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難治性疾患等政策研究事業（難治性疾患政策研究事業）

自己免疫疾患に関する調査研究

平成 30 年度　統括・分担研究報告書

研究代表者　森　雅亮

平成 31（2019）年　3 月

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Ⅱ．総括研究報告

平成 30 年度厚生労働科学研究費補助金
難治性疾患等政策研究事業（難治性疾患政策研究事業）
統括研究報告書

自己免疫疾患に関する研究

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研究要旨
本研究 2 年目である平成 30 年度は、多診療領域の専門家 37 名が集結しつつ 5 つの分科会を組織し、①全身性エリテマトーデス（SLE、疾病番号 49)、②多発性筋炎・皮膚筋炎（PM/DM、同 50)、③混合性結合織病（MCTD、同 52)、④シェーグレン症候群（SS、同 53)、⑤成人スチル病（ASD、同 54)、⑥若年性特発性関節炎（JIA、同 107）の 6 疾病に関し、１）診断基準や重症度分類の検証と改訂、国際分類基準の検証および関連学会承認獲得、２）診療ガイドライン(GL)の策定と改訂、関連学会承認獲得、３）臨床個人調査票の解析や検証と難病レジストリ構築への協力、4）早期診断や診療施設紹介のための自己免疫疾患難病診療ネットワーク構築５）AMED 実用化研究事業との連携等を、昨年度に引き続いて活発な研究活動が行われた。
具体的には、本年度は以下の成果が得られた。
①SLE 分科会：(1)診療 GL の推奨文・解説文の執筆、(2) パブリックコメントや Minds による AGREEII を用いた評価、(3) 出版社による校正後に来年度早期に公開予定、②PM/DM 分科会:(1) 我が国の既存の治療 GL の国際化と診療 GL 改訂への拡充（推奨文草案作成まで終了）、(2)小児と成人の GL の統合（小児例では、既存の GL を基盤とした専門家の意見を統合した記述的な項目で補完)、③MCTD 分科会：(1) 厚生労働省研究班で作成した 1996 年、2004 年の診断の手引きの検証による MCTD の定義の再考、(2) (1)の結果に基づいた診断基準の改訂、(3)重症度分類(2011)の妥当性の検証、(4)治療 GL(診断+治療)の策定作業、④SS 分科会:(1)国際診断（分類）基準の検定、(2)(1)の結果に基づいた診断基準の検証、(3)重症度分類の検証・改訂案の検討、(4)診療ガイドライン 2017 年版の検証・改訂の準備および英語版の発刊、(5)臨床調査個人票の誤記の指摘、(6)疫学調査と臨床調査個人票との比較、(7)公開講座の企画、(8)小児慢性特定疾患としての小児 SS との transition に関する検討の準備、(9)難病プラットフォーム作成の準備、⑤JIA/ ASD 分科会: (1) ASD 診療 GL 2017 年度版の見直しと今後の改訂ポイントの抽出、(2) ASD 呼称変更の検討、(3) 関節型 JIA の指定難病登録とその後の対応、(4)抗 IL-6 抗体投与下のマクロファージ活性化症候群(MAS)の検討、(5)公開講座の研究分担者地域での開催(金沢市)。

A. 研究目的

主な全身性自己免疫疾患である指定難病、①全身性エリテマトーデス（SLE、疾病番号 49)、②多発性筋炎・皮膚筋炎(PM/DM、同 50)、③混合性結合織病(MCTD、同 52)、④シェーグレン症候群（SS、同 53)、⑤成人スチル病（ASD、同 54)、および平成 30 年度から指定難病に登録された⑥若年性特発性関節炎（JIA、同 107）の 6 疾病に関し、SLE 分科会、PM/DM 分科会、MCTD 分科会、JIA/ASD 分科会の 5 分科会がそれぞれ担当し、研究を進める。前記の体制で、１）診断基準や重症度分類の検証と改訂、国際分類基準の検証、関連学会承認獲得、２）Minds に原則準拠した診療ガイドライン（GL）の策定と改訂、関連学会承認獲得、３）臨床個人調査票の解析や検証と難病レジストリ構築への協力、４）早期診断や診療施設紹介のための自己免疫疾患難病診療ネットワーク構築、５）AMED 実用化研究事業との連携、等を、小児・成人で一体的して行うことを目的とした。

B. 研究方法

多診療領域の専門家37名が集結しつつ分科会を形成し、１）診断基準や重症度分類の検証と改訂、国際分類基準の検証、及び関連学会承認獲得、２）診療ガイドライン（GL）の策定と改訂、関連学会承認獲得、３）臨床個人調査票の解析や改訂案提案と難病レジストリ構築、４）早期診断と治療のための啓発活動と自己免疫疾患難病診療ネットワーク構築、５）AMED実用化研究事業との連携、などを小児・成人一体的に実施した。

（倫理面への配慮）
1)「人を対象とする医学系研究に関する倫理指針」に則して、研究を行う。研究内容は、研究代表者および分担研究者の施設での倫理審査の承認後、診療録の後方視学的解析および患者あるいは保護者の同意済の保存血清を使用する。各施設で貼付するポスターに記載する等して倫理的配慮を行っていく。
2)個人情報の保護に関する法律（平成15年5月法律第57号）第50条の規定に沿い、得られた患者の情報は外部に一切漏れないように厳重に管理した。研究結果の公表に際しては、個人の特定が不可能であるよう配慮した。

C. 研究結果

①SLE 分科会：(1)診療 GL の推奨文・解説文の執筆、(2) パブリックコメントや Minds による AGREEII を用いた評価、(3) 出版社による校正後に来年度早期に公開予定、

②PM/DM 分科会：(1) 我が国の既存の治療 GL の国際化と診療 GL 改訂への拡充（推奨文草案作成まで終了）、(2)小児と成人の GL の統合（小児例では、既存の GL を基盤とした専門家の意見を統合した記述的な項目で補完）、

③MCTD 分科会：(1) 厚生労働省研究班で作成した 1996 年、2004 年の診断の手引きの検証による疾患定義の再考、(2) (1)の結果に基づいた診断基準の改訂、(3)重症度分類（2011）の妥当性の検証、(4)治療 GL(診断+治療)の策定作業、

④SS 分科会：(1)国際診断（分類）基準の検定、(2)(1)の結果に基づいた診断基準の検証、(3)重症度分類の検証・改訂案の検討、 (4)診療ガイドライン 2017 年版の検証・改訂の準備および英語版の発刊、(5)臨床調査個人票の誤記の指摘、(6)疫学調査と臨床調査個人票との比較、(7)公開講座の企画、(8)小児慢性特定疾患としての小児 SS との transition に関する検討の準備、(9)難病プラットフォーム作成の準備、

⑤JIA/ ASD 分科会：(1) ASD 診療 GL 2017 年度版の見直しと今後の改訂ポイントの抽出、(2) ASD 呼称変更の検討、(3) 関節型 JIA の指定難病登録とその後の対応、(4)抗 IL-6 抗体投与下のマクロファージ活性化症候群（MAS）の検討、(5)公開講座の研究分担者地域での開催（金沢市）。

D. 考察

本研究 2 年目の平成 30 年度は、当初から目標として掲げてきた、１）診断基準や重症度分類の検証と改訂、国際分類基準の検証、及び関連学会承認獲得、２）診療ガイドライン（GL）の策定と改訂、関連学会承認獲得、３）臨床個人調査票の解析や改訂案提案と難病レジストリ構築、４）早期診断と治療のための啓発活動と自己免疫疾患難病診療ネットワーク構築、５）AMED 実用化研究事業との連携について、各分科会が精力的に挑み、先進的な成果を挙げることができた。特に、小児・成人を一体化して検討を行えていることで、難病対策として重要視されている移行医療を十分意識した成果となっている。

E. 結論

E. 結論

本研究体制は、SLE、PM/DM、MCTD、SS、 JIA/ASD の５つの分科会に、成人内科医と小児科医が配置された形態で行われた小児・成人一体化研究である。それぞれの分科会は、必要に応じて他の分科会メンバーを動員して各分科会を開催して、様々な課題に取り組んだ。詳細については、各班の分担研究報告書をご参照頂きたい。

F. 健康危険情報

特記すべき事項無し

G. 研究発表

各分担研究報告書参照

H. 知的財産権の出願・登録状況（予定を含む）

各分担研究報告書参照

Ⅲ. 分担研究報告

平成 30 年度厚生労働科学研究費補助金
難治性疾患等政策研究事業（難治性疾患政策研究事業）
分担研究報告書

多発性筋炎・皮膚筋炎に関する調査研究

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研究要旨

本研究プロジェクトにおいては、指定難病の一つである多発性筋炎・皮膚筋炎（PM/DM）に関して、我が国の既存の治療ガイドラインの国際化と診療ガイドラインへの拡充、また小児と成人のガイドラインの統合を目指した改訂を行うことを目的とした。

改訂に向けた作業では、治療に関して設定した、GRADE 法に準拠したClinical Questions（小児例対象を含む）に対し、P（Patients, Problem, Population）、I （Interventions）、C （Comparisons, Controls）、O（Outcomes）を設定した。これに基づいた文献検索の上、システマティックレビューを行い、エビデンス評価の上、レポートを作成、レポートを基に推奨文草案作成までを終了した。

希少疾患であり、古典的薬剤による経験的治療が確立していてコントロールスタディの計画が倫理的に許可されにくいPM/DMにおいては、なかんづく小児例では、コントロールスタディの報告に乏しく、GRADE法に準拠したシステマティックレビューのみで診療ガイドラインを構成することは困難であることから、既存のガイドラインを基盤とした、専門家の意見を統合した記述的な項目で、補完する必要があるものと考えられた。

A. 研究目的

指定難病の一つである、自己免疫疾患の多発性筋炎・皮膚筋炎（PM/DM）に関して、診療の標準化、医療の質の向上・患者のQOL の改善を目指すために、我が国の既存の治療ガイドラインの改訂を行うことを目的とする。

改訂にあたっては、下記の点を重点的項目に挙げた。

1. GRADE 法に準拠したPM/DMガイドライン改訂：膠原病･リウマチ内科医、神経内科医、皮膚科医が学会レベルで合意した、我が国の既存の PM/DM 治療ガイドラインは、世界に類を見ない内容ではあるが、GRADE 法に準拠していないため、準拠した改訂を行い、国際的に通用する診療ガイドラインへの改定を目指した作業を行う。

2. 小児PM/DMガイドラインと成人例に対するPM/DMガイドラインの統合：既存のガイドラインは、日本小児科学会発行のものと、上述の日本リウマチ学会、日本神経内科学会、日本皮膚科学会承認の成人用PM/DM 治療ガイドラインがある。本分科会では、小児PM/DMに関するガイドラインを含めた既存のガイドライン改訂を行う。

B. 研究方法

1. GRADE 法に準拠したPM/DMガイドライン改訂

2017年度より本作業に着手しており、GRADE法に準拠して、治療に関して、Clinical Question（CQ）が設定済である。それぞれのCQに対し、P（Patients, Problem, Population）、O（Outcomes）とその重要度、I （Interventions）／C（Comparisons, Controls）のリスト化を行う。そののちに、日本医学図書館協会の協力を得て、PubMed, Cochrane Library、医中誌Webをデータベースとした1990～2017年までの文献検索を行ったうえで、システマティックレビューを施行する。システマティックレビューを基に、それぞれのCQに対する推奨文草案を作成する。この作業のため、研究協力員を増員する。

2. 小児PM/DMガイドラインと成人例に対するPM/DMガイドラインの統合

本分科会には小児科医の参加も得ており、ガイドライン改訂のために、2017年度に設定したCQには、小児PM/DMを対象としたものも、成人PM/DMと同様に含めた。1. のGRADE法に準拠したPICO設定、文献検索、システマティックレビューと推奨文草案作成も、同様に行う。

（倫理面への配慮）

特記すべきことなし。

C. 研究結果

1. GRADE 法に準拠したPM/DMガイドライン改訂

CQに対するPは、性別の指定なく、18歳以上で、疾患・病態はPM/DM、地理的要件には医療体制の確立した地域を挙げた。

Iは、副腎皮質ステロイド、アザチオプリン、メトトレキサート、タクロリムス、シクロスポリン、ミコフェノール酸モフェチル、シクロホスファミド、トファチニブ、生物学的製剤、大量ガンマグロブリン療法を挙げた。Cはプラセボとした。

Oは、益となるものとして、筋力回復、筋原性酵素正常化、QOL改善、筋電図の改善、ステロイド減量効果、MRIの改善、筋生検の改善を挙げ、それぞれの重要度は9, 9, 9, 7, 9, 7, 7点とした。害となるものとしては、副作用発現と重症合併症発現を挙げ、それぞれの重要度は8, 8 点としている。

日本医学図書館協会の協力を得て、PubMed, Cochrane Library、医中誌Webをデータベースとした1990～2017年までの文献検索を行ったうえで、システマティックレビューを開始したところ、多くのIに対して、コントロールスタディは一つずつしか見出されなかった。絞り込まれた文献に対して、GRADE法に準拠したシステマティックレビューを行い、エビデンスを評価の上、レポートをまとめた。

レポートを基に、システマティックレビュー担当者と別の担当者が推奨文草案を作成した。

2. 小児PM/DMガイドラインと成人例に対するPM/DMガイドラインの統合

1. と同様にPICOを設定したが、Pの条件として18歳未満とした。

GRADE法に準拠したシステマティックレビューを開始したところ、設定したCQ3つのうち2つでコントロールスタディが一つも見出されず、推奨文草案はCQ一つに対してのみ作成した。

D. 考察

国際的なガイドライン作成法であるGRADE法に準拠したガイドライン改訂に対する作業が進行した。2019年度には、推奨文承認や公開による意見募集などを行う予定である。

ただし、希少疾患であり、古典的薬剤による経験的治療がすでに確立していてコントロールスタディの計画が倫理的に許可されにくいPM/DMにおいては、なかんづく小児例では、コントロールスタディの報告に乏しく、GRADE法に準拠したシステマティックレビューのみで診療ガイドラインを構成することは困難である。既存のガイドラインを基盤とし、専門家の意見を統合した記述的な項目で補完する必要があるものと考える。

E. 結論

GRADE 法に準拠したガイドライン改訂作業を完成させると共に、専門家の意見統合による記述的ガイドライン作成の作業も進める。

F. 健康危険情報

なし

G. 研究発表

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2. 学会発表
特記すべきものなし

H. 知的財産権の出願・登録状況
（予定を含む）

1. 特許取得
なし

2. 実用新案登録
なし

3. その他
特記事項なし

平成 30 年度厚生労働科学研究費補助金
難治性疾患等政策研究事業（難治性疾患政策研究事業）
分担研究報告書

シェーグレン症候群に関する調査研究

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研究要旨

本研究プロジェクトにおいては、指定難病の一つであるシェーグレン症候群（SS）に焦点を当て、疫学調査、予防因子・予後予測因子の解析、診断基準の検証・改訂、重症度分類の検証・改訂、診療ガイドライン 2017 年版の検証などを目的とした。本研究成果により、効率的で安全性の高いスタンダード医療が確立でき、普及することにより患者の予後、QOL の改善、医療費の節約化につながると期待される。

本年度の研究課題として具体的には以下の項目を進めた。1)国際診断（分類）基準の検定、2)1)の結果に基づいた診断基準の検証。現行の厚労省基準が一次性および二次性 SS の診断基準として最適であることが判明した。3)重症度分類の検証・改訂案の検討、4)診療ガイドライン 2017 年版の検証・改訂の準備および英語版の発刊、5)臨床調査個人票の誤記の指摘、6)疫学調査と臨床調査個人票との比較、7)公開講座の企画、8)小児慢性特定疾患としての小児 SS との transition に関する検討の準備、9)難病プラットフォーム作成の準備、などを行った。

A. 研究目的

自己免疫疾患診療の標準化、医療の質の向上・患者の QOL の改善を目指すために、1)疫学調査及び個人調査票に基づく統計学的病態解析による予防因子・予後予測因子の提唱、2)実践的かつ国際的視野に立った診断基準の検定・改訂、3)重症度分類の確立、4)臨床現場で活用できる診療ガイドラインの作成、5)臨床調査個人票の検証、6)疫学調査結果と本指定難病制度による認定患者数の比較検証、7)本疾患の啓発のために公開講座を企画、8)小児慢性特定疾患としての小児 SS と成人 SS との transition の問題を解決する、9)難病プラットフォーム作成に向けた議論、などを目的とした。

本研究は、自己免疫疾患の医療の向上、患者の QOL の改善を目指すために必要不可欠な研究プロジェクトである。本研究では、SS を対象疾患とし、各分野の専門家から研究体制を構築し、効率のよい建設的な研究班を組織、運営した。

過去の実績として、SS に関する一次、二次疫学調査を 2010-2011 年にすでに終了し、そのデータに

基づく予防・予後予測因子を提唱してきた。

2015年1月からSSが指定難病に指定された時点では、1)感度及び特異度が最も優れていた旧厚生省診断基準(現厚労省基準、1999 年)を公式の基準と制定し、2)重症度分類としてESSDAIを提唱した。この診断基準と重症度分類に基づいた臨床調査個人票（新規、更新）案を提唱し、厚労省の指定難病の評価基準として活用されている。

診断基準に関しては、厚労省基準(1999 年)に加えて、世界的には改訂アメリカ・ヨーロッパ基準（2002年)、アメリカリウマチ基準(2012年)、ACR-EULAR基準（2016年）が使用されている。本研究班において、4つの基準に関して、日本のSS患者を用いた検証をした結果、日本のSS患者においては、特異度は厚労省基準において最も高く(90.9%)、感度はACR-EULAR基準が最も優れていること(95.4%)を明らかにしてきた。しかしながら、口腔検査および眼科検査において上記２つの基準には異なる点が存在しているため、同一検査結果での比較検討が課題として残っている。

また、2014～2017年にかけて、Minds2014に準拠した診療ガイドライン2017年版を作成し厚労省HPで公表している。英語論文として発表することにより、日本のエビデンスを世界に発することが可能となる。

このように、本班の独創的な点は、サイエンスと臨床データに基づき、診療ガイドラインを作成し、SS医療の標準化を目指していることである。

B. 研究方法

1)国際診断（分類）基準の検定：

ACR-EULAR基準（2016年）と厚労省基準(1999年)を日本人SS患者を対象として比較検討した結果、前者において感度が最も高く、後者において特異度が最も高い事を明らかにしてきた(添付表1～3)[1)]。しかし、二つの基準において、細かな判定基準が異なる点が問題であり、本班において、前向き研究による検証を行うこととした。

対象者は、SS分科会の構成メンバーが所属する13施設から抽出した、一次性SS患者376名、非SS患者211名を、二次性SS患者190名、非SS患者33名を対象とした。

ACR-EULAR基準と厚労省基準における検査の相違点は、２点である（添付表4)。

一点目は、唾液分泌量がACR-EULAR基準では無刺激唾液量（0.1ml/分以下）を使用しているのに対して、厚労省基準ではガムテスト（10ml/10分以下）あるいはサクソンテスト(2g/2分以下)と刺激唾液量を測定している点である。そこで、前向き研究では、無刺激唾液量と刺激唾液量の両者を測定することとした。

二点目の違いは、角結膜の傷を数字化した van Bijsterveld scoreの陽性とする基準点数である。ACR-EULAR基準では、4点以上を陽性しているが、厚労省基準では3点以上を陽性としてやや甘い基準となっている。そこで、前向き研究では陽性陰性の判定記載だけではなく、実際の点数を記載することにより比較検討することとした。

2)1)の結果に基づく国内診断基準の改訂準備：

1)の結果に基づき国内の診断基準の改訂も視野に入れる。

3)重症度分類の検証・改訂の準備：

現在の重症度分類は、ESSDAIを応用している。ESSDAIは一次性SSを対象とした活動性評価指標であるため、二次性SSを対象とした重症度分類の必要性を検討する。また、乾燥症状や乾燥所見がESSDAI項目に含まれていないため、乾燥症状および所見の強い患者が重症と評価されない可能性もあり、より幅の広い重症度分類の提案を試みた。
具体的には、一次性SS87名、二次性SS32名を対象として、(1)ESSDAが5点以上、(2)ESSPRIが5点以上、(3)ESSPRIの乾燥症状が5点以上、をそれぞれ重症度と定義した際の重症者の割合を検討した。

4)診療ガイドライン2017年版の検証・改訂の準備：

2017年度版[2)]を作成したばかりなので、今後のエビデンス（RCTやメタアナライシスなど）を踏まえて検討する。また、世界に発信するために英語論文として発表する。

5)臨床調査個人票の誤記の指摘：

2017年に臨床個人票はフォーマットが統一され改訂されたが、その際に誤記が多く認められた。改訂版を作成し本班のH29年度報告書で報告済みであるが、まだHP上で改訂されていないため、継続して改訂依頼に努める。

6)疫学調査と臨床調査個人票との比較：

本研究班で2011年に施行した「2010年のシェーグレン症候群患者の全国疫学一次調査、二次調査」の結果と、指定難病認定後の重症シェーグレン症候群患者数を比較検討する。

7)公開講座の準備：

本症の理解と指定難病認定に関して、市民講座を

開催して患者、医師、コメデイカルなどに啓発、周知する。

8)小児慢性特定疾患としての小児 SS との transition に関する検討の準備：
小児慢性特定疾患の小児 SS の人数の把握、診断基準、重症度分類などを成人 SS と比較検討し、transition に向けて現実的な対策を提案する。

9)難病プラットフォーム作成の準備：
SS 患者のデータベース作成を目的とするが、全難病における基本的戦略の作成を待って進めることとする。

C.研究結果

1)国際診断（分類）基準の検定：
(1)一次性 SS：厚労省基準においては、感度、特異度がそれぞれ 87.0%および 88.6%であり、ACR-EULAR 基準では、それぞれ 92.0%および 74.9%であった(図 5)。一次性 SS 患者を対象とした場合、特異度は厚労省基準が最も高く、感度は ACR-EULAR 基準が最も優れていた。
(2)二次性 SS：厚労省基準においては、感度、特異度がそれぞれ 75.8%および 84.8%であり、ACR-EULAR 基準では、それぞれ 90.5%および 45.5%であった（図 6)。二次性 SS 患者を対象とした場合においても、特異度は厚労省基準が最も高く、感度は ACR-EULAR 基準が最も優れていた。

2)1)の結果に基づく国内診断基準の改訂の検定：
分類基準としては、特異度が高い基準が求められている。一方、診断基準としては、感度と特異度の両方が高いものが望ましいとされている。その観点から、1)の結果に基づくと、一次性 SS および二次性 SS の診断基準としては、現行の厚労省基準が最も適切であることが判明した。

3)重症度分類の検証・改訂の準備：
(1)ESSDA が 5 点以上:一次性 SS では 24.1%が重症、二次性 SS では 40.6%が重症、全体では 28.6%が重症となった（図 7)。
(2)ESSDAI and/or ESSPRI が 5 点以上：一次性 SS では 51.7%が重症、二次性 SS では 84.4%が重症、全体では 57.1%が重症となった（図 8)。
(3)ESSDAI and/or ESSPRI の乾燥症状が 5 点以上：一次性 SS では 74.7%が重症、二次性 SS では 71.9%が重症、全体では 77.3%が重症となった（図 9)。
以上の結果から、ESSDAI に ESSPRI あるいは乾燥症状を加えた場合、重症者の頻度が上昇することが判明した。今後、口腔乾燥検査所見、眼科乾燥検査所見を加味した検討を進め、より実臨床に近い有益な重症度分類案を提唱したい。

4)診療ガイドライン 2017 年版の検証・改訂の準備：
診療ガイドライン 2017 年版の英語版を作成し、日本リウマチ学会誌 Modern Rheumatology に掲載した（図 10）[3]。また、ヨーロッパで作成中の SS に関する recommendation が発表された際には、本診療ガイドラインとの比較検討を予定するである。

5)臨床調査個人票の誤記の指摘：
すでに本班の H29 年度報告書により厚労省へ報告済みであるが、HP 上はまだ改訂はされていない。

6)疫学調査と臨床調査個人票との比較：
2010 年の全国一次疫学調査では、66,317 人であった。一方、重症 SS 患者数は 2016 年度末時点で 11,201 人である。両者のギャップの原因は、幾つか考えられる。1)SS 患者のうち重症患者(ESSDAI５点以上)の割合が約 30%と推定されること、2)診断には侵襲性のある検査や他科での検査が必要なため確定診断に至っていないこと、3)SS が周知されていないこと、などであろう。

7)公開講座の準備：
市民公開講座は、本班主催で 2019 年 6 月 9 日に東京で開催されることとなった。その際に、SS 分科会としても SS 患者を対象とした公開講座を企画開催することとした。

8)小児慢性特定疾患としての小児 SS との transition に関する検討の準備：
小児 SS の実態把握と共に、すでに厚労省や日本小児リウマチ学会で承認されている小児 SS の診断基準、重症度分類と成人 SS との比較検討をスタートし、対策を検討していきたい。

9)難病プラットフォーム作成の準備：
難病全体の方向性および具体的な戦略を待つこととした。

D.結論、E.考察

1)厚労省基準と ACR-EULAR 分類基準の比較検証：
特異度は厚労省基準（1999 年）が最も高く、感度は ACR-EULAR 基準（2016 年）が最も高い事を明らかにした。本研究成果は Ann Rheum Dis 誌上(2017)で発表し、世界で高く評価されている。
今年度は、同一検査基準で評価した SS 症例を追

加して検証した結果、同様の結果であった。診断基準としては、一次性 SS では感度、特異度ともに 87%以上、二次性 SS では共に 75%以上の現行の厚労省基準が最適であることが判明した。

2)診療ガイドライン 2017 年版の英語論文作成：
エビデンスに基づく診療ガイドライン 2017 年版の英語版を Modren Rheumatology 誌上で発表し、世界に発信した。

F. 健康危険情報

なし

G. 研究発表

論文発表

1.Tsuboi, H., Hagiwara, S., Asashima, H., Takahashi, H., Hirota, T., Umihara, H., Kawakami, A., Nakamura, H., Sano, H., Tsubota, K., Ogawa, Y., Takamura, E., Saito, I., Inoue, H., Nakamura, S., Moriyama, M., Takeuchi, T., Tanaka, Y., Hirata, S., Mimori, T., Matsumoto, I., and Sumida, T. Comparison of the performance of new ACR-EULAR classification criteria for primary Sjögren's syndrome with former sets of criteria in Japanese patients. *Ann Rheum Dis. 76:1980-1985, 2017.*

2.シェーグレン症候群診療ガイドライン 2017 年版、住田孝之編集、診断と治療社、2017 年

3. Sumida, T., Azuma, N., Moriyama, M., Takahashi, H., Asashima, H., Honda, F., Abe, S., Ono, Y., Hirota, T., Hirata, S., Tanaka, Y., Shimizu, T., Nakamura, H., Kawakami, A., Sano, H., Ogawa, Y., Tsubota, K., Koufuchi, R., Ssaito, I., Tanaka, A., Nakamura, S., Takamura, E., Tanaka, M., Suzuki, K., Takeuchi, T., Yamakawa, N., Mimori, T., Ohta, A., Nishiyama, S., Yoshihara, T., Suzuki, Y., Kawano, M., Tomiita, M., and Sumida, T. Clinical practice guideline for Sjögren's syndrome 2017. *Mod. Rheumatol. 28:383-408, 2018.*

H. 知的財産権の出願・登録状況（予定も含む）

1. **特許取得：**なし
2. **実用新案登録：**なし
3. **その他：**特記事項なし

表 1

シェーグレン症候群の改訂診断基準

（厚生省1999）

1 生検病理組織検査で次のいずれかの陽性所見を認めること
A 口唇腺組織4mm²当たり1focus（導管周囲に50個以上のリンパ球浸潤）以上
B 涙腺組織4mm²当たり1focus（導管周囲に50個以上のリンパ球浸潤）以上

2 口腔検査で次のいずれかの陽性所見を認めること
A 唾液腺造影でStage1（直径1mm未満の小点状陰影）以上の異常所見
B 唾液分泌量低下（ガム試験にて10分間で10ml以下またはサクソンテストにて2分間で2g以下）があり、かつ唾液腺シンチグラフィにて機能低下の所見

3 眼科検査で次のいずれかの陽性所見を認めること
A シルマー試験で5分間に5mm以下で、かつローズベンガル試験でvan Bijsterveld score3以上
B シルマー試験で5分間に5mm以下で、かつ蛍光色素（フルオレセイン）試験で陽性

4 血清検査で次のいずれかの陽性所見を認めること
A 抗SS-A抗体陽性　B 抗SS-B抗体陽性

診断基準：上記4項目のうち、いずれか2項目以上を満たす

（藤林孝司ほか：厚生省特定疾患免疫疾患調査研究班平成10年度研究報告、1999より引用）
(Fujibayashi T, et al. Mod Rheumatol 14:425-434, 2004)

表 2

ACR/EULAR基準(2016) for primary SS

項目	Weight/Score
口唇唾液腺の巣状リンパ球性唾液腺炎でフォーカススコア≧1	3
抗SS-A（Ro）抗体陽性	3
少なくとも一方の目でOSS≧5（あるいはvan Bijsterveld≧4）	1
少なくとも一方の目でシルマー試験≦5 mm/5分	1
無刺激唾液分泌量≦0.1 ml/分	1
合計4点以上でSSと分類	

適応基準：眼あるいは口腔乾燥症状のある患者、あるいはESSDAI questionnaireでSS疑いの患者（少なくとも1つのドメインが陽性）

除外基準：頭頸部の放射線療法の既往、活動性HCV感染（PCR陽性）、AIDS、サルコイドーシス、アミロイドーシス、GVHD、IgG4関連疾患

OSS（Ocular staining score）：角膜は蛍光色素染色、結膜はリサミングリーン染色、0～12点/片眼のスコアリング（Am J Ophthalmol 149:405-415, 2010）

(Ann Rheum Dis 76:9-16, 2017) (Arthritis Rheumatol 69:35-45, 2016)

表 3

厚労省基準の4項目＋無刺激唾液実施したSS患者(383名)

基準	感度（%）（95%CI）	特異度（%）（95%CI）
厚労省基準（Shirmer試験＋Rose-bengal試験vBS≧3 and/or 蛍光色素陽性）	74.9	90.6
ACR-EULAR基準（vBS≧4）	94.1	76.7

Tsuboi H, et al. Ann Rheu Dis 2018

表 4

厚労省基準とACR/EUALR基準の方法の違い

・主治医による臨床診断をゴールドスタンダード
・調査票を用いて、ACR-EULAR新基準（2016年）、厚生省基準（1999年）、AECG基準（2002年）、ACR基準（2012年）の満足度に関して後ろ向きに解析

基準	評価方法	
	唾液分泌量	眼染色
厚労省基準	ガム≦10 ml/10分 or サクソン≦2g/2分（基準通り）	vBS≧3（ローズ or リサミン or 蛍光色素）and/or 蛍光色素陽性（基準通り）
AECG基準	無刺激唾液≦0.1ml/分（基準通り）	vBS≧4（ローズ or リサミン or 蛍光色素）（基準通り）
ACR基準	採用なし	vBS≧3（ローズ or リサミン or 蛍光色素）and/or 蛍光色素陽性
ACR-EULAR新基準	無刺激唾液≦0.1ml/分（基準通り）	vBS≧4（ローズ or リサミン or 蛍光色素）

表 5

一次性SS患者の感度、特異度（合計587例）

（主治医診断：一次性SS376例/非SS211例）

基準	唾液量・眼科評価方法	感度（%）（95%CI）	特異度（%）（95%CI）
厚労省	サクソン陽性 and/or ガム陽性 vBS≧3 and/or 蛍光色素陽性	87.0	88.6
ACR-EULAR 4点以上	無刺激唾液陽性 vBS≧4	92.0	74.9

表 6

二次性SSにおける感度、特異度（合計223症例）

（主治医判断：二次性SS190例/非SS33例）

基準	唾液量・眼科評価方法	感度（%）（95%CI）	特異度（%）（95%CI）
厚労省	サクソン陽性 and/or ガム陽性 vBS≧3 and/or 蛍光色素陽性	75.8	84.8
ACR-EULAR 4点以上	無刺激唾液陽性 vBS≧4	90.5	45.5
ACR-EULAR 5点以上		75.3	69.7
ACR-EULAR 6点以上		61.6	97.0

表 7

ESSDAIを重症度基準とした場合

厚労省基準を満たしたSSのうち、ESSDAI、ESSPRIの両方のデータが揃った症例119例（一次性SS87例、二次性SS32例）

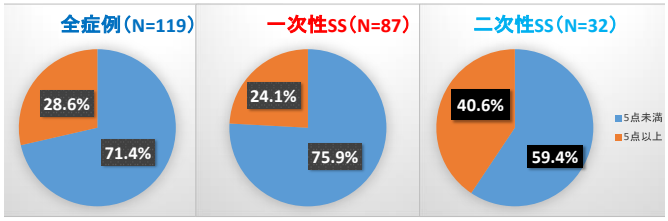

表 8

ESSDAI and/or ESSPRIを重症度基準とした場合

厚労省基準を満たしたSSのうち、ESSDAI、ESSPRIの両方のデータが揃った症例119例（一次性SS87例、二次性SS32例）

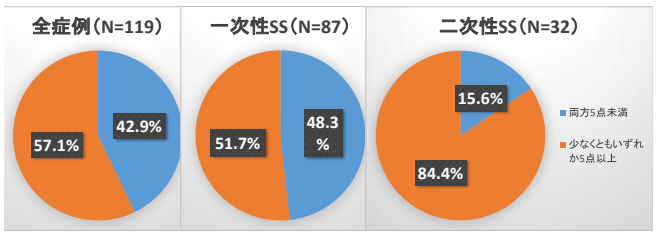

表 9

ESSDAI and/or 乾燥を重症度基準とした場合

厚労省基準を満たしたSSのうち、ESSDAI、ESSPRIの両方のデータが揃った症例119例（一次性SS87例、二次性SS32例）

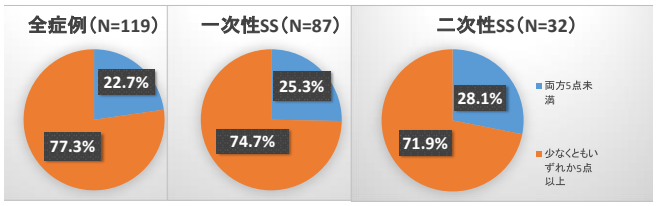

表 10

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REVIEW ARTICLE

OPEN ACCESS

Clinical practice guideline for Sjögren's syndrome 2017

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ABSTRACT

Objectives: The objective of this study is to develop clinical practice guideline (CPG) for Sjögren's syndrome (SS) based on recently available clinical and therapeutic evidences.

Methods: The CPG committee for SS was organized by the Research Team for Autoimmune Diseases, Research Program for Intractable Disease of the Ministry of Health, Labor and Welfare (MHLW), Japan. The committee completed a systematic review of evidences for several clinical questions and developed CPG for SS 2017 according to the procedure proposed by the Medical Information Network Distribution Service (Minds). The recommendations and their strength were checked by the modified Delphi method. The CPG for SS 2017 has been officially approved by both Japan College of Rheumatology and the Japanese Society for SS.

Results: The CPG committee set 38 clinical questions for clinical symptoms, signs, treatment, and management of SS in pediatric, adult and pregnant patients, using the PICO (P: patients, problem, population, I: interventions, C: comparisons, controls, comparators, O: outcomes) format. A summary of evidence, development of recommendation, recommendation, and strength for these 38 clinical questions are presented in the CPG.

Conclusion: The CPG for SS 2017 should contribute to improvement and standardization of diagnosis and treatment of SS.

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KEYWORDS
Sjögren's syndrome; clinical practice guideline; clinical question; systematic review; Medical Information Network Distribution Service (Minds)

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難治性疾患等政策研究事業（難治性疾患政策研究事業）
分担研究報告書

全身性エリテマトーデスの診療ガイドライン作成に関する研究

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研究要旨
本研究は全身性エリテマトーデス(SLE)の総合的な診療ガイドラインを中心とした活動を行ってきた。本年度は、診療ガイドラインの推奨文・解説文を執筆し、パブリックコメントや M-inds による AGREEII を用いた評価をしていただき、出版社での校正後に公開予定である。

A. 研究目的

本研究は全身性エリテマトーデ.(SLE)の本邦における初めての診療ガイドラインを作成することを目的とする。SLE は代表的自己免疫疾患で全身の臓器を冒し、その病態像は多様性に富む。その為、専門家の間でも治療方針の決定に難渋することが多い。更に近年、新規治療薬の開発や健康保険認可がなされた。これらが為に希少性疾患であるが、本疾患の診療を整理し、専門医を対象とした指針を出す事は非常に重要である。

本邦においてこれは最初の SLE のガイドラインである。一方、海外においては、世界の二大学会であるアメリカリウマチ学会、ヨーロッパリウマチ学会では 10 年以上ガイドラインが作成されていない。2018年1月に英国リウマチ学会から成人 SLE の疾患管理(management)に関するガイドラインの論文が掲載されたが、現在我々が作成している小児・成人・産褥婦における診断・評価・治療に指標を示す包括的なガイドラインはこれまで他国にもない。

研究方法
本事業班参加各施設を中心に、診療ガイドライン作成グループを作成し、診療ガイドライン作成の標準的手法となっている Grading of Recommendations Assessment, Development and Evaluation(GRADE)システムを用いてシステマティックレビュー(SR)に基づいたガイドラインを作成した。
平成 27 年度はガイドライン作成の前提として、SLE の診断基準の検証を行った。現在診断に流用されているアメリカリウマチ学会(ACR)分類基準(表1)と 2012 年に SLE 臨床研究専門家集団(SLICC)が提出した新分類基準(表2)を本邦の症例シナリオ 495 例を用いて 27 名のエキスパートの診断を基準に感度、特異度を検討した。即ち、それぞれの施設を実際に受診した患者(SLE 及び非 SLE 膠原病患者)の病歴、検査結果、身体所見を同一のフォーマットにまとめ、それらを事務局に集積して、全 495 例のシナリオ集を各施設に分配した。シナリオの例を図1に示す。ガイドライン作成の具体的方法としては、作成グループの編成と Clinical Questions(CQ)の設定を行ない、ガイドライン作成グループでは膠原病専門医及び一般内科を含む他科医師、患者、看護師などの医師以外の医療関係者、医療統計学専門家、医療経済学専門家の参加を決定した。平成 28 年度には、CQ のうちいくつかについて推奨文作成を開始した。平成 29 年度は、すべての治療関連 CQ に関してシステマティックレビューを行い、推奨文を作成した。平成30年度はパネル会議を行い、推奨文を決定し、外部評価・パブリックコメント募集・Minds(公益法人財団日本医療機能評価機構)での評価を経てガイドラインが完成した。平成31年3月現在、出版社にて校正作業が行われており、平成31年度内に書籍で公開予定である。

B. 研究結果
平成 27 年度には SLICC 分類基準と ACR 分類基準の本邦の実症例による検証を行い、SLICC 分類が高感度で同程度の特異度を有するとのデータを得て、論文発表した。ガイドライン作成委員会は、各科専門医及び医療統計専門家を加えて編成し、CQ はガイドライン作成委員会で認証された。それに基づき、すべての CQ に推奨文が作成された。平成30年度はパネル会議でそれらの最終的な承認をえて平成31年度に公表する。一部の CQ については並行して論文化を進めており平成31年度中に投稿する。

D.考察
SLICC 基準の検証については報告によってその評価が異なり、それらを解析した。また、症例シナリオの専門医の診断において診断が分かれる病態像がいくつかあることが判明しそれらを解析し、今後の SLE 分類・診断基準の改訂・作成に提言する形で論文作成し、発表した。なお、新たなアメリカリウマチ学会・ヨーロッパリウマチ学会共同の分類基準の提案が平成29年11月のアメリカリウマチ学会年次集会であり、正式な分類基準の改定となった時点で本研究班での評価を予定する。
ガイドラインは、国際的に発表することを目的とし、現在公表に向けた最終的な調整を行なっている。

E.結論
本邦での検証では SLE の診断(分類)において SLICC 新分類基準は旧来の ACR 分類基準に並ぶ診断(分類)能を認めた。本邦ではじめて作成する包括的な SLE 診療ガイドラインは、来年度早期の公表の予定で最終的な調整を行なっている。

F.健康危険情報
特記事項なし

G.研究発表
1.論文発表

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2.学会発表

該当なし

H.知的財産権の出願・登録状況（予定を含む）

1. 特許取得　なし

実用新案登録

その他

平成 30 年度厚生労働科学研究費補助金
難治性疾患等政策研究事業(難治性疾患政策研究事業)
分担研究報告書

混合性結合組織病(MCTD)の診断基準、重症度分類、診断ガイドラインに関する研究

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研究要旨

厚生労働省の研究班で作成した 1996 年、2004 年の MCTD 診断の手引きを検証し、MCTD の定義を再考した。その結果を基に、MCTD の診断基準の改訂を行い。重症度分類(2011)の妥当性の検証、治療ガイドライン(診断+治療)の策定作業に着手した。診断基準に関しては、MCTD の概念、共通所見、免疫学的所見、特徴的な臓器障害を冒頭に記載することにより、本疾患の全体像を捕らえやすくした。特徴的な臓器所見としては肺動脈性高血圧症に加え、無菌性髄膜炎、三叉神経障害などもあげられ、混合所見を満たさなかった場合も、特徴的臓器病変があれば、診断可能とした。さらに、実際の症例を用いて診断基準の検証を行い、日本リウマチ学会などの関連学会から意見を求め、論文の peer review を経て最終的に改定診断基準とする。

A.研究目的

混合性結合組織病(MCTD; 指定難病 52)は 11000 人の患者が登録される代表的な全身性自己免疫疾患の一つである。本分科会においては MCTD に関して、1)診断基準や重症度分類の検証と改訂、2)診療ガイドラインの策定と改訂、3)臨床個人調査票の解析や検証を通じた指定難病データベース構築、4)患者への臨床情報の還元などを目的とする。

欧米には MCTD という疾患概念が十分に認知されているとは言い難く、日本でも共通認識に欠け、経過中に病態が変遷する症例ではどこまでを MCTD として捉えるか、SLE と MCTD のオーバーラップなども認めるかなどについてはコンセンサスが得られていない。そこで、平成 29 年度には日本のエキスパートの考え方を把握し、分科会として本疾患に対する共通認識を作るために、典型的な MCTD 症例と境界領域の症例を各施設から提出して、症例を検討、議論して、MCTD の定義を再考した。その結果をもとに、平成 30 年度には厚生労働省の研究班で作成した 1996 年、2004 年の MCTD 診

断の手引きの改訂作業を行なった。また、重症度分類についても見直し、修正作業を行なった。

B.研究方法

MCTD の定義を再考を目的として、分科会として本疾患に対する共通認識を作るために典型的な MCTD 症例と境界領域の症例を研究分担者、協力者の全 11 施設から提出して、症例検討を介して MCTD の定義を再考し、1996 年、2004 年の MCTD 診断の手引きの改訂作業を行なった。さらに、日本リウマチ学会などの関連学会において、改定診断基準案に対するパブリックコメントを求めた。その結果も踏まえて、MCTD の 2018 改訂診断基準案を策定した。また、重症度分類についても修正を行い、診療ガイドラインの作成に着手した。

（倫理面への配慮）

臨床検体を使用する場合には、所属機関の倫理委員会、或は、IRB で承認を得た研究に限定し、患者からインフォームドコンセントを得た上で、倫理委員会の規約を遵守し、所属機関の現有設備を用いて行う。患者の個人情報が所属機関外に漏洩せぬよう、試料や解析データは万全の安全システムをもって厳重に管理し、人権擁護に努めると共に、患者は、経済的負担を始め如何なる不利益や危険性も被らない事を明確にする。

C.研究結果

1）診断基準の改定について

平成 29 年度に実施した症例を用いた定義の再考作業の結果に基づいて MCTD の診断基準の改定について議論した。その結果、疾患の基本的概念は堅持しつつ、特徴的な共通所見や臓器障害、重症度や治療方針を意識しながら診断を行う必要性を確認した（別添参照）。MCTD 改訂診断基準案に対して、日本リウマチ学会などで実施したパブリックコメントでも概ね高い評価が得られた。

共通所見は MCTD で 9 割認められる所見を集めたものであり、MCTD に特徴的な障害である肺高血圧症は共通所見とされていたが、診断の感度・特異度には殆ど影響しないとのことで削除されることになった。一方、MCTD に特徴的な臓器所見としては肺動脈性高血圧症に加え、無菌性髄膜炎、三叉神経障害などもあげ、混合所見を満たさなかった場合も、これらの特徴的臓器病変があれば、MCTD と診断可能とした。概念、共通所見、免疫学的所見、特徴的な臓器障害を冒頭に記載することにより、本疾患の全体像を捕らえやすくした。

混合所見についても一部を見直した。強皮症所見のにおける肺線維症は間質性肺疾患と表記を変更し、CT でも検出できるため呼吸機能検査の項目は削除した。指尖部潰瘍やネイルフォールドキャピラロスコピーについても言及されたが、MCTD の診断基準としての意味づけを考慮して含有しなかった。筋炎所見について、ゴットロン、ヘリオトープなどの皮膚所見も含めるべきかについては、予後や治療反応性を考慮した場合、MCTD の診断基準としては該当しないとした。また筋原性酵素に「CK 等」と表記されているが、ミオグロビン、アルドラーゼのみも上昇症例もあることからこの文言は除いた。筋力低下が明確でない症例も多く、筋電図に加え、MRI などの高感度画像検査について診断基準への追加が望ましいが、国際的には経済的な問題から撮影は難しく、撮影方法、条件などの統一も必要であり、MRI は必須項目とはしないことにした。

以上の議論を踏まえ、全身性エリテマトーデスや強皮症、多発性筋炎/皮膚筋炎などと診断された症例においては、MCTD の診断は慎重に行うとの従来の方針で同意を得た。現在の保険診療の範囲内で測定可能で、かつ、予後および臓器障害に関与すると考えられる全身性エリテマトーデスや強皮症、多発性筋炎/皮膚筋炎のそれぞれに特徴的な疾患標識抗体として、①抗二本鎖 DNA 抗体、抗 Sm 抗体、②抗トポイソメラーゼ I 抗体（抗 Scl-70 抗体)、抗 RNA ポリメラーゼ III 抗体、③抗 ARS 抗体、抗 MDA-5 抗体を付記した。また、従来の診断基準の付記において示されていた肺高血圧症を伴う抗 U1-RNP 抗体陽性例は MCTD に分類される可能性が高いという表記については、新診断基準において特徴的な臓器所見に肺高血圧症を加えたことにより、削除する方針となった。

一方、小児領域における従来の MCTD の診断基準に対してのオンラインアンケート結果が示された。多くの小児科医が抗 U1-RNP 抗体陽性、レイノー現象を重視している一方で、混合所見については小児領域では半数の医師が同意していないことがわかった。アンケート結果は全体的に、共通所見が小児でも重視されるレイノー現象と手指の腫脹に絞られた今回の改

定診断基準案に合致するとのコメントがあった。よって、『混合性』という概念は維持するも、小児領域においては必ずしも混合所見が揃わないことがあり、小児においては混合所見の1項目で1所見以上満たせば診断可能とする旨を付記することとした。なお、小児発症、成人移行症例については、改定規準の妥当性に関して疫学調査が必要との発言があった。以上から、小児の扱いについては、付記に「小児の場合はⅣの A、B、C 項のうち、1 項目以上につき、それぞれ 1 所見以上が陽性およびⅠ＋Ⅱを満たす場合を混合性結合組織病と診断する」と明記する方針となった。

2）重症度分類の改訂について

重症度分類については他の自己免疫疾患との共通化は困難であり、現行の重症度分類を今後も継続して使用する方針とした。一方、新診断基準において変更した表記もあり(間質性肺炎、肺線維症など)、それらは新診断基準の表記に合わせ文言を修正する。また誤記が複数見つかり、これは修正を急ぐこととした（別添参照）。

3）MCTD 診療ガイドラインについて

GRADE システムを用いて診療ガイドライン作成を進めることが報告された。MINDs2017 に準拠してしっかりやったほうが良いが、文献検索は必ずしも外部に依頼しなくても良い等の発言を踏まえ、CQ に関しては三森班(2008 年)のものを新たな文献も踏まえ見直し、適宜 CQ を削除、追加する方針とし、SLR については、2019 年 6 月を目標に各施設で二次スクリーニングと並行して推奨文を作成する予定とした。2019 年 8-9 月に分科会を再度行い、検討する方針とした。

D.考察

MCTD の診断基準の改定について議論し、疾患の基本的概念は堅持しつつ、特徴的な共通所見や臓器障害、重症度や治療方針を意識しながら診断を行う必要性を確認した。多数症例を用いた検証で、診断基準の正当性が実証され、日本リウマチ学会などの関連学会からパブリッシュコメントでも概ね高い評価を得た。今後は、Modern Rheumatology に投稿し、論文の peer review を経て最終的に改定診断基準とし、疫学調査を行う予定とした。米国/欧州リウマチ学会への抄録提出は疫学調査を行って理論武装をしてからが望ましいとの発言があり、疫学調査方法については、自己免疫班の他の疫学調査を参考にしてくこととした。

2011 年に発刊された「混合性結合組織病の診療ガイドライン（改訂第3版）」に記載された重症度分類では、重症、中等症、軽症に分類され、この分類が指定難病の申請および更新時に使用されている。しかし、これらはあくまで専門医の意見に基づいた分類で、患者予後の研究などは行われていない。また全身性エリテマトーデスの SLEDAI などで計算されるように、複数の臨床症状があったときに、それらを総合して点数化することも考慮されていないことから、再度その項目の妥当性と生命予後・後遺障害との関連を検討すべきと考えた。

ガイドライン策定については、本邦における MCTD の診療ガイドラインは、1987 年に厚生省特定疾患 混合性結合組織病研究班（粕川 禮司 班長）より「混合性結合組織病診断の手引きと治療指針」として初めて公表され、2005 年、2011 年には「混合性結合組織病の診療ガイドライン」改訂第 2 版、第 3 版が出版された。第 3 版ではエビデンスレベルと推奨度が表示されているが、その作成は GRADE 法に基づいてはいない。MCTD は、その治療が SLE や強皮症、多発性筋炎/皮膚筋炎の治療と共通している部分が多く、MCTD に特異的な治療内容はきわめて限られる。これは海外において、MCTD という疾患概念を認めていない学者が存在し論文数が少ないことにも起因する。したがって MCTD のガイドラインでは、他の膠原病のエビデンスを参考にしている場合が多い。今後ガイドラインを改定する場合には、MCTD として記載されたものと他の膠原病のエビデンスを MCTD に流用したものの区別を明確として作成すべきである。したがって、まずは MINDS 等を用いて GRADE システムを使った診療ガイドライン（診断と治療）の作成を目指す。いずれにしてもきっちりとしたガイドラインを作成すれば、世界に先駆けて MCTD の疾患概念を確立し、普及させることも可能となる。

患者対応としては、難病情報センターのホームページでは混合性結合組織病の項目があり、一般利用者向けとして「病気の解説」が行われている。ホームページの作成、質問に対する回答、膠原病友の会への対応は、本分科会にてどこまで対応するかは、今後の議論を要する。また、臨床個人調査票による疫学調査を体系的に実施し、論文として纏め、ホームページなどを通じて患

者に臨床情報を還元する必要がある。現状の患者調査票について議論し、現状では大きな修正は不要であるとした。難病情報センターの HP の診断基準は 2004 年作成版なので 2011 年版へ変更を依頼する。患者対応については、平成 30 年 6 月に東京医科歯科大学において市民公開講座を開催した。

E.結論

分科会としてMCTD に対する共通認識を作るために、多数症例から MCTD としての診断の妥当性を議論し、MCTD の定義を再考した。また、厚労省 MCTD 診断基準、Alarcon-Segovia 基準、Sharp 基準などとの合致点を比較検討した。これらの議論を通して MCTD の基本的概念を固め、今後の活動である診断の手引きの妥当性の検証、診断基準の改訂、付記事項の追記、重症度分類の改訂を行なった。

F.健康危険情報

なし

G.研究発表

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H.知的財産権の出願・登録状況
(予定を含む)

1. 特許取得

なし

2. 実用新案登録

なし

3. その他

なし

MCTD の 2018 改訂診断基準(案)

Ⅰ 共通所見

1. Raynaud 現象
2. 指ないし手背の腫脹

Ⅱ. 免疫学的所見

抗 U1-RNP 抗体陽性

Ⅲ. 特徴的な臓器所見

1. 肺動脈性肺高血圧症
2. 無菌性髄膜炎，三叉神経障害

Ⅳ. 混合所見

A. 全身性エリテマトーデス様所見

1. 多発関節炎
2. リンパ節腫脹
3. 顔面紅斑
4. 心膜炎または胸膜炎
5. 白血球減少(4,000/μl以下)または血小板減少(100,000/μl以下)

B. 強皮症様所見

1. 手指に限局した皮膚硬化
2. 間質性肺疾患
3. 食道蠕動低下または拡張

C. 多発性筋炎様所見

1. 筋力低下
2. 筋原性酵素上昇
3. 筋電図における筋原性異常所見

診断:

1. Ⅰの 1 所見以上が陽性
2. Ⅱの所見が陽性
3. Ⅰ＋Ⅱ＋Ⅲの 1 項目を満たす場合を混合性結合組織病と診断する
4. Ⅳの A、B、C 項のうち、2 項目以上につき、それぞれ 1 所見以上が陽性およびⅠ＋Ⅱを満たす場合を混合性結合組織病と診断する

付記

1. 抗 U1-RNP 抗体の検出は二重免疫拡散法あるいは酵素免疫測定法(ELISA)のいずれでもよい。ただし、二重免疫拡散法が陽性で ELISA の結果と一致しない場合には、二重免疫拡散法を優先する。
2. 以下の予後および臓器障害と関与する疾患標識抗体が陽性の場合は混合性結合組織病の診断は慎重に行う。
   ① 抗二本鎖 DNA 抗体、抗 Sm 抗体
   ② 抗トポイソメラーゼⅠ抗体 (抗 Scl-70 抗体)、抗 RNA ポリメラーゼ III 抗体
   ③ 抗 ARS 抗体、抗 MDA5 抗体
3. 小児の場合はⅣの A、B、C 項のうち、1 項目以上につき、それぞれ 1 所見以上が陽性およびⅠ＋Ⅱを満たす場合を混合性結合組織病と診断する

＜重症度分類＞2018 年度改定

MCTD の臓器障害別の重症度分類

中等度以上を対象とする。

重症度	臓器障害	臨床所見
重症:	中枢神経症状	痙攣、器質性脳障害、精神病、脳血管障害(頻度はまれ)
	無菌性髄膜炎	頭痛、嘔気、嘔吐(NSAID 誘発性に注意)
	肺動脈性肺高血圧症(最も重要な予後規定因子)	息切れ、動悸、胸骨後部痛
	急速進行性間質性肺疾患	急速に進行する呼吸困難、咳嗽
	進行した間質性肺疾患	動悸、息切れ、咳嗽
	血小板減少	出血傾向、紫斑
	溶血性貧血	高度の貧血
	下部消化管機能不全	吸収不良症候群、偽性腸閉塞
中等症:	発熱	疾患活動性の高い時に見られる
	リンパ節腫脹	疾患活動性の高い時に見られる
	筋炎	筋力低下、筋痛、筋原性酵素上昇。時に重症例あり
	食道運動機能不全	逆流性食道炎、胸やけ、心窩部痛
	漿膜炎	胸水、心嚢液貯留
	腎障害	蛋白尿(ネフローゼ症候群、腎不全もまれではあるがみられる)
	皮膚血管炎	紫斑、爪床出血、皮膚梗塞
	皮膚潰瘍、壊死	重度の末梢循環障害による
	間質性肺疾患	進行は緩徐であるが、比較的早く進行する例もある
	末梢神経障害	三叉神経障害が多い
	骨破壊性関節炎	関節リウマチ様の関節破壊が時に見られる
軽症:	レイノー現象	寒冷刺激による血管攣縮により手指の色調変化。時に難治性
	手指ないし手背の腫脹	MCTD の診断上重要だが臨床的に問題となることはない
	紅斑	顔面、手掌などに多い
	手指に限局する皮膚硬化	軽度にとどまるが、手指の屈曲拘縮を来たしうる
	非破壊性関節炎	関節破壊は通常ないが時に見られる

平成 30 年度厚生労働科学研究費補助金
難治性疾患等政策研究事業(難治性疾患政策研究事業)
分担研究報告書

JIA/AOSD分科会「若年性特発性関節炎/成人発症スチル病に関する調査研究」

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研究協力者　松本　拓美　　東京医科歯科大学 膠原病・リウマチ内科（大学院生)

研究要旨
本研究２年目となった 2018 年度は、本分科会として下記の 5 項目について検討を行い、それぞれ成果を得た。
1) 成人スチル病診療ガイドライン 2017 年度版の見直しと今後の改訂ポイントの抽出、
2) AOSD 呼称変更(資料収集と日本リウマチ学会の承認取得から、指定難病名の改称を目指す)、
3) 関節型若年性特発性関節炎の指定難病登録とその後の対応、
4) 抗 IL-6 抗体投与下のマクロファージ活性化症候群(MAS)の検討、
5) 本年度内に患者向けの公開講座の研究分担者地域での開催(金沢市)

A. 研究目的
本研究では、本年度、1）成人スチル病診療ガイドライン 2017 年度版の見直しと今後の改訂ポイントの抽出、2）AOSD 呼称変更（資料収集と日本リウマチ学会の承認取得から、指定難病名の改称を目指す)、3）関節型若年性特発性関節炎の指定難病登録とその後の対応、4）抗 IL-6 抗体投与下のマクロファージ活性化症候群(MAS)の検討、5）本年度内に患者向けの公開講座の研究分担者地域での開催(金沢市)、の 5 項目の実現を活動目的とした。

B. 研究方法
1）「成人スチル病診療ガイドライン 2017 年度版」の見直しと今後の改訂ポイントの抽出
・分科会内で、ガイドライン公表後に指摘いただいた点を中心に、全体の見直しと今後の改訂ポイントを抽出する。
2）AOSD 呼称変更
＜背景と呼称変更の必要性＞
・「成人スチル病」は、「成人発症スチル病」と「スチル病小児が成人した症例」の両者を含むとこれまで認識されてきた。しかし、現在、小児科では「スチル病」という診断名は殆ど使われることはなく、全身型 JIA が用いられている。
・「スチル病小児が成人した症例」は、全身型 JIA の成人移行に相当し、既存の指定難病「全身型 JIA」で認定されることが可能である。
・現在同じ病態が 2 つの異なった指定難病名で認定されうる状態であり、患者や医療関係者に不必要な誤解や混乱を与えている虞がある。
・国際的にも、ICD-10 version（2016 年版）では、M06.01 「Adult-onset Still disease」と記載され、「Adult Still's disease」名の表示は存在しない。
・2012 年に住田班で施行した全国調査の二次調査において、本症 169 名の返答のうち 8 名が小児発症例であり（4.7%）、これら小児症例が「全身型 JIA」で指定替えされても、修正による影響は少ない。
・以上の現状を踏まえて、今後の正確な調査研究を担保するためにも、「成人スチル病」は「成人発症スチル病」と成人スチル病のみに限る名称に変更すべきと考え、厚生労働省難病対策課と検討していくことを今後の見直し課題とした。
3）関節型若年性特発性関節炎の指定難病登録とその後の対応
＜背景＞
・2015 年 1 月に、全身型 JIA が指定難病に認定。(若年性）乾癬性関節炎、付着部炎関連関節炎（若年性脊椎関節炎）と関連する疾患を扱う難病研究班との連携を開始し、その検討を行う体制を構築した結果、2018 年 4 月から関節型 JIA も認定基準を満たすと判断され、全身型と統合され「若年性特発性関節炎（JIA）（指定難病１０７）」として指定難病に認定となった。
4）抗 IL-6 抗体投与下のマクロファージ活性化症候群(MAS)の検討：
＜対象と方法＞
・国内の小児リウマチ専門施設において、抗 IL-6 抗体投与下のマクロファージ活性化症候群(MAS)の検討を行う。これまで、抗 IL-6 抗体投与下では MAS の典型的な症状や検査所見が見いだせない状況が認識されており、治療のタイミング・使用薬に苦慮する場面が臨床の場で問題になっていた。
5）本年度内に患者向けの公開講座の研究分担者地域での開催（金沢）
＜背景と目的＞
・難治性疾患政策研究事業において患者への啓蒙活動は必須課題であり、とくに JIA では移行期医療も含めた啓蒙が重要と考えられる。このような活動を進めることは臨床個人調査票からの疫学調査や指定難病データベースの構築の基盤にも繋がることから、研究分担者地域での開催（金沢市）を検討した。

C. 研究結果
1）「成人スチル病診療ガイドライン 2017 年度版」の見直しと今後の改訂ポイントの抽出
・ガイドライン公表後に指摘いただいた点を中心に、全体の見直しと今後の改訂ポイントを抽出し、今後の改訂作業を分科会で進めていくことになった。
2）AOSD 呼称変更
・日本リウマチ学会理事会で上記要望が承認され、学会の総意として変更が受け入れられた。同用語委員会でも、正式に「成人スチル」→「成人発症スチル病」の用語変更となった。しかし、まだ社会への周知度が低いため、厚生労働省難病対策課と協議の上社会的事情も鑑みて AOSD 呼称変更を引き続き検討していくこととなった。
3）関節型若年性特発性関節炎の指定難病登録とその後の対応
・2018 年 1 月に関節型 JIA が承認され、全身型 JIA と疾患名が統合となり、2018 年 4 月「JIA」として本疾患の個票や概要が公表された。その後の対応を分科会として随時行い、質問にも回答し周知を図ることに成功した。
4）抗 IL-6 抗体投与下のマクロファージ活性化症候群(MAS)の検討
・明日 12 月 8 日、国内の小児リウマチ専門施設において報告された抗 IL-6 抗体投与下のマクロファ

ージ活性化症候群(MAS)症例を持ち合い、臨界点の検出や治療のタイミング・使用薬についての議論がなされることになった。成人例との相違点についても議論する予定。
5) 第 2 回 JIA/AOSD 医療講演会の開催
・2018 年 11 月 18 日、「JIA/AOSD」をテーマとした患者向け医療講演会を金沢大学にて開催した。以下、行われた講演会の概要を資料 1 に記す。

D. 考察
本研究２年目となった 2018 年度の本分科会の成果として、上述した 5 項目が挙げられる。
いずれも、本研究班全体の目標・方向性に即した活動結果を示すこととなり、順調に研究が進んでいると考えている。

E. 結論
2018 年度の本分科会の成果として、1) 成人スチル病診療ガイドライン 2017 年度版の見直しと今後の改訂ポイントの抽出、2) AOSD 呼称変更（資料収集と日本リウマチ学会の承認取得から、指定難病名の改称を目指す)、3) 関節型若年性特発性関節炎の指定難病登録とその後の対応、4) 抗 IL-6 抗体投与下のマクロファージ活性化症候群(MAS)の検討、5) 本年度内に患者向けの公開講座の研究分担者地域での開催(金沢市)、が得られた。当初の予定の通り、順調に研究は進んでいる。

F. 健康危険情報
なし

G. 研究発表
1. 論文発表

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4) 森　雅亮. 特集 私の処方. 若年性特発性関節炎. 小児科臨床 17:985-92,2018

5) 森　雅亮. 特集 ＜Clinical Science＞リウマチ・膠原病の診療において注意すべき難治性疾患. 血球貪食症候群/マクロファージ活性化症候群. 炎症と免疫 26:31-5,2018.

6) 森　雅亮. 特集 リウマチ・膠原病の診療において注意すべき難治性疾患. 血球貪食症候群/マクロファージ活性化症候群. 炎症と免疫 26:31-5, 2018.

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H.知的財産権の出願・登録状況
（予定を含む）

1. 特許取得
該当なし。

2. 実用新案登録
該当なし。

3. その他
該当なし

資料 1　　2018 年 11 月 18 日

厚生労働省難治性疾患政策研究事業自己免疫疾患に関する調査研究班

若年性特発性関節炎・成人スチル病分科会

若年性特発性関節炎・成人スチル病　医療講演会

1. 背景と目的

難治性疾患政策研究事業において患者への啓蒙活動は必須課題であり、疾病そのものだけではなく、診療の手引き・ガイドラインの策定といった近年の活動について周知することは重要と考えられます。また、若年性特発性関節炎では移行期医療に関する啓蒙も重要と考えられます。このような活動を進めることは臨床個人調査票からの疫学調査や指定難病データベースの構築にも繋がると考えられます。今回我々は、若年性特発性関節炎・成人スチル病をテーマとした患者向け医療講演会を開催致しましたので、ご報告致します。

2. 開催概要

日時：平成 30 年 11 月 18 日（日）10:00～12:30

場所：金沢大学附属病院 CPD センター

参加費：無料、事前申し込み無し

参加者数：53 名

講演内容

第一部：医療講演

座長：東京医科歯科大学　生涯免疫難病学講座　教授　森雅亮

1）講演 1 「若年性特発性関節炎の手引きの概要」

演者：大阪医科大学小児科　助教　岡本奈美

2）講演 2 「成人スチル病手引きの概要」

演者：埼玉医科大学病院　リウマチ膠原病科　教授　三村俊英

3）講演 3 「リウマチ性疾患の移行期医療の展望」

演者：聖マリアンナ医科大学病院　リウマチ・膠原病・アレルギー内科

教授　川畑仁人

第二部：医療相談会

参加者のうち、希望の方を対象に個別に相談に応じた。

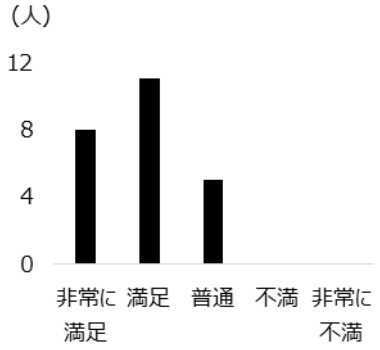
若年性特発性関節炎：森雅亮、岡本奈美、清水正樹

成人スチル病：三村俊英、川畑仁人

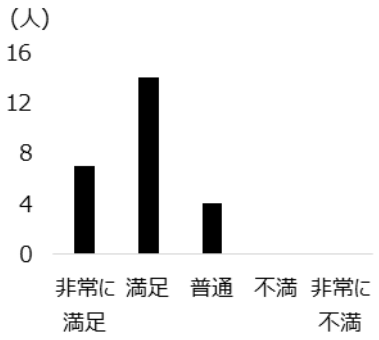
当日の様子：予想よりも多くの方が参加されたが、会場の準備、受付、参加者の案内、アンケートの回収は問題なくスムーズに行われた。講医療講演、医療相談会はほぼ予定の時間通り進行した。体調不良者等はいなかった。

3. 参加者からのアンケート集計結果

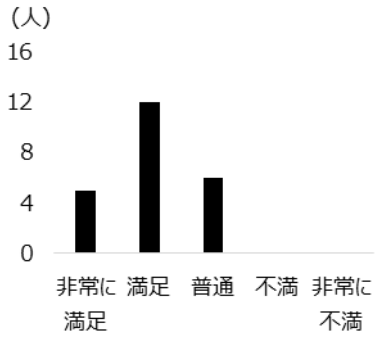
・会全体について



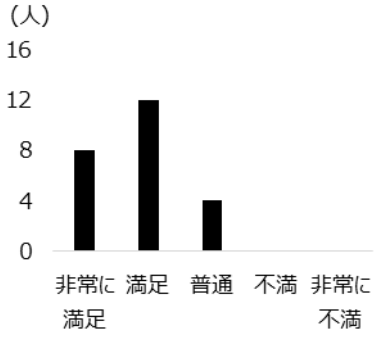
・「若年性特発性関節炎の手引き概要」について



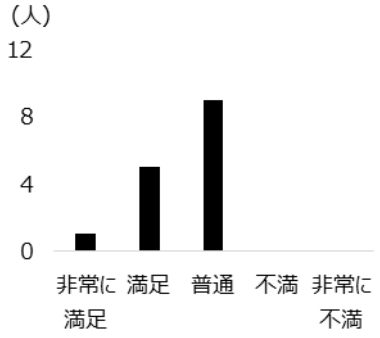
・「成人発症スティル病の手引き概要」について



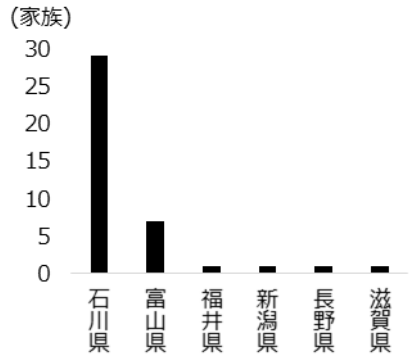
・「リウマチの移行期医療の展望」について



・質疑応答について



・出席者の出身県（家族単位での集計）



患者さんからの感想（自由記載）

- 病気の経過など具体的な例など紹介して頂けたら助かります。
- 薬を長く飲み続けなくてはいけない病気なので、成人した時に何か副作用とかがおきないか心配です。薬に関する説明も聞きたいです。
- 薬の副作用の実例（小児から成人になってからの副作用でどのようなことがあったか、特に女性に関する内容）が知りたい。
- 移行期の詳しい説明、具体的な説明（医療機関、先生の名前など）が欲しい。
- 助成金について教えて欲しい。
- 高齢でスティル病になった人を対象にした講演会をしてほしい。
- スクリーンのみの解説でなく、ペーパー資料があれば良いと思います。
- 時間が全体として少し長い気がしました。内容も難しい部分が多かったと思います。
- 先生方がはるばる金沢までお越し下さったことにとても感謝しています。講演会に参加できて良かったです。
- 話をきいていてよく理解できました。質問にも適確に答えを頂き非常に感謝しています。
- ぜひ、また北陸で講演会をして下さい。

Ⅳ．研究成果の刊行に関する一覧表

別紙４

研究成果の刊行に関する一覧表

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Akizuki S., Ishigaki K., Kochi Y., Law S. M., Matsuo K., Ohmura K., Suzuki A., Nakayama M., Iizuka Y., Koseki H., Ohara O., Hirata J., Kamatani Y., Matsuda F., Sumida T., Yamamoto K., Okada Y., Mimori T. and Terao C.	PLD4 is a genetic determinant to systemic lupus erythematosus and involved in murine autoimmune phenotypes	***Ann Rheum Dis***	78(4)	509-518	2019
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岡本奈美	腺障害の検査	厚生労働科学研究費補助金難治性疾患等政策研究事業若年性特発性関節炎を主とした小児リウマチ性疾患の診断基準・重症度分類の標準化とエビデンスに基づいたガイドラインの策定に関する研究班	小児期シェーグレン症候群診療の手引き2018年版	羊土社	東京	2018	27-30
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平成３１年１月２４日

国立保健医療科学院長　殿

機関名　国立大学法人東京医科歯科大学

所属研究機関長　職　名　学　長

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次の職員の平成３０年度厚生労働科学研究費の調査研究における、倫理審査状況及び利[redacted]ついては以下のとおりです。

１．研究事業名　難治性疾患等政策研究事業（難治性疾患政策研究事業）

２．研究課題名　自己免疫疾患に関する調査研究

３．研究者名　（所属部局・職名）　大学院医歯学総合研究科 生涯免疫難病学講座・寄附講座教授

（氏名・フリガナ）　森　雅亮（モリ マサアキ）

４．倫理審査の状況

	該当性の有無	左記で該当がある場合のみ記入（※1）		
	有　無	審査済み	審査した機関	未審査（※2）
ヒトゲノム・遺伝子解析研究に関する倫理指針	□　■	□		□
遺伝子治療等臨床研究に関する指針	□　■	□		□
人を対象とする医学系研究に関する倫理指針（※3）	■　□	■	東京医科歯科大学	□
厚生労働省の所管する実施機関における動物実験等の実施に関する基本指針	□　■	□		□
その他、該当する倫理指針があれば記入すること（指針の名称：　）	□　■	□		□

（※1）当該研究者が当該研究を実施するに当たり遵守すべき倫理指針に関する倫理委員会の審査が済んでいる場合は、「審査済み」にチェックし一部若しくは全部の審査が完了していない場合は、「未審査」にチェックすること。

その他（特記事項）

（※2）未審査に場合は、その理由を記載すること。
（※3）廃止前の「疫学研究に関する倫理指針」や「臨床研究に関する倫理指針」に準拠する場合は、当該項目に記入すること。

５．厚生労働分野の研究活動における不正行為への対応について

研究倫理教育の受講状況	受講 ■　未受講 □

６．利益相反の管理

当研究機関におけるＣＯＩの管理に関する規定の策定	有 ■　無 □（無の場合はその理由：　）
当研究機関におけるＣＯＩ委員会設置の有無	有 ■　無 □（無の場合は委託先機関：　）
当研究に係るＣＯＩについての報告・審査の有無	有 ■　無 □（無の場合はその理由：　）
当研究に係るＣＯＩについての指導・管理の有無	有 □　無 ■（有の場合はその内容：　）

（留意事項）　・該当する□にチェックを入れること。
・分担研究者の所属する機関の長も作成すること。

平成31年　1月21日

国立保健医療科学院長　殿

機関名　国立大学法人筑
所属研究機関長　職　名　国立大学法人筑
氏　名　永田恭

次の職員の平成３０年度厚生労働科学研究費の調査研究における、倫理審査状況及び利益相
いては以下のとおりです。

１．研究事業名　難治性疾患等政策研究事業（難治性疾患政策研究事業）

２．研究課題名　自己免疫疾患に関する調査研究

３．研究者名　（所属部局・職名）医学医療系内科（膠原病・リウマチ・アレルギー）・教授

（氏名・フリガナ）住田　孝之・スミダ　タカユキ

４．倫理審査の状況

	該当性の有無	左記で該当がある場合のみ記入（※1）		
	有　無	審査済み	審査した機関	未審査（※2）
ヒトゲノム・遺伝子解析研究に関する倫理指針	□　■	□		□
遺伝子治療等臨床研究に関する指針	□　■	□		□
人を対象とする医学系研究に関する倫理指針（※3）	□　■	□		□
厚生労働省の所管する実施機関における動物実験等の実施に関する基本指針	□　■	□		□
その他、該当する倫理指針があれば記入すること（指針の名称：　　）	□　■	□		□

（※1）当該研究者が当該研究を実施するに当たり遵守すべき倫理指針に関する倫理委員会の審査が済んでいる場合は、「審査済み」にチェックし一部若しくは全部の審査が完了していない場合は、「未審査」にチェックすること。

その他（特記事項）

（※2）未審査に場合は、その理由を記載すること。
（※3）廃止前の「疫学研究に関する倫理指針」や「臨床研究に関する倫理指針」に準拠する場合は、当該項目に記入すること。

５．厚生労働分野の研究活動における不正行為への対応について

研究倫理教育の受講状況	受講 ■　未受講 □

６．利益相反の管理

当研究機関におけるＣＯＩの管理に関する規定の策定	有 ■　無 □（無の場合はその理由：　　）
当研究機関におけるＣＯＩ委員会設置の有無	有 ■　無 □（無の場合は委託先機関：　　）
当研究に係るＣＯＩについての報告・審査の有無	有 ■　無 □（無の場合はその理由：　　）
当研究に係るＣＯＩについての指導・管理の有無	有 □　無 ■（有の場合はその内容：　　）

（留意事項）　・該当する□にチェックを入れること。
・分担研究者の所属する機関の長も作成すること。

平成31年3月29日

国立保健医療科学院長　殿

機関名　北海道大学

所属研究機関長　職　名　総長職務代理

氏　名　笠原　正典

次の職員の平成３０年度厚生労働科学研究費の調査研究における、倫理審査状況及び利益相反等の管理については以下のとおりです。

１．研究事業名　難治性疾患等政策研究事業（難治性疾患政策研究事業）

２．研究課題名　自己免疫疾患に関する調査研究

３．研究者名　（所属部局・職名）大学院医学研究院・教授

（氏名・フリガナ）渥美　達也・アツミ　タツヤ

４．倫理審査の状況

	該当性の有無	左記で該当がある場合のみ記入（※1）		
	有　無	審査済み	審査した機関	未審査（※2）
ヒトゲノム・遺伝子解析研究に関する倫理指針	□　■	□		□
遺伝子治療等臨床研究に関する指針	□　■	□		□
人を対象とする医学系研究に関する倫理指針（※3）	□　■	□		□
厚生労働省の所管する実施機関における動物実験等の実施に関する基本指針	□　■	□		□
その他、該当する倫理指針があれば記入すること（指針の名称：　）	□　■	□		□

（※1）当該研究者が当該研究を実施するに当たり遵守すべき倫理指針に関する倫理委員会の審査が済んでいる場合は、「審査済み」にチェックし一部若しくは全部の審査が完了していない場合は、「未審査」にチェックすること。

その他（特記事項）

（※2）未審査に場合は、その理由を記載すること。

（※3）廃止前の「疫学研究に関する倫理指針」や「臨床研究に関する倫理指針」に準拠する場合は、当該項目に記入すること。

５．厚生労働分野の研究活動における不正行為への対応について

研究倫理教育の受講状況	受講 ■　未受講 □

６．利益相反の管理

当研究機関におけるＣＯＩの管理に関する規定の策定	有 ■　無 □（無の場合はその理由：　）
当研究機関におけるＣＯＩ委員会設置の有無	有 ■　無 □（無の場合は委託先機関：　）
当研究に係るＣＯＩについての報告・審査の有無	有 ■　無 □（無の場合はその理由：　）
当研究に係るＣＯＩについての指導・管理の有無	有 □　無 ■（有の場合はその内容：　）

（留意事項）　・該当する□にチェックを入れること。
・分担研究者の所属する機関の長も作成すること。

2019年 3月 5日

国立保健医療科学院長　殿

機関名　産業医[redacted]

所属研究機関長　職　名　学[redacted]

氏　名　東　敏[redacted]

次の職員の平成３０年度厚生労働科学研究費の調査研究における、倫理審査状況及び利益相反等の管理については以下のとおりです。

１．研究事業名　難治性疾患等政策研究事業（難治性疾患政策研究事業）

２．研究課題名　自己免疫疾患に関する調査研究

３．研究者名　（所属部局・職名）　医学部第１内科学講座・教授

（氏名・フリガナ）　田中良哉・タナカヨシヤ

４．倫理審査の状況

	該当性の有無		左記で該当がある場合のみ記入（※1）		
	有	無	審査済み	審査した機関	未審査（※2）
ヒトゲノム・遺伝子解析研究に関する倫理指針	□	■	□		□
遺伝子治療等臨床研究に関する指針	□	■	□		□
人を対象とする医学系研究に関する倫理指針（※3）	■	□	■	産業医科大学	□
厚生労働省の所管する実施機関における動物実験等の実施に関する基本指針	□	■	□		□
その他、該当する倫理指針があれば記入すること（指針の名称：　）	□	■	□		□

（※1）当該研究者が当該研究を実施するに当たり遵守すべき倫理指針に関する倫理委員会の審査が済んでいる場合は、「審査済み」にチェックし一部若しくは全部の審査が完了していない場合は、「未審査」にチェックすること。

その他（特記事項）

（※2）未審査に場合は、その理由を記載すること。
（※3）廃止前の「疫学研究に関する倫理指針」や「臨床研究に関する倫理指針」に準拠する場合は、当該項目に記入すること。

５．厚生労働分野の研究活動における不正行為への対応について

研究倫理教育の受講状況	受講 ■　未受講 □

６．利益相反の管理

当研究機関におけるＣＯＩの管理に関する規定の策定	有 ■　無 □（無の場合はその理由：　）
当研究機関におけるＣＯＩ委員会設置の有無	有 ■　無 □（無の場合は委託先機関：　）
当研究に係るＣＯＩについての報告・審査の有無	有 ■　無 □（無の場合はその理由：　）
当研究に係るＣＯＩについての指導・管理の有無	有 □　無 ■（有の場合はその内容：　）

（留意事項）　・該当する□にチェックを入れること。
・分担研究者の所属する機関の長も作成すること。

平成31年3月26日

国立保健医療科学院長　殿

機関名　　国立大学
所属研究機関長　職　名　　大学院医
氏　名　　金田　安

次の職員の平成３０年度厚生労働科学研究費の調査研究における、倫理審査状況及び利益相反等の管理については以下のとおりです。

１．研究事業名　難治性疾患等政策研究事業（難治性疾患政策研究事業）

２．研究課題名　自己免疫疾患に関する調査研究

３．研究者名　（所属部局・職名）　大学院医学系研究科　情報統合医学講座皮膚科学教室・教授

（氏名・フリガナ）　藤本　学・フジモトマナブ

４．倫理審査の状況

	該当性の有無	左記で該当がある場合のみ記入（※1）		
	有　無	審査済み	審査した機関	未審査（※2）
ヒトゲノム・遺伝子解析研究に関する倫理指針	□　■	□		□
遺伝子治療等臨床研究に関する指針	□　■	□		□
人を対象とする医学系研究に関する倫理指針（※3）	□　■	□		□
厚生労働省の所管する実施機関における動物実験等の実施に関する基本指針	□　■	□		□
その他、該当する倫理指針があれば記入すること（指針の名称：　　）	□　■	□		□

（※1）当該研究者が当該研究を実施するに当たり遵守すべき倫理指針に関する倫理委員会の審査が済んでいる場合は、「審査済み」にチェックし一部若しくは全部の審査が完了していない場合は、「未審査」にチェックすること。

その他（特記事項）

（※2）未審査に場合は、その理由を記載すること。
（※3）廃止前の「疫学研究に関する倫理指針」や「臨床研究に関する倫理指針」に準拠する場合は、当該項目に記入すること。

５．厚生労働分野の研究活動における不正行為への対応について

研究倫理教育の受講状況	受講 ■　　未受講 □

６．利益相反の管理

当研究機関におけるＣＯＩの管理に関する規定の策定	有 ■　無 □（無の場合はその理由：　　）
当研究機関におけるＣＯＩ委員会設置の有無	有 ■　無 □（無の場合は委託先機関：　　）
当研究に係るＣＯＩについての報告・審査の有無	有 ■　無 □（無の場合はその理由：　　）
当研究に係るＣＯＩについての指導・管理の有無	有 □　無 ■（有の場合はその内容：　　）

（留意事項）　・該当する□にチェックを入れること。
・分担研究者の所属する機関の長も作成すること。

平成３１年　３月１５日

国立保健医療科学院長　殿

機関名　山口大学

所属研究機関長　職　名　学長

氏　名　岡　正朗

次の職員の平成３０年度厚生労働科学研究費の調査研究における、倫理審査状況及び利益
いては以下のとおりです。

１．研究事業名　難治性疾患等政策研究事業（難治性疾患政策研究事業）

２．研究課題名　自己免疫疾患に関する調査研究

３．研究者名　（所属部局・職名）　大学院医学系研究科　・　教授

（氏名・フリガナ）　神田　隆　・　カンダ　タカシ

４．倫理審査の状況

	該当性の有無	左記で該当がある場合のみ記入（※1）		
	有　無	審査済み	審査した機関	未審査（※2）
ヒトゲノム・遺伝子解析研究に関する倫理指針	□　■	□		□
遺伝子治療等臨床研究に関する指針	□　■	□		□
人を対象とする医学系研究に関する倫理指針（※3）	□　■	□		□
厚生労働省の所管する実施機関における動物実験等の実施に関する基本指針	□　■	□		□
その他、該当する倫理指針があれば記入すること（指針の名称：　）	□　■	□		□

（※1）当該研究者が当該研究を実施するに当たり遵守すべき倫理指針に関する倫理委員会の審査が済んでいる場合は、「審査済み」にチェックし一部若しくは全部の審査が完了していない場合は、「未審査」にチェックすること。

その他（特記事項）

（※2）未審査に場合は、その理由を記載すること。
（※3）廃止前の「疫学研究に関する倫理指針」や「臨床研究に関する倫理指針」に準拠する場合は、当該項目に記入すること。

５．厚生労働分野の研究活動における不正行為への対応について

研究倫理教育の受講状況	受講 ■　未受講 □

６．利益相反の管理

当研究機関におけるＣＯＩの管理に関する規定の策定	有 ■　無 □（無の場合はその理由：　）
当研究機関におけるＣＯＩ委員会設置の有無	有 ■　無 □（無の場合は委託先機関：　）
当研究に係るＣＯＩについての報告・審査の有無	有 ■　無 □（無の場合はその理由：　）
当研究に係るＣＯＩについての指導・管理の有無	有 □　無 ■（有の場合はその内容：　）

（留意事項）　・該当する□にチェックを入れること。
・分担研究者の所属する機関の長も作成すること。

平成 31 年 3 月 5 日

国立保健医療科学院長　　殿

機関名　東京女子医科大学

所属研究機関長　職　名　学長

氏　名　吉岡　俊正

次の職員の平成３０年度厚生労働科学研究費の調査研究における、倫理審査状況及び利益相反
ついては以下のとおりです。

１．研究事業名　難治性疾患等政策研究事業（難治性疾患政策研究事業）

２．研究課題名　自己免疫疾患に関する調査研究

３．研究者名　（所属部局・職名）　膠原病リウマチ痛風センター ・ 臨床教授

（氏名・フリガナ）　川口　鎮司 ・ カワグチ　ヤスシ

４．倫理審査の状況

	該当性の有無		左記で該当がある場合のみ記入　(※1)		
	有	無	審査済み	審査した機関	未審査(※2)
ヒトゲノム・遺伝子解析研究に関する倫理指針	□	■	□		□
遺伝子治療等臨床研究に関する指針	□	■	□		□
人を対象とする医学系研究に関する倫理指針（※3）	■	□	■	東京女子医科大学	□
厚生労働省の所管する実施機関における動物実験等の実施に関する基本指針	□	■	□		□
その他、該当する倫理指針があれば記入すること（指針の名称：　　）	□	■	□		□

（※1）当該研究者が当該研究を実施するに当たり遵守すべき倫理指針に関する倫理委員会の審査が済んでいる場合は、「審査済み」にチェックし一部若しくは全部の審査が完了していない場合は、「未審査」にチェックすること。

その他（特記事項）

（※2）未審査に場合は、その理由を記載すること。

（※3）廃止前の「疫学研究に関する倫理指針」や「臨床研究に関する倫理指針」に準拠する場合は、当該項目に記入すること。

５．厚生労働分野の研究活動における不正行為への対応について

研究倫理教育の受講状況	受講 ■　未受講 □

６．利益相反の管理

当研究機関におけるＣＯＩの管理に関する規定の策定	有 ■　無 □（無の場合はその理由　：　）
当研究機関におけるＣＯＩ委員会設置の有無	有 ■　無 □（無の場合は委託先機関：　）
当研究に係るＣＯＩについての報告・審査の有無	有 ■　無 □（無の場合はその理由　：　）
当研究に係るＣＯＩについての指導・管理の有無	有 □　無 ■（有の場合はその内容　：　）

（留意事項）・該当する□にチェックを入れること。
・分担研究者の所属する機関の長も作成すること。

平成３１年3月２９日

国立保健医療科学院長　殿

機関名　和歌山県立医科大学

所属研究機関長　職　名　学長

氏　名　宮下　和久

次の職員の平成３０年度厚生労働科学研究費の調査研究における、倫理審査状況及び利益
いては以下のとおりです。

１．研究事業名　厚生労働科学研究費補助金（難治性疾患等政策研究事業（難治性疾患政策研究事業））

２．研究課題名　自己免疫疾患に関する調査研究

３．研究者名　（所属部局・職名）　和歌山県立医科大学医学部・教授

（氏名・フリガナ）　神人正寿・ジンニンマサトシ

４．倫理審査の状況

	該当性の有無	左記で該当がある場合のみ記入（※1）		
	有　無	審査済み	審査した機関	未審査（※2）
ヒトゲノム・遺伝子解析研究に関する倫理指針	□　■	□		□
遺伝子治療等臨床研究に関する指針	□　■	□		□
人を対象とする医学系研究に関する倫理指針（※3）	□　■	□		□
厚生労働省の所管する実施機関における動物実験等の実施に関する基本指針	□　■	□		□
その他、該当する倫理指針があれば記入すること（指針の名称：　）	□　■	□		□

（※1）当該研究者が当該研究を実施するに当たり遵守すべき倫理指針に関する倫理委員会の審査が済んでいる場合は、「審査済み」にチェックし一部若しくは全部の審査が完了していない場合は、「未審査」にチェックすること。

その他（特記事項）

（※2）未審査に場合は、その理由を記載すること。
（※3）廃止前の「疫学研究に関する倫理指針」や「臨床研究に関する倫理指針」に準拠する場合は、当該項目に記入すること。

５．厚生労働分野の研究活動における不正行為への対応について

研究倫理教育の受講状況	受講 ■　未受講 □

６．利益相反の管理

当研究機関におけるＣＯＩの管理に関する規定の策定	有 ■　無 □（無の場合はその理由：　）
当研究機関におけるＣＯＩ委員会設置の有無	有 ■　無 □（無の場合は委託先機関：　）
当研究に係るＣＯＩについての報告・審査の有無	有 ■　無 □（無の場合はその理由：　）
当研究に係るＣＯＩについての指導・管理の有無	有 □　無 ■（有の場合はその内容：　）

（留意事項）　・該当する□にチェックを入れること。
・分担研究者の所属する機関の長も作成すること。

平成 31 年 3 月 31 日

国立保健医療科学院長　殿

機関名　京都大学
所属研究機関長 職　名　医学研究
氏　名　岩井 一

次の職員の平成３０年度厚生労働科学研究費の調査研究における、倫理審査状況及び利益相反等の管理については以下のとおりです。

１．研究事業名　難治性疾患等政策研究事業（難治性疾患政策研究事業）

２．研究課題名　自己免疫疾患に関する調査研究

３．研究者名　（所属部局・職名）京都大学大学院医学研究科内科学講座臨床免疫学・助教

（氏名・フリガナ）中嶋　蘭・ナカシマ　ラン

４．倫理審査の状況

	該当性の有無		左記で該当がある場合のみ記入（※1）		
	有	無	審査済み	審査した機関	未審査（※2）
ヒトゲノム・遺伝子解析研究に関する倫理指針	□	☑	□		□
遺伝子治療等臨床研究に関する指針	□	☑	□		□
人を対象とする医学系研究に関する倫理指針（※3）	□	☑	□		□
厚生労働省の所管する実施機関における動物実験等の実施に関する基本指針	□	☑	□		□
その他、該当する倫理指針があれば記入すること（指針の名称：　）	□	☑	□		□

（※1）当該研究者が当該研究を実施するに当たり遵守すべき倫理指針に関する倫理委員会の審査が済んでいる場合は、「審査済み」にチェックし一部若しくは全部の審査が完了していない場合は、「未審査」にチェックすること。

その他（特記事項）

（※2）未審査に場合は、その理由を記載すること。
（※3）廃止前の「疫学研究に関する倫理指針」や「臨床研究に関する倫理指針」に準拠する場合は、当該項目に記入すること。

５．厚生労働分野の研究活動における不正行為への対応について

研究倫理教育の受講状況	受講 ☑　未受講 □

６．利益相反の管理

当研究機関におけるＣＯＩの管理に関する規定の策定	有 ☑　無 □（無の場合はその理由：　）
当研究機関におけるＣＯＩ委員会設置の有無	有 ☑　無 □（無の場合は委託先機関：　）
当研究に係るＣＯＩについての報告・審査の有無	有 ☑　無 □（無の場合はその理由：　）
当研究に係るＣＯＩについての指導・管理の有無	有 □　無 ☑（有の場合はその内容：　）

（留意事項）　・該当する□にチェックを入れること。
・分担研究者の所属する機関の長も作成すること。

平成31年3月29日

国立保健医療科学院長　殿

機関名　北海道大学

所属研究機関長　職　名　　総長職務代

氏　名　笠原　正典

次の職員の平成３０年度厚生労働科学研究費の調査研究における、倫理審査状況及び利益相反等の管理については以下のとおりです。

１．研究事業名　難治性疾患等政策研究事業（難治性疾患政策研究事業）

２．研究課題名　自己免疫疾患に関する調査研究

３．研究者名　（所属部局・職名）　大学院医学研究院・客員教授

（氏名・フリガナ）　小林　一郎・コバヤシ　イチロウ

４．倫理審査の状況

	該当性の有無		左記で該当がある場合のみ記入（※1）		
	有	無	審査済み	審査した機関	未審査（※2）
ヒトゲノム・遺伝子解析研究に関する倫理指針	□	■	□		□
遺伝子治療等臨床研究に関する指針	□	■	□		□
人を対象とする医学系研究に関する倫理指針（※3）	■	□	■	北海道大学病院	□
厚生労働省の所管する実施機関における動物実験等の実施に関する基本指針	□	■	□		□
その他、該当する倫理指針があれば記入すること（指針の名称：　　）	□	■	□		□

（※1）当該研究者が当該研究を実施するに当たり遵守すべき倫理指針に関する倫理委員会の審査が済んでいる場合は、「審査済み」にチェックし一部若しくは全部の審査が完了していない場合は、「未審査」にチェックすること。

その他（特記事項）

（※2）未審査に場合は、その理由を記載すること。

（※3）廃止前の「疫学研究に関する倫理指針」や「臨床研究に関する倫理指針」に準拠する場合は、当該項目に記入すること。

５．厚生労働分野の研究活動における不正行為への対応について

研究倫理教育の受講状況	受講 ■　未受講 □

６．利益相反の管理

当研究機関におけるＣＯＩの管理に関する規定の策定	有 ■　無 □（無の場合はその理由：　　）
当研究機関におけるＣＯＩ委員会設置の有無	有 ■　無 □（無の場合は委託先機関：　　）
当研究に係るＣＯＩについての報告・審査の有無	有 ■　無 □（無の場合はその理由：　　）
当研究に係るＣＯＩについての指導・管理の有無	有 □　無 ■（有の場合はその内容：　　）

（留意事項）　・該当する□にチェックを入れること。
・分担研究者の所属する機関の長も作成すること。

平成３１年3月３１日

国立保健医療科学院長　　殿

機関名　国立大学法人長崎大学

所属研究機関長　職　名　学長

氏　名　河野　[redacted]

次の職員の平成３０年度厚生労働科学研究費の調査研究における、倫理審査状況及[redacted]については以下のとおりです。

１．研究事業名　難治性疾患等政策研究事業（難治性疾患政策研究事業）

２．研究課題名　自己免疫疾患に関する調査研究

３．研究者名　（所属部局・職名）大学院医歯薬学総合研究科・教授

（氏名・フリガナ）川上　純・カワカミ　アツシ

４．倫理審査の状況

	該当性の有無		左記で該当がある場合のみ記入（※1）		
	有	無	審査済み	審査した機関	未審査（※2）
ヒトゲノム・遺伝子解析研究に関する倫理指針	□	■	□		□
遺伝子治療等臨床研究に関する指針	□	■	□		□
人を対象とする医学系研究に関する倫理指針（※3）	■	□	■	長崎大学	□
厚生労働省の所管する実施機関における動物実験等の実施に関する基本指針	□	■	□		□
その他、該当する倫理指針があれば記入すること（指針の名称：　　）	□	■	□		□

（※1）当該研究者が当該研究を実施するに当たり遵守すべき倫理指針に関する倫理委員会の審査が済んでいる場合は、「審査済み」にチェックし一部若しくは全部の審査が完了していない場合は、「未審査」にチェックすること。

その他（特記事項）

（※2）未審査に場合は、その理由を記載すること。
（※3）廃止前の「疫学研究に関する倫理指針」や「臨床研究に関する倫理指針」に準拠する場合は、当該項目に記入すること。

５．厚生労働分野の研究活動における不正行為への対応について

研究倫理教育の受講状況	受講 ■　未受講 □

６．利益相反の管理

当研究機関におけるＣＯＩの管理に関する規定の策定	有 ■　無 □（無の場合はその理由：　　）
当研究機関におけるＣＯＩ委員会設置の有無	有 ■　無 □（無の場合は委託先機関：　　）
当研究に係るＣＯＩについての報告・審査の有無	有 ■　無 □（無の場合はその理由：　　）
当研究に係るＣＯＩについての指導・管理の有無	有 □　無 ■（有の場合はその内容：　　）

（留意事項）　・該当する□にチェックを入れること。
・分担研究者の所属する機関の長も作成すること。

平成31年 3月13日

国立保健医療科学院長　殿

機関名　金沢医科
所属研究機関長　職　名　学長
氏　名　神田　享

次の職員の平成３０年度厚生労働科学研究費の調査研究における、倫理審査状況及び
いては以下のとおりです。

１．研究事業名　難治性疾患等政策研究事業（難治性疾患政策研究事業）

２．研究課題名　自己免疫疾患に関する調査研究

３．研究者名　（所属部局・職名）血液免疫内科学・教授

（氏名・フリガナ）正木　康史・マサキ　ヤスフミ

４．倫理審査の状況

	該当性の有無		左記で該当がある場合のみ記入（※1）		
	有	無	審査済み	審査した機関	未審査（※2）
ヒトゲノム・遺伝子解析研究に関する倫理指針	□	■	□		□
遺伝子治療等臨床研究に関する指針	□	■	□		□
人を対象とする医学系研究に関する倫理指針（※3）	■	□	■	金沢医科大学	□
厚生労働省の所管する実施機関における動物実験等の実施に関する基本指針	□	■	□		□
その他、該当する倫理指針があれば記入すること（指針の名称：　）	□	■	□		□

（※1）当該研究者が当該研究を実施するに当たり遵守すべき倫理指針に関する倫理委員会の審査が済んでいる場合は、「審査済み」にチェックし一部若しくは全部の審査が完了していない場合は、「未審査」にチェックすること。

その他（特記事項）

（※2）未審査に場合は、その理由を記載すること。
（※3）廃止前の「疫学研究に関する倫理指針」や「臨床研究に関する倫理指針」に準拠する場合は、当該項目に記入すること。

５．厚生労働分野の研究活動における不正行為への対応について

研究倫理教育の受講状況	受講 ■　未受講 □

６．利益相反の管理

当研究機関におけるＣＯＩの管理に関する規定の策定	有 ■　無 □（無の場合はその理由：　）
当研究機関におけるＣＯＩ委員会設置の有無	有 ■　無 □（無の場合は委託先機関：　）
当研究に係るＣＯＩについての報告・審査の有無	有 ■　無 □（無の場合はその理由：　）
当研究に係るＣＯＩについての指導・管理の有無	有 □　無 ■（有の場合はその内容：　）

（留意事項）　・該当する□にチェックを入れること。
・分担研究者の所属する機関の長も作成すること。

平成31 年 2月 27 日

国立保健医療科学院長　殿

機関名　国立大学法[redacted]

所属研究機関長　職　名　総長

氏　名　久保　千[redacted]

次の職員の平成３０年度厚生労働科学研究費の調査研究における、倫理審査状況及び利[redacted]いては以下のとおりです。

１．研究事業名　難治性疾患等政策研究事業（難治性疾患政策研究事業）

２．研究課題名　自己免疫疾患に関する調査研究

３．研究者名　（所属部局・職名）　大学院歯学研究院・教授

（氏名・フリガナ）　中村　誠司・ナカムラ　セイジ

４．倫理審査の状況

	該当性の有無		左記で該当がある場合のみ記入（※1）		
	有	無	審査済み	審査した機関	未審査（※2）
ヒトゲノム・遺伝子解析研究に関する倫理指針	□	■	□		□
遺伝子治療等臨床研究に関する指針	□	■	□		□
人を対象とする医学系研究に関する倫理指針（※3）	■	□	■	九州大学	□
厚生労働省の所管する実施機関における動物実験等の実施に関する基本指針	□	■	□		□
その他、該当する倫理指針があれば記入すること（指針の名称：　）	□	■	□		□

（※1）当該研究者が当該研究を実施するに当たり遵守すべき倫理指針に関する倫理委員会の審査が済んでいる場合は、「審査済み」にチェックし一部若しくは全部の審査が完了していない場合は、「未審査」にチェックすること。

その他（特記事項）

（※2）未審査に場合は、その理由を記載すること。
（※3）廃止前の「疫学研究に関する倫理指針」や「臨床研究に関する倫理指針」に準拠する場合は、当該項目に記入すること。

５．厚生労働分野の研究活動における不正行為への対応について

研究倫理教育の受講状況	受講 ■　未受講 □

６．利益相反の管理

当研究機関におけるＣＯＩの管理に関する規定の策定	有 ■　無 □（無の場合はその理由：　）
当研究機関におけるＣＯＩ委員会設置の有無	有 ■　無 □（無の場合は委託先機関：　）
当研究に係るＣＯＩについての報告・審査の有無	有 ■　無 □（無の場合はその理由：　）
当研究に係るＣＯＩについての指導・管理の有無	有 □　無 ■（有の場合はその内容：　）

（留意事項）　・該当する□にチェックを入れること。
・分担研究者の所属する機関の長も作成すること。

平成３１年３月３１日

国立保健医療科学院長 殿

機関名　慶應義塾大[redacted]

所属研究機関長　職　名　学長

氏　名　長谷山　[redacted]

次の職員の平成３０年度厚生労働科学研究費の調査研究における、倫理審査状況及び利益相反等の管理については以下のとおりです。

１．研究事業名　難治性疾患等政策研究事業（難治性疾患政策研究事業）

２．研究課題名　自己免疫疾患に関する調査研究

３．研究者名　（所属部局・職名）　慶應義塾大学医学部・教授

（氏名・フリガナ）　坪田　一男・ツボタ　カズオ

４．倫理審査の状況

	該当性の有無		左記で該当がある場合のみ記入（※1）		
	有	無	審査済み	審査した機関	未審査（※2）
ヒトゲノム・遺伝子解析研究に関する倫理指針	□	■	□		□
遺伝子治療等臨床研究に関する指針	□	■	□		□
人を対象とする医学系研究に関する倫理指針（※3）	■	□	■	慶應義塾大学医学部	□
厚生労働省の所管する実施機関における動物実験等の実施に関する基本指針	□	■	□		□
その他、該当する倫理指針があれば記入すること（指針の名称：　　）	□	■	□		□

（※1）当該研究者が当該研究を実施するに当たり遵守すべき倫理指針に関する倫理委員会の審査が済んでいる場合は、「審査済み」にチェックし一部若しくは全部の審査が完了していない場合は、「未審査」にチェックすること。

その他（特記事項）

（※2）未審査に場合は、その理由を記載すること。

（※3）廃止前の「疫学研究に関する倫理指針」や「臨床研究に関する倫理指針」に準拠する場合は、当該項目に記入すること。

５．厚生労働分野の研究活動における不正行為への対応について

研究倫理教育の受講状況	受講 ■　未受講 □

６．利益相反の管理

当研究機関におけるＣＯＩの管理に関する規定の策定	有 ■　無 □（無の場合はその理由：　　）
当研究機関におけるＣＯＩ委員会設置の有無	有 ■　無 □（無の場合は委託先機関：　　）
当研究に係るＣＯＩについての報告・審査の有無	有 ■　無 □（無の場合はその理由：　　）
当研究に係るＣＯＩについての指導・管理の有無	有 □　無 ■（有の場合はその内容：　　）

（留意事項）　・該当する□にチェックを入れること。
・分担研究者の所属する機関の長も作成すること。

5037

平成 31 年 3 月 7 日

国立保健医療科学院長　　殿

機関名　東京女子医科大学

所属研究機関長　職　名　学長

氏　名　吉岡　俊正

次の職員の平成３０年度厚生労働科学研究費の調査研究における、倫理審査状況及び利益相反
ついては以下のとおりです。

１．研究事業名　難治性疾患等政策研究事業（難治性疾患政策研究事業）

２．研究課題名　自己免疫疾患に関する調査研究

３．研究者名　（所属部局・職名）　医学部医学科眼科学 ・ 教授

（氏名・フリガナ）　高村　悦子 ・ タカムラ　エツコ

４．倫理審査の状況

	該当性の有無		左記で該当がある場合のみ記入　(※1)		
	有	無	審査済み	審査した機関	未審査(※2)
ヒトゲノム・遺伝子解析研究に関する倫理指針	□	■	□		□
遺伝子治療等臨床研究に関する指針	□	■	□		□
人を対象とする医学系研究に関する倫理指針（※3）	■	□	■	東京女子医科大学	□
厚生労働省の所管する実施機関における動物実験等の実施に関する基本指針	□	■	□		□
その他、該当する倫理指針があれば記入すること（指針の名称：　　）	□	■	□		□

（※1）当該研究者が当該研究を実施するに当たり遵守すべき倫理指針に関する倫理委員会の審査が済んでいる場合は、「審査済み」にチェックし一部若しくは全部の審査が完了していない場合は、「未審査」にチェックすること。

その他（特記事項）

（※2）未審査に場合は、その理由を記載すること。

（※3）廃止前の「疫学研究に関する倫理指針」や「臨床研究に関する倫理指針」に準拠する場合は、当該項目に記入すること。

５．厚生労働分野の研究活動における不正行為への対応について

研究倫理教育の受講状況	受講 ■　未受講 □

６．利益相反の管理

当研究機関におけるＣＯＩの管理に関する規定の策定	有 ■　無 □（無の場合はその理由　：　）
当研究機関におけるＣＯＩ委員会設置の有無	有 ■　無 □（無の場合は委託先機関：　）
当研究に係るＣＯＩについての報告・審査の有無	有 ■　無 □（無の場合はその理由　：　）
当研究に係るＣＯＩについての指導・管理の有無	有 □　無 ■（有の場合はその内容　：　）

（留意事項）・該当する□にチェックを入れること。
・分担研究者の所属する機関の長も作成すること。

2019 年 3 月 25 日

国立保健医療科学院長　殿

機関名　国立病院機構下志津[redacted]

所属研究機関長　職　名　院長

氏　名　石毛尚走[redacted]

次の職員の平成３０年度厚生労働科学研究費の調査研究における、倫理審査状況及び利益相反等の管理については以下のとおりです。

１．研究事業名　難治性疾患等政策研究事業（難治性疾患政策研究事業）

２．研究課題名　自己免疫疾患に関する調査研究

３．研究者名　（所属部局・職名）　国立病院機構下志津病院小児科医長

（氏名・フリガナ）　冨板美奈子（トミイタミナコ）

４．倫理審査の状況

	該当性の有無		左記で該当がある場合のみ記入 (※1)		
	有	無	審査済み	審査した機関	未審査 (※2)
ヒトゲノム・遺伝子解析研究に関する倫理指針	□	■	□		□
遺伝子治療等臨床研究に関する指針	□	■	□		□
人を対象とする医学系研究に関する倫理指針 (※3)	■	□	■	千葉県こども病院 下志津病院	□
厚生労働省の所管する実施機関における動物実験等の実施に関する基本指針	□	■	□		□
その他、該当する倫理指針があれば記入すること （指針の名称：　　）	□	■	□		□

(※1) 当該研究者が当該研究を実施するに当たり遵守すべき倫理指針に関する倫理委員会の審査が済んでいる場合は、「審査済み」にチェックし一部若しくは全部の審査が完了していない場合は、「未審査」にチェックすること。

その他（特記事項）

(※2) 未審査に場合は、その理由を記載すること。
(※3) 廃止前の「疫学研究に関する倫理指針」や「臨床研究に関する倫理指針」に準拠する場合は、当該項目に記入すること。

５．厚生労働分野の研究活動における不正行為への対応について

研究倫理教育の受講状況	受講 ■　未受講 □

６．利益相反の管理

当研究機関におけるＣＯＩの管理に関する規定の策定	有 ■　無 □(無の場合はその理由：　　)
当研究機関におけるＣＯＩ委員会設置の有無	有 ■　無 □(無の場合は委託先機関：　　)
当研究に係るＣＯＩについての報告・審査の有無	有 ■　無 □(無の場合はその理由：　　)
当研究に係るＣＯＩについての指導・管理の有無	有 □　無 ■ (有の場合はその内容：　　)

（留意事項）　・該当する□にチェックを入れること。
・分担研究者の所属する機関の長も作成すること。

平成３１年３月３１日

国立保健医療科学院長 殿

機関名　慶應義塾大[redacted]

所属研究機関長　職　名　学長

氏　名　長谷山　彰[redacted]

次の職員の平成３０年度厚生労働科学研究費の調査研究における、倫理審査状況及び利[redacted]ついては以下のとおりです。

１．研究事業名　難治性疾患等政策研究事業（難治性疾患政策研究事業）

２．研究課題名　自己免疫疾患に関する調査研究

３．研究者名　（所属部局・職名）　慶應義塾大学医学部・教授

（氏名・フリガナ）　竹内　勤・タケウチ　ツトム

４．倫理審査の状況

	該当性の有無		左記で該当がある場合のみ記入 (※1)		
	有	無	審査済み	審査した機関	未審査 (※2)
ヒトゲノム・遺伝子解析研究に関する倫理指針	□	■	□		□
遺伝子治療等臨床研究に関する指針	□	■	□		□
人を対象とする医学系研究に関する倫理指針 (※3)	■	□	■	慶應義塾大学医学部	□
厚生労働省の所管する実施機関における動物実験等の実施に関する基本指針	□	■	□		□
その他、該当する倫理指針があれば記入すること（指針の名称：　　）	□	■	□		□

(※1) 当該研究者が当該研究を実施するに当たり遵守すべき倫理指針に関する倫理委員会の審査が済んでいる場合は、「審査済み」にチェックし一部若しくは全部の審査が完了していない場合は、「未審査」にチェックすること。

その他（特記事項）

(※2) 未審査に場合は、その理由を記載すること。
(※3) 廃止前の「疫学研究に関する倫理指針」や「臨床研究に関する倫理指針」に準拠する場合は、当該項目に記入すること。

５．厚生労働分野の研究活動における不正行為への対応について

研究倫理教育の受講状況	受講 ■　未受講 □

６．利益相反の管理

当研究機関におけるＣＯＩの管理に関する規定の策定	有 ■　無 □(無の場合はその理由：　　)
当研究機関におけるＣＯＩ委員会設置の有無	有 ■　無 □(無の場合は委託先機関：　　)
当研究に係るＣＯＩについての報告・審査の有無	有 ■　無 □(無の場合はその理由：　　)
当研究に係るＣＯＩについての指導・管理の有無	有 □　無 ■(有の場合はその内容：　　)

（留意事項）　・該当する□にチェックを入れること。
・分担研究者の所属する機関の長も作成すること。

平成31年4月8日

国立保健医療科学院長　殿

機関名　順天堂大学

所属研究機関長　職　名　学長

氏　名　新井　一

次の職員の平成30年度厚生労働科学研究費の調査研究における、倫理審査状況及び利益[redacted]ついては以下のとおりです。

1．研究事業名　難治性疾患等政策研究事業（難治性疾患政策研究事業）

2．研究課題名　自己免疫疾患に関する調査研究

3．研究者名　（所属部局・職名）　医学部・准教授

（氏名・フリガナ）　天野　浩文（アマノ　ヒロフミ）

4．倫理審査の状況

	該当性の有無		左記で該当がある場合のみ記入（※1）		
	有	無	審査済み	審査した機関	未審査（※2）
ヒトゲノム・遺伝子解析研究に関する倫理指針	□	■	□		□
遺伝子治療等臨床研究に関する指針	□	■	□		□
人を対象とする医学系研究に関する倫理指針（※3）	■	□	■	順天堂大学	□
厚生労働省の所管する実施機関における動物実験等の実施に関する基本指針	□	■	□		□
その他、該当する倫理指針があれば記入すること（指針の名称：　）	□	■	□		□

（※1）当該研究者が当該研究を実施するに当たり遵守すべき倫理指針に関する倫理委員会の審査が済んでいる場合は、「審査済み」にチェックし一部若しくは全部の審査が完了していない場合は、「未審査」にチェックすること。

その他（特記事項）

（※2）未審査に場合は、その理由を記載すること。

（※3）廃止前の「疫学研究に関する倫理指針」や「臨床研究に関する倫理指針」に準拠する場合は、当該項目に記入すること。

5．厚生労働分野の研究活動における不正行為への対応について

研究倫理教育の受講状況	受講 ■　未受講 □

6．利益相反の管理

当研究機関におけるＣＯＩの管理に関する規定の策定	有 ■　無 □（無の場合はその理由：　）
当研究機関におけるＣＯＩ委員会設置の有無	有 ■　無 □（無の場合は委託先機関：　）
当研究に係るＣＯＩについての報告・審査の有無	有 ■　無 □（無の場合はその理由：　）
当研究に係るＣＯＩについての指導・管理の有無	有 □　無 ■（有の場合はその内容：　）

（留意事項）　・該当する□にチェックを入れること。
・分担研究者の所属する機関の長も作成すること。

平成 31 年 1 月 30 日

国立保健医療科学院長　殿

機関名 国立大学法人東北大学

所属研究機関長　職　名

氏　名 総長 大野英男

次の職員の平成３０年度厚生労働科学研究費の調査研究における、倫理審査状況及び利益相反等の[illegible]いては以下のとおりです。

１．研究事業名　難治性疾患等政策研究事業（難治性疾患政策研究事業）

２．研究課題名　自己免疫疾患に関する調査研究

３．研究者名　（所属部局・職名）　病院・特任教授

（氏名・フリガナ）　石井　智徳（イシイ　トモノリ）

４．倫理審査の状況

	該当性の有無		左記で該当がある場合のみ記入（※1）		
	有	無	審査済み	審査した機関	未審査（※2）
ヒトゲノム・遺伝子解析研究に関する倫理指針	□	■	□		□
遺伝子治療等臨床研究に関する指針	□	■	□		□
人を対象とする医学系研究に関する倫理指針（※3）	■	□	■	東北大学	□
厚生労働省の所管する実施機関における動物実験等の実施に関する基本指針	□	■	□		□
その他、該当する倫理指針があれば記入すること（指針の名称：　）	□	■	□		□

（※1）当該研究者が当該研究を実施するに当たり遵守すべき倫理指針に関する倫理委員会の審査が済んでいる場合は、「審査済み」にチェックし一部若しくは全部の審査が完了していない場合は、「未審査」にチェックすること。

その他（特記事項）

（※2）未審査に場合は、その理由を記載すること。
（※3）廃止前の「疫学研究に関する倫理指針」や「臨床研究に関する倫理指針」に準拠する場合は、当該項目に記入すること。

５．厚生労働分野の研究活動における不正行為への対応について

研究倫理教育の受講状況	受講 ■　未受講 □

６．利益相反の管理

当研究機関におけるＣＯＩの管理に関する規定の策定	有 ■　無 □（無の場合はその理由：　）
当研究機関におけるＣＯＩ委員会設置の有無	有 ■　無 □（無の場合は委託先機関：　）
当研究に係るＣＯＩについての報告・審査の有無	有 ■　無 □（無の場合はその理由：　）
当研究に係るＣＯＩについての指導・管理の有無	有 ■　無 □（有の場合はその内容：研究実施の際の留意点を示した　）

（留意事項）　・該当する□にチェックを入れること。
・分担研究者の所属する機関の長も作成すること。

2019年　1月　9日

国立保健医療科学院長　殿

機関名　北里大学

所属研究機関長　職　名　学長

氏　名　伊藤 智夫

次の職員の平成３０年度厚生労働科学研究費の調査研究における、倫理審査状況及び利益相反等の管理については以下のとおりです。

１．研究事業名　難治性疾患等政策研究事業（難治性疾患政策研究事業）

２．研究課題名　自己免疫疾患に関する調査研究

３．研究者名　（所属部局・職名）　北里大学医学部　・　客員教授

（氏名・フリガナ）　廣畑 俊成　・　ヒロハタ・シュンセイ

４．倫理審査の状況

	該当性の有無	左記で該当がある場合のみ記入（※1）		
	有　無	審査済み	審査した機関	未審査（※2）
ヒトゲノム・遺伝子解析研究に関する倫理指針	□　■	□		□
遺伝子治療等臨床研究に関する指針	□　■	□		□
人を対象とする医学系研究に関する倫理指針（※3）	□　■	□		□
厚生労働省の所管する実施機関における動物実験等の実施に関する基本指針	□　■	□		□
その他、該当する倫理指針があれば記入すること（指針の名称：　）	□　■	□		□

（※1）当該研究者が当該研究を実施するに当たり遵守すべき倫理指針に関する倫理委員会の審査が済んでいる場合は、「審査済み」にチェックし一部若しくは全部の審査が完了していない場合は、「未審査」にチェックすること。

その他（特記事項）

（※2）未審査に場合は、その理由を記載すること。
（※3）廃止前の「疫学研究に関する倫理指針」や「臨床研究に関する倫理指針」に準拠する場合は、当該項目に記入すること。

５．厚生労働分野の研究活動における不正行為への対応について

研究倫理教育の受講状況	受講 ■　未受講 □

６．利益相反の管理

当研究機関におけるＣＯＩの管理に関する規定の策定	有 ■　無 □（無の場合はその理由：　）
当研究機関におけるＣＯＩ委員会設置の有無	有 ■　無 □（無の場合は委託先機関：　）
当研究に係るＣＯＩについての報告・審査の有無	有 ■　無 □（無の場合はその理由：　）
当研究に係るＣＯＩについての指導・管理の有無	有 □　無 ■（有の場合はその内容：　）

（留意事項）　・該当する□にチェックを入れること。
・分担研究者の所属する機関の長も作成すること。

2019年3月11日

国立保健医療科学院長　殿

機関名　藤田医科大学

所属研究機関長　職　名　学長

氏　名　星長　清隆

次の職員の平成３０年度厚生労働科学研究費の調査研究における、倫理審査状況及び利益相反等の管理については以下のとおりです。

１．研究事業名　難治性疾患等政策研究事業（難治性疾患政策研究事業）

２．研究課題名　自己免疫疾患に関する調査研究

３．研究者名　（所属部局・職名）[i1]　医学部・教授

（氏名・フリガナ）　湯澤由紀夫・ユザワユキオ

４．倫理審査の状況

	該当性の有無		左記で該当がある場合のみ記入（※1）		
	有	無	審査済み	審査した機関	未審査（※2）
ヒトゲノム・遺伝子解析研究に関する倫理指針	□	■	□		□
遺伝子治療等臨床研究に関する指針	□	■	□		□
人を対象とする医学系研究に関する倫理指針（※3）	□	■	□		□
厚生労働省の所管する実施機関における動物実験等の実施に関する基本指針	□	■	□		□
その他、該当する倫理指針があれば記入すること（指針の名称：　）	□	■	□		□

（※1）当該研究者が当該研究を実施するに当たり遵守すべき倫理指針に関する倫理委員会の審査が済んでいる場合は、「審査済み」にチェックし一部若しくは全部の審査が完了していない場合は、「未審査」にチェックすること。

その他（特記事項）

（※2）未審査に場合は、その理由を記載すること。
（※3）廃止前の「疫学研究に関する倫理指針」や「臨床研究に関する倫理指針」に準拠する場合は、当該項目に記入すること。

５．厚生労働分野の研究活動における不正行為への対応について

研究倫理教育の受講状況	受講 ■　未受講 □

６．利益相反の管理

当研究機関におけるＣＯＩの管理に関する規定の策定	有 ■　無 □（無の場合はその理由：　）
当研究機関におけるＣＯＩ委員会設置の有無	有 ■　無 □（無の場合は委託先機関：　）
当研究に係るＣＯＩについての報告・審査の有無	有 ■　無 □（無の場合はその理由：　）
当研究に係るＣＯＩについての指導・管理の有無	有 □　無 ■（有の場合はその内容：　）

（留意事項）　・該当する□にチェックを入れること。
・分担研究者の所属する機関の長も作成すること。

H３１年　４月　９日

国立保健医療科学院長　殿

機関名　国立大学法人[redacted]

所属研究機関長　職　名　学長

氏　名　佐　野　[redacted]

次の職員の平成３０年度厚生労働科学研究費の調査研究における、倫理審査状況及び利益[redacted]いては以下のとおりです。

１．研究事業名　難治性疾患等政策研究事業（難治性疾患政策研究事業）

２．研究課題名　自己免疫疾患に関する調査研究

３．研究者名　（所属部局・職名）大学院医歯学総合研究科・客員研究員

（氏名・フリガナ）武井　修治　・　タケイ　シュウジ

４．倫理審査の状況

	該当性の有無		左記で該当がある場合のみ記入（※1）		
	有	無	審査済み	審査した機関	未審査（※2）
ヒトゲノム・遺伝子解析研究に関する倫理指針	□	■	□		□
遺伝子治療等臨床研究に関する指針	□	■	□		□
人を対象とする医学系研究に関する倫理指針（※3）	□	■	□		□
厚生労働省の所管する実施機関における動物実験等の実施に関する基本指針	□	■	□		□
その他、該当する倫理指針があれば記入すること（指針の名称：　　）	□	■	□		□

（※1）当該研究者が当該研究を実施するに当たり遵守すべき倫理指針に関する倫理委員会の審査が済んでいる場合は、「審査済み」にチェックし一部若しくは全部の審査が完了していない場合は、「未審査」にチェックすること。

その他（特記事項）

（※2）未審査に場合は、その理由を記載すること。

（※3）廃止前の「疫学研究に関する倫理指針」や「臨床研究に関する倫理指針」に準拠する場合は、当該項目に記入すること。

５．厚生労働分野の研究活動における不正行為への対応について

研究倫理教育の受講状況	受講 ■　未受講 □

６．利益相反の管理

当研究機関におけるＣＯＩの管理に関する規定の策定	有 ■　無 □（無の場合はその理由：　　）
当研究機関におけるＣＯＩ委員会設置の有無	有 ■　無 □（無の場合は委託先機関：　　）
当研究に係るＣＯＩについての報告・審査の有無	有 ■　無 □（無の場合はその理由：　　）
当研究に係るＣＯＩについての指導・管理の有無	有 □　無 ■（有の場合はその内容：　　）

（留意事項）　・該当する□にチェックを入れること。
・分担研究者の所属する機関の長も作成すること。

2019年　4月　4日

国立保健医療科学院長　殿

機関名　和歌山県立医科大学

所属研究機関長　職　名　学長

氏　名　宮下　和久

次の職員の平成３０年度厚生労働科学研究費の調査研究における、倫理審査状況及び利益相
いては以下のとおりです。

１．研究事業名　難治性疾患等政策研究事業（難治性疾患政策研究事業）

２．研究課題名　自己免疫疾患に関する調査研究

３．研究者名　（所属部局・職名）医学部リウマチ・膠原病科学講座・教授

（氏名・フリガナ）藤井　隆夫・フジイ　タカオ

４．倫理審査の状況

	該当性の有無	左記で該当がある場合のみ記入（※1）		
	有　無	審査済み	審査した機関	未審査（※2）
ヒトゲノム・遺伝子解析研究に関する倫理指針	□　■	□		□
遺伝子治療等臨床研究に関する指針	□　■	□		□
人を対象とする医学系研究に関する倫理指針（※3）	□　■	□		□
厚生労働省の所管する実施機関における動物実験等の実施に関する基本指針	□　■	□		□
その他、該当する倫理指針があれば記入すること（指針の名称：　　）	□　■	□		□

（※1）当該研究者が当該研究を実施するに当たり遵守すべき倫理指針に関する倫理委員会の審査が済んでいる場合は、「審査済み」にチェックし一部若しくは全部の審査が完了していない場合は、「未審査」にチェックすること。

その他（特記事項）

（※2）未審査に場合は、その理由を記載すること。
（※3）廃止前の「疫学研究に関する倫理指針」や「臨床研究に関する倫理指針」に準拠する場合は、当該項目に記入すること。

５．厚生労働分野の研究活動における不正行為への対応について

研究倫理教育の受講状況	受講 ■　未受講 □

６．利益相反の管理

当研究機関におけるＣＯＩの管理に関する規定の策定	有 ■　無 □（無の場合はその理由：　　）
当研究機関におけるＣＯＩ委員会設置の有無	有 ■　無 □（無の場合は委託先機関：　　）
当研究に係るＣＯＩについての報告・審査の有無	有 ■　無 □（無の場合はその理由：　　）
当研究に係るＣＯＩについての指導・管理の有無	有 □　無 ■（有の場合はその内容：　　）

（留意事項）　・該当する□にチェックを入れること。
・分担研究者の所属する機関の長も作成すること。

平成 31 年 3 月 1 日

国立保健医療科学院長　殿

機関名　日本医科大学

所属研究機関長　職　名　　学長

氏　名　　弦 間　昭 [redacted]

次の職員の平成３０年度厚生労働科学研究費の調査研究における、倫理審査状況及び利益相反等の管理については以下のとおりです。

１．研究事業名　難治性疾患等政策研究事業（難治性疾患政策研究事業）

２．研究課題名　自己免疫疾患に関する調査研究

３．研究者名　（所属部局・職名）大学院医学研究科・教授

（氏名・フリガナ）桑名　正隆（クワナ　マサタカ）

４．倫理審査の状況

	該当性の有無	左記で該当がある場合のみ記入（※1）		
	有　無	審査済み	審査した機関	未審査（※2）
ヒトゲノム・遺伝子解析研究に関する倫理指針	□　■	□		□
遺伝子治療等臨床研究に関する指針	□　■	□		□
人を対象とする医学系研究に関する倫理指針（※3）	□　■	□		□
厚生労働省の所管する実施機関における動物実験等の実施に関する基本指針	□　■	□		□
その他、該当する倫理指針があれば記入すること（指針の名称：　　）	□　■	□		□

（※1）当該研究者が当該研究を実施するに当たり遵守すべき倫理指針に関する倫理委員会の審査が済んでいる場合は、「審査済み」にチェックし一部若しくは全部の審査が完了していない場合は、「未審査」にチェックすること。

その他（特記事項）

（※2）未審査に場合は、その理由を記載すること。

（※3）廃止前の「疫学研究に関する倫理指針」や「臨床研究に関する倫理指針」に準拠する場合は、当該項目に記入すること。

５．厚生労働分野の研究活動における不正行為への対応について

研究倫理教育の受講状況	受講 ■　未受講 □

６．利益相反の管理

当研究機関におけるＣＯＩの管理に関する規定の策定	有 ■　無 □（無の場合はその理由：　　）
当研究機関におけるＣＯＩ委員会設置の有無	有 ■　無 □（無の場合は委託先機関：　　）
当研究に係るＣＯＩについての報告・審査の有無	有 ■　無 □（無の場合はその理由：　　）
当研究に係るＣＯＩについての指導・管理の有無	有 □　無 ■（有の場合はその内容：　　）

（留意事項）　・該当する□にチェックを入れること。
・分担研究者の所属する機関の長も作成すること。

2019 年 3 月 19 日

国立保健医療科学院長　殿

機関名　東邦大学
所属研究機関長　職名　学長
氏名　高松　研

次の職員の平成３０年度厚生労働科学研究費の調査研究における、倫理審査状況及び利益相反等の管理については以下のとおりです。

１．研究事業名　難治性疾患等政策研究事業（難治性疾患政策研究事業）

２．研究課題名　自己免疫疾患に関する調査研究

３．研究者名　（所属部局・職名）　医学部内科学講座膠原病学分野・教授

（氏名・フリガナ）　亀田秀人　・　カメダヒデト

４．倫理審査の状況

	該当性の有無		左記で該当がある場合のみ記入（※1）		
	有	無	審査済み	審査した機関	未審査（※2）
ヒトゲノム・遺伝子解析研究に関する倫理指針	□	■	□		□
遺伝子治療等臨床研究に関する指針	□	■	□		□
人を対象とする医学系研究に関する倫理指針（※3）	■	□	■	東邦大学医療センター 大橋病院倫理委員会	□
厚生労働省の所管する実施機関における動物実験等の実施に関する基本指針	□	■	□		□
その他、該当する倫理指針があれば記入すること （指針の名称：　）	□	■	□		□

（※1）当該研究者が当該研究を実施するに当たり遵守すべき倫理指針に関する倫理委員会の審査が済んでいる場合は、「審査済み」にチェックし一部若しくは全部の審査が完了していない場合は、「未審査」にチェックすること。

その他（特記事項）

（※2）未審査に場合は、その理由を記載すること。
（※3）廃止前の「疫学研究に関する倫理指針」や「臨床研究に関する倫理指針」に準拠する場合は、当該項目に記入すること。

５．厚生労働分野の研究活動における不正行為への対応について

研究倫理教育の受講状況	受講 ■　未受講 □

６．利益相反の管理

当研究機関におけるＣＯＩの管理に関する規定の策定	有 ■　無 □（無の場合はその理由：　）
当研究機関におけるＣＯＩ委員会設置の有無	有 ■　無 □（無の場合は委託先機関：　）
当研究に係るＣＯＩについての報告・審査の有無	有 ■　無 □（無の場合はその理由：　）
当研究に係るＣＯＩについての指導・管理の有無	有 □　無 ■（有の場合はその内容：　）

（留意事項）　・該当する□にチェックを入れること。
・分担研究者の所属する機関の長も作成すること。

平成　31　年 4 月 3 日

国立保健医療科学院長　殿

機関名　東京大[redacted]

所属研究機関長　職　名　総長

氏　名　五神[redacted]

次の職員の平成30年度厚生労働科学研究費の調査研究における、倫理審査状況及び利益相反等の管理については以下のとおりです。

1．研究事業名　難治性疾患等政策研究事業（難治性疾患政策研究事業）

2．研究課題名　自己免疫疾患に関する調査研究

3．研究者名　（所属部局・職名）　医学部附属病院・教授

（氏名・フリガナ）　藤尾　圭志・フジオ　ケイシ

4．倫理審査の状況

	該当性の有無		左記で該当がある場合のみ記入（※1）		
	有	無	審査済み	審査した機関	未審査（※2）
ヒトゲノム・遺伝子解析研究に関する倫理指針	□	■	□		□
遺伝子治療等臨床研究に関する指針	□	■	□		□
人を対象とする医学系研究に関する倫理指針（※3）	□	■	□		□
厚生労働省の所管する実施機関における動物実験等の実施に関する基本指針	□	■	□		□
その他、該当する倫理指針があれば記入すること（指針の名称：　　）	□	■	□		□

（※1）当該研究者が当該研究を実施するに当たり遵守すべき倫理指針に関する倫理委員会の審査が済んでいる場合は、「審査済み」にチェックし一部若しくは全部の審査が完了していない場合は、「未審査」にチェックすること。

その他（特記事項）

（※2）未審査に場合は、その理由を記載すること。
（※3）廃止前の「疫学研究に関する倫理指針」や「臨床研究に関する倫理指針」に準拠する場合は、当該項目に記入すること。

5．厚生労働分野の研究活動における不正行為への対応について

研究倫理教育の受講状況	受講 ■　未受講 □

6．利益相反の管理

当研究機関におけるＣＯＩの管理に関する規定の策定	有 ■　無 □（無の場合はその理由：　　）
当研究機関におけるＣＯＩ委員会設置の有無	有 ■　無 □（無の場合は委託先機関：　　）
当研究に係るＣＯＩについての報告・審査の有無	有 ■　無 □（無の場合はその理由：　　）
当研究に係るＣＯＩについての指導・管理の有無	有 □　無 ■（有の場合はその内容：　　）

（留意事項）　・該当する□にチェックを入れること。
・分担研究者の所属する機関の長も作成すること。

平成31年 2 月 26 日

国立保健医療科学院長　殿

機関名　名古屋大学

所属研究機関長　職　名　大学院医学系研究

氏　名　門松健治

次の職員の平成３０年度厚生労働科学研究費の調査研究における、倫理審査状況及び利益相反等
いては以下のとおりです。

１．研究事業名　難治性疾患等政策研究事業（難治性疾患政策研究事業）

２．研究課題名　自己免疫疾患に関する調査研究

３．研究者名　（所属部局・職名）　大学院医学系研究科　皮膚科学・准教授

（氏名・フリガナ）　室　慶直・ムロ　ヨシナオ

４．倫理審査の状況

	該当性の有無	左記で該当がある場合のみ記入（※1）		
	有　無	審査済み	審査した機関	未審査（※2）
ヒトゲノム・遺伝子解析研究に関する倫理指針	□　■	□		□
遺伝子治療等臨床研究に関する指針	□　■	□		□
人を対象とする医学系研究に関する倫理指針（※3）	□　■	□		□
厚生労働省の所管する実施機関における動物実験等の実施に関する基本指針	□　■	□		□
その他、該当する倫理指針があれば記入すること（指針の名称：　）	□　■	□		□

（※1）当該研究者が当該研究を実施するに当たり遵守すべき倫理指針に関する倫理委員会の審査が済んでいる場合は、「審査済み」にチェックし一部若しくは全部の審査が完了していない場合は、「未審査」にチェックすること。

その他（特記事項）

（※2）未審査に場合は、その理由を記載すること。
（※3）廃止前の「疫学研究に関する倫理指針」や「臨床研究に関する倫理指針」に準拠する場合は、当該項目に記入すること。

５．厚生労働分野の研究活動における不正行為への対応について

研究倫理教育の受講状況	受講 ■　未受講 □

６．利益相反の管理

当研究機関におけるＣＯＩの管理に関する規定の策定	有 ■　無 □（無の場合はその理由：　）
当研究機関におけるＣＯＩ委員会設置の有無	有 ■　無 □（無の場合は委託先機関：　）
当研究に係るＣＯＩについての報告・審査の有無	有 ■　無 □（無の場合はその理由：　）
当研究に係るＣＯＩについての指導・管理の有無	有 □　無 ■（有の場合はその内容：　）

（留意事項）　・該当する□にチェックを入れること。
・分担研究者の所属する機関の長も作成すること。

平成 31 年 3 月 1 日

国立保健医療科学院長　　殿

機関名　日本医科大学

所属研究機関長　職　名　　学長

氏　名　　弦 間　昭 

次の職員の平成３０年度厚生労働科学研究費の調査研究における、倫理審査状況及び利益相反等の管理については以下のとおりです。

１．研究事業名　難治性疾患等政策研究事業(難治性疾患政策研究事業)

２．研究課題名　自己免疫疾患に関する調査研究

３．研究者名　（所属部局・職名）大学院医学研究科・教授

（氏名・フリガナ）伊藤　保彦 ・ イトウ　ヤスヒコ

４．倫理審査の状況

	該当性の有無	左記で該当がある場合のみ記入（※1）		
	有　無	審査済み	審査した機関	未審査（※2）
ヒトゲノム・遺伝子解析研究に関する倫理指針	□　■	□		□
遺伝子治療等臨床研究に関する指針	□　■	□		□
人を対象とする医学系研究に関する倫理指針（※3）	□　■	□		□
厚生労働省の所管する実施機関における動物実験等の実施に関する基本指針	□　■	□		□
その他、該当する倫理指針があれば記入すること（指針の名称：　　）	□　■	□		□

（※1）当該研究者が当該研究を実施するに当たり遵守すべき倫理指針に関する倫理委員会の審査が済んでいる場合は、「審査済み」にチェックし一部若しくは全部の審査が完了していない場合は、「未審査」にチェックすること。

その他（特記事項）

（※2）未審査に場合は、その理由を記載すること。

（※3）廃止前の「疫学研究に関する倫理指針」や「臨床研究に関する倫理指針」に準拠する場合は、当該項目に記入すること。

５．厚生労働分野の研究活動における不正行為への対応について

研究倫理教育の受講状況	受講 ■　　未受講 □

６．利益相反の管理

当研究機関におけるＣＯＩの管理に関する規定の策定	有 ■　無 □（無の場合はその理由：　　）
当研究機関におけるＣＯＩ委員会設置の有無	有 ■　無 □（無の場合は委託先機関：　　）
当研究に係るＣＯＩについての報告・審査の有無	有 ■　無 □（無の場合はその理由：　　）
当研究に係るＣＯＩについての指導・管理の有無	有　無 ■（有の場合はその内容：　　）

（留意事項）　・該当する□にチェックを入れること。

・分担研究者の所属する機関の長も作成すること。

平成　31　年　1　月　31　日

国立保健医療科学院長　殿

機関名　　埼玉医科大学
所属研究機関長　職　名　　学　長
氏　名　　別　所　正　[redacted]

次の職員の平成３０年度厚生労働科学研究費の調査研究における、倫理審査状況及び利益相反等の管理については以下のとおりです。

１．研究事業名　難治性疾患等政策研究事業（難治性疾患政策研究事業）

２．研究課題名　自己免疫疾患に関する調査研究

３．研究者名　（所属部局・職名）　医学部　リウマチ膠原病科　・教授

（氏名・フリガナ）　三村（みむら）　俊英（としひで）

４．倫理審査の状況

	該当性の有無		左記で該当がある場合のみ記入（※1）		
	有	無	審査済み	審査した機関	未審査（※2）
ヒトゲノム・遺伝子解析研究に関する倫理指針	■	□	■	埼玉医科大学	□
遺伝子治療等臨床研究に関する指針	□	■	□		□
人を対象とする医学系研究に関する倫理指針（※3）	■	□	■	埼玉医科大学	□
厚生労働省の所管する実施機関における動物実験等の実施に関する基本指針	□	■	□		□
その他、該当する倫理指針があれば記入すること（指針の名称：　　）	□	■	□		□

（※1）当該研究者が当該研究を実施するに当たり遵守すべき倫理指針に関する倫理委員会の審査が済んでいる場合は、「審査済み」にチェックし一部若しくは全部の審査が完了していない場合は、「未審査」にチェックすること。

その他（特記事項）

（※2）未審査に場合は、その理由を記載すること。
（※3）廃止前の「疫学研究に関する倫理指針」や「臨床研究に関する倫理指針」に準拠する場合は、当該項目に記入すること。

５．厚生労働分野の研究活動における不正行為への対応について

研究倫理教育の受講状況	受講 ■　未受講 □

６．利益相反の管理

当研究機関におけるＣＯＩの管理に関する規定の策定	有 ■　無 □（無の場合はその理由：　　）
当研究機関におけるＣＯＩ委員会設置の有無	有 ■　無 □（無の場合は委託先機関：　　）
当研究に係るＣＯＩについての報告・審査の有無	有 ■　無 □（無の場合はその理由：　　）
当研究に係るＣＯＩについての指導・管理の有無	有 □　無 ■（有の場合はその内容：　　）

（留意事項）　・該当する□にチェックを入れること。
・分担研究者の所属する機関の長も作成すること。

２０１９年４月１日

国立保健医療科学院長　殿

機関名　聖マリアン[redacted]

所属研究機関長　職　名　学長

氏　名　尾崎　承一[redacted]

次の職員の平成３０年度厚生労働科学研究費の調査研究における、倫理審査状況及び利益相反等の管理については以下のとおりです。

１．研究事業名　難治性疾患等政策研究事業（難治性疾患政策研究事業）

２．研究課題名　自己免疫疾患に関する調査研究

３．研究者名　（所属部局・職名）医学部(内科学(ﾘｳﾏﾁ・膠原病・ｱﾚﾙｷﾞｰ内科))・教授

（氏名・フリガナ）川畑　仁人・カワハタ　キミト

４．倫理審査の状況

	該当性の有無	左記で該当がある場合のみ記入（※1）		
	有　無	審査済み	審査した機関	未審査（※2）
ヒトゲノム・遺伝子解析研究に関する倫理指針	□　☑	□		□
遺伝子治療等臨床研究に関する指針	□　☑	□		□
人を対象とする医学系研究に関する倫理指針（※3）	□　☑	□		□
厚生労働省の所管する実施機関における動物実験等の実施に関する基本指針	□　☑	□		□
その他、該当する倫理指針があれば記入すること（指針の名称：　　）	□　☑	□		□

（※1）当該研究者が当該研究を実施するに当たり遵守すべき倫理指針に関する倫理委員会の審査が済んでいる場合は、「審査済み」にチェックし一部若しくは全部の審査が完了していない場合は、「未審査」にチェックすること。

その他（特記事項）

（※2）未審査に場合は、その理由を記載すること。
（※3）廃止前の「疫学研究に関する倫理指針」や「臨床研究に関する倫理指針」に準拠する場合は、当該項目に記入すること。

５．厚生労働分野の研究活動における不正行為への対応について

研究倫理教育の受講状況	受講 ☑　未受講 □

６．利益相反の管理

当研究機関におけるＣＯＩの管理に関する規定の策定	有 ☑　無 □（無の場合はその理由：　　）
当研究機関におけるＣＯＩ委員会設置の有無	有 ☑　無 □（無の場合は委託先機関：　　）
当研究に係るＣＯＩについての報告・審査の有無	有 ☑　無 □（無の場合はその理由：　　）
当研究に係るＣＯＩについての指導・管理の有無	有 ☑　無 □（有の場合はその内容：企業より得ている研究費等については自己申告がなされており、その情報により利益相反は適切に管理されている）

（留意事項）　・該当する□にチェックを入れること。
・分担研究者の所属する機関の長も作成すること。

平成31年3月28日

国立保健医療科学院長　殿

機関名　大阪医科
所属研究機関長　職　名　学長
氏　名　大槻 [redacted]

次の職員の平成３０年度厚生労働科学研究費の調査研究における、倫理審査状況及び利益相反等の管理については以下のとおりです。

１．研究事業名　難治性疾患等政策研究事業（難治性疾患政策研究事業）

２．研究課題名　自己免疫疾患に関する調査研究

３．研究者名　（所属部局・職名）　小児科学・助教

（氏名・フリガナ）　岡本　奈美　・　オカモト ナミ

４．倫理審査の状況

	該当性の有無	左記で該当がある場合のみ記入（※1）		
	有　無	審査済み	審査した機関	未審査（※2）
ヒトゲノム・遺伝子解析研究に関する倫理指針	□　■	□		□
遺伝子治療等臨床研究に関する指針	□　■	□		□
人を対象とする医学系研究に関する倫理指針（※3）	□　■	□		□
厚生労働省の所管する実施機関における動物実験等の実施に関する基本指針	□　■	□		□
その他、該当する倫理指針があれば記入すること（指針の名称：　）	□　■	□		□

（※1）当該研究者が当該研究を実施するに当たり遵守すべき倫理指針に関する倫理委員会の審査が済んでいる場合は、「審査済み」にチェックし一部若しくは全部の審査が完了していない場合は、「未審査」にチェックすること。

その他（特記事項）

（※2）未審査に場合は、その理由を記載すること。
（※3）廃止前の「疫学研究に関する倫理指針」や「臨床研究に関する倫理指針」に準拠する場合は、当該項目に記入すること。

５．厚生労働分野の研究活動における不正行為への対応について

研究倫理教育の受講状況	受講 ■　未受講 □

６．利益相反の管理

当研究機関におけるＣＯＩの管理に関する規定の策定	有 ■　無 □（無の場合はその理由：　）
当研究機関におけるＣＯＩ委員会設置の有無	有 ■　無 □（無の場合は委託先機関：　）
当研究に係るＣＯＩについての報告・審査の有無	有 ■　無 □（無の場合はその理由：　）
当研究に係るＣＯＩについての指導・管理の有無	有 □　無 ■（有の場合はその内容：　）

（留意事項）　・該当する□にチェックを入れること。
・分担研究者の所属する機関の長も作成すること。

平成31年　2月　15日

国立保健医療科学院長　殿

機関名　金沢大学

所属研究機関長　職　名　学　長

氏　名　山崎　光

次の職員の平成３０年度厚生労働科学研究費の調査研究における、倫理審査状況及び[redacted]ついては以下のとおりです。

１．研究事業名　難治性疾患等政策研究事業（難治性疾患政策研究事業）

２．研究課題名　自己免疫疾患に関する調査研究

３．研究者名　（所属部局・職名）　附属病院小児科・講師

（氏名・フリガナ）　清水　正樹・シミズ　マサキ

４．倫理審査の状況

	該当性の有無		左記で該当がある場合のみ記入（※1）		
	有	無	審査済み	審査した機関	未審査（※2）
ヒトゲノム・遺伝子解析研究に関する倫理指針	□	■	□		□
遺伝子治療等臨床研究に関する指針	□	■	□		□
人を対象とする医学系研究に関する倫理指針（※3）	■	□	■	金沢大学	□
厚生労働省の所管する実施機関における動物実験等の実施に関する基本指針	□	■	□		□
その他、該当する倫理指針があれば記入すること（指針の名称：　）	□	■	□		□

（※1）当該研究者が当該研究を実施するに当たり遵守すべき倫理指針に関する倫理委員会の審査が済んでいる場合は、「審査済み」にチェックし一部若しくは全部の審査が完了していない場合は、「未審査」にチェックすること。

その他（特記事項）

（※2）未審査に場合は、その理由を記載すること。

（※3）廃止前の「疫学研究に関する倫理指針」や「臨床研究に関する倫理指針」に準拠する場合は、当該項目に記入すること。

５．厚生労働分野の研究活動における不正行為への対応について

研究倫理教育の受講状況	受講 ■　未受講 □

６．利益相反の管理

当研究機関におけるＣＯＩの管理に関する規定の策定	有 ■　無 □（無の場合はその理由：　）
当研究機関におけるＣＯＩ委員会設置の有無	有 ■　無 □（無の場合は委託先機関：　）
当研究に係るＣＯＩについての報告・審査の有無	有 ■　無 □（無の場合はその理由：　）
当研究に係るＣＯＩについての指導・管理の有無	有 □　無 ■（有の場合はその内容：　）

（留意事項）　・該当する□にチェックを入れること。
・分担研究者の所属する機関の長も作成すること。

２０１９年　３月　２０日

国立保健医療科学院長　殿

機関名　埼玉医科大学

所属研究機関長　職　名　学長

氏　名　別所　[redacted]　印

次の職員の平成３０年度厚生労働科学研究費の調査研究における、倫理審査状況及び利益相反等の管理については以下のとおりです。

１．研究事業名　難治性疾患等政策研究事業（難治性疾患政策研究事業）

２．研究課題名　自己免疫疾患に関する調査研究

３．研究者名　（所属部局・職名）　医学部　准教授

（氏名・フリガナ）　太田　晶子（オオタ　アキコ）

４．倫理審査の状況

	該当性の有無		左記で該当がある場合のみ記入（※1）		
	有	無	審査済み	審査した機関	未審査（※2）
ヒトゲノム・遺伝子解析研究に関する倫理指針	□	■	□		□
遺伝子治療等臨床研究に関する指針	□	■	□		□
人を対象とする医学系研究に関する倫理指針（※3）	■	□	■	埼玉医科大学	□
厚生労働省の所管する実施機関における動物実験等の実施に関する基本指針	□	■	□		□
その他、該当する倫理指針があれば記入すること（指針の名称：　）	□	■	□		□

（※1）当該研究者が当該研究を実施するに当たり遵守すべき倫理指針に関する倫理委員会の審査が済んでいる場合は、「審査済み」にチェックし一部若しくは全部の審査が完了していない場合は、「未審査」にチェックすること。

その他（特記事項）

（※2）未審査に場合は、その理由を記載すること。

（※3）廃止前の「疫学研究に関する倫理指針」や「臨床研究に関する倫理指針」に準拠する場合は、当該項目に記入すること。

５．厚生労働分野の研究活動における不正行為への対応について

研究倫理教育の受講状況	受講 ■　未受講 □

６．利益相反の管理

当研究機関におけるＣＯＩの管理に関する規定の策定	有 ■　無 □（無の場合はその理由：　）
当研究機関におけるＣＯＩ委員会設置の有無	有 ■　無 □（無の場合は委託先機関：　）
当研究に係るＣＯＩについての報告・審査の有無	有 ■　無 □（無の場合はその理由：　）
当研究に係るＣＯＩについての指導・管理の有無	有 □　無 ■（有の場合はその内容：　）

（留意事項）　・該当する□にチェックを入れること。
・分担研究者の所属する機関の長も作成すること。

平成31年3月29日

国立保健医療科学院長 殿

機関名　京都大学
所属研究機関長　職　名　医学研究
氏　名　岩井 一

次の職員の平成30年度厚生労働科学研究費の調査研究における、倫理審査状況及び利益相反等の管理については以下のとおりです。

1．研究事業名　難治性疾患等政策研究事業（難治性疾患政策研究事業）

2．研究課題名　自己免疫疾患に関する調査研究（H29-難治等（難）-一般-008）

3．研究者名　（所属部局・職名）　医学研究科・教授

（氏名・フリガナ）　山田　亮（ヤマダ　リョウ）

4．倫理審査の状況

	該当性の有無		左記で該当がある場合のみ記入（※1）		
	有	無	審査済み	審査した機関	未審査（※2）
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遺伝子治療等臨床研究に関する指針	□	■	□		□
人を対象とする医学系研究に関する倫理指針（※3）	□	■	□		□
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その他、該当する倫理指針があれば記入すること（指針の名称：　）	□	■	□		□

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5．厚生労働分野の研究活動における不正行為への対応について

研究倫理教育の受講状況	受講 ■　未受講 □

6．利益相反の管理

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平成３１年１月２４日

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機関名　国立大学法人東京医科歯科大学

所属研究機関長　職　名　学　長

氏　名　吉　澤　靖　[redacted]

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２．研究課題名　自己免疫疾患に関する調査研究

３．研究者名　（所属部局・職名）　大学院医歯学総合研究科 膠原病・リウマチ内科学分野・助教

（氏名・フリガナ）　溝口　史高　（ミゾグチ フミタカ）

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（氏名・フリガナ）　平野　史生（ヒラノ　フミオ）

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CLINICAL SCIENCE

PLD4 is a genetic determinant to systemic lupus erythematosus and involved in murine autoimmune phenotypes

Shuji Akizuki,[1] Kazuyoshi Ishigaki,[2] Yuta Kochi,[3] Sze-Ming Law,[1] Keitaro Matsuo,[4,5] Koichiro Ohmura,[1] Akari Suzuki,[3] Manabu Nakayama,[6] Yusuke Iizuka,[7] Haruhiko Koseki,[7] Osamu Ohara,[8] Jun Hirata,[9,10,11] Yoichiro Kamatani,[2,12] Fumihiko Matsuda,[12] Takayuki Sumida,[13] Kazuhiko Yamamoto,[3] Yukinori Okada,[2,9,14] Tsuneyo Mimori,[1] Chikashi Terao[1,2,15,16]

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ABSTRACT

Objectives Systemic lupus erythematosus (SLE) is an autoimmune disease that is characterised by autoantibody production and widespread inflammation damaging many organs. Previous genome-wide association studies (GWASs) have revealed over 80 genetic determinants of SLE, but they collectively explain a fraction of the heritability, and only a few were proven in vivo for the involvement in SLE. We conducted a meta-analysis of SLE GWAS in the Japanese population, followed by functional analyses of a susceptibility gene with use of mutant mice.

Methods We conducted a meta-analysis of two GWASs comprising a total of 1363 cases and 5536 controls using the 1000 Genome Project data as an imputation reference. Enrichment analyses for functional annotations were conducted. We examined Phospholipase D4 (Pld4) mutant mice to assess functional involvement of a genetic determinant.

Results We found a total of 14 significant loci, which included rs2582511 in *AHNAK2/PLD4* recently reported in a Chinese study and a novel locus of rs143181706 in *MAMLD1* ($p=7.9\times10^{-11}$ and 3.7×10^{-8}, respectively). PLD4 risk allele was associated with anti-dsDNA antibody production. Enrichment analysis of genetic signals revealed involvement of a wide range of immune-related cells and pathways. Pld4 mutant mice revealed remarkably low body weight. The mice demonstrated autoimmune phenotypes compatible with SLE, including splenomegaly and lymphadenopathy, expansion of B cells and hypersecretion of BAFF and production of autoantibodies especially anti-nuclear antibody and anti-dsDNA antibody.

Conclusions We found a novel susceptibility gene to SLE. Pld4 mutant mice revealed autoimmune phenotypes suggesting functional involvement of PLD4 with the basics of SLE.

Key messages

What is already known about this subject

► Genetic studies, mainly genome wide association study (GWAS), for SLE so far have identified more than 80 susceptibility loci. However, a quite few of them have been shown their functional involvement in SLE in vivo.

What does this study add

► We conducted a meta-analysis of GWAS for SLE in Japanese population, and identified two new susceptibility genes, PLD4 andMAMLD1. PLD4 is a susceptibility gene to RA and SSc.
► PLD4 risk allele was associated withproduction of anti-dsDNA antibody, suggesting that PLD4 contributes to SLE pathophysiology by activating B cells.
► Pld4 mutant mice demonstrated autoimmune phenotypes corresponding to SLE, including the production of anti-nuclear antibody and pathology of nephritis.

How might this impact on clinical practice or future developments

► PLD4 is a causative gene shared by multiple human autoimmune diseases (RA, SSc, SLE) and seems to have a role in the general immune system beyond species.
► Since PLD4 biological function has not been fully elucidated, clarification of biology of PLD4 would deepen our understanding of autoimmune diseases and lead to development of new therapeutic strategies.

INTRODUCTION

Systemic lupus erythematosus (SLE) is an autoantibody-mediated autoimmune disease characterised by systemic organ involvement.[1] A variety of autoantibodies including anti-nuclear antibody (ANA), anti-DNA antibody, anti-Ro antibody and anti-RNP antibody frequently accompany SLE.[1] More than 80% of the patients with SLE are young women at the onset of this disease.[1] Severe organ damages include renal failure and central nervous system (CNS) lupus, both of which are sometimes fatal. Serologically, type I interferon, especially interferon alpha signature, is assumed to play critical roles in SLE.[2 3] Elevated levels of B cell–activating factor of the TNF family (BAFF), cytokine activating B-cell expansion and functional proliferation are features of SLE.[4] Belimumab, a monoclonal antibody targeting BAFF, was approved to be the first molecular target agent for SLE.[4]

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GUIDELINE

Treatment consensus for management of polymyositis and dermatomyositis among rheumatologists, neurologists and dermatologists

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ABSTRACT

Although rheumatologists, neurologists and dermatologists see patients with polymyositis (PM) and dermatomyositis (DM), their management appears to vary depending on the physician's specialty. The aim of the present study was to establish the treatment consensus among specialists of the three fields to standardize the patient care. We formed a research team supported by a grant from the Ministry of Health, Labor and Welfare, Japan. Clinical questions (CQ) on the management of PM and DM were raised. A published work search on CQ was performed primarily using PubMed. Using the nominal group technique, qualified studies and results in the published work were evaluated and discussed to reach consensus recommendations. They were sent out to the Japan College of Rheumatology, Japanese Society of Neurology and Japanese Dermatological Association for their approval. We reached a consensus in 23 CQ and made recommendations and a decision tree for management was proposed. They were officially approved by the three scientific societies. In conclusion, a multidisciplinary treatment consensus for the management of PM and DM was established for the first time.

Key words: **consensus, dermatomyositis, management, polymyositis, treatment.**

INTRODUCTION

It has been known that rheumatologists, dermatologists and neurologists often have different views not only on the classification but on the disease concept of idiopathic inflammatory myopathy (IIM), which includes polymyositis (PM) and dermatomyositis (DM). Dr Chistopher-Stein compared rheumatologists and neurologists to creatures from Mars and Venus.[1]

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"Treatment consensus for management of polymyositis and dermatomyositis among rheumatologists, neurologists and dermatologists" in Japanese was published in 2015 from *Shindan to Chiryo Sha* in Japan (ISBN 978-4-7878-2226-0). This is the English-language version of that report with summary and clinical questions, which is published here to enhance our non-Japanese colleagues' and other interested parties' understanding of this topic. This article is jointly published in *Neurology and Clinical Neuroscience* (the official English-language journal of the Japanese Society of Neurology: doi: 10.1111/ncn3.12223), the *Journal of Dermatology* (the official English-language journal of the Japanese Dermatological Association: doi: 10.1111/1346-8138.14604) and *Modern Rheumatology* (the official English-language journal of the Japan College of Rheumatology: doi: 10.1080/14397595.2018.1521185).
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REVIEW ARTICLE

Treatment consensus for management of polymyositis and dermatomyositis among rheumatologists, neurologists and dermatologists

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ABSTRACT

Although rheumatologists, neurologists and dermatologists see patients with polymyositis (PM) and dermatomyositis (DM), their management appears to vary depending on the physician's specialty. The aim of the present study was to establish the treatment consensus among specialists of the three fields to standardize the patient care. We formed a research team supported by a grant from the Ministry of Health, Labor and Welfare, Japan. Clinical questions (CQ) on the management of PM and DM were raised. A published work search on CQ was performed primarily using PubMed. Using the nominal group technique, qualified studies and results in the published work were evaluated and discussed to reach consensus recommendations. They were sent out to the Japan College of Rheumatology, Japanese Society of Neurology and Japanese Dermatological Association for their approval. We reached a consensus in 23 CQ and made recommendations and a decision tree for management was proposed. They were officially approved by the three scientific societies. In conclusion, a multidisciplinary treatment consensus for the management of PM and DM was established for the first time.

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KEYWORDS
consensus; dermatomyositis; management; polymyositis; treatment

Introduction

It has been known that rheumatologists, dermatologists and neurologists often have different views not only on the classification but on the disease concept of idiopathic inflammatory myopathy (IIM), which includes polymyositis (PM) and dermatomyositis (DM). Dr Chistopher-Stein compared rheumatologists and neurologists to creatures from Mars and Venus [1]. In the past, muscle pathological findings have been the only solid evidence for subset classification except for clinical findings. Recently, quite a few myositis-specific autoantibodies (MSA) have been discovered and help to characterize subsets of the IIM patients.

In Japan, we have a parable of the blind men and an elephant. It is originally an Indian story of several blind men, who have no idea what the elephant is like, and have tried to learn the elephant by touching it. They feel different parts of the elephant, such as the ear, leg, trunk and tail, and describe what they think the elephant is. They were inevitably in total disagreement, and even became not to believe each other. This parable tells us that we are only partially right when we take only partial information into account. IIM can be classified now by deference to clinical findings, muscle pathological features or autoantibody profiles. However, one subset classified by one method is not necessarily the same subset classified by another method.

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Placenta Specific 8 Suppresses IL-18 Production through Regulation of Autophagy and Is Associated with Adult Still Disease

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Adult Still disease (ASD) is a systemic disorder of unknown etiology characterized by high spiking fever, rash, and arthritis. The purpose of this study was to identify genes specifically associated with the active phase of the disease. In this study, we have reported that placenta specific 8 (PLAC8) was a newly specific gene involved in ASD. DNA microarray and validation analysis using human monocytes revealed that the expression of PLAC8 was significantly higher in active-ASD patients than in inactive-ASD patients and healthy controls. In ASD, PLAC8 expression level correlated with serum levels of CRP, ferritin, IL-1β, and IL-18. Stimulation of monocytes with LPS results in PLAC8 upregulation. LPS or nigericin stimulation of PLAC8-overexpressing human monocytic cell line (THP-1), but not mock THP-1 cells, was associated with a significant decrease in IL-1β and IL-18 production. PLAC8 overexpression in THP-1 cells was associated with enhanced autophagy and suppression of IL-1β and IL-18 production. Therefore, we found that PLAC8 was upregulated in activated monocytes, as was IL-1β and IL-18. The upregulated PLAC8 acts on the synthesis of inactive precursors of IL-1β and IL-18 and seemed to suppress the production of IL-1β and IL-18 by negative feedback through enhanced autophagy, resulting in the suppression of ASD. The results highlight the role of PLAC8 in the pathogenesis of ASD and suggest its potential suitability as an activity marker and therapeutic target in ASD. *The Journal of Immunology*, **2018, 201: 3534–3545.**

Adult Still disease (ASD) is a rare multisystemic autoinflammatory disorder of unknown etiology. The clinical features correlate with systemic manifestations, such as a high spiking fever, arthralgia or arthritis, and an evanescent salmon-pink maculopapular skin rash (1, 2). Although the pathogenesis of ASD is not clear, the interplay of viral infections, genetic factors, and immune dysregulation, including cytokine-mediated inflammation and enhanced apoptosis, may contribute to the development of this disease (3).

Previous reports investigated the pathogenic roles of several proinflammatory cytokines in ASD, including IL-1β, IL-6, IL-18, TNF-α, and IFN-β (3). Among these cytokines, IL-18 is thought to be the upstream initiator of the proinflammatory cytokine cascades, and serum IL-18 levels are particularly elevated in ASD, unlike in other inflammatory conditions (4–8). Furthermore, higher levels of IL-18 correlate with ASD activity (6, 8). Thus, IL-18 is thought to be one of the most important factors in the pathogenesis of ASD. However, there is little or no information on the regulatory process involved in the production of IL-18 and other inflammatory cytokines in ASD.

Activation of myeloid cells, including monocytes, macrophages, dendritic cells, and neutrophils, is the hallmark of ASD. Especially, several markers and cytokines that reflect macrophage activation correlate with ASD activity (3). In contrast, activated monocytes are known to produce IL-6, TNF-α, IL-1β, and IL-18 through several stimuli including viral and bacterial components (9, 10). In patients with ASD, uncontrolled activation of monocytes could induce cytokine storms and several systemic disorders. However, the genes involved in the regulation of monocyte activation remain unidentified in ASD. Therefore, identification of specific genes in

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S.S. and T.S. designed the study. S.S., Y.K., A.I., S.K., M.Y., K.F., D.G., and I.M. performed analysis and collected the data. Y.K. and H.T. oversaw patient recruitment. Y.N. performed DNA microarray analysis. S.S. analyzed the data and wrote the manuscript. All authors have read and approved the manuscript for publication.

The microarray data presented in this article have been submitted to the Gene Expression Omnibus (http://www.ncbi.nlm.nih.gov/geo/) under accession number GSE113645.

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The online version of this article contains supplemental material.

Abbreviations used in this article: ASD, adult Still disease; BCL2A1, BCL2-related protein A1; CD55, CD55 molecule; CLU, clusterin; CRP, C-reactive protein; CYP1B1, cytochrome P450 family 1 subfamily B polypeptide 1; FARMS, Factor Analysis for Robust Microarray Summarization; FCGR1B, Fc fragment of IgG high affinity Ib; GO, Gene Ontology; HC, healthy control; IL1RN, IL-1 receptor antagonist; ISD, immunosuppressive drug; 3-MA, 3-methyladenine; MBL, Medical and Biological Laboratories; mSAM, modified SAM; PCA, principal component analysis; PIM1, Pim-1 proto-oncogene; PLAC8, placenta specific 8; PLAC8–THP-1, PLAC8-overexpressing THP-1; PLSCR1, phospholipid scramblase 1; PM/DM, polymyositis/dermatomyositis; qPCR, quantitative PCR; RA, rheumatoid arthritis; S100A12, S100 calcium binding protein A12; SAM, Significance Analysis of Microarrays; SLE, systemic lupus erythematosus; SOD2, superoxide dismutase 2; SS, Sjögren syndrome; STEAP4, STEAP family member 4.

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REVIEW ARTICLE

Evidence-based clinical practice guideline for adult Still's disease

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ABSTRACT

Objectives: Using an expert- and data-driven methodology, we have constructed the first clinical practice guidelines (CPGs) for adult Still's disease (ASD) after complete systematic review (SR) of the literature based upon the Medical Information Network Distribution Service (Minds) procedure.

Methods: The CPG committee for ASD organized by the Research Team for Autoimmune Diseases, the Research Program for Intractable Disease of the Japanese Ministry of Health, Labour, and Welfare has developed CPG for ASD 2017, according to the procedure proposed by Minds. The CPG development process includes (1) clarification of the purpose of CPG, (2) organization of the steering committee, (3) organization of the CPG committee and secretariat, (4) defining the scope (setting of clinical questions (CQs)), (5) SR, (6) development of recommendations, (7) drafting the CPG, (8) external evaluation and public comments, and (9) release. Because we wanted to construct CPG for ASD to encompass both adult-onset Still's disease (AOSD) and adult patients with systemic juvenile idiopathic arthritis (sJIA), we also included SR data from sJIA in this study.

Results: Twenty-six CQs were selected and roughly divided into the following items: (1) clinical findings (CQs 1–4), (2) laboratory findings (CQs 5–8), (3) complications (CQs 9–13), (4) treatment with oral medicine (CQs 14–19), (5) treatment with biological reagents (CQs 20–23), and (6) treatments for sJIA (CQs 25–26). Recommendations and the strength of the recommendations for these CQs were decided by a modified Delphi method.

Conclusion: We have developed the first published CPG for ASD including AOSD and sJIA, which includes 26 CQs and recommendations. This guideline will help rheumatologists, non-specialized physicians, other healthcare providers, medical and health-related students, and patients and their family members to understand and treat ASD.

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KEYWORDS
Diagnosis; management; treatment; arthritis; recommendation

Introduction

Adult-onset Still's disease (AOSD) is a rare systemic autoinflammatory disorder that was first reported in 1971 [1], approximately 74 years after the initial description of its childhood counterpart [2], systemic juvenile idiopathic arthritis (sJIA). AOSD is characterized by a daily high spiking fever, evanescent rash, arthritis, sore throat, lymphadenopathy, splenomegaly, leukocytosis with predominant neutrophils, liver dysfunction, and elevated inflammatory markers and serum ferritin [3,4]. It is generally accepted that AOSD and sJIA are the same disease entity but occur in different age groups, although they show some differences in prevalence and clinical profiles [5,6].

The pathogenesis of AOSD remains obscure; however, recent progress in molecular genetics, especially in the field of innate immunity and autoinflammatory disorders, has mainly contributed to a better understanding of its pathophysiology [5,7]. AOSD is considered a multifactorial disease in which an individual with susceptible polygenes develops sustained autoinflammatory conditions in response to multiple environmental factors. According to different pathogenic mechanisms, AOSD is heterogeneous in terms of clinical features, disease course, severity, and prognosis. In this context, AOSD can be divided into multiple clinical subtypes and was recently classified into systemic and articular (rheumatic) subtypes according to clinical

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EXTENDED REPORT

Splicing variant of *WDFY4* augments MDA5 signalling and the risk of clinically amyopathic dermatomyositis

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ABSTRACT

Objectives Idiopathic inflammatory myopathies (IIMs) are a heterogeneous group of rare autoimmune diseases in which both genetic and environmental factors play important roles. To identify genetic factors of IIM including polymyositis, dermatomyositis (DM) and clinically amyopathic DM (CADM), we performed the first genome-wide association study for IIM in an Asian population.

Methods We genotyped and tested 496 819 single nucleotide polymorphism for association using 576 patients with IIM and 6270 control subjects. We also examined the causal mechanism of disease-associated variants by in silico analyses using publicly available data sets as well as by in in vitro analyses using reporter assays and apoptosis assays.

Results We identified a variant in *WDFY4* that was significantly associated with CADM (rs7919656; OR=3.87; $P=1.5\times10^{-8}$). This variant had a cis-splicing quantitative trait locus (QTL) effect for a truncated *WDFY4*isoform (tr-*WDFY4*), with higher expression in the risk allele. Transexpression QTL analysis of this variant showed a positive correlation with the expression of NF-κB associated genes. Furthermore, we demonstrated that both WDFY4 and tr-WDFY4 interacted with pattern recognition receptors such as TLR3, TLR4, TLR9 and MDA5 and augmented the NF-κB activation by these receptors. WDFY4 isoforms also enhanced MDA5-induced apoptosis to a greater extent in the tr-WDFY4-transfected cells.

Conclusions As CADM is characterised by the appearance of anti-MDA5 autoantibodies and severe lung inflammation, the WDFY4 variant may play a critical role in the pathogenesis of CADM.

INTRODUCTION

Idiopathic inflammatory myopathies (IIMs) are autoimmune conditions characterised by muscle weakness and inflammation, and the most common types are polymyositis (PM) and dermatomyositis (DM).[1 2] Clinically amyopathic DM (CADM), a subset of DM, lacks distinct muscle features but often manifests rapidly progressive interstitial pneumonia (RPIP).[3–6] The mortality rate of CADM at 6 months from diagnosis reaches approximately 50%, making it one of the most fatal autoimmune diseases.[7 8] The appearance of autoantibodies such as anti-MDA5 antibodies in CADM suggests a role for autoimmunity in the pathogenesis.[9–11] Although the aetiology of IIM remains unknown, virus infection may be the major environmental factor.[12] In addition, patients with IIM and their close relatives are more likely to develop other autoimmune diseases, suggesting shared genetic factors.[13–15] In fact, a previous genome-wide association studies (GWAS) and candidate gene analyses in European populations demonstrated multiple loci that were shared with other autoimmune diseases.[15–18]

However, when compared with other autoimmune diseases, little is known about the genetic background of IIM. This may be due to the rarity of disease, precluding researchers from designing sufficiently powered studies. In addition, because IIMs are a heterogenous group of rare disorders, an overall pooled analysis might also reduce the power for detecting loci specific to certain subtypes. Therefore, as suggested,[19] studies of disease subsets are needed to increase the power for detecting subset-specific genetic components. Here, to elucidate genetic loci associated with IIM, we performed a GWAS for IIM in the Japanese population. This study was the first GWAS for IIM in an Asian population. We also performed a GWAS for CADM as a subset analysis, which was the first such study in the world.

METHODS

Subjects

We enrolled 592 IIM cases (mean age, 55.5±14.2 years; female, 74.6%) from 18 medical institutes

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REVIEW

Transcriptional Regulation of CD4+ T Cell Differentiation in Experimentally Induced Arthritis and Rheumatoid Arthritis

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Rheumatoid arthritis (RA) is an autoimmune disorder characterized by chronic inflammation of the joint synovium and infiltration by activated inflammatory cells. CD4+ T cells form a large proportion of the inflammatory cells invading the synovial tissue, and are involved in the RA pathologic process. In general, CD4+ T cells differentiate into various T helper cell subsets and acquire the functional properties to respond to specific pathogens, and also mediate some autoimmune disorders such as RA. Because the differentiation of T helper cell subsets is determined by the expression of specific transcription factors in response to the cytokine environment, these transcription factors are considered to have a role in the pathology of RA. Treg cells control an excess of T cell–mediated immune response, and the transcription factor FoxP3 is critical for the differentiation and function of Treg cells. Treg cell dysfunction can result in the development of systemic autoimmunity. In this review, we summarize how the expression of transcription factors modulates T helper cell immune responses and the development of autoimmune diseases, especially in RA. Understanding the role of transcription factors in the pathogenesis of autoimmunity may lead to novel therapeutic strategies to control the differentiation and function of both T helper cells and Treg cells.

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Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disorder characterized by autoimmunity, infiltration of activated inflammatory cells into the joint synovium, synovial hyperplasia, neoangiogenesis, and progressive destruction of cartilage and bone. CD4+ T cells constitute a large proportion of the inflammatory cells invading the synovial tissue. Upon antigenic stimulation and cytokine signaling, naive CD4+ T cells activate and differentiate into various T helper cell subsets.

Classically, interferon-γ (IFNγ)–producing Th1 cells had been considered to play a predominant role in the development of RA. However, studies have demonstrated that the Th1 phenotype does not explain all of the mechanisms involved in RA (1).

The pathogenic role of interleukin-17 (IL-17)–producing Th17 cells has intrigued rheumatologists, because IL-17 is spontaneously produced by rheumatoid synovium (2), and Th17 cells are increased among peripheral blood mononuclear cells of RA patients compared with those of healthy control subjects (3). Th17 cells also appear to play a critical role in the generation of autoimmune arthritis in several experimental models. In addition, some studies have shown that the frequency of follicular helper T (Tfh) cells, which support high-affinity and long-term antibody response, is increased in the peripheral blood of RA patients and correlates with disease activity (4), suggesting that these cells also play a role in RA pathology. More recently, it was reported that PD-1^{high}CXCR5−CD4+ T cells were markedly expanded and activated in synovium, and appeared to be poised to promote B cell response and antibody production through expression of IL-21–like Tfh cells within pathologically inflamed nonlymphoid tissue in patients with RA (5).

Differentiation of naive CD4+ T cells into T helper cell subsets is dependent on the expression of specific transcription factors induced by specific cytokines. Each

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ORIGINAL ARTICLE

Evaluation of the alternative classification criteria of systemic lupus erythematosus established by Systemic Lupus International Collaborating Clinics (SLICC)

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ABSTRACT

Objective: To evaluate the performance of the 2012 Systemic Lupus International Collaborating Clinics criteria (SLICC-12) on classifying systemic lupus erythematosus (SLE) in an uncontrolled multi-centered study with real-life scenario of the patients in Japan.

Methods: This study comprised 495 patients with SLE or non-SLE rheumatic diseases and allied conditions from 12 institutes in Japan. Chart review of each patient was performed by the 27 expert rheumatologists and diagnosis of 487 cases reached to the consensus. Value of the SLICC-12 on SLE classification was analyzed comparing with the 1997 revised American College of Rheumatology SLE classification criteria (ACR-97) employing the expert-consented diagnoses.

Results: Compared to the ACR-97, the SLICC-12 had a higher sensitivity (ACR-97 vs. SLICC-12: 0.88 vs. 0.99, $p < .01$) and comparable specificity (0.85 vs. 0.80). The rate of misclassification (0.14 vs. 0.11) or the area under the receiver operating characteristic curves (0.863 vs. 0.894) was not statistically different. In the cases that diagnoses corresponded in high rates among experts, both criteria showed high accordance of SLE classification over 85% with the expert diagnoses.

Conclusion: Although employment of SLICC-12 for the classification for SLE should be carefully considered, the SLICC-12 showed the higher sensitivity on classifying SLE in Japanese population.

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Systemic lupus erythematosus (SLE); classification criteria; systemic lupus erythematosus established by Systemic Lupus International Collaborating Clinics (SLICC); American College of Rheumatology (ACR)

Introduction

Systemic lupus erythematosus (SLE) is a representative systemic autoimmune disease that has various types of manifestations in multiple organs. For the purpose of research and surveillance, classification criteria for SLE have been developed. The most widely used criteria for SLE were developed by the American College of Rheumatology (ACR) in 1982 [1], later revised in 1997 (ACR-97) [2]. Many research groups have attempted to refine the ACR criteria, but they failed to generalize. The Cleveland Clinic criteria applied Bayes theorem to develop a weighting system [3]. Boston criteria were developed on the basis of the Cleveland Clinic criteria, but it included new supplemental criteria such as antiphospholipid antibodies [4]. These new criteria have been reported to provide a more accurate differentiation of lupus, but an analysis of the criteria's use was only performed in small cohorts of patients with lupus. By analyzing with an independent cohort, Sanchez et al. reported that

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REVIEW ARTICLE

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Clinical practice guideline for Sjögren's syndrome 2017

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ABSTRACT

Objectives: The objective of this study is to develop clinical practice guideline (CPG) for Sjögren's syndrome (SS) based on recently available clinical and therapeutic evidences.

Methods: The CPG committee for SS was organized by the Research Team for Autoimmune Diseases, Research Program for Intractable Disease of the Ministry of Health, Labor and Welfare (MHLW), Japan. The committee completed a systematic review of evidences for several clinical questions and developed CPG for SS 2017 according to the procedure proposed by the Medical Information Network Distribution Service (Minds). The recommendations and their strength were checked by the modified Delphi method. The CPG for SS 2017 has been officially approved by both Japan College of Rheumatology and the Japanese Society for SS.

Results: The CPG committee set 38 clinical questions for clinical symptoms, signs, treatment, and management of SS in pediatric, adult and pregnant patients, using the PICO (P: patients, problem, population, I: interventions, C: comparisons, controls, comparators, O: outcomes) format. A summary of evidence, development of recommendation, recommendation, and strength for these 38 clinical questions are presented in the CPG.

Conclusion: The CPG for SS 2017 should contribute to improvement and standardization of diagnosis and treatment of SS.

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KEYWORDS
Sjögren's syndrome; clinical practice guideline; clinical question; systematic review; Medical Information Network Distribution Service (Minds)

Introduction

Sjögren's syndrome (SS) is an autoimmune disease characterized by lymphocytic infiltration into the exocrine glands and other organs, leading to dry mouth, dry eyes, and various extra-glandular symptoms [1]. SS is categorized into primary SS (pSS) which is not associated with other well defined connective tissue diseases (CTDs), and secondary SS, which is associated with other well defined CTDs [1]. Moreover, pSS is further subdivided into the glandular form, with involvement of the exocrine glands only, and the extra-glandular form, with the involvement of organs other than exocrine glands.

In Japan, SS was certified as a designated intractable disease by the Ministry of Health, Labor and Welfare (MHLW) in January 2015. Researches on designated intractable

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ORIGINAL ARTICLE

Histopathological classification of anti-neutrophil cytoplasmic antibody-associated glomerulonephritis in a nationwide Japanese prospective 2-year follow-up cohort study

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Abstract

Background The prognostic value of the EUVAS-proposed histopathological classification of anti-neutrophil cytoplasmic antibody (ANCA)-associated glomerulonephritis has been evaluated throughout the world. Here, we performed a Japanese nationwide biopsy survey to assess the association between this histopathological classification and renal prognosis after 2-year follow-up in ANCA-associated glomerulonephritis.

Methods We collected 67 renal biopsy materials of the 321 entries in the RemIT-JAV-RPGN cohort study, and assessed their histologies. Based on the EUVAS-proposed histopathological classification and some histological parameters, we statistically evaluated renal survival and the comparison of renal function for 2 years.

Results Based on the histopathological classification, the largest number of biopsy samples belonged to the Focal class, followed by the Mixed, Crescentic, and Sclerotic classes ($n=30$, 19, 10, 8, respectively). Although the number of events might be too low (four patients with renal death) to make this conclusion, the Focal and Mixed classes had higher renal-survival rates compared to the others in the renal-survival curve. Comparing renal function among all classes, the estimated glomerular filtration rate (eGFR) throughout 2-year follow-up period was significantly higher in the Focal class compared to the other 3 classes. The eGFR-values in the Crescentic, Mixed, and Sclerotic classes increased with time. Based on both combined results, the Focal class could be the best prognosis.

Conclusion This histopathological classification was valuable for both the stratification of renal function and the estimation of partial renal survival during 2-year follow-up in ANCA-associated glomerulonephritis.

Keywords Anti-neutrophil cytoplasmic antibody (ANCA)-associated glomerulonephritis · Histopathological classification · Renal prognosis · Nationwide prospective cohort study · Rapidly progressive glomerulonephritis

Introduction

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a systemic form of vasculitis that affects the small vasculatures in multiple organs but primarily the kidneys. Histopathologically, the typical renal involvement in AAV is characterized by pauci-immune necrotizing and crescentic glomerulonephritis [1]. In recent years, the European Vasculitis Study Group (EUVAS) has proposed a classification based on glomerular lesions as the new histopathological classification for ANCA-associated

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RHEUMATOLOGY

Concise report

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Efficacy of dual antiplatelet therapy for preventing recurrence of arterial thrombosis in patients with antiphospholipid syndrome

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Abstract

Objective. Warfarin is regarded as the standard treatment for preventing thrombotic events in APS, but the recurrence rate is still high. Dual antiplatelet therapy (DAPT) has been shown to be effective for the prevention of acute coronary syndrome or stroke. The objective of this study was to evaluate the efficacy of DAPT for the prevention of thrombosis recurrence in APS patients with history of arterial thrombosis.

Methods. This retrospective cohort study of APS patients was conducted at Hokkaido University Hospital between 1990 and 2016. The secondary prophylactic effects and safety of warfarin monotherapy (Wf), antiplatelet monotherapy (AP), warfarin and antiplatelet combination therapy (Wf + AP) and DAPT were evaluated. The primary endpoints were set as thrombosis-free and adverse events-free survival period. Adverse events were defined as severe bleeding and death.

Results. A total of 90 APS patients were enrolled. Thrombotic recurrence was found in 40 patients (35 arterial and 5 venous thromboses) and serious adverse events in 20 patients (9 severe bleeding events and 14 deaths). Kaplan–Meier analysis demonstrated a 10-year recurrence-free survival rate of 62%. The recurrence rate per 100 patient-years was as follows: Wf: 11.6, AP: 5.5, Wf: + AP: 3.7, DAPT: 1.8. We demonstrated that DAPT significantly reduced the rate of recurrence compared with Wf (log-rank $P = 0.001$). There were no significant differences in the rate of serious adverse events among the groups.

Conclusion. DAPT might be considered as an effective and safe option for the prophylaxis of recurrent arterial thrombosis in APS.

Key words: antiphospholipid syndrome (APS), dual antiplatelet therapy (DAPT), arterial thrombosis, venous thrombosis, prophylaxis, safety

Rheumatology key messages

- This is the first study exploring dual antiplatelet therapy (DAPT) for APS patients.
- DAPT might be considered as an effective and safe option for APS patients.

Introduction

APS is an autoimmune disease characterized by thrombotic events and pregnancy complications with persistently positive aPL [1]. APS patients suffer from thrombosis in both arteries and veins, while protein C deficiency, Factor V Leiden, and other thrombophilia mostly affect the venous circulation.

According to the guidelines for the management of patients with APS, anticoagulation using warfarin is recommended for secondary prophylaxis of arterial/venous thrombosis by targeting the PT-International normalized ratio (PT-INR) between 2.0 and 3.0 [2]. On the other hand, the APS Workshop guidelines recommend that APS patients with an arterial thrombotic event should be treated with warfarin at PT-INR >3.0 or with antiplatelet plus warfarin combination therapy at PT-INR between 2.0 and 3.0 [3]. The difference between these recommendations may be due to the discrepancy in their main objectives of avoiding treatment-related bleeding events [4] or

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UPDATE

Pathogenic role of antiphospholipid antibodies: an update

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The antiphospholipid syndrome (APS) is a systemic disorder clinically characterized by widespread thrombosis and obstetric complications associated with the persistence of antiphospholipid antibodies (aPL).[1] Because of their strong association with clinical symptoms, aPL have been considered pathogenic antibodies. Dysregulation of coagulation and fibrinolytic pathways mediated by aPL, along with activation of endothelial cells, monocytes, platelets and the complement system, contribute to the development of thrombosis in patients with APS.[2] The aPs recognize phospholipid-binding proteins located on endothelial cells and induce p38 mitogen-activated protein kinase (MAPK) phosphorylation, leading to the transcription of procoagulant substances, adhesion molecules and, subsequently, thrombus formation. However, the biological and pathological roles of aPL production, and the mechanism of aPL recognition for cryptic epitopes are not fully understood. A novel antigen presentation mechanism recently proposed that misfolded proteins are transported to the cell surface by major histocompatibility complex (MHC) class II molecules without protein degradation, thus becoming 'neo-self-antigens'. APS is a representative disease of this concept, suggesting that β2glycoprotein I (β2GPI)/MHC class II complex is a major target antigen for autoantibodies in patients with APS. In this update, we briefly highlight recent findings regarding antigen presentation of the new/conventional theory in APS.

Misfolded proteins localized in the endoplasmic reticulum (ER) are degraded promptly inside cells. The newly reported theory is that misfolded proteins are rescued from protein degradation in the ER through transportation to the cell surface by MHC class II molecules without being processed into peptides.[3] Under normal physiological conditions, the expression of MHC class II is restricted to specific antigen-presenting cells such as dendritic cells and B cells. However, it is widely accepted that MHC class II molecules are expressed by most cell types following stimulation with certain cytokines in response to infection or inflammation. Newly synthesized MHC class II molecules are associated with the invariant chain, which blocks the binding peptide antigen in the ER, and MHC-invariant chain complexes pass from the rough ER to the Golgi body. In general, the invariant chain is degraded before MHC class II molecules are shuttled to the cell surface, and a peptide derived from the endocytic compartment is presented as antigen to $CD4^+$ T cells. However, misfolded proteins can associate with MHC class II molecules in the ER instead of the invariant chain,[3] depending on allelic polymorphisms of MHC class II genes. As the misfolded proteins do not contain endolysosomal-targeting signals, they are transported as complexes with MHC class II directly to the cell surface without degradation.[4] The misfolded proteins/MHC class II complexes transported to the cell surface behave as 'neo-self-antigens', and activate the antigen-specific B cells. These complexes of misfolded proteins with MHC class II molecules are considered major targets of autoantibodies in multiple autoimmune diseases, including rheumatoid arthritis.[5]

Based on these findings, the roles of β2GPI and MHC class II molecules in APS were analyzed.[6] The presentation of whole intact β2GPI, no peptide, with MHC class II molecules on the cell surface was confirmed by overexpression assay in the 293T cell line (cell-based assay). These proteins are recognized by aPL and over 80% of APS patients possessed autoantibodies against whole β2GPI/APS-associated HLA-DR complexes, suggesting that β2GPI/MHC class II complexes are major target antigens in patients with APS. More importantly, β2GPI/MHC class II complexes have been detected in uterine decidual tissues from patients with APS. Notably, β2GPI is produced not only from hepatocytes, but also from some endothelial

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REVIEW

Clinical profiles and risk assessment in patients with antiphospholipid antibodies

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ABSTRACT

Introduction: Antiphospholipid syndrome (APS) is an acquired autoimmune thrombophilia associated with the presence of persistent antiphospholipid antibodies (aPL). Owing to recent studies, not only APS patients but also incidentally-identified, asymptomatic aPL carriers are able to be stratified in terms of the risk of future thrombotic events, according to the variety and the titer of positive aPL tests and to the non-thrombotic, aPL-associated clinical manifestations.

Areas covered: Here, we critically review (1) criteria manifestations of APS, (2) non-criteria manifestations of APS, (3) risk assessment in patients with APS and in aPL carriers, and (4) the potential role of primary thrombosis prophylaxis in aPL carriers. In addition, we discuss what we are currently able to do and what we need to do in the future for primary prophylaxis against a first thrombotic event.

Expert commentary: We suggest a comprehensive algorithm to stratify thrombotic risk in aPL carriers, including criteria aPL, non-criteria aPL, their scoring systems, and non-criteria manifestations. However, further studies, particularly prospective randomized controlled trials, are highly warranted to establish an effective and tolerable treatment regimen for high risk aPL carriers.

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KEYWORDS
Antiphospholipid syndrome; antiphospholipid antibodies; vascular thrombosis; pregnancy morbidity; risk assessment

1. Introduction

Antiphospholipid syndrome (APS) is a systemic autoimmune disease characterized by vascular thrombosis and pregnancy morbidity in the presence of persistent antiphospholipid antibodies (aPL). Thrombosis occurs in both arteries and veins, whereas other thrombophilia, such as factor V Leiden, protein S deficiency, protein C deficiency, and antithrombin III deficiency, predominantly affects veins. Pregnancy morbidity includes fetal loss after the 10th week of gestation, severe preeclampsia, placental insufficiency, and recurrent early miscarriages. Patients with APS may also have thrombocytopenia, renal microangiopathy, heart valve disease, livedo reticularis, or neurological manifestations, which are called as non-criteria manifestations of APS. Catastrophic APS is a rare, with its prevalence of less than 1% in patients with APS, but most severe form of APS which should be suspected in front of a patients with severe multiorgan involvement with thrombotic microangiopathy over a short period of time [1]. APS occurs primarily (so-called primary APS) in approximately half of the patients, whereas the other half is associated with other autoimmune diseases (so-called secondary APS), particularly with systemic lupus erythematosus (SLE), with similar clinical and immunological profiles in both groups [2].

In this review, we start with an overview of the clinical profiles and underlying pathogenesis of APS, focusing on both criteria and non-criteria manifestations. We will then highlight the recent progress in the risk assessment of APS patients as well as asymptomatic aPL carriers in terms of future thrombotic and obstetric events and finally discuss the potential role of primary prophylaxis against vascular thrombosis in asymptomatic aPL carriers.

2. Criteria manifestations of APS

The Sydney-revised Sapporo criteria for definite APS include vascular thrombosis and pregnancy morbidity as clinical criteria manifestations [3]. Stroke and transient ischemic attack are the most common arterial events whereas ischemic heart disease less occurs in patients with APS, although the reason for the organ susceptibility remains unclear. Venous events are commonly lower extremity deep vein thrombosis, pulmonary embolism, or both. The prevalence of arterial and venous thrombotic events in patients with APS may vary in different ethnic populations, with large cohort data showing a venous event predominance in Europe [4] in contrast with an arterial event predominance in Japan [5]. Pregnancy events are deaths of fetus at or beyond the 10th week of gestation, premature births of neonate before the 34th week of gestation, or recurrent pregnancy loss before the 10th week of gestation. Nonrecurring fetal loss before 10 weeks is more commonly attributed to other causes such as chromosomal defects. Clinical manifestations of APS are summarized in Table 1.

2.1. Pathogenesis

A number of clinical, ex vivo, *in vitro*, and animal studies have so far supported aPL as pathogenic autoantibodies through inducing a procoagulant and proinflammatory state in APS and/or in SLE.

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ORIGINAL ARTICLE

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Potential therapeutics for antiphospholipid antibody associated thrombocytopenia: A systematic review and meta-analysis

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ABSTRACT

Objectives: Thrombocytopenia is frequently observed in antiphospholipid antibody (aPL) carriers. Due to the paradoxical risks of thrombosis and hemorrhage, the management of aPL-associated thrombocytopenia (APAT) is often deductive. We aimed to investigate the efficacy and safety of therapeutic approaches for APAT through a systematic review.

Methods: Four therapeutic approaches for APAT, including antiplatelet agents, glucocorticoids, splenectomy and thrombopoietin receptor agonists, were selected. Clinical trials evaluating therapeutic outcomes including the remission, complications, mortality and relapse, were searched in MEDLINE, EMBASE and CENTRAL from the inception dates to 28 November 2016. A meta-analysis was performed to calculate risk ratios (RRs) and 95% confidence intervals (CIs) using random-effects models.

Results: Out of 1407 papers, eight controlled clinical trials were included. In patients with APAT, the remission rates were higher in patients on glucocorticoids (RR 8.33 [95% CI 3.07–22.6]) or splenectomy (RR 8.37 [95% CI 1.61–43.7]) than in patients without those treatments. There was no significant association between glucocorticoids and thrombosis (RR 1.57 [95% CI, 0.17–14.9]) or between splenectomy and hemorrhage (RR 0.17 [95% CI 0.02–1.28]). The extracted data of mortality and relapse rate were not available for synthesis.

Conclusion: Glucocorticoids or splenectomy seemed suitable therapeutic approaches for APAT.

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Antiphospholipid antibody; meta-analysis; splenectomy; systematic review; thrombocytopenia

Introduction

Antiphospholipid syndrome (APS) is a systemic autoimmune disorder characterized by venous, arterial or small vessel thrombosis and pregnancy morbidity with the persistent positivity of antiphospholipid antibodies (aPLs). Besides thrombotic and pregnancy complications, clinical manifestations of APS extend beyond the revised Sapporo classification criteria [1–3]. In these extra-criterial symptoms, thrombocytopenia is a representative condition observed in APS patients and non-APS patients with aPL, with an estimated prevalence ranging from 22% to 42% [4,5]. Thrombocytopenia associated with aPL is generally mild, but severe thrombocytopenia with hemorrhagic complications may occur. Although the pathogenesis has been even unclear, antibody-mediated destruction in the blood-stream and bone marrow, as well as platelet consumption due to micro thrombus formation with aPL-interacted-platelet are considered to play a critical role in the development of thrombocytopenia in patients with APS [6].

Based on the classification criteria for APS [1] and diagnostic criteria for immune thrombocytopenia (ITP) [7,8], patients with thrombocytopenia and aPL in the absence of thrombosis and pregnancy morbidity are diagnosed and treated as ITP. Although the presence of aPL was reported to have an insignificant effect on the clinical course of ITP [1], a growing body of evidence is accumulating to demonstrate that aPL positivity in patients with ITP is a risk factor for thrombosis [9–11]. Thrombotic events may occur even in aPL positive patients with severe thrombocytopenia [12]. Considering the conflicted status with thrombotic and hemorrhagic tendency, thrombocytopenia in non-APS patients with aPL should be classified differently from the diagnosis of ITP. Thus, we proposed the term 'aPL-associated thrombocytopenia (APAT)' [13]. By definition, the platelet counts in patients with APAT are lower than $1.0 \times 10^5/\mu L$ confirmed at least twice 12 weeks apart with the positivity of aPL including anti-cardiolipin antibody, lupus anticoagulant and anti-β2 glycoprotein I antibody. The diagnosis of APAT requires that other causes of thrombocytopenia, such as thrombotic thrombocytopenic purpura, disseminated intravascular coagulation, pseudo-thrombocytopenia and heparin-induced thrombocytopenia are excluded [1].

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Supplemental data for this article can be accessed here.

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LETTER TO THE EDITOR

Thrombopoietin mimetics for systemic lupus erythematosus with antiphospholipid antibodies should be discussed separately

Sir,

The clinical question has been raised as to whether or not the thrombopoietin (TPO) mimetics, eltrombopag and romiplostim, could be applicable for refractory immune thrombocytopenia purpura (ITP) patients with systemic lupus erythematosus (SLE) or antiphospholipid syndrome (APS). The effectiveness and safety of TPO mimetics for those patients have not been conclusively demonstrated, but TPO mimetics do have some effects for platelet increments or steroid sparing in SLE patients concurrent with ITP (SLE-TP) in case series.[1–4] Furthermore, Lusa, et al. have recently reported the efficacy of TPO mimetics for SLE-TP.[1] This supports the effectiveness of TPO mimetics for treating SLE-TP.

One of the main concerns regarding the use of TPO mimetics is the possible triggering of thromboembolic events (TEEs).[5] To ensure the safe use of TPO mimetics to treat SLE-TP/ITP, we have to pay attention to the presence of antiphospholipid antibodies (aPL) because aPL (especially in lupus anticoagulants) carriers are at risk of TEEs.[6,7] Lusa, et al. show that there is a possibility of the safe and effective use of romiplostim for patients with APS, but we have experienced an aPL-positive rheumatoid arthritis case concurrent with ITP who suffered from deep venous thromboembolism after eltrombopag therapy.[8] In addition, other groups have also expressed concern about the risk of TEEs during treatment with TPO mimetics in patients with APS.[9,10] Together, these cases suggest that TPO mimetics are not safe for patients with aPL.

There have not yet been any clinical trials to prove the efficacy and safety of TPO mimetics to treat SLE-TP, especially concerning aPL positivity. Until we acquire evidence of this kind, we should consider aPL-positive SLE-TP as a separate subgroup for TPO mimetics and exercise particular caution with them, so as to avoid long-term use of TPO mimetics, or consider combination therapy with antiplatelet drugs after the acute phase, given the risk of TEEs.

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REVIEW ARTICLE

Systemic lupus erythematosus: nothing stale her infinite variety

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ABSTRACT

Systemic lupus erythematosus (SLE) is a representative systemic autoimmune disease that has various types of manifestations in multiple organs. Additionally, SLE is one of the most variable diseases in its epidemiology and etiology with heterogenous types of immune dysfunction. Since the word 'lupus' has first appeared in the literature in the Middle Ages, clinical/pathological knowledges have massively accumulated that contributed to the establishments and improvements of classification criteria, therapeutic agents or assessments of disease activity. Along with them, the survival rate of patients with SLE has dramatically improved. However, the mortality rate is still higher compared with the healthy population and the progress in basic, translational and clinical research are expected to lead to new insights into pathogenesis and identifying novel targets for therapy.

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KEYWORDS
Systematic lupus erythematosus; lupus nephritis; neuropsychiatric lupus; review

Introduction

Systemic lupus erythematosus (SLE) is a representative systemic autoimmune disease that has various types of manifestations in multiple organs. Systemic inflammation and tissue damage contribute to the clinical picture of SLE and can cause severe sequelae that may result in disability or death.

After a period of major improvement, mortality in SLE has plateaued since mid 1990s despite the rapid progress of disease understanding or development of new treatment modalities. SLE still is a retractable disease with deficient prognosis [1]. In recent years, new findings in etiology, pathology or treatment as well as new definition of disease itself are proposed and hopefully expected to become breakthroughs.

History

Hippocrates was reported to be the first to document the cutaneous ulcers of SLE and named it as herpes entheogens (gnawing dermatosis) [2]. Since then, many physicians have added knowledges or definitions to this complicated disease with wide range of manifestations. The word lupus has come up to the literature in 855AD by French archibishop Hebernus in his writing "The Miracles of Saint Martin". He has described the bishop of Liege (in current Belgium) who was suffering the disease called 'lupus' and described that the disease miraculously healed after he spend some time in Basillique of Saint Martin. Paracelsus, a 16th century Swiss German physician also known as an alchemist or philosopher, considered SLE to be a dermatosis with 'greater blood supply' and recommended phlebotomy. He compared the ulcer to a hungry wolf eating flesh as he considered that the lesions were taking up excessive blood supply, leaving less for surrounding tissue [3]. In 19th century, Rudolph Virchow reviewed systemically the history of SLE at the first time. According to this multitalented pathologist, lupus has become a common term since the Middle Ages and having caught on later became more generalized and entered to the language of Medicine. The name lupus erythematosus (or *lupus érythémateux)* was given in by Pierre Louis Cazenave, the French dermatologist, in 1833 indicating the facial erythema. Sir William Osler was the first to use the name 'Systemic lupus erythematosus' and realize the multi-organ damages of this disease such as the kidney, lung or heart manifestations. In 1948, lupus erythematosus cells (LE cells) were first reported from the hematologists in the Mayo Clinic, Malcom Hargraves and Robert Morton [4]. The investigators observed these cells in the bone marrow of individuals with acute disseminated lupus erythematosus and postulated that the cell '*... is the result of... phagocytosis of free nuclear material with a resulting round vacuole containing this partially digested and lysed nuclear material...*'.

In 1967, George Friou found that the antibodies against DNA exists in the serum of SLE [5]. Also in middle of 20th century, corticosteroid was introduced as a treatment of lupus which presently is the primary therapy of most of the lupus patients. Antimararial was first used by Payne in 1894 for lupus and now is widely used for lupus not only for skin or joint problems but to prevent flares or accumulation of disease damages. Immunosuppressants and in 21st century, the more targeted therapy such as biologics has been used for severe cases.

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RHEUMATOLOGY

Concise report

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Antiphospholipid score is a novel risk factor for idiopathic osteonecrosis of the femoral head in patients with systemic lupus erythematosus

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Abstract

Objectives. Idiopathic osteonecrosis of the femoral head (ION) is a common complication of SLE associated with CS therapy. Although the pathogenesis of ION involves local bone ischaemia favoured by thrombophilia, the involvement of aPL in lupus ION remains to be elucidated. We have previously reported the aPL score (aPL-S) as a quantitative marker of aPL and the development of thrombotic events in autoimmune diseases. The aim of this study was to identify the impact of aPL on the development of ION using aPL-S.

Methods. This was a single-centre retrospective study comprising 88 consecutive SLE patients who underwent MRI of the hip joints from January 2000 to March 2017. Baseline characteristics, pharmacotherapy and total hip arthroplasty performed during follow-up were evaluated.

Results. The presence of ION was confirmed by MRI scan in 38 patients (43.1%). Male gender, positivity of any aPL, aPL-S, high aPL-S (≥30) and high dose of CS were identified as risk factors for ION by univariate analysis. Multivariate analysis revealed high aPL-S (odds ratio 5.12, 95% CI 1.18–29.79) and use of high-dose CS (odds ratio 10.25, 95% CI 3.00–48.38) as independent variables. Kaplan–Meier analysis showed that patients with high aPL-S received total hip arthroplasty more frequently than those without aPL ($P = 0.010$).

Conclusion. We newly identified high aPL-S as an important risk factor for ION development in SLE, suggesting the involvement of aPL-induced coagulopathy in the pathophysiology of lupus ION.

Key words: systemic lupus erythematosus, antiphospholipid antibodies, antiphospholipid score, idiopathic osteonecrosis, magnetic resonance imaging.

Rheumatology key messages

- High aPL score was newly identified as a risk factor for idiopathic osteonecrosis in SLE.
- Patients with high aPL score were at high risk of total hip arthroplasty.

Introduction

Idiopathic osteonecrosis of the femoral head (ION) remains a serious complication of SLE associated with CS therapy due to the lack of established prophylaxis. ION leads to a significant decrease in quality of life associated with pain and disability, with advanced cases requiring major surgical procedures such as total hip arthroplasty (THA). The diagnosis of ION can be made using radiographs, skeletal scintigraphy, CT and MRI. Among these, MRI may be used to detect a very early stage of ION with high specificity. A prospective MRI study has revealed that ION can be found in about 40% of SLE patients [1], which is much higher than in patients with other autoimmune or rheumatic diseases, suggesting the

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EXTENDED REPORT

Tocilizumab in patients with adult-onset still's disease refractory to glucocorticoid treatment: a randomised, double-blind, placebo-controlled phase III trial

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ABSTRACT

Objective To evaluate the efficacy and safety of tocilizumab, an interleukin-6 receptor antibody, in patients with adult-onset Still's disease.

Methods In this double-blind, randomised, placebo-controlled phase III trial, 27 patients with adult-onset Still's disease refractory to glucocorticoids were randomised to tocilizumab at a dose of 8 mg/kg or placebo given intravenously every 2 weeks during the 12-week, double-blind phase. Patients received open-label tocilizumab for 40 weeks subsequently. The primary outcome was American College of Rheumatology (ACR) 50 response at week 4. The secondary outcomes included ACR 20/50/70, systemic feature score, glucocorticoid dose and adverse events at each point.

Results In the full analysis set, ACR50 response at week 4 was achieved in 61.5% (95% CI 31.6 to 86.1) in the tocilizumab group and 30.8% (95% CI 9.1 to 61.4) in the placebo group (p=0.24). The least squares means for change in systemic feature score at week 12 were −4.1 in the tocilizumab group and −2.3 in the placebo group (p=0.003). The dose of glucocorticoids at week 12 decreased by 46.2% in the tocilizumab group and 21.0% in the placebo group (p=0.017). At week 52, the rates of ACR20, ACR50 and ACR70 were 84.6%, 84.6% and 61.5%, respectively, in both groups. Serious adverse events in all participants who received one dose of tocilizumab were infections, aseptic necrosis in the hips, exacerbation of adult-onset Still's disease, drug eruption and anaphylactic shock.

Conclusion The study suggests that tocilizumab is effective in adult-onset Still's disease, although the primary endpoint was not met and solid conclusion was not drawn.

Key messages

What is already known about this subject?

► Suppression of pro-inflammatory cytokines has been reported to be effective in many case reports with adult-onset Still's disease, however, there has been no placebo-controlled trial on these drugs.

What does this study add?

► This is the first double-blinded, randomised placebo-controlled trial conducted in patients with adult-onset Still's disease that suggests tocilizumab, an anti-interleukin-6 receptor monoclonal antibody, is effective in improving systemic symptoms and decreasing glucocorticoid dose.

How might this impact on clinical practice or future developments?

► Our findings provide useful insights in the management of adult-onset Still's disease and in designing and conducting future clinical trials on adult-onset Still's disease.

INTRODUCTION

Adult-onset Still's disease is a rare, systemic inflammatory disorder of unknown aetiology characterised by high spiking fever, evanescent rash and polyarthritis.[1] In addition to these major symptoms, other features simultaneously occur with multiple organ involvement, including sore throat, lymphadenopathy, hepatosplenomegaly, and elevated serum liver enzymes and ferritin. Glucocorticoids are the first-line treatment for this disease, and the initial response to glucocorticoids is generally good despite intensive systemic inflammation. Overall treatment, however, remains challenging because high-dose glucocorticoids sometimes fail to cause remission, with occasionally fatal consequences, and dependence on glucocorticoids is frequently observed with a relapse of symptoms along with dose tapering or discontinuation, which leads to organ damage accrual and long-term side effects.[2 3]

Immunosuppressive agents, such as methotrexate and ciclosporin, have been used as a steroid-sparing drug, but their effectiveness is limited.[4 5] Progress in the understanding of the critical role of proinflammatory cytokines in the pathogenesis of adult-onset Still's disease has led to pilot use of anticytokine agents, resulting in an increasing number of successful case reports in patients who were unresponsive to conventional treatments.[6–10] Furthermore, systemic juvenile idiopathic arthritis, previously known as Still's disease, has responded significantly better to canakinumab, an anti-interleukin-1β monoclonal antibody, and tocilizumab, an anti-interleukin-6 receptor monoclonal antibody, than to placebo in several randomised controlled trials.[11–16] Since adult-onset Still's disease closely resembles systemic juvenile idiopathic arthritis in terms of pathogenesis and cytokine profiles, these anticytokine inhibitors are promising treatments for adult-onset Still's disease. However, there have been no randomised, placebo-controlled trials on these anti-interleukin-1β or anti-interleukin-6 treatments in patients with adult-onset Still's disease.

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ORIGINAL ARTICLE
Pulmonary Circulation

Predictors of Favorable Responses to Immunosuppressive Treatment in Pulmonary Arterial Hypertension Associated With Connective Tissue Disease

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Background: The potential efficacy of immunosuppressive (IS) treatment has been reported in patients with pulmonary arterial hypertension (PAH) associated with connective tissue disease (CTD), but its positioning in the treatment algorithm remains uncertain. The aim of this study was to identify predictors of favorable responses to first-line IS treatment.

Methods and Results: This single-center retrospective study included 30 patients with PAH accompanied by systemic lupus erythematosus (SLE), mixed CTD (MCTD), or primary Sjögren's syndrome (SS) who received first-line IS treatment alone or in combination with pulmonary vasodilators. When short-term treatment response was defined as an improvement in World Health Organization functional class at 3 months, 16 patients (53%) were short-term responders. Simultaneous diagnosis of PAH and CTD, and the use of immunosuppressants, especially intravenous cyclophosphamide, in addition to glucocorticoids were identified as independent predictors of a short-term response (P=0.004 and 0.0002, respectively). Cumulative rates free of PAH-related death were better in short-term responders than non-responders (P=0.04), and were best in patients with a simultaneous diagnosis of PAH and CTD who were treated initially with a combination of glucocorticoids and immunosuppressants.

Conclusions: Patients with a simultaneous diagnosis of PAH and CTD, including SLE, MCTD, and primary SS, should receive intensive IS treatment regimens to achieve better short- and long-term outcomes.

Key Words: Collagen; Immunology; Pulmonary arterial hypertension; Survival

Pulmonary arterial hypertension (PAH) is a refractory manifestations of connective tissue disease (CTD), even though a number of selective pulmonary vasodilators have become available.[1] Recent data from large registries of PAH patients have revealed that survival rates are better in patients with systemic lupus erythematosus (SLE) or mixed connective tissue disease (MCTD) than in those with systemic sclerosis (SSc).[2,3] A possible reason for the better prognosis in patients with SLE- or MCTD-PAH is that immune and inflammatory mechanisms, rather than fibrotic processes, have a primary role in remodeling the pulmonary vasculature, resulting in favorable responses to immunosuppressive (IS) treatment.[4] In fact, several cohort studies and case series have described the potential efficacy of IS treatment for PAH associated with SLE, MCTD, or even primary Sjögren's syndrome (SS), although the treatment regimens and response criteria differ among these reports.[5-9] Notably, a short-term response to IS treatment predicts favorable long-term outcomes.[5,7] However, updated guidelines proposed by a joint task force for the diagnosis and treatment of pulmonary hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS) recommend that therapy for CTD-PAH should follow the same treatment algorithm as that described for idiopathic PAH.[10] IS treatment is not included in the recommendations, although there is a brief comment that the combination of glucocorticoids (GC) and cyclophosphamide may result in clinical improvement in some patients with PAH associated with SLE or MCTD.[10] Nevertheless, in clinical practice, patients with SLE- or MCTD-PAH often receive IS treatment alone or in combination with pulmonary vasodilators,[8,9,11,12] although we still do not know which patients benefit from IS treatment. In this regard, it is recognized that SSc-PAH patients respond poorly to IS treatment unless their disorder overlaps with other CTDs, including SS or myositis.[5,8] In addition, patients with less severe functional disabilities or only mild hemodynamic impairment at baseline are more likely to respond to IS treatment.[5,6] Based on these findings, Jais et al proposed a treatment algorithm for patients with

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ORIGINAL ARTICLE

Myositis-specific autoantibodies in Japanese patients with juvenile idiopathic inflammatory myopathies

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ABSTRACT

Objectives: The aim of our study is to clarify the association of myositis-specific autoantibodies (MSAs) with clinical and laboratory features in Japanese patients with juvenile idiopathic inflammatory myopathies (JIIMs).

Methods: We retrospectively analyzed the frequency of MSAs and their association with clinical or laboratory findings in 25 Japanese patients with JIIMs in Hokkaido district.

Results: Eighteen of the 25 patients (72%) were positive for MSAs; seven with anti-melanoma differentiation associated gene (MDA) 5 (28%), five with anti-transcriptional intermediary factor (TIF)-1γ (20%), four with anti-MJ/nuclear matrix protein (NXP)-2 (16%), two with anti-Jo-1 (8%), one with anti- HMG-CoA reductase, one with anti-signal recognition peptide (SRP) antibodies (4% each), including co-existence and transition of MSAs in one patient each. Anti-MDA5 antibodies were related to interstitial lung disease (ILD) and arthritis but not to amyopathic juvenile dermatomyositis. Drug-free remission was achieved, once ILD was overcome in this group. Anti-TIF-1γ antibodies were associated with typical rashes and mild myositis. Anti-MJ/NXP2 and anti-SRP antibodies were associated with severe muscle weakness. No patient was complicated with malignancy.

Conclusion: Anti-MDA5 antibodies are prevalent and closely associated with ILD in our series compared with other countries. There was no apparent difference in clinical features associated with other MSAs among races.

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KEYWORDS
Juvenile idiopathic inflammatory myopathies; myositis-specific autoantibody

Introduction

Juvenile idiopathic inflammatory myopathy (JIIM) is an entity of myositis of unknown etiology comprising juvenile dermatomyositis (JDM), juvenile polymyositis (JPM), immune-mediated necrotizing myopathy (IMNM), and myositis associated with other connective tissue diseases [1,2]. JDM is the most common form of JIIMs mainly affecting both the striated muscle and skin. Recent reports have demonstrated association of clinical features with myositis-specific autoantibodies (MSAs) such as anti-transcriptional intermediary factor (TIF)-1γ, anti-melanoma differentiation associated gene (MDA) 5, anti-MJ/nuclear matrix protein (NXP) 2, anti-Mi-2, anti-signal recognition particle (SRP), and anti-aminoacyl-tRNA synthetase (ARS) antibodies in JIIMs [3–5]. Although we have reported a strong correlation of anti-MDA5 antibodies with interstitial lung diseases (ILD) [6,7], clinical characteristics and frequency of other MSAs have not been elucidated in Japanese patients with JIIMs. In the present study, we analyzed the frequency of the MSAs and association of MSAs with clinical and laboratory features in Japanese patients in Hokkaido district.

Method

Patients

Medical records of patients with JIIMs who presented to Hokkaido University Hospital, KKR Sapporo Medical Center and affiliated hospitals in Hokkaido district between 1990 and 2016 were retrospectively reviewed for their clinical and laboratory features at their initial visit. This study was approved by Institutional Review Board of Hokkaido University Hospital (016-0382).

Diagnosis

Patients were divided into three groups according to the presence or absence of clinical and laboratory myositis; classical JDM, hypomyopathic JDM (JHDM) which lacks muscle weakness but shows typical skin lesions and objective evidence of myositis such as biochemical, radiological, or electrophysiological abnormalities, and amyopathic JDM (JADM) which lacks any of clinical or objective myositis despite clinicopathological evidence of skin lesions. The diagnosis of classical JDM was made according to Bohan

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Case report

Anti-MDA5 antibody-positive rapidly progressive interstitial pneumonia without cutaneous manifestations

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ABSTRACT

A 47-year-old man was referred to our hospital with a 1-month history of fever and dyspnea after inhalation of insecticide in a confined space. We diagnosed rapidly progressive interstitial pneumonia. High-dose methylprednisolone, tacrolimus, and intermittent infusion of cyclophosphamide were administered. His condition rapidly deteriorated; therefore, extracorporeal membrane oxygenation therapy was performed. Unfortunately, he died 69 days after admission. Although typical skin findings suggestive of dermatomyositis were absent, anti-melanoma differentiation-associate gene (anti-MDA5) antibody was positive. Our findings suggest that in patients with hyperferritinemia and rapidly progressive interstitial lung disease (RP-ILD) demonstrating random ground glass shadows and peripheral consolidations by high-resolution computed tomography (HRCT) even if skin manifestations related to dermatomyositis are not complicated, we should assume anti-MDA5 antibody-positive interstitial pneumonia.

1. Introduction

Clinically amyopathic dermatomyositis (CADM) is a subset of dermatomyositis showing typical skin manifestations without myositis. Patients with CADM do not have apparent muscle weakness or elevated serum muscle enzymes. CADM may be complicated by rapidly progressive interstitial lung disease (RP-ILD) [1,2]. Approximately 60–70% of CADM patients have anti-melanoma differentiation-associated gene 5 (anti-MDA5) antibodies. To date, the mechanism of the production of anti-MDA5 antibodies and their pathogenic roles has not been fully elucidated [3]. The mortality rate of anti-MDA5-positive patients with respiratory failure is high. Rapid intervention with immunosuppressive therapy including high-dose corticosteroids, cyclosporine, and intermittent intravenous cyclophosphamide (IVCY) is recommended immediately after diagnosis of RP-ILD with anti-MDA5 antibody [3].

In this case, we report an anti-MDA5 antibody positive patient without the cutaneous symptoms of CADM but exhibiting treatment-resistant RP-ILD.

2. Case report

A 47-year-old Japanese man with a history of bronchial asthma and allergic rhinitis presented with cough and fever. He had no history of smoking and no family history of bronchial asthma or allergy. When helping with house cleaning, he was exposed to a large amount of pyrethroid insecticide in a confined space without a mask. Approximately 1 week after pyrethroid exposure, he complained of cough and fever and visited a neighboring doctor. No person had reported similar symptoms in the surrounding area. He was treated with azithromycin (500 mg/day) and garenoxacin (400 mg/day). His symptoms did not improve; therefore, he visited our hospital 4 weeks after the insecticide exposure. On admission, he was alert. His vital signs were: blood pressure, 110/68 mmHg; pulse rate, 113/min; and body temperature, 37.3 °C. Percutaneous arterial blood oxygen

Abbreviations: Anti-MDA5, anti-melanoma differentiation-associate gene; ARS, anti-aminoacyl-tRNA synthetase; CADM, clinically amyopathic dermatomyositis; IVCY, intravenous cyclophosphamide; HRCT, high-resolution computed tomography; RIG-I, retinoic acid inducible gene-I; RP-ILD, rapidly progressive interstitial lung disease

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Original article

Initial predictors of poor survival in myositis-associated interstitial lung disease: a multicentre cohort of 497 patients

Shinji Sato[1,*], Kenichi Masui[2,3,*], Naoshi Nishina[4], Yasushi Kawaguchi[5], Atsushi Kawakami[6], Maasa Tamura[7], Kei Ikeda[8], Takahiro Nunokawa[9], Yoshinori Tanino[10], Katsuaki Asakawa[11], Yuko Kaneko[12], Takahisa Gono[4,13], Taro Ukichi[14], Shinjiro Kaieda[15], Taio Naniwa[16] and Masataka Kuwana[4]; A Multicentre Retrospective Cohort of Japanese Patients with Myositis-associated ILD Investigators[a]

Abstract

Objective. To identify initial predictors of poor survival in patients with PM/DM-associated interstitial lung disease (ILD).

Methods. We established a multicentre retrospective cohort of incident cases of PM/DM-associated ILD from 44 institutions across Japan (Multicentre Retrospective Cohort of Japanese Patients with Myositis-associated ILD, JAMI). Inclusion criteria were an onset age ⩾16 years; PM/DM or clinically amyopathic DM according to the published criteria; imaging evidence of ILD; and availability of serum samples for assays of autoantibodies such as anti-melanoma differentiation-associated gene 5 and anti-aminoacyl tRNA synthetase. We collected demographic data and clinical characteristics recorded at the time of diagnosis, as well as follow-up survival data. Predictors of ILD-related mortality were identified by univariate and multivariate analyses.

Results. JAMI enrolled a cohort of 497 patients with PM (15%), classic DM (32%) and clinically amyopathic DM (53%). During the observation period (median 20 months), 76 died of respiratory insufficiency directly related to ILD. Univariate analysis revealed several initial parameters associated with ILD mortality, including demographic, clinical, laboratory, imaging and autoantibody variables. We used multivariate analysis with a stepwise selection of parameters to generate an appropriate predictive model, and identified the following independent risk factors for ILD mortality: age at onset ⩾60 years [hazard ratio (HR) = 4.3, 95% CI: 2.4, 7.5], CRP ⩾1 mg/dl (HR = 2.6, 95% CI: 1.5, 4.8), peripheral capillary oxygen saturation <95% (HR = 2.0, 95% CI: 1.2, 3.4) and anti-melanoma differentiation-associated gene 5 antibody (HR = 7.5, 95% CI: 2.8, 20.2).

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CLINICAL SCIENCE

Association of Serum Soluble CD163 with Polymyositis and Dermatomyositis, Especially in Anti-MDA5 Antibody–positive Cases

Hidenaga Kawasumi, Yasuhiro Katsumata, Akira Nishino, Shinya Hirahara, Yasushi Kawaguchi, Masataka Kuwana, and Hisashi Yamanaka

ABSTRACT. ***Objective.*** We elucidated the association of serum soluble CD163 (sCD163) with rapidly progressive interstitial lung disease (RP-ILD), autoantibody profiles, and serum ferritin in patients with polymyositis (PM), classic dermatomyositis (DM), and clinical amyopathic dermatomyositis (CADM).

Methods. Serum sCD163 levels were retrospectively measured by ELISA in patients with PM, classic DM, and CADM, as well as in healthy controls (HC). Repeat sera samples were obtained posttreatment from available patients. The associations between serum sCD163 levels and clinical information were analyzed.

Results. Serum sCD163 levels in patients with PM/classic DM/CADM were significantly higher than those in HC (n = 72, 56, 34, and 68, respectively; $p < 0.001$ for all comparisons). No significant difference was observed between serum sCD163 levels in patients with and without ILD ($p = 0.16$) or between those with RP-ILD and chronic ILD ($p = 0.21$). Serum sCD163 levels were significantly higher in patients with anti-MDA5 antibodies (n = 27) than in those without ($p = 0.001$). Serum sCD163 levels were weakly correlated with serum ferritin levels in the patients with PM, classic DM, and CADM ($r = 0.21$). Serum sCD163 levels decreased significantly following treatment in all patient groups ($p = 0.003$).

Conclusion. The present results suggest an association of serum sCD163 with PM, classic DM, and CADM, especially in anti-MDA5 antibody–positive cases. However, serum sCD163 levels were not specifically associated with ILD or RP-ILD. (First Release April 15 2018; J Rheumatol 2018;45:947–55; doi:10.3899/jrheum.170997)

Key Indexing Terms:
POLYMYOSITIS DERMATOMYOSITIS MDA5
INTERSTITIAL LUNG DISEASE FERRITINS

Polymyositis (PM) and dermatomyositis (DM) are characterized clinically by weakness and low skeletal muscle endurance and histopathologically by the presence of T cells, macrophages, dendritic cells, B cells, and plasma cells in muscle tissue[1,2]. In addition, a subset of patients with DM have cutaneous lesions in the absence of muscle weakness, known as clinically amyopathic dermatomyositis (CADM)[2]. PM/DM is often complicated by interstitial lung disease (ILD)[3]. Although therapeutic strategies have improved the clinical courses of patients with PM/DM[4,5,6], ILD is a major prognostic factor for PM/DM[7]. In particular, rapidly progressive (RP)-ILD, mostly complicated with CADM and/or antimelanoma differentiation-associated gene 5 (anti-MDA5) antibodies, is a life-threatening complication[8].

Predicting disease progression, the prognosis, and treatment response are important when making treatment decisions, given the heterogeneity of the clinical course of PM/DM-associated ILD[9]. We have reported previously that high levels of serum ferritin, an iron-binding protein, are associated with the severity and prognosis of ILD with PM/classic DM/CADM, particularly in a patient with anti-MDA5 antibodies[8,10,11]. In addition, we demonstrated that accumulated macrophages synthesize ferritin in the lung and bone marrow of a patient with RP-ILD associated with

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ORIGINAL ARTICLE

Beneficial use of serum ferritin and heme oxygenase-1 as biomarkers in adult-onset Still's disease: A multicenter retrospective study

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ABSTRACT

Background: Heme oxygenase (HO)-1 is a heme-degrading enzyme highly expressed in monocyte/macrophage, serum levels of which may be promising biomarker for adult-onset Still's disease (AOSD). We here report data on the use of serum ferritin and HO-1 levels in AOSD.

Methods: Under the Hypercytokinemia Study Group collaboration, we collected sera from a total of 145 AOSD patients. Three independent experts judged whether the patients were definite AOSD depending on the clinical information. These 91 'definite AOSD' patients were further divided into active, remission, and relapse groups. Forty-six cases of systemic vasculitis, sepsis, etc. were included as disease controls. Serum ferritin and HO-1 levels were measured using ELISA. Associations between clinical symptoms, serum ferritin, and HO-1 were explored. Multivariate regression analysis was performed to identify independent variables associated with definite AOSD diagnosis.

Results: Serum ferritin and HO-1 levels were significantly higher in active and relapsed AOSD cases compared to disease controls, and were reduced by the treatment. Although a significant correlation was found between serum ferritin and HO-1 levels, a discrepancy was found in some cases such as iron-deficiency anemia. Receiver operating characteristic analysis identified optimal levels of serum ferritin (>819 ng/ml; sensitivity 76.1% and specificity 73.8%), and serum HO-1 (>30.2 ng/ml; sensitivity 84.8% and specificity 83.3%) that differentiated AOSD from controls. Interestingly, 88.9% of patients with AOSD who relapsed exceeded the cut-off value of serum HO-1 > 30.2 ng/ml, but only 50.0% exceeded serum ferritin >819 ng/ml ($p = .013$), suggesting that serum HO-1 levels may be a convenient indicator of AOSD disease status. Multivariate analysis identified neutrophilia, RF/ANA negativity, sore throat, and elevated serum HO-1 as independent variables associated with AOSD diagnosis.

Conclusion: We confirmed that serum ferritin and HO-1 serve as highly specific and sensitive biomarkers for AOSD. A future prospective study with large sample size is necessary to determine whether these biomarkers could be included in Yamaguchi's Criteria.

ARTICLE HISTORY
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KEYWORDS
Adult-onset Still's disease; ferritin; heme oxygenase-1

Background

Adult-onset Still's disease (AOSD) is a heterogeneous autoinflammatory disease that manifests with high-grade fever, arthritis, salmon-pink skin rash, etc. [1,2]. Although the cause of AOSD is still unknown, abnormal macrophage activation and natural killer cell dysfunction, triggered by various stimuli including infection, are thought to play critical roles in AOSD pathogenesis [3,4].

To date, there is no disease-specific clinical feature or laboratory test to make a diagnosis of AOSD: its diagnosis is dependent upon combinations of non-specific clinical features. A few criteria have been proposed for the classification of AOSD [5–7]; among them, Yamaguchi's criteria, in which several co-authors of the current article had participated in the proposal process, have widely been applied in clinics worldwide [5]. The criteria employ clinical and laboratory information including high-grade fever, typical skin rash, arthralgia, leukocytosis, sore throat, lymphadenopathy/splenomegaly, liver dysfunction, and rheumatoid factor (RF)/anti-nuclear antibody (ANA) negativity. However,

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Supplemental data for this article can be accessed here.

RHEUMATOLOGY

Original article

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Serum matrix metalloproteinase levels in polymyositis/dermatomyositis patients with interstitial lung disease

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Abstract

Objective. We aimed to clarify the clinical significance of serum levels of MMPs in interstitial lung disease (ILD) complicated with PM/DM (PM/DM-ILD).

Methods. We retrospectively analysed serum levels of seven subsets of MMPs in 52 PM/DM-ILD patients diagnosed at Kyoto University Hospital or Tenri Hospital from January 2005 to December 2014. The patients were sub-grouped based on the presence of anti-amimoacyl-tRNA synthetase antibody (anti-ARS antibody), anti-melanoma differentiation-associated protein 5 antibody (anti-MDA5 antibody) or lack of the antibodies (ARS-ILD, MDA5-ILD and other-ILD groups, respectively) and independently analysed. Eighteen PM/DM patients without ILD and 55 healthy control were also analysed. Associations between serum levels of MMPs and clinical findings including mortality were analysed.

Results. Among the MMPs analysed, MMP-7 serum levels in the ARS-ILD group were significantly higher compared with those in any of the other groups of PM/DM patients or in healthy controls. On the other hand, in the MDA5-ILD group, serum MMP-7 levels >5.08 ng/ml were associated with worse overall survival both in univariate (P = 0.017; odds ratio 18.0; 95% CI 1.69, 192.00) and multivariate (P = 0.027; odds ratio 14.60; 95% CI 1.11, 192.00) analyses. Immunohistochemical analysis suggested that MMP-7 was expressed in type II alveolar epithelial cells adjacent to the fibrotic lesions.

Conclusion. Serum MMP-7 levels were higher in anti-ARS antibody-positive PM/DM-ILD patients, while higher serum MMP-7 levels among anti-MDA5 antibody-positive PM/DM-ILD patients were associated with a worse prognosis. Fibrotic processes may be associated with the elevation of serum MMP-7 levels.

Key words: polymyositis/dermatomyositis, interstitial lung disease, anti-MDA5 antibody, anti-ARS antibody, matrix metalloproteinase, fibrosis

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ORIGINAL ARTICLE

Serum neopterin as well as ferritin, soluble interleukin-2 receptor, KL-6 and anti-MDA5 antibody titer provide markers of the response to therapy in patients with interstitial lung disease complicating anti-MDA5 antibody-positive dermatomyositis

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ABSTRACT

Objective: This study identified biomarkers that can be used to assess disease activity and response to therapy in patients with interstitial lung disease complicating anti-melanoma differentiation-associated gene 5 (MDA5) antibody (Ab)-positive clinically amyopathic dermatomyositis (CADM).

Methods: In 15 patients with interstitial lung disease complicating anti-MDA5 Ab-positive CADM, anti-MDA5 Ab, neopterin, interleukin (IL)-18, ferritin, and soluble interleukin 2 receptor (sIL-2R) levels were measured in cryopreserved serum specimens before and at multiple times after remission induction therapy, and their correlations were assessed.

Results: Anti-MDA5 Ab, neopterin, IL-18, ferritin, and sIL-2R levels did not differ significantly between patients who survived and those who succumbed to the disease. In many cases, serum anti-MDA5 Ab titers were over the upper limit (over 150 index value) before treatment in the usual measuring method, and gradually decreased to the normal range at stable phase. Meanwhile, serum neopterin levels (21.6 [15.3–48.3] nmol/L) were significantly elevated in newly diagnosed patients and fell to 6.8 (5–11.4) nmol/L at 6 months after treatment introduction.

Conclusions: Elevated serum neopterin as well as ferritin, sIL-2R, KL-6, and anti-MDA5 Ab titer might help identify patients with interstitial lung disease complicated with DM and might be useful in monitoring response to therapy.

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KEYWORDS
Anti-MDA5 antibody; clinically amyopathic dermatomyositis; neopterin; ferritin; soluble interleukin-2 receptor

1. Introduction

Dermatomyositis is an inflammatory myopathy accompanied by rash. Autoantibodies are present in the serum of patients with dermatomyositis and their association with clinical symptoms described [1,2]. While autoantibodies specific for the melanoma differentiation-associated gene 5 (MDA5) protein are typically found in patients with myositis, these autoantibodies are also present in patients with clinically amyopathic dermatomyositis (CADM) characterized by the absence of limited clinical muscle involvement but who frequently develop rapid progressive interstitial lung disease (RP-ILD) [1,2].

Anti-MDA5 antibody (Ab)-positive Asian patients with CADM commonly have abnormally increased levels of serum anti-MDA5 Ab. Anti-MDA5 Ab-positive advanced RP-ILD has a poor prognosis. It is refractory to treatment and patients frequently succumb to respiratory failure [3–6]. Even in patients with few respiratory symptoms and minimal findings in imaging studies, interstitial lung disease can worsen rapidly and without notice. Thus, prompt diagnosis and early intervention are key to improving outcome.

The clinical features of CADM are typically limited to the skin, and CADM is especially associated with the presence of the Gottron's sign with skin ulceration or reverse Gottron's sign. Serological features include elevations in hepatobiliary enzymes and high serum ferritin, the latter reportedly correlating with disease activity [2,7]. In addition, serum studies suggest that the levels of pro-inflammatory cytokines, including interleukin (IL)-6, tumor necrosis factor (TNF)-α, and IL-18, are high in patients with active disease and decrease over the course of treatment [8–11]. The observation that serum ferritin and IL-18 levels are elevated suggests that macrophages may be involved in the development of CADM pathology [2,9]. This study, therefore, examined a set of proteins produced by activated monocytes/macrophages. Using cryopreserved serum samples obtained from patients with anti-MDA5 Ab-positive CADM who developed interstitial lung disease controlled by treatment, we retrospectively monitored the levels of anti-MDA5

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Efficacy of Glucocorticoids and Calcineurin Inhibitors for Anti-aminoacyl-tRNA Synthetase Antibody–positive Polymyositis / dermatomyositis–associated Interstitial Lung Disease: A Propensity Score–matched Analysis

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ABSTRACT. ***Objective.*** The optimal treatment strategy for anti-aminoacyl-tRNA synthetase antibody–positive polymyositis/dermatomyositis-associated interstitial lung disease (anti-ARS-PM/DM-ILD) is yet to be established. We aimed to evaluate the efficacy of glucocorticoids and calcineurin inhibitors (CNI) in patients with ARS-PM/DM-ILD.

Methods. Progression-free survival (PFS) and overall survival rates were retrospectively evaluated in 32 consecutive patients with ARS-PM/DM-ILD. Disease progression was defined as deterioration in PM/DM-ILD (including recurrence). Predictive factors associated with PFS were analyzed by Cox hazards analysis. The efficacy of first-line prednisolone (PSL) plus CNI therapy was compared with that of PSL monotherapy using propensity score–matched analysis.

Results. Overall, 20 (62.5%) and 12 (37.5%) patients received first-line therapy with PSL + CNI and PSL, respectively. The 2-year PFS and 5-year survival rates in the overall cohort were 68.8% and 96.9%, respectively. On multivariate analysis, arterial oxygen pressure (HR 0.86) and PSL monotherapy (vs PSL + CNI; HR 7.29) showed an independent association with PFS. Baseline characteristics of propensity score-matched PSL + CNI and PSL groups were similar. The 2-year PFS rate was significantly higher in the matched PSL + CNI group than in the matched PSL group. All patients who experienced disease progression during first-line therapy were subsequently treated with second-line therapies. The 5-year survival rates of both the matched PSL + CNI and PSL groups were favorable.

Conclusion. Propensity score–matched analysis demonstrated that first-line PSL + CNI therapy for patients with ARS-PM/DM-ILD significantly improved the PFS compared with PSL monotherapy, although there was no significant difference regarding longterm survival. (J Rheumatol First Release January 15 2019; doi:10.3899/jrheum.180778)

Key Indexing Terms:
DERMATOMYOSITIS POLYMYOSITIS INTERSTITIAL LUNG DISEASE
ANTI-AMINOACYL TRNA-SYNTHETASE ANTIBODY CALCINEURIN INHIBITOR

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RESEARCH ARTICLE Open Access

Anti-CD11b antibody treatment suppresses the osteoclast generation, inflammatory cell infiltration, and autoantibody production in arthritis-prone FcγRIIB-deficient mice

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Abstract

Background: Previously we established an arthritis-prone FcγRIIB-deficient mouse strain (designated KO1). Anti-mouse CD11b mAb (5C6) has been reported to inhibit the recruitment of peripheral CD11b$^+$ myelomonocytic cells from the blood to the inflammatory site. These cells include neutrophils and monocytes, both of which play important roles in the development of arthritis. Here we treated KO1 mice with 5C6 mAb in order to study its effect on arthritis development.

Methods: To evaluate the disease-preventive effect of 5C6, 4-month-old preclinical KO1 mice were divided into three groups: the first treated with 5C6 for 6 months, the second treated with normal rat IgG for 6 months, as a control, and the third left untreated. Arthritis severity and immunological abnormalities were compared among the groups, along with transcriptional levels of several important arthritis-related factors in ankle joints, spleen, and peripheral blood cells.

Results: The 5C6 treatment ameliorated arthritis in KO1 mice, showing decreases in inflammatory cell infiltration and osteoclast formation. Analysis of transcriptional levels in ankle joints revealed that compared with the two control groups, the 5C6-treated group showed downregulated expression of RANK, RANKL, MCP-1, RANTES, TNFα, and IL-6, and at the same time showed significantly up-regulated expression of the decoy receptor for RANKL, *i.e.* osteoprotegerin. In addition, the disease suppression was associated with the lower serum levels of autoantibodies, and the decreased frequencies of activated B cells and plasma cells. The expression levels of B cell activation/differentiation-related cytokines were suppressed in spleen and peripheral leukocytes of the 5C6-treated mice. Intriguingly, while untreated KO1 mice spontaneously developed marked monocytosis, the 5C6-treated mice showed the significantly down-regulated frequency of monocytes.

Conclusions: The outcome of 5C6 treatment was complex, in which the 5C6-mediated disease-preventive effect is likely due on one hand to the decrease in the recruitment of inflammatory cells and osteoclast precursor monocytes from the periphery into the joints, and on the other hand to the suppression of B cell activation/maturation and of autoantibody production via the suppression of B cell stimulating cytokine production. The lower levels of these cytokines may be the secondary effect of the lower frequency of monocytes, since monocytes/macrophages are the major producers of these cytokines.

Keywords: Rheumatoid arthritis, FcγRIIB deficiency, Osteoclast, Monocytes, B cell activation

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FcγRIIb on B Cells and Myeloid Cells Modulates B Cell Activation and Autoantibody Responses via Different but Synergistic Pathways in Lupus-Prone *Yaa* Mice

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C57BL/6 (B6).FcγRIIb$^{-/-}$.*Yaa* mice spontaneously develop lethal lupus nephritis. To define the cell type–specific role of FcγRIIb in *Yaa*-associated lupus, we established B cell– (CD19^{Cre}.*Yaa*), myeloid cell– (C/EBPα^{Cre}.*Yaa*), and dendritic cell– (DC) (CD11c^{Cre}.*Yaa*) specific FcγRIIb-deficient B6.*Yaa* mouse strains. CD19^{Cre}.*Yaa* mice developed milder lupus than B6.FcγRIIb$^{-/-}$.*Yaa* mice, indicating that FcγRIIb deficiency on B cells is not sufficient for the development of severe disease. Surprisingly, C/EBPα^{Cre}.*Yaa* mice also showed autoantibody production and mild lupus similar to that in CD19^{Cre}.*Yaa* mice, whereas CD11c^{Cre}.*Yaa* mice stayed disease free. These observations indicate that FcγRIIb deficiency in B cells and myeloid cells, but not DCs, contributes to the severe disease in B6.FcγRIIb$^{-/-}$.*Yaa* mice. Flow cytometric analysis showed that the frequency of peripheral Gr-1^{-} but not Gr-1^{+} monocyte was increased in B6.FcγRIIb$^{-/-}$.*Yaa* and C/EBPα^{Cre}.*Yaa* but not CD19^{Cre}.*Yaa* mice, suggesting a link between FcγRIIb deficiency on myeloid cells and the high frequency of Gr-1^{-} monocytes. RNA sequencing revealed that compared with Gr-1^{+} monocytes, Gr-1^{-} monocytes expressed higher levels of the B cell–stimulating cytokines BSF-3, IL-10, and IL-1β, the DC markers CD11c, CD83, and Adamdec1, and the antiapoptotic factors Bcl2 and Bcl6. In conclusion, in *Yaa*-associated lupus nephritis, FcγRIIb on B cells and myeloid cells modulates B cell activation via different but synergistic pathways. Gr-1^{-} monocytes are the most likely candidate myeloid cells involved. *The Journal of Immunology*, **2018, 201: 3199–3210.**

Mice have four types of IgG Fc receptors, FcγRI, FcγRIII, FcγRIV, and FcγRIIb (1, 2). The former three are activating receptors composed of a ligand-binding α-chain and a dimer of the FcR γ-chain (FcR γ) that mediates activation signals. FcγRIIb is a single-chain receptor, which inhibits cell activation upon coengagement with the activating FcγR by immune complexes (ICs). The balance of stimulatory and inhibitory signals determines the outcome of FcγR signaling in myeloid effector cells, which controls IC-mediated cellular responses such as Ab-dependent cell-mediated cytotoxicity, Ab-dependent cellular phagocytosis, and release of inflammatory mediators. On B cells, coengagement of FcγRIIb and the BCR downregulates the production of Abs.

Lupus nephritis, the characteristic feature of systemic lupus erythematosus (SLE), is an IC-mediated renal glomerular and vascular inflammatory disease. FcγRIIb encoding gene is identified as a susceptibility locus for SLE both in mice and humans (3–5). We previously found that the *Fcgr2b* gene is polymorphic and that SLE-prone strains, such as NZB, BXSB, and MRL all share deletion polymorphism in the *Fcgr2b* promoter region (3). This causes downregulation of FcγRIIb expression particularly on activated B cells, which results in increased IgG Ab production (6, 7). The SLE-prone BXSB strain contains not only the autoimmune-type *Fcgr2b* locus but also the Y chromosome–linked autoimmune acceleration gene (*Yaa*) mutation. The etiologic basis of *Yaa* is a duplication of the TLR7 gene due to a

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Q.L., H.F., J.S.V., and S.H. designed, conducted, and analyzed experiments and wrote the manuscript; M.O., H.T., N.T., and R.S. conducted and analyzed experiments and approved the manuscript; H.A. and H.N. designed and interpreted experiments and approved the manuscript.

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The online version of this article contains supplemental material.

Abbreviations used in this article: ACR, albumin/creatinine ratio; B6, C57BL/6; BSF-3, B cell–stimulating factor-3; DC, dendritic cell; FcR γ, FcR γ-chain; FPKM, fragment per kilobase of exon per million reads; GC, germinal center; GO, gene ontology; GSEA, Gene Set Enrichment Analysis; IC, immune complex; MOMA-1, metallophilic macrophage Ab; PANTHER, protein analysis through evolutionary relationships; PAS, periodic acid–Schiff; PNA, peanut agglutinin; RNP, ribonucleoprotein; SLAM, signaling lymphocytic activation molecule; SLE, systemic lupus erythematosus; *Yaa*, Y chromosome–linked autoimmune accelerating gene.

The sequences presented in this article have been submitted to the National Center for Biotechnical Information's Gene Expression Omnibus (https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE116757) under accession number GSE116757.

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Original Articles

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Outcomes of the Re-classification of WHO Class IV Lupus Nephritis Using the ISN/RPS Classification: a Single Center Retrospective Observational Study from the JUDE Study

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Objective: The International Society of Nephrology-Renal Pathology Society (ISN/RPS) 2003 classification of lupus nephritis (LN) was designed to provide beneficial pathologic information relevant to the renal outcome. We conducted a retrospective observational study to investigate the baseline characteristics and renal response to treatment for patients with LN, comparing the World Health Organization (WHO) and ISN/RPS classification systems.

Materials: A total of 39 Japanese patients (2 men; 37 women) with LN who underwent percutaneous needle renal biopsy between 1998 and 2012 were evaluated.

Methods: Renal biopsy samples were classified using the 1995 WHO and 2003 ISN/RPS criteria.

Results: Among WHO class IV patients, a higher number of patients reclassified into ISN/RPS class III achieved complete response to treatment compared to those reclassified into class IV at 6 months follow-up. Twenty patients in WHO class IVc were reclassified into ISN/RPS classes III, III+V, IV-S, IV-S+V, IV-G and IV-G+V. No patients developed end-stage renal failure requiring renal replacement therapy.

Conclusions: The results suggest that the ISN/RPS classification system is more advantageous in predicting renal outcome and guiding treatment, especially for those previously classified with WHO class IVc LN.

Key words: systemic lupus erythematosus, lupus nephritis (LN), renal biopsy, renal outcome

Introduction

Systemic lupus erythematosus (SLE) is a clinically and serologically diverse multisystem autoimmune disease[1]. SLE may affect any organ, but mainly affects the skin, joints, blood cells, nervous system, and kidneys. Renal involvement is the most important risk factor associated with a poor prognosis in SLE. Lupus nephritis (LN) occurs in approximately 50-60% of patients with SLE[2) 3)]. LN plays a key role in the prognosis of SLE and nearly 10% of patients with LN develop end-stage renal failure requiring dialysis or renal transplantation[4)-6)]. Moreover, LN and the chronic use of corticosteroids and immunosuppressive agents contribute significantly to mortality. The world Health Organization (WHO) classification for LN was introduced in 1974, defined in 1982, and revised

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ORIGINAL ARTICLE

Disease flare patterns and predictors of systemic lupus erythematosus in a monocentric cohort of 423 Japanese patients during a long-term follow-up: The JUDE study

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Abstract

Objective: To clarify the clinical features of systemic lupus erythematosus (SLE) patients, factors associated with flares, and changes over time.
Methods: Patients having SLE with a visiting history were entered into the Juntendo University Database of Erythematosus. We included 423 cases in the long-term follow-up analysis, and 383 cases were followed for 10 years after the initiation of any therapeutic intervention (comparative analysis: 1973–1982, 82 cases; 1983–1992, 141, and 1993–2002, 160). We assessed changes in the patients' background characteristics, disease symptoms, flare rates, etc.
Results: Among the 423 cases, the mean follow-up period was 25.9 years, and mean number of flares was 0.51. Of those, 31.9% had ≥1 flares. Thrombocytopenia at onset contributed to the flares. For disease symptoms at onset, a recent trend in increasing thrombocytopenia was observed. The combination rate of immunosuppressive agents for diseases other than lupus nephritis was slightly increased, and there was no improvement until the first flare or in the flare rate.
Conclusions: Thrombocytopenia at onset is predictive factor for flares. Since SLE is a diverse disease with varying symptoms at recurrence, the treatment guidelines should be improved for thrombocytopenia from a long-term perspective.

Keywords

Clinical features, Cohort, Lupus nephritis, Systemic lupus erythematosus, Thrombocytopenia

History

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Introduction

Recently, the prognosis of systemic lupus erythematosus (SLE) has improved from a <50% five-year survival in 1955 [1] to a >90% 10-year survival [2,3]. Various factors have affected this improvement. Generally, the progressive treatment for lupus nephritis (e.g. introducing steroid pulse in the 1970s and intravenous cyclophosphamide [IVCY] in the 1980s) is considered to have largely contributed to the prognosis improvement [4,5]. Other possible factors include changes in patients' background because of an increased diagnostic efficiency in mild/failure cases and the recent progress in the treatment of complications such as infection, etc. by spreading awareness of SLE conditions and advanced diagnostic techniques.

SLE has diverse manifestations in multiple organ systems. Therefore, subjects were narrowed in a recent randomized control trial. This causes difficulty in comprehensively assessing the progress of overall SLE treatment, and as a result, the prognosis improvement of lupus nephritis and overall SLE has not been clarified. In cohort studies, there have been reports on the disease activity patterns and flare occurrence during a short follow-up period of several years [6–8]; however, there are few reports on long-term follow-up. Thus, overall changes in SLE over time are unclear. Studies on changes in SLE over time have been conducted at the Juntendo University School of Medicine using its own experimental cases [9,10].

The current study targeted long-term follow-up cases that were continuously followed for at least >10 years starting in 2012. We evaluated patients' background characteristics and the clinical features to study the predictive factors for flares. In addition, we assessed changes in patients' background characteristics, disease symptoms, and progress every 10 years since the 1970s. Furthermore, we investigated whether changes in patients' background characteristics and disease symptoms at onset were due to recent advancements in diagnostic techniques and treatment, as well as whether flares were decreasing. Lastly, we discussed future issues with SLE treatment from a comprehensive viewpoint.

Materials and methods

This study received ethical approval from the institutional ethics committee of Juntendo University (No. 20-72-2). The study participants provided informed consent, and the study was conducted in accordance with the 2008 Declaration of Helsinki. SLE patients who had a visiting history were entered into the Juntendo University Database of Erythematosus (JUDE) at the Department of Internal Medicine and Rheumatology, Juntendo University School of Medicine. To date, 2390 cases have been entered. Of them, 423 cases were continuously followed for at

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Innovative Techniques and Technology

A novel and innovative paper-based analytical device for assessing tear lactoferrin of dry eye patients

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ABSTRACT

Purpose: To elucidate the correlation between lactoferrin concentration in the tear film and signs and symptoms of severe dry eye disease (DED) using a novel microfluidic paper-based analytical device (μPAD) and enzyme-linked immunosorbent assay (ELISA).

Methods: Twenty-four patients were recruited at the Keio University Hospital. Using a novel μPAD, lactoferrin concentrations were measured in 4 patients with GVHD-related DED, 3 patients with other types of DED and 2 controls (Group A). For validation by ELISA, 22 patients (7 patients from Group A) comprising 9 patients with GVHD-related DED, 6 patients with other types of DED and 7 controls were examined (Group B). The link between lactoferrin concentration and clinical data about the severity of aqueous tear deficient DED was also investigated by both μPAD and ELISA.

Results: The lactoferrin concentration in tear fluid of the DED patients was positively correlated between μPAD and ELISA ($p = 0.006$, $r = 0.886$). The tear fluid of the GVHD patients showed low or undetectable lactoferrin concentration. Analysis by ELISA demonstrated that lactoferrin concentrations in the tear film from the GVHD patients were significantly lower than those from the non-GVHD patients ($p = 0.010576$). ELISA revealed lactoferrin concentration correlated with the value of Schirmer test and tear film breakup time, whereas it was inversely correlated with OSDI, fluorescein and rose bengal scores.

Conclusions: The novel μPAD may pave the way for measuring lactoferrin concentration in tear fluid from DED patients. Our results suggested that lactoferrin concentration in tear fluid reflect the severity of DED.

1. Introduction

Tear film plays an indispensable role in maintaining corneal and conjunctival homeostasis by protecting against foreign body microbial invasion and preserving visual acuity [1]. Tear fluid is composed of a variety of proteins, enzymes, water, lipids, and electrolytes [1–3]. Lactoferrin as well as lysozyme, lipocalin, secretory IgA, phospholipase A, and secretory and membrane-associated mucins are important tear components that protect against invading pathogens [4]. Lactoferrin, a protein secreted from lacrimal gland acini, exerts a bactericidal, anti-tumor, and anti-viral/-fungal effect; exhibits immunomodulatory properties, and maintains homeostasis of ocular surface health [5]. Lactoferrin binds to iron in tear fluid; thus, bacteria cannot colonize the ocular surface due to the lack of this nutrient [4]. Lactoferrin levels in tear fluid are reduced in SS and non-SS dry eye patients [2,4,6–8].

The Tear Film Ocular Surface Society Dry Eye Workshop II (TFOS DEWS II) recently revised the definition of dry eye as "a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles" [9]. On the other hand, the Asia Dry Eye Society proposed a new consensus definition of dry eye disease as "a multifactorial disease characterized by unstable tear film causing a variety of symptoms and/or visual impairment, potentially accompanied by ocular surface damage" [10]. Both definitions indicate that an understanding of tear film, including tear dynamics and components, is essential for dry eye disease.

The diagnosis of dry eye disease is based on a combination of signs and symptoms. The ocular surface disease index (OSDI), fluorescein and rose bengal staining, and tear film breakup time (TFBUT) are used as

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Review

Interferons and Dry Eye in Sjögren's Syndrome

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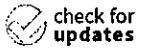

Abstract: Various cytokines, including interferon (IFN)-γ and IL-17, are augmented, and autoreactive T cells and B cells are activated in the immune pathogenesis of Sjögren's syndrome (SS). In particular, IFNs are involved in both the early stages of innate immunity by high level of type I IFN in glandular tissue and sera and the later stages of disease progression by type I and type II IFN producing T cells and B cells through B cell activating factor in SS. Genetically modified mouse models for some of these molecules have been reported and will be discussed in this review. New findings from human SS and animal models of SS have elucidated some of the mechanisms underlying SS-related dry eye. We will discuss IFN-γ and several other molecules that represent candidate targets for treating inflammation in SS-related dry eye.

Keywords: Sjögren's syndrome; dry eye; animal model; Interferon-γ

1. Introduction

Sjögren's syndrome (SS) is an intractable autoimmune disease, characterized by chronic lymphocytic infiltration of the lacrimal gland, salivary gland, and other exocrine glands, which lead to dry eye, dry mouth, and extraglandular syndrome [1,2].

SS is categorized into primary SS, which is not associated with other autoimmune diseases, and secondary SS, which is associated with other diseases including rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis, autoimmune liver cirrhosis, and mixed connective tissue disease [3,4]. Moreover, primary SS is further subdivided into the glandular form, which exclusively affects the exocrine glands, and the extraglandular form, which affects organs beyond the exocrine glands [1].

Animal models that reflect clinical findings have been studied to elucidate the pathogenic processes of SS-related dry eye disease, using modern, cutting-edge technology. The comparison of SS animal models to controls has enabled researchers to investigate the detailed mechanisms underlying SS-related dry eye; these pathogenic processes cannot be examined using human samples, which are limited in terms of their availability and applications. On the other hand, the pathophysiology of SS-related dry eye has been controversial because the available animal models do not completely reproduce all of the clinical aspects of dry eye related to SS or its clinical settings [5].

Nevertheless, recent advances in basic research have increased our understanding of the dry eye disease caused by SS [5]. It is reported that various cytokines produced by immunocompetent cells including IFN-γ and interleukin (IL)-17 are augmented and autoreactive T cells and B are activated by IFN in the immune pathogenesis of SS exocrine glands [6]. In particular, IFNs are involved in both the early stage of innate immunity, during which the type I IFN is elevated in glandular tissue and sera [7] and the later phase of disease progression, by type I and type II IFN producing T cells and B cells [8], which is stimulated by B-cell-activating factor (BAFF) in SS [2] (Figure 1). BAFF is

Foreword

Dry Eye Research Update in Japan in Celebration of the 25th Anniversary of the Dry Eye Society and the 10th Anniversary of Hakone Dry Eye Club

The Dry Eye Society was founded in 1990, serving this field for more than 25 years. The purpose of the Society is to develop a consensus on the definition and classification of dry eye, promote basic and clinical research, and perform public education on dry eye. Until around 1990, dry eye disease was not well understood by Japanese society. Several diagnostic names such as Sjögren syndrome, aqueous deficiency, and keratoconjunctivitis sicca were used for the disease by many ophthalmologists, but a consensus was absent among researchers. Moreover, around 1990, the symptoms of dry eye were considered as minor, and dry eye was not an established disease category. Since the establishment of our Society, we have dedicated our work to public education, explaining the importance of eye fatigue, irritation, and visual impairment due to dry eye. Through these endeavors, the recognition of dry eye terminology had increased to 73% by 1999—9 years after the establishment of our Society.[1] In 1995, we reported the first definition and diagnostic criteria by our Society.[2] At that time, the diagnosis could be made without symptoms. The most important components were decreased tear production, and abnormalities on the ocular surface shown by rose bengal or fluorescein staining, or squamous metaplasia. After increasing our understanding on the importance of dry eye symptoms, we revised the definition of dry eye in 2006, in which the symptoms became a mandatory factor for the diagnosis of dry eye.[3] Recently, in 2016, we have again revised the definition to include only two components (i.e., subjective symptoms and unstable tear film, which can provide a diagnosis of dry eye).[4] Since the understanding of dry eye has been changing worldwide over the last 25 years, it is essential that we revise the definition and diagnostic criteria accordingly. As of 2018, our Society has 700 members and the Governing Board consists of 13 officers and 15 council members (in the public domain, http://www.dryeye.ne.jp/en/doctor/index.html). We hold an annual educational seminar in February, and luncheon seminars at meetings held by the Japanese Ophthalmological Society, including the dry eye research award ceremony to recognize the contributions made by the most active dry eye researchers of the year. The list of the past awardees is shown in the Table.

In addition, we established the Hakone Dry Eye Club, which focuses on research and education on dry eye during an annual overnight retreat. Every year, all active dry eye researchers gather and hold in-depth discussions about dry eye, as well as impart current knowledge to the budding dry eye researchers. This annual event has greatly contributed to the consensus on the definition and diagnostic criteria of dry eye, as well as encouraging active research. In addition, we have promoted dry eye research in Asia from 2012 by sponsoring the first Asia Dry Eye Society (ADES) meeting in Tokyo (in the public domain, http://asia-dry-eye.biz/). The ADES is now growing rapidly thanks to the enthusiastic cooperation of China, Korea, and other countries; in addition, we are very active in determining the definition and classification of dry eye, collaborative research, and the exchange of knowledge.[5] Each autumn, we hold a scientific meeting, and the membership has grown from the founding 3 countries to 11 countries in 2018.

We are proud of publishing the dry eye research special issue in *Investigative Ophthalmology & Visual Science* on the occasion of the 25th anniversary of the Japan Dry Eye Society and 10th anniversary of Hakone Dry Eye Club. The contents of this special issue on dry eye by the Dry Eye Society were planned by the editorial committee: Drs Shiro Amano, Jun Shimazaki, Yuichi Hori, Norihiko Yokoi, and Yuichi Uchino. We have selected active dry eye researchers from the Dry Eye Society, defined as those who have published several articles on dry eye as a first or corresponding author. We have chosen 28 researchers to cover seven categories according to their subspecialties. Each article reports on the history and current findings of the subject in Japan and other parts of the world, as well as future directions. We are very proud of the contributions made by our Society to dry eye research worldwide, especially in the area of diagnosis and therapy, including the importance of the measurement of tear film break-up time to the development of mucin-secreting eye drops such as diquafosol sodium or rebamipide. I hope this special issue on dry eye enables dry eye researchers in Asia and worldwide to appreciate the contributions made by the Japanese research community.

Kazuo Tsubota
President
Dry Eye Society

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Original Contribution

The clinicopathological comparison among nodal cases of idiopathic multicentric Castleman disease with and without TAFRO syndrome☆,☆☆

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Keywords:
Idiopathic multicentric Castleman disease (iMCD);
TAFRO syndrome;
Follicular dendritic cell (FDC), interleukin-6 (IL-6);
Immunoglobulin G4 (IgG4);
Creatinine (Cre)

Summary Multicentric Castleman disease (MCD) is a systemic inflammatory disease potentially caused by an increase in the serum interleukin-6 (IL-6) level. Idiopathic MCD (iMCD) is histopathologically classified into three types: plasmacytic (PC), mixed, and hypervascular (hyperV) types. Recently, a unique clinical phenotype with a poor prognosis overlap with iMCD, thrombocytopenia, anasarca, fever, renal failure or reticulin fibrosis, and organomegaly (TAFRO syndrome), has been reported from Japan, but its detailed clinicopathological features remain unclear. In this study, we performed a clinicopathological analysis of 70 nodal cases of iMCD with and without TAFRO syndrome (n = 37 versus n = 33). Compared with iMCD without TAFRO, iMCD with TAFRO showed more atrophic lymphoid follicles (LF), greater distances between follicles, increased glomeruloid vascular proliferation within the germinal center, and increased follicular dendritic cells. In addition, the hyperV type in particular demonstrated severe atrophic LF and interfollicular vascular proliferation. Among the mixed-type cases, the serum IL-6 levels in iMCD with TAFRO were significantly higher than those in iMCD without TAFRO. Furthermore, compared to iMCD without TAFRO, the numbers of immunoglobulin G4 (IgG4)–positive and CD38-positive plasma cells were significantly decreased in iMCD with TAFRO.

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Original Article

The diagnostic utility of submandibular gland sonography and labial salivary gland biopsy in IgG4-related dacryoadenitis and sialadenitis: its potential application to the diagnostic criteria

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Cytidine deaminase enables Toll-like receptor 8 activation by cytidine or its analogs

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Abstract

Toll-like receptor 8 (TLR8), a sensor for pathogen-derived single-stranded RNA (ssRNA), binds to uridine (Uri) and ssRNA to induce defense responses. We here show that cytidine (Cyd) with ssRNA also activated TLR8 in peripheral blood leukocytes (PBLs) and a myeloid cell line U937, but not in an embryonic kidney cell line 293T. Cyd deaminase (CDA), an enzyme highly expressed in leukocytes, deaminates Cyd to Uri. CDA expression enabled TLR8 response to Cyd and ssRNA in 293T cells. CDA deficiency and a CDA inhibitor both reduced TLR8 responses to Cyd and ssRNA in U937. The CDA inhibitor also reduced PBL response to Cyd and ssRNA. A Cyd analogue, azacytidine, is used for the therapy of myelodysplastic syndrome and acute myeloid leukemia. Azacytidine with ssRNA induced tumor necrosis factor-α expression in U937 and PBLs in a manner dependent on CDA and TLR8. These results suggest that CDA enables TLR8 activation by Cyd or its analogues with ssRNA through deaminating activity. Nucleoside metabolism might impact TLR8 responses in a variety of situations such as the treatment with nucleoside analogues.

Keywords: 5-azacytidine, CDA, TLR8

Introduction

Toll-like receptors (TLRs) sense viral and bacterial products including microbial membrane components, flagellin and nucleic acids (NAs) to initiate defense responses (1). NAs such as double-stranded (ds) RNA, single-stranded (ss) RNA and ssDNA are recognized by TLR3, TLR7/TLR8 and TLR9, respectively (2). dsRNA and ssDNA directly bind to TLR3 and TLR9, respectively (3–5). In contrast, the structures of TLR7 and TLR8 show that these sensors bind to a combination of oligoribonucleotides and nucleosides such as guanosine (Guo) or uridine (Uri), respectively (6, 7). Functional analyses further show that TLR7 and TLR8 are activated by a combination of ssRNA and nucleosides (8). These results suggest that nucleosides might impact TLR7 and TLR8 responses in innate immune cells.

Nucleosides are generated by RNA degradation by RNases in lysosomes. In addition to Guo and Uri, adenosine (Ado) and cytidine (Cyd) are generated by RNA degradation. Cyd is deaminated to Uri by Cyd deaminase (CDA) (9). The role of CDA in the metabolism of Cyd analogues has been extensively studied (10). A variety of Cyd analogues have been developed as therapeutic agents to control myeloid leukemias and related diseases such as myelodysplastic syndrome. 5-Azacytidine is used in the treatment of myelodysplastic syndrome and acute myeloid leukemia (AML). The toxicity of these drugs is influenced by the activity of CDA (11, 12), suggesting that these Cyd analogues are rapidly deaminated to Uri analogues *in vivo*.

We hypothesized that Cyd deamination might enable TLR8 activation by Cyd and ssRNA. We here studied the role of CDA in TLR8 responses. TLR8 in peripheral blood leukocytes (PBLs) and a myeloid leukemia line U937 was activated by Cyd with ssRNA in addition to Uri with ssRNA.

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ORIGINAL ARTICLE

Tentative diagnostic criteria and disease severity classification for Castleman disease: A report of the research group on Castleman disease in Japan

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ABSTRACT

Objectives: To determine the tentative diagnostic criteria and disease severity classification for Castleman disease (CD) and describe the clinical and pathologic features among human herpesvirus 8 (HHV-8) negative idiopathic multicentric CD (iMCD) in the Japanese population.

Methods: We established the working groups for the research of CD in Japan and had meetings to discuss and define the tentative diagnostic criteria and disease severity classification for CD. We subsequently analyzed 142 patients classified into iMCD by using the nationwide Japanese patient registry.

Results: We proposed the preliminary diagnostic criteria and disease severity classification for CD based on our discussion. In addition, we made a proposal for the disease activity score. We identified clinical and pathological features of patients with iMCD diagnosed by these diagnostic criteria. In the disease severity classification, 37, 33 and 30% patients were categorized into mild, moderate and severe diseases, respectively.

Conclusion: This is the first proposal for diagnosis and classification of CD by the Japanese group. Further studies are required to validate whether they can distinguish CD from other inflammatory diseases and to determine their sensitivity and specificity.

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KEYWORDS
Castleman disease; idiopathic multicentric Castleman disease; diagnostic criteria; disease severity classification; TAFRO syndrome

Introduction

Castleman disease (CD) is a refractory lymphoproliferative disorder of unknown origin [1,2] and is present as two distinct clinical entities: the localized form (unicentric CD (UCD)) and the multicentric form (multicentric CD (MCD)) [3,4]. In addition, this disease is pathologically classified into the hyaline-vascular (HV), plasma cell (PC) and mixed types [5]. Most cases of UCD exhibit the HV type, whereas patients with MCD predominantly have the PC type or mixed type [5]. Depending on the clinical and pathologic subtypes, the clinical manifestations and management strategies of this disease are distinct. Patients with UCD typically have localized lymph nodes and are generally asymptomatic or mildly symptomatic [6,7]. Unlike UCD, MCD is a systemic disease with peripheral lymphadenopathy and systemic symptoms include fever, night sweats, weight loss and fatigue [6,7]. Although the pathogenesis of MCD is poorly understood, these manifestations are essentially resulted from proinflammatory hypercytokinemia including interleukin-6 (IL-6) [8,9]. In addition, a part of MCD is associated with the human immunodeficiency virus (HIV) [10] and human herpesvirus 8 (HHV-8) infection [11]. Some HHV8-positive MCD patients complicate with Kaposi's sarcoma and rare B cell lymphomas called primary effusion lymphoma occurring in the body cavities [12,13]. Of note, there is also a group of HIV-negative and

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Supplemental data for this article can be accessed here.

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Podocyte foot process width is a prediction marker for complete renal response at 6 and 12 months after induction therapy in lupus nephritis

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ABSTRACT

Morphological change that includes diffuse effacement of podocyte foot processes is correlated with proteinuria in patients with lupus nephritis (LN). We collected the data of clinico-pathological parameters and assessed foot process width (FPW) as an index of podocyte effacement in 73 patients with LN who had undergone renal biopsy. The multivariate analysis revealed that female gender (OR: 5.288; 95%CI: 1.197–37.29; $p = .0267$) and FPW (OR = 0.999, 95%CI = 0.997–0.999, $p = .0150$) were significantly predictive of a complete renal response (CR) at 6 months, while lymphocyte counts (OR = 1.002; 95%CI = 1.001–1.003, $p = .0028$) and FPW (OR = 0.998, 95%CI = 0.996–0.999, $p = .0027$) were significantly predictive of CR at 12 months. The cut-off point determined by the Classification and Regression Trees algorithm showed that FPW < 908.3 nm provides the best performance for predicting patients who achieve CR at 12 months. A smaller FPW appears to be a predictive factor for CR at 6 and 12 months after induction therapy.

1. Introduction

Lupus nephritis (LN) is one of the most important predictors of morbidity and mortality in patients with systemic lupus erythematosus (SLE) [1]. In a large multicenter and multi-ethnic inception cohort study, LN occurred in 38.8% of the SLE patients, and 10%–20% of the patients were predicted to progress to end-stage renal disease (ESRD) within 5 years of diagnosis [2,3]. Several studies have suggested predictive factors for the progression to ESRD in patients with LN; proteinuria, elevated creatinine, anemia, hypertension, and histological activity at the initial presentation of LN have each been reported to indicate progression to ESRD" in patients with LN [4–9].

Histopathology samples from patients with LN can demonstrate injury to almost any cell type, including mesangial, endothelial, podocyte, tubulointerstitial and vascular cells, and each type of injured cell is associated with different pathogeneses, clinical presentations, therapeutic responses, and outcomes in LN patients [3]. Fenestrated endothelial cells, the glomerular basement membrane (GBM), and the foot processes and slit diaphragms of the podocytes are all involved in maintenance of the glomerular filtration barrier. Podocytes are important to the structure that forms the final glomerular filtration barrier to prevent albumin and larger plasma proteins from crossing into the urine. The degree of podocyte foot process effacement as a result of podocyte injury has been associated with the development of proteinuria and nephrotic syndrome without evidence of mesangial proliferation or immune deposition [10,11]. It has also been shown that in

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Review

Modulation of Apoptosis by Cytotoxic Mediators and Cell-Survival Molecules in Sjögren's Syndrome

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Abstract: The pathogenesis of Sjögren's syndrome (SS) involves multiple factors including genetic background, cell death, and exocrine dysfunction. We here discuss apoptotic control in exocrine glands in SS by showing various pro- and anti-apoptotic pathways. Although the membrane-bound and soluble form of the Fas/Fas ligand system is a leading player with activation of the death domain and caspase 8/3 cleavage, the role of soluble Fas/FasL (including its polymorphism) in apoptosis is controversial. The tumor necrosis factor related apoptosis-inducing ligand (TRAIL)-mediated apoptosis of salivary gland epithelial cells (SGECs) involves a mitochondrial pathway that includes caspase 9 cleavage. The involvement of innate immunity cells such as toll-like receptors (TLRs) has been investigated; TLR2-4 and TLR7-9 are associated with the induction of inflammation in exocrine glands of SS patients. TLR3 has the potential to induce the apoptosis of SS patients' SGECs. Linkage of epidermal growth factor (EGF) was shown in exocrine glands in SS, and it inhibited the Fas/FasL system with the help of cell-survival factors. TLR3 has dual actions to cause inflammation as well as apoptosis, which are inhibited by EGF. In conclusion, apoptosis in exocrine glands of SS patients is tightly controlled by balance of pro-apoptotic signals and growth factor.

Keywords: Sjögren's syndrome; apoptosis; Fas; TLR; EGF; salivary gland epithelial cells; cell survival molecule

1. Introduction

Sjögren's syndrome (SS) is an autoimmune disease characterized by sicca symptoms including xerophthalmia and xerostomia, extraglandular manifestations such as interstitial pneumonia and interstitial nephritis, and the appearance of autoantibodies such as anti-Ro/SS-A, La/SS-B antibodies [1–5]. Because of the activation of the B-cell system in concert with T cells that respond to autoantigens, T or B cell-targeting therapies including abatacept, rituximab, and belimumab are possible beneficial biologics for the treatment for SS [6–9]. With regard to SS patients' genetic backgrounds, genome-wide association studies (GWAS) for SS patients showed susceptible loci in major histocompatibility complex and in regions for GTF21, along with differences among ethnic groups [10,11]. Although interferon-γ and Th2 cytokines are pathologically major factors for T cell-related immunological dysfunction in SS [12,13], a recent study showed the importance of the involvement of Th17 cells in SS [14].

In contrast, other studies showed that B-cell activation in the ectopic germinal center (GC) was also mediated by C-X-C motif chemokine 13 (CXCL13), and that B-cell activating factor of the tumor necrosis factor (TNF) family (BAFF) is also involved in the pathology of SS [15–17]. CD40-CD40 ligand expression on lymphocytes is also involved in T-cell activation after T–B cell interaction [18,19].

Clinical Case Report

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Recurrence of anti-MDA5 antibody-positive clinically amyopathic dermatomyositis after long-term remission

A case report

Yushiro Endo, MD[a], Tomohiro Koga, MD, PhD[a,*], Midori Ishida, MD[a], Yuya Fujita, MD[a], Sosuke Tsuji, MD[a], Ayuko Takatani, MD[a], Toshimasa Shimizu, MD[a], Remi Sumiyoshi, MD[a], Takashi Igawa, MD[a], Masataka Umeda, MD, PhD[a], Shoichi Fukui, MD, PhD[a], Ayako Nishino, MD, PhD[a], Shin-ya Kawashiri, MD, PhD[a], Naoki Iwamoto, MD, PhD[a], Kunihiro Ichinose, MD, PhD[a], Mami Tamai, MD, PhD[a], Hideki Nakamura, MD, PhD[a], Tomoki Origuchi, MD, PhD[a], Masataka Kuwana, MD, PhD[b], Yuji Hosono, MD, PhD[c], Tsuneyo Mimori, MD, PhD[c], Atsushi Kawakami, MD, PhD[a]

Abstract

Rationale: Among all dermatomyositis (DM) patients, antimelanoma differentiation-associated gene 5 antibody (anti-MDA5 Ab) positive patients have significantly poor short-term mortality, whereas they experience less relapses over the long term after the remission. We report the case of a patient with anti-MDA5 Ab-positive clinically amyopathic dermatomyositis (CADM) with the recurrence of interstitial lung disease (ILD) after 7 years of remission. There has been no case report of an anti-MDA5 Ab-positive DM patient with the recurrence of ILD after 7 years of long-term remission.

Patient concerns: A 70-year-old Japanese woman was diagnosed with anti-MDA5 Ab-positive CADM and ILD. After achieving 7 years long-term remission, she was admitted to our department with erythema on the fingers and interstitial pneumonia. Her anti-MDA5 Ab titer was elevated.

Diagnoses: We diagnosed recurrent CADM complicated with ILD.

Interventions: We successfully treated her with 1,000 mg of methyl-prednisolone pulse and intravenous cyclophosphamide therapy followed by prednisolone 50 mg/day and an increase of cyclosporine.

Outcomes: After that treatment, the patient's skin symptoms and interstitial pneumonia were relieved. All laboratory investigations such as ferritin, the serum markers of interstitial pneumonia (i.e., SP-A, SP-D), and the titer of anti-MDA5 Ab showed signs of improvement.

Lessons: Her case suggests that careful physical examinations and monitoring the serum markers are important even after long-term remission is achieved.

Abbreviations: anti-MDA5 Ab = antimelanoma differentiation-associated gene 5 antibody, anti-SFPQ Ab = anti-splicing factor proline/glutamine-rich protein antibody, CADM = clinically amyopathic dermatomyositis, CyA = cyclosporine., DM = dermatomyositis, ILD = interstitial lung disease, IVCY = intravenous cyclophosphamide therapy, mPSL = methyl-prednisolone, PSL = prednisolone, RPILD = rapidly progressive interstitial lung disease.

Keywords: anti-MDA5 antibody, clinically amyopathic dermatomyositis, dermatomyositis, interstitial pneumonia

Editor: N/A.

Patient Consent: Written informed consent was obtained from the patient by the corresponding author.

Conflicts of Interest: KM holds a patent on anti-MDA5 antibody-measuring kits and the other authors have no conflicts of interest to disclose.

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Clinical Case Report

Medicine

OPEN

Successful treatment of plasma exchange for rapidly progressive interstitial lung disease with anti-MDA5 antibody-positive dermatomyositis

A case report

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Abstract

Rationale: As the initial treatment of rapidly progressive interstitial lung disease (RPILD) with antimelanoma differentiation-associated gene 5 antibody (anti-MDA5 Ab)-positive dermatomyositis (DM) patients, a combination of corticosteroids, cyclophosphamide, and calcineurin inhibitor is recommended. However, some of these patients have poor prognoses despite such intensive treatment. Other more effective treatments are desired. We report the case of an anti-MDA5 Ab-positive DM patient who had developed RPILD despite intensive treatments; she was treated successfully by a short-term plasma exchange (PE).

Patient concerns: A 71-year-old Japanese woman was admitted to the rheumatology department of another hospital with progressive muscle weakness of the limbs and erythema on both upper eyelids and the fingers of both hands. She was suspected of having classical DM (CDM) based on the findings of typical skin and myositis. Although a chest computed tomography (CT) examination showed no findings of interstitial pneumonia at the first visit to the department, she newly presented interstitial pneumonia during her admission and her anti-MDA5 Ab titer was elevated.

Diagnoses: She was diagnosed with interstitial lung disease (ILD) with anti-MDA5 Ab-positive DM.

Interventions: She was treated with 1000 mg of methyl-prednisolone pulse, 500 mg of intravenous cyclophosphamide therapy (IVCY) followed by prednisolone 40 mg/day with tapering, and oral cyclosporine 200 mg/day. However, her interstitial pneumonia worsened with increasing breathing difficulty and an increasing serum ferritin level. She was transferred to our department, and we initiated PE as an additional treatment.

Outcomes: After the PE treatment, all laboratory findings, for example, ferritin, KL-6, and the titer of anti-MDA5 Ab showed marked improvement, and the patient's skin symptoms and active interstitial pneumonia were relieved.

Lessons: Our patient's case suggests that PE may be effective for RPILD in anti-MDA5 Ab-positive DM patients.

Abbreviations: anti-MDA5 Ab = antimelanoma differentiation-associated gene 5 antibody, CADM = clinically amyopathic dermatomyositis, DM = dermatomyositis, ILD = interstitial lung disease, IVCY = intravenous cyclophosphamide therapy, PE = plasma exchange, RPILD = rapidly progressive interstitial lung disease.

Keywords: anti-MDA5 antibody, clinically amyopathic dermatomyositis, dermatomyositis, interstitial pneumonia, plasma exchange

Editor: N/A.

Written informed consent was obtained from the patient by the corresponding author.

MK holds a patent on anti-MDA5 antibody-measuring kits.

The authors have no funding and conflicts of interest to disclose.

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Activation of Toll-like receptor 7 signaling in labial salivary glands of primary Sjögren's syndrome patients

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Summary

The aim of this study was to determine the expressions of Toll-like receptors (TLRs) 7–9 and type I interferon (IFN) signal in labial salivary glands (LSGs) and cultured salivary gland epithelial cells (SGECs) from primary Sjögren's syndrome (pSS) patients. We performed an immunohistochemistry analysis of LSGs from 11 patients with pSS as defined by American–European Consensus Group classification criteria and five healthy subjects. The pSS patients' SGECs were analyzed by immunofluorescence and western blotting. IFN-α expression was examined by immunosorbent assay and flow cytometry. Mononuclear cells (MNCs) from pSS patients' LSGs showed TLR-7-dominant expression. B cells, plasma cells and plasmacytoid dendritic cells (pDCs) co-expressed with TLR-7. Myeloid differentiation primary response gene 88 (MyD88), tumor necrosis factor receptor-associated factor 6 (TRAF6) and interferon regulatory factor 7 (IRF7) co-expressed with the pDC marker CD303 in LSGs. Ducts from pSS patients dominantly expressed TLR-7, and TLR-7 in the ducts co-expressed with MyD88, TRAF6 and IRF7. Type I IFNs including IFN-α and IFN-β were detected in MNCs and ducts in pSS patients' LSGs. Increased TRAF6 expression and the nuclear translocation of IRF7 in SGECs were detected by immunofluorescence following loxoribine (a TLR-7 ligand) stimulation despite IFN-β pretreatment. Western blotting showed increased TRAF6 expression in SGECs following IFN-β and loxoribine stimulation. Although no increase in IFN-α was detected in supernatant from stimulated SGECs, the IFN-α in supernatant from stimulated peripheral blood pDCs from pSS patients was significantly increased. Our findings suggest that TLR-7 is dominantly expressed in both MNCs and ducts with downstream signals for type I IFNs, indicating that TLR7-dominant innate immunity is related to the development of sialadenitis in pSS.

Keywords: plasmacytoid dendritic cells, Sjögren's syndrome, TLR-7, type I interferons

Introduction

Primary Sjögren's syndrome (pSS) is a systemic autoimmune disease characterized by periductal lymphocytic infiltration of the salivary and lacrimal glands, which results in reduced secretory functions and oral and ocular dryness [1]. Although the pathogenesis of pSS is not yet established, innate immune responses including type I interferon (IFN) activity were shown to be associated with the pathogenesis of pSS [2,3], as were the conventional acquired immunity responses, including major histocompatibility class II-mediated antigen presentation [4]. Toll-like receptors (TLRs), especially TLRs 7–9, are important innate immune receptors that recognize a range of RNA and DNA molecules from viruses and self-antigens, and lead to the production of type I IFN via downstream molecules such as myeloid differentiation primary response gene 88 (MyD88), tumor necrosis factor receptor-associated factor 6 (TRAF6) and interferon regulatory factor 7 (IRF7) signaling [5]. The expressions of TLR-7 and TLR-9 were high in the peripheral blood mononuclear cells (PBMCs)

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PAPER

Complete renal response at 12 months after induction therapy is associated with renal relapse-free rate in lupus nephritis: a single-center, retrospective cohort study

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Background: Lupus nephritis (LN) is a major risk factor for overall morbidity and mortality in systemic lupus erythematosus (SLE). **Methods:** We retrospectively analyzed cases of proliferative and membranous LN patients who underwent a renal biopsy at our hospital in 1993–2016. We analyzed the association between complete renal response (CR) rates at 12 months after induction therapy and predictive factors for CR and their association with renal flares. **Results:** Of the 95 cases analyzed, we were able to track the therapeutic responses of 81 patients at 12 months after their induction therapy. The median follow-up duration after renal biopsy was 51 months (interquartile range: 16.5–154.5 months). The Cox proportional hazards model showed that, compared to not attaining CR at 12 months, the attainment of CR at 12 months was correlated with being free from renal flares. The multivariate logistic analysis revealed that the predictive factors for CR at 12 months were the anti-La/SSB antibodies (U/ml) (odds ratio (OR) 1.22, 95% confidence interval (CI) 1.01–1.63, $p=0.0220$), blood urea nitrogen (BUN) (OR 0.68, 95% CI 0.44–0.90, $p=0.00048$) and serum β2 microglobulin (MG) (OR 0.26, 95% CI 0.06–0.74, $p=0.00098$) levels. **Conclusions:** Among LN patients, being free from renal flares was associated with attaining CR at 12 months after induction therapy. Anti-La/SSB antibodies were a positive predictive factor, and BUN and serum β2MG levels were negative predictive factors of CR at 12 months. *Lupus* (2019) **0**, 1–9.

Key words: Anti-La/SSB antibodies; complete renal response; proliferative and membranous lupus nephritis; serum β2 microglobulin

Introduction

In patients with systemic lupus erythematosus (SLE), lupus nephritis (LN) is a common and serious complication that often requires aggressive immunosuppressive therapy.[1] LN remains a major determinant of morbidity and mortality, and approximately 5%–15% of patients with LN will progress to end-stage renal disease (ESRD) within 10 years after diagnosis despite expert care and access to contemporary therapy.[2–4] Renal flares are disadvantageous to the renal function of patients with severe LN, and the flares contribute to morbidity in patients with SLE.[5–7] The reported incidence of renal flares has varied with the populations studied, the distribution of histological classes of LN, the treatment administered and the definitions of renal flare. It has been reported that 27%–66% of LN patients experienced at least one renal flare during their follow-up period.[8]

There has been no simple test than can be used to predict renal outcomes and guide the treatment of patients with LN. The recommendations for LN management published by the European League

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PAPER

Factors predictive of long-term mortality in lupus nephritis: a multicenter retrospective study of a Japanese cohort

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Background: Lupus nephritis (LN) is a major determinant of mortality in systemic lupus erythematosus (SLE). Here we evaluated the association between complete renal response (CR) and mortality in LN. **Methods:** We retrospectively analyzed the cases of 172 of 201 patients with LN for whom data on the therapeutic response at 6 and 12 months after induction therapy were available. The patients underwent a renal biopsy at Nagasaki University Hospital and community hospitals in Nagasaki between the years 1990 and 2016. We determined the CR rates at 6 and 12 months after induction therapy initiation and evaluated the predictive factors for CR and their relationship with mortality. We performed univariate and multivariable competing risks regression analyses to determine the factors predictive of CR. The patients' survival data were analyzed by the Kaplan–Meier method with a log-rank test. **Results:** The median follow-up duration after renal biopsy was 120 months (interquartile range: 60.3–191.8 months). The 5-, 10-, 15- and 20-year survival rates of our cohort were 99.3, 94.6, 92.0 and 85.4%, respectively. During follow-up, nine patients (5.2%) died from cardiovascular events, infection, malignancy and other causes. The multivariate analysis revealed that the following factors were predictive of CR. At 6 months: male gender (odds ratio (OR) 0.23, 95% confidence interval (CI) 0.08–0.65, $p=0.0028$), proteinuria (g/gCr) (OR 0.83, 95% CI 0.71–0.97, $p=0.0098$) and index of activity (0–24) (OR 0.84, 95% CI 0.71–0.99, $p=0.0382$). At 12 months: male gender (OR 0.25, 95% CI 0.09–0.67, $p=0.0043$) and index of activity (0–24) (OR 0.82, 95% CI 0.69–0.98, $p=0.0236$). The Kaplan–Meier analysis showed that compared to not achieving CR at 12 months, achieving CR at 12 months was significantly correlated with the survival rate (OR 0.18, 95% CI 0.04–0.92, $p=0.0339$). **Conclusions:** Our results suggest that the survival rate of patients with LN is associated with the achievement of CR at 12 months after induction therapy, and that male gender and a higher index of activity (0–24) are the common predictive factors for failure to achieve CR at 6 and 12 months. *Lupus* (2019) **28**, 295–303.

Key words: Complete renal response; lupus nephritis; survival rate; systemic lupus erythematosus

Introduction

Systemic lupus erythematosus (SLE) is a complex autoimmune disorder with a broad spectrum of clinical and immunologic manifestations, among which lupus nephritis (LN) is the most common cause of morbidity and mortality.[1] Indeed, SLE patients with LN have 6–6.8-fold higher standardized mortality rates compared to those without

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Clinical Case Report

Medicine

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Sjögren's syndrome manifesting as clinicopathological features of TAFRO syndrome

A case report

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Abstract

Rationale: TAFRO syndrome is a newly proposed disorder that manifests as thrombocytopenia, anasarca, fever, reticulin myelofibrosis, renal dysfunction, and organomegaly. In this report, we describe the development of severe TAFRO syndrome-like systemic symptoms during the clinical course of juvenile-onset Sjögren's syndrome in a 32-year-old woman.

Patient concerns: The patient was admitted due to dyspnea, fever, polyarthralgia, and generalized edema. She had been diagnosed with Sjögren's syndrome at the age of 14 years, based on histopathological examination of a biopsy of the minor salivary glands and the development of Raynaud's phenomenon, with no follow-up treatment required. On admission, she presented with anemia, elevated C-reactive protein levels, anasarca, and hepato-splenomegaly. A bone marrow examination revealed increased megakaryocytes with reticulin fibrosis, and the histopathology of an axillary lymph node was consistent with mixed-type Castleman disease. Eventually, she developed thrombocytopenia.

Interventions: Her symptoms fulfilled all of the major and minor categories of the diagnostic criteria for TAFRO syndrome. However, considering her prior diagnosis, we assumed that the clinical presentation was consistent with an acute exacerbation of Sjögren's syndrome. Unlike typical cases of TAFRO syndrome, the administration of relatively low-dose prednisolone relieved her symptoms.

Lessons: Differentiation between TAFRO syndrome and exacerbation of an autoimmune disease is clinically important, although this can be challenging. Identification of specific biomarkers for TAFRO syndrome would be clinically beneficial.

Abbreviations: β2MG = β2-microgloburin, CRP = C-reactive protein, iMCD = idiopathic multicentric Castleman disease, IP-10 = interferon γ-induced protein 10 kDa, NAG = *N*-acetyl-β-D-glucosaminidase, SLE = systemic lupus erythematosus.

Keywords: Castleman disease, Sjögren's syndrome, TAFRO syndrome

1. Introduction

TAFRO syndrome is a newly proposed disorder that manifests as thrombocytopenia, anasarca (pleural effusion/ascites and systemic edema), fever, reticulin myelofibrosis, renal dysfunction, and organomegaly (hepatosplenomegaly and lymph node swelling).[1,2] In most cases, the onset of this syndrome is acute or subacute, and leads to rapid deterioration in health status. According to the diagnostic criteria that were proposed for TAFRO syndrome in 2015,[3] all 3 major categories, that is, anasarca (pleural effusion, ascites, and/or generalized edema), thrombocytopenia, and inflammatory signs/symptoms should be met; and at least 2 of the 4 minor categories, that is, Castleman disease-like lymph node histopathology, reticulin myelofibrosis or increased megakaryocytes in the bone marrow, organomegaly, and progressive renal insufficiency, should be met for diagnosis.[3] In addition, malignancies, autoimmune diseases, infectious diseases, POEMS syndrome, IgG4-related disease, hepatic cirrhosis, and thrombotic microangiopathies should be excluded. In fact, patients with autoimmune diseases, such as systemic lupus erythematosus (SLE) and vasculitis syndrome, sometimes show systemic inflammatory symptoms similar to those of TAFRO syndrome,[4] probably due to an overproduction of inflammatory cytokines. In this report, we describe the case of a patient who presented with severe TAFRO syndrome-like systemic symptoms, which developed during the clinical course of juvenile-onset Sjögren's syndrome, a common autoimmune disease.

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Role of serum autoantibodies in blood brain barrier damages in neuropsychiatric systemic lupus erythematosus

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Abstract

Objective

The present study was carried out to elucidate the roles of serum autoantibodies in the development of blood-brain barrier (BBB) damages in neuropsychiatric systemic lupus erythematosus (NPSLE).

Methods

Paired serum and CSF samples were obtained from 101 SLE patients when they presented active neuropsychiatric manifestations (69 patients with diffuse psychiatric/neuropsychological syndromes [diffuse NPSLE] and 32 patients with neurologic syndromes or peripheral neuropathy [focal NPSLE]). IgG anti-NR2 subunit of NMDA receptor (anti-NR2), anti-Sm, anti-ribosomal P and IgG anti-cardiolipin in sera and albumin in CSF and sera were measured by ELISA. Blood-brain barrier (BBB) function was evaluated by Q albumin (CSF/serum albumin quotient x 1,000).

Results

Q albumin was significantly higher in acute confusional state (ACS) than in non-ACS diffuse NPSLE (anxiety disorder, cognitive dysfunction, mood disorder and psychosis) or in focal NPSLE. Anti-Sm, but not anti-NR2, anti-P or anti-cardiolipin, was significantly elevated in ACS compared with the other 2 groups of NPSLE, although serum anti-NR2 was significantly higher in ACS than that in focal NPSLE. Multiple regression analysis confirmed the significant contribution of anti-Sm ($p=0.0040$), but not anti-NR2 ($p=0.5023$), anti-P ($p=0.2651$), or anti-cardiolipin ($p=0.6769$) in the elevation of Q albumin.

Conclusion

The data demonstrate that serum anti-Sm antibodies play a most important role in the disruption of BBB in NPSLE.

Key words

NPSLE, blood-brain barrier, autoantibodies, anti-Sm

LUPUS SCIENCE & MEDICINE

Elevation of serum anti-glucose-regulated protein 78 antibodies in neuropsychiatric systemic lupus erythematosus

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ABSTRACT

Objective Recent studies have demonstrated that autoantibodies directed against glucose-regulated protein 78 (GRP78) on endothelial cells promote blood–brain barrier (BBB) damages. The present study examined whether serum anti-GRP78 antibodies might be involved in the pathogenesis of neuropsychiatric SLE (NPSLE).

Methods Serum samples were obtained from 129 patients with SLE (58 patients with diffuse psychiatric/neuropsychological syndromes of NPSLE (diffuse NPSLE), 30 with neurological syndromes (focal NPSLE), 21 with lupus nephritis (LN), 20 without NPSLE or LN (SLE alone)), from 35 patients with non-SLE rheumatic diseases (non-SLE RD) and from 24 healthy controls (HC). Anti-GRP78 levels were measured with an ELISA, using recombinant GRP78 as antigens. Cerebrospinal fluid (CSF) samples were also obtained from 88 patients with NPSLE. The BBB function was evaluated by Q albumin ((CSF albumin/serum albumin)$\times 10^3$).

Results Serum anti-GRP78 levels were significantly elevated in SLE compared with non-SLE RD or HC. There were no significant differences in serum anti-GRP78 levels among NPSLE, LN and SLE alone. Of note, serum anti-GRP78 levels were significantly higher in acute confusional state (ACS) than in non-ACS diffuse NPSLE ($p=0.0001$) or in focal NPSLE ($p=0.0002$). Finally, serum anti-GRP78 levels were significantly correlated with Q albumin ($r=0.294$, $p=0.0054$) in NPSLE.

Conclusion These results indicate that anti-GRP78 antibodies are associated with the development of diffuse NPSLE, especially ACS. Thus, the data suggest that anti-GRP78 antibodies might contribute to the development of ACS through the damages of BBB.

INTRODUCTION

Neuropsychiatric SLE (NPSLE) is one of the recalcitrant complications of the disease, leading to substantial impairment of quality of life as well as disability.[1] Among a variety of manifestations in NPSLE, acute confusional state (ACS) in diffuse psychiatric/neuropsychological syndromes (diffuse NPSLE) is the most serious one, requiring extensive immunosuppressive therapy and sometimes resulting in poor prognosis.[1 2]

N-Methyl-D-aspartate (NMDA) receptors are one of the glutamate receptor families.[3] Recently, it has been disclosed that autoantibodies to NMDA receptor subunit NR2 (anti-NR2) play an important role in the development of brain damages in mouse.[4] More importantly, it was shown that such neuronal damage requires the influx of anti-NR2 into the central nervous system (CNS) through a breakdown of the blood–brain barrier (BBB).[5]

In human, it was also found that cerebrospinal fluid (CSF) anti-NR2, but not serum anti-NR2, were significantly higher in diffuse NPSLE than in focal NPSLE.[6] Furthermore, CSF anti-NR2 were shown to be elevated in patients with ACS compared with those in non-ACS diffuse NPSLE or in focal NPSLE.[7] More importantly, the elevation of CSF anti-NR2 in patients with ACS has been shown to result from the damage of BBB, but not from the increased intrathecal production thereof.[7] Thus, it has been demonstrated that BBB damages play a crucial role in the pathogenesis of diffuse NPSLE, especially ACS. However, the mechanism of the BBB breakdown in NPSLE remained unclear.

Neuromyelitis optica spectrum disorder (NMOSD) is a severe inflammatory autoimmune disorder of the CNS.[8] Previous studies discovered that serum IgG from patients with NMOSD contained autoantibodies specific for aquaporin-4 (anti-AQP4), the brain's main water channel protein, primarily expressed on CNS astrocytes.[9] Thus, detection of anti-AQP4 in sera from patients facilitates clinical diagnosis of NMOSD.[10] However, it remained unclear how anti-AQP4 penetrates BBB to access astrocytes.

Glucose-regulated protein 78 (GRP78) is a stress protein belonging to the Hsp70 multigene family.[11] Previous studies demonstrated that GRP78 is expressed on the surface of cell

Clinical Case Report

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Progression of immunoglobulin G4-related disease to systematic lupus erythematosus after gastric cancer surgery

A case report

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Abstract

Rationale: Immunoglobulin G4 related disease (IgG4-RD) rarely coexists with other autoimmune diseases, though we had a patient whose primary clinical problem was shifted from IgG4-RD to systemic lupus erythematosus (SLE) after gastrectomy. The present paper aimed to report pathological findings and clinical course of the patient.

Patient concerns: The patient was a male aged 74 years old with gastric cancer characterized by the following symptoms: Raynaud phenomenon, polyarthralgia, and swollen parotid glands on both sides. Before gastrectomy, laboratory examination results showed renal dysfunction, hypocomplementemia, antinuclear antibodies (ANAs) positivity, and elevated serum IgG and IgG4 levels.

Diagnosis: Based on postoperative renal biopsy showing severe plasma cell infiltration with tubulointerstitial fibrosclerosis, the patient was diagnosed with IgG4-RD. Despite significant improvement in renal function and reduction in parotid gland swelling during the postoperative follow-up period, after 7 months of the gastrectomy, anti-DNA antibody levels were increased and serositis was detected, which indicated the onset of SLE. IgG4-type ANA were also detected in the sera of the patient.

Interventions: Treatment by oral prednisolone at 30 mg/day was initiated.

Outcomes: Pericardial fluid, pleural effusions, and thickening of the gallbladder wall improved after 3 months of treatment according to computed tomography.

Lessons: This study presented a rare case of comorbidity, wherein the patient's primary problem progressed from IgG4-type ANA-positive IgG4-RD to SLE after excision of gastric cancer.

Abbreviations: ANAs = antinuclear antibodies, Cr = creatinine, CT = computed tomography, IgG4-RD = immunoglobulin G4-related disease, IgG4-RKD = immunoglobulin G4-related kidney disease, PSL = prednisolone, SLE = systemic lupus erythematosus.

Keywords: anti-nuclear antibody, IgG4-related disease, systemic lupus erythematosus

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Drs Arai, Hayashi, Saegusa, Ogata, Takahashi, Koide, Profs. Inaguma, Hasegawa, Yuzawa, and Mr Uto declare that they have no relevant financial interests.

Consent to publication: The patient provided written informed consent for this study.

There are no financial interests and there are no conflict of interest to declare.

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1. Introduction

Immunoglobulin G4-related disease (IgG4-RD) is a systemic condition in which IgG4-positive plasma cell infiltration and fibrosis cause organ swelling and the development of nodular and thickened lesions,[1] leading to a wide variety of clinical presentations. The diagnostic criteria for IgG4-RD, as proposed by the Japanese Ministry of Health, Labour and Welfare IgG4-RD Research Committee,[1] state that autoimmune diseases must be excluded. Generally, no disease-specific autoantibodies are detected in IgG4-RD, and therefore, the condition can easily be differentiated from systemic lupus erythematosus (SLE). Furthermore, in IgG4-RD, excessive plasma cell infiltration is detected and characteristics of sclerotic fibrosis are observed. Here, we report a male patient with gastric cancer in whom IgG4-RD progressed to SLE after gastrectomy.

2. Case report

2.1. Patient concerns

A 74-year-old male patient presented with 1-year history of illness, including Raynaud phenomenon and polyarthralgia. Preoperative laboratory examination of gastric cancer identified

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ORIGINAL ARTICLE

Early prediction for over two years efficacy of the first biologic agent for polyarticular juvenile idiopathic arthritis: A multi-institutional study in Japan

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ABSTRACT

Objective: To estimate target of treatment for long-term efficacy of the first biologic agent used to treat polyarticular juvenile idiopathic arthritis (pJIA).

Methods: A retrospective cohort of patients with pJIA treated at six medical institutions in Japan between 1 March 2005 and 31 October 2014 was identified. The patients were divided by 2-year treatment periods with the first biologic agent into continuous treatment group and switching group. Three markers were examined: matrix metalloproteinase-3 (MMP-3), erythrocyte sedimentation rate (ESR), and disease activity score (DAS) 28-ESR.

Results: Thirty-two pJIA patients (8 boys, 24 girls) from 43 recruited patients were included in this study. The treatment periods with the first biologic agent in continuous treatment group (24 patients, 75%) was 40 months (median, range 24–119) and switching group (8 patients; 25%) was 9.5 months (median, 6–18). Markers [odds ratio (95% confidence interval)] at 3 months were MMP-3 [1.02 (0.99–1.05), $p = .219$], ESR [1.00 (0.78–1.30), $p = .998$], and DAS28-ESR [13.9 (2.08–409.82), $p = .035$]. The cut-off point for DAS28-ESR at 3 months to distinguish the two groups was 2.49 (sensitivity, 87.5%; specificity, 87.5%).

Conclusion: DAS28-ESR of 2.49 at 3 months after initiating the first biologic agent can be a target of sustained treatment in pJIA patients.

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KEYWORDS
Biologic agents; DAS28-ESR; juvenile idiopathic arthritis; polyarticular type; treat to target

Introduction

Juvenile idiopathic arthritis (JIA) is a heterogeneous group of diseases characterized by arthritis of unknown origin, with onset before 16 years of age [1]. JIA is the most common rheumatologic condition of childhood and consists of seven subtypes, including rheumatoid factor (RF)-negative or RF-positive polyarticular types [2]. Patients with polyarticular JIA (pJIA) tend to experience a more refractory disease course than those who have fewer affected joints. Due to a prolonged course of active disease, patients with pJIA are at increased risk for joint damage, which results in poorer functional outcomes and a decreased quality of life [3]. The earlier the treatment is started, the more likely it is to achieve inactive disease by 6 months and clinical remission by 12 months [4]. To control radiologic progression in patients with rheumatoid arthritis (RA), there is a window of opportunity of at least 12–24 months after diagnosis within which aggressive therapy should be started [5]. Some studies have suggested that the European League Against Rheumatism response and disease activity score (DAS) 28 are predictive factors for the long-term effectiveness of treatment for patients with RA [6,7]. Takeuchi et al. reported that an early response to the biologic agent at week 12 as measured by DAS28-ESR changes predicts long-term probability of low disease activity [8]. To confirm the accuracy of DAS28-ESR, it is important to check the ESR because DAS28-ESR is not accurate when the ESR is very low (<2 mm/h) [9]. Matrix metalloproteinase-3 (MMP-3) level is one of the predictive factors for joint damage in patients with RA and JIA [10,11].

It is very important for disease activity to be controlled in patients with pJIA in the early phase of the disease and to switch biologic agents if the initial treatment is ineffective [12]. For the rheumatologists, it is easy to decide to switch the first biologic agent to the second one, when the first one is ineffective obviously, i.e. primary failure. However, it is difficult to switch the biologic agent when the agent was partially effective in early phase. Treat-to-target strategy for RA patients improves patient's outcome and helps physicians to change or adjust the treatment in a short period [13]. However, there have been few studies in patients with

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INFLAMMATORY MUSCLE DISEASE (I LUNDBERG, SECTION EDITOR)

Immune Checkpoint Inhibitor-Induced Myositis: a Case Report and Literature Review

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Abstract

Purpose of the Review We clarify clinical characteristics of patients with immune checkpoint inhibitor (ICI)-induced myositis.

Recent Findings In 13 of 15 cases with ICI-induced myositis, the type of malignancy was melanoma. Eight, 4, and 3 patients received anti-PD-1 alone, anti-CTLA4 alone, and a combination of those, respectively. The mean period to the onset of ICI-induced myositis from the initiation of ICI was 4 weeks. Myocarditis was a complication in five patients. Seven of the patients died. The causes of death were myocarditis in three patients, respiratory muscle paralysis in two patients, and cancer progression in two patients. In patients without myocarditis or respiratory muscle paralysis, the prognosis for myositis was favorable with normalization of the CK levels occurring upon the cessation of ICI and the administration of immunosuppressive agents.

Summary Myocarditis and respiratory muscle paralysis are the major causes of death as immune-related adverse events in patients with ICI-induced myositis.

Keywords Immune checkpoint inhibitor · Programed cell death-1 · Cytotoxic T lymphocyte antigen 4 · Autoreactive T cell · Myositis

Introduction

Polymyositis or dermatomyositis (PM/DM) is an idiopathic inflammatory myopathy (IIMs) that is caused by exaggerated activity of the autoimmune system. Myositis-specific autoantibodies (MSAs) are found in approximately 80% of patients with PM/DM [1]. PM/DM is also complicated with extramuscular manifestations such as interstitial lung disease (ILD), myocarditis, and arthritis. Cancer occurs more frequently in patients with PM/DM than in the general population [2]. Cancer-associated myositis (CAM) has been considered to be a paraneoplastic syndrome, and the anti-tumor immune response is involved in the development of myositis in CAM [3].

Recently, immune checkpoint inhibitors (ICIs) that target programmed cell death-1 (PD-1), such as nivolumab, or target cytotoxic T lymphocyte-associated protein 4 (CTLA4), such as ipilimumab, have improved the survival of patients with advanced malignancies, such as melanoma and non-small cell lung cancer [4, 5]. ICIs have the ability to potentiate T cell cytotoxicity against cancer cells [6]. Anti-PD-1 monoclonal antibodies selectively block the interaction between the PD-1 on T cells and the PD-ligand 1 (PD-L1) on the surface of the cancer cells in the tumor microenvironment. The blockade of PD-1-PD-L1 engagement restores T cell activation and proliferation and consequently enhances the anti-tumor immune response by the T cells. In contrast, CTLA4 is expressed transiently on activated T cells and usually serves to bind to CD80/86 on antigen-presenting cells (APCs) with greater affinity and avidity than CD28, which transmits a stimulatory signal to T cells. Thus, CTLA4 enables the outcompeting of CD28 for the binding of CD80/86 and subsequently inhibits T cell priming and activation. CTLA4 is also expressed constitutively on Foxp3$^+$ regulatory CD4$^+$ T cells and is involved in their inhibitory function. The blockade of CTLA4 accelerates the activation of T cells via CD28-CD80/86 signaling and, more directly, causes the inactivation and/or depletion of the regulatory T cells, which

This article is part of the Topical Collection on *Inflammatory Muscle Disease*

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ORIGINAL ARTICLE

Improved quantification of a commercial enzyme-linked immunosorbent assay kit for measuring anti-MDA5 antibody

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ABSTRACT

Objectives: To compare the quantitative performance for measuring anti-MDA5 antibody titer of two enzyme-linked immunosorbent assay (ELISA) systems: an in-house ELISA and the commercial MESACUP™ anti-MDA5 test.

Methods: Anti-MDA5 antibody titer was measured in sera from 70 patients with dermatomyositis using an in-house ELISA and the MESACUP™ anti-MDA5 test side-by-side. For the commercial ELISA kit, serum samples diluted 1:101 were used according to the manufacturer's protocol, but serial dilutions of sera were also examined to identify the optimal serum dilution for quantification.

Results: The anti-MDA5 antibody titers measured by the in-house and commercial ELISAs were positively correlated with each other ($r = 0.53$, $p = .0001$), but the antibody titer measured by the commercial ELISA was less sensitive to change after medical treatment, and 37 (80%) of 46 anti-MDA5-positive sera had antibody titer exceeding the quantification range specified by the manufacturer (≥150 index). Experiments using diluted serum samples revealed that diluting the sera 1:5050 improved the quantitative performance of the MESACUP™ anti-MDA5 test, including a better correlation with the in-house ELISA results and an increased sensitivity to change.

Conclusion: We improved the ability of the commercial ELISA kit to quantify anti-MDA5 antibody titer by altering its protocol.

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KEYWORDS
anti-MDA5 antibody; biomarker; dermatomyositis; enzyme-linked immunosorbent assay; interstitial lung disease

Introduction

Dermatomyositis (DM) is an idiopathic inflammatory myopathy, characterized by myositis and skin rash, such as heliotrope rash and Gottron's papules/sign. Patients with DM often also suffer from extra-muscular manifestations, including interstitial lung disease (ILD), myocarditis, arthritis and concomitant malignancy. In particular, ILD is a major cause of death in DM patients; however, the clinical course, treatment responses, and prognosis of this disease are highly variable [1,2]. Myositis-specific autoantibodies are useful biomarkers for predicting clinical phenotypes, including the treatment responses and survival of patients with idiopathic inflammatory myopathies [3]. Of the well-characterized autoantibodies, anti-aminoacyl-transfer RNA synthetase and anti-melanoma differentiation-associated gene 5 (MDA5) antibodies are known to be strongly correlated with ILD [1–3].

Sato and coworkers discovered an autoantibody in patients with clinically amyopathic DM (CADM) that was reactive with a 140 kD protein in a protein immunoprecipitation (IP) assay, which they called the anti-CADM-140 antibody [4]. Later, the target antigen recognized by the anti-CADM-140 antibody was identified as a cytoplasmic protein MDA5, which is involved in the host immune defense against double-stranded RNA viruses [5]. The presence of anti-MDA5 antibody is strongly associated with CADM and with rapidly progressive ILD (RP-ILD) [3–5]. Studies showed that approximately one-third of DM patients with anti-MDA5 antibody died within 6 months after the diagnosis, despite intensive treatment [6,7]. The association between anti-MDA5 antibody and RP-ILD has been replicated in many studies in Japan and other countries, including China and the United States [8,9]. Therefore, the anti-MDA5 antibody is presently considered the best biomarker for predicting the development of RP-ILD, which has a poor prognosis, in patients with DM [3]. To make anti-MDA5 antibody measurements available for routine clinical practice, we previously developed an 'in-house' enzyme-linked immunosorbent assay (ELISA) system [5]. The sensitivity and specificity of this ELISA system compared with the 'gold-standard' IP assay are 85% and 100%, respectively [5]. Since one advantage of an ELISA over an IP assay is its ability to provide quantitative results, several studies evaluating the clinical significance of anti-MDA5 antibody titer have been published using the in-house ELISA [6,10–12]. These studies showed that higher anti-MDA5 antibody titer before treatment can predict a poor treatment response and poor survival [10,11] and that a rapid decline in anti-MDA5 antibody titer after treatment is associated with a favorable prognosis [6,10,12]. Currently, a commercial kit applying the same principle as our in-house ELISA (MESACUP™ anti-MDA5 test; Medical and Biological Laboratories, Nagoya,

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Original article

Low positive titer of anti-melanoma differentiation-associated gene 5 antibody is not associated with a poor long-term outcome of interstitial lung disease in patients with dermatomyositis

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ABSTRACT

Background: Anti-melanoma differentiation-associated gene 5 antibody (anti-MDA5-Ab) is associated with fatal rapidly progressive interstitial lung disease (RP-ILD) in patients with dermatomyositis (DM). We attempted to clarify whether anti-MDA5-Ab is associated with long-term outcomes in patients with DM-ILD.

Methods: Thirty-six patients with DM-ILD were retrospectively analyzed for their serum anti-MDA5-Ab by using an enzyme-linked immunosorbent assay. We analyzed the association between clinical parameters, including the serum levels of anti-MDA5-Ab and ferritin.

Abbreviations: ARS-Ab, aminoacyl-transfer RNA synthetase antibody; AUC, area under the curve; CADM, clinically amyopathic dermatomyositis; CI, confidence interval; CRP, C-reactive protein; $\%D_{LCO}$, diffusing capacity of the lungs for carbon monoxide, predicted; DM-ILD, dermatomyositis-interstitial lung disease; ELISA, enzyme-linked immunosorbent assay; %FVC, forced vital capacity, predicted; HRCT, high-resolution computed tomography; IP, immunoprecipitation; KL-6, Krebs von den Lungen 6; LDH, lactate dehydrogenase; MDA5-Ab, melanoma differentiation-associated gene 5 antibody; NPV, negative predictive value; NSIP, non-specific interstitial pneumonia; OP, organizing pneumonia; OS, overall survival; PPV, positive predictive value; ROC, receiver operating characteristic; RP-ILD, rapidly progressive interstitial lung disease; RR, relative risk; UIP, usual interstitial pneumonia

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Anti-Aminoacyl tRNA Synthetases Antibodies in Japanese Patients with Interstitial Lung Disease

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Abstract

Objectives: In the present study, we have sought to establish the clinical and immunological characteristics of Japanese patients with interstitial lung disease (ILD). **Methods:** Serum samples from 35 patients of ILD were screened for autoantibodies using RNA and protein immunoprecipitation assays. Patients with or without serum antibodies to aminoacyl tRNA synthetases (ARS) were assessed clinically and compared. **Results:** Sera from 12 of 35 (34%) patients with ILD (mean age at onset = 49.7 yrs; range 27 - 65 yrs) were found to contain anti-ARS antibodies (anti-EJ: 3 patients; anti-OJ: 2 patients; anti-PL-12: 3 patients; anti-KS: 4 patients). Nine of the 12 (75%) were female. Six (50%) had Raynaud's phenomenon, 5 (42%) had arthralgia/arthritis and four (33%) had rheumatoid factor. Lung biopsy specimens of 8 patients with anti-ARS antibodies were examined histologically in detail. The following was determined: Two patients had usual interstitial pneumonia; 3 had non-specific interstitial pneumonia; one had organizing pneumonia; one had lymphocyte interstitial pneumonia and the remaining patient had desquamative interstitial pneumonia. Age at disease onset was significantly lower and the frequency of Raynaud's phenomenon was significantly greater in these patients compared to anti-ARS-negative patients (49.7 yrs vs. 62.6 yrs, $p = 0.004$; 50% vs. 4%, $p = 0.003$, respectively). **Conclusions:** These results indicate that the presence of anti-ARS autoantibodies correlates with ILD without definite diagnosis of connective tissue diseases as well as polymyositis/dermatomyositis (PM/DM) with ILD in Japanese patients.

Keywords

Interstitial Lung Disease (ILD), Anti-Aminoacyl tRNA Synthetases (ARS) Antibodies, Autoantibody, Interstitial Pneumonia with Autoimmune

Prognosis of dysphagia in dermatomyositis

Sirs,

Dysphagia is relatively common complication in dermatomyositis (DM), with 18–58% of patients reported to have this manifestation (1-4). Although risk factors of dysphagia in DM and polymyositis are reported to be age, male gender, anti-TIF1-γ antibody, muscle weakness, and malignancy (5, 6), there is very little published data on the prevalence, treatment outcomes and prognosis of dysphagia in patients with DM.

In this research, which features a cohort of patients with DM, our aims were to (i) reveal the appropriate treatment types and intervention timing for dysphagia recovery, and (ii) identify risk factors for non-recovery from dysphagia.

Serum samples were obtained from adult Japanese patients with DM followed at each medical centre from 2003 to 2016. Detailed medical histories of every patient were retrospectively gathered by unified questionnaire. Eighty-five patients fulfilled the "definite to probable" criterion of Bohan and Peter (7). Autoantibody detection and statistical methods were the same as in our previous study (8). This study was approved by the Ethics Committee of the Nagoya University Graduate School of Medicine and by the individual participating centres.

Of 85 DM patients, 57 (67%) were female. The mean age at DM diagnosis was 61.0±13.9 years. 30 patients were considered to have dysphagia as determined by subjective symptoms judged by their physician's evaluation (10 of 30), examination by otolaryngologists (14 of 30), or examination by speech therapists (5 of 30). The clinical and laboratory characteristics of the 85 DM patients with and without dysphagia are detailed in Supplementary Table S1.

Of the 30 DM patients with dysphagia, we analysed 29 patients' data, excluding one patient with insufficient data (Table I). Sixteen of the 29 patients showed recovery with dysphagia. Survival rates showed strong association with dysphagia recovery (p=0.000003), and high initial dose of prednisolone (PSL) seemed to influence the recovery rate (p=0.045). There was a significant negative correlation between cancer and dysphagia recovery (p=0.025). Other factors, such as age, sex, periods from onset to hospital visit or treatment, intravenous immunoglobulin (IVIG) or other immunosuppressive therapy use did not significantly correlate with dysphagia recovery.

Of the 29 dysphagia-complicated DM patients, 13 patients (33%) died during the follow-up period: 5 from cancer complications (38%), 3 from aspiration pneumonia, and 5 from various other causes. The mean follow-up duration was 15.1±15.5 months. Kaplan-Meier survival curves show the survival probability for patients with or without dysphagia recovery (Supplementary Fig. S1). The mortality rate is significantly higher in patients without recovery from dysphagia than in patients with recovery from dysphagia (p<0.000001).

We had predicted that treatment delay might affect dysphagia recovery, but no such relation was found (Table I). Since the initial dose of PSL was significantly higher in the dysphagia recovery group, early intensive treatment may be effective for recovery. However, in the unrecovered group, 76.9% of patients (10 of 13) had cancer, and this factor may lead clinicians to choose mild immunosuppressive treatments. Medications other than oral PSL, including IVIG, were not significantly related to dysphagia recovery. All but 1 of the 15 surviving patients (93.7%) showed dysphagia recovery. These results suggest that dysphagia in DM might often be reversible without any specific medication.

A major limitation in our study is the lack of standardised dysphagia evaluation methods. Given this limitation, we were unable to compare and discuss the extent of dysphagia recovery between cases. Another limitation was that we did not collect the dates on which the clinician discovered the dysphagia recovery. Future prospective studies on dysphagia recovery and time course are necessary.

Table I. Association between recovery from dysphagia and clinical/laboratory features.

	Improvement of dysphagia		p-value
	(+) n=16 (%)	(-) n=13 (%)	
Age	69.1 ± 7.3	72.5 ± 7.7	0.50
Sex (female)	7 (44)	6 (46)	1
Period (months)			
DM onset to dysphagia*	2.4 ± 2.5	1.6 ± 0.9	0.11
Visit to dysphagia**	0.6 ± 1.1	1.4 ± 2.6	0.77
Treatment to dysphagia***	-0.2 ± 0.9	0.8 ± 2.4	0.39
Visits up to death****	13	5. ± 5.2	0.39
Survival rate	15 (94)	1 (8)	<0.000001
Cancer	5 (31)	10 (76)	0.025
Anti-TIF1-γ	6 (38)	10 (76)	0.06
CK max	3010 ± 2721	2854 ± 3063	0.91
Initial dose of PSL (mg/day)	44.4 ± 19.2	29.2 ± 18.1	0.045
IVIG	3 (18)	0 (0)	0.25
Other medications*****	8 (50)	4 (30)	0.45

*DM onset to dysphagia: period (months) from DM onset to dysphagia onset, **Visit to dysphagia: period (months) from first hospital visit to dysphagia onset, ***Treatment to dysphagia: period (months) from treatment to dysphagia onset, ****Visits up to death: period (months) from first hospital visit up to death. *****Other medications: intravenous steroid pulse therapy, azathioprine, tacrolimus, methotrexate other than oral PSL and IVIG.
CK: creatine kinase; IVIG: Intravenous immunoglobulin; PSL: prednisolone

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Strong correlation between cancer progression and anti-transcription intermediary factor 1γ antibodies in dermatomyositis patients

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Abstract

Objective

Transcription intermediary factor 1γ (TIF1γ) protein is known as a tumour suppressor that promotes cellular differentiation. Autoantibodies to TIF1γ have a strong clinical association with cancers associated with dermatomyositis (DM). This study aims to identify the clinical characteristics of cancers in anti-TIF1γ antibody-positive adult patients with DM.

Methods

This retrospective analysis covered 160 adult DM patients who visited Nagoya University Hospital or collaborating medical centres between 2003 and 2016. Anti-TIF1γ antibody and other myositis-specific autoantibodies were detected by ELISA. Based on a review of medical charts, the cancers were staged according to the TNM Classification of Malignant Tumours of the Union for International Cancer Control and were divided into the two groups of "advanced" or "non-advanced" according to the stage classification.

Results

Forty-one of the 160 (26%) patients had cancer. The incidence was significantly higher in the anti-TIF1γ-positive patients than in the anti-TIF1γ-negative patients (23/34=68% vs. 18/126=14%, $p<1x10^{-6}$). Anti-TIF1γ-positive patients with cancer were found more frequently in the "advanced" group than in the "non-advanced" group (21/23=91% vs. 9/18=50%, $p<0.0046$). The intervals between DM diagnosis and cancer diagnosis were significantly shorter in the anti-TIF1γ-positive patients than in the anti-TIF1γ-negative patients ($p=0.047$).

Conclusion

Not only did anti-TIF1γ antibodies correlate strongly with malignancy in DM patients, but cancers were also significantly more advanced in anti-TIF1γ-positive DM patients than in anti-TIF1γ-negative patients. Cancers in such cases were very frequently found close to the time of the DM diagnosis.

Key words

advanced cancer, anti-TIF1γ antibody, cancer-associated dermatomyositis, dermatomyositis

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CORRESPONDENCE

Anti-transcription intermediary factor 1γ antibody titer correlates with clinical symptoms in a patient with recurrent dermatomyositis associated with ovarian cancer

Dear Editor,

A 42-year-old Japanese woman presented with erythema on the face and scattered erythematous lesions on the trunk. Histological findings taken from an erythema on the upper arm showed vacuolar change in basal keratinocytes and infiltration of lymphocytes around vessels in the upper dermis. The patient complained of muscle weakness in her upper arm. Serum examination revealed elevated levels of creatine phosphokinase (CPK: 500 IU/L). Anti-nuclear and anti-Jo1 antibodies were negative. She was diagnosed with dermatomyositis (DM). While screening the entire body for malignant growth, breast cancer (medullary carcinoma) was detected. The breast

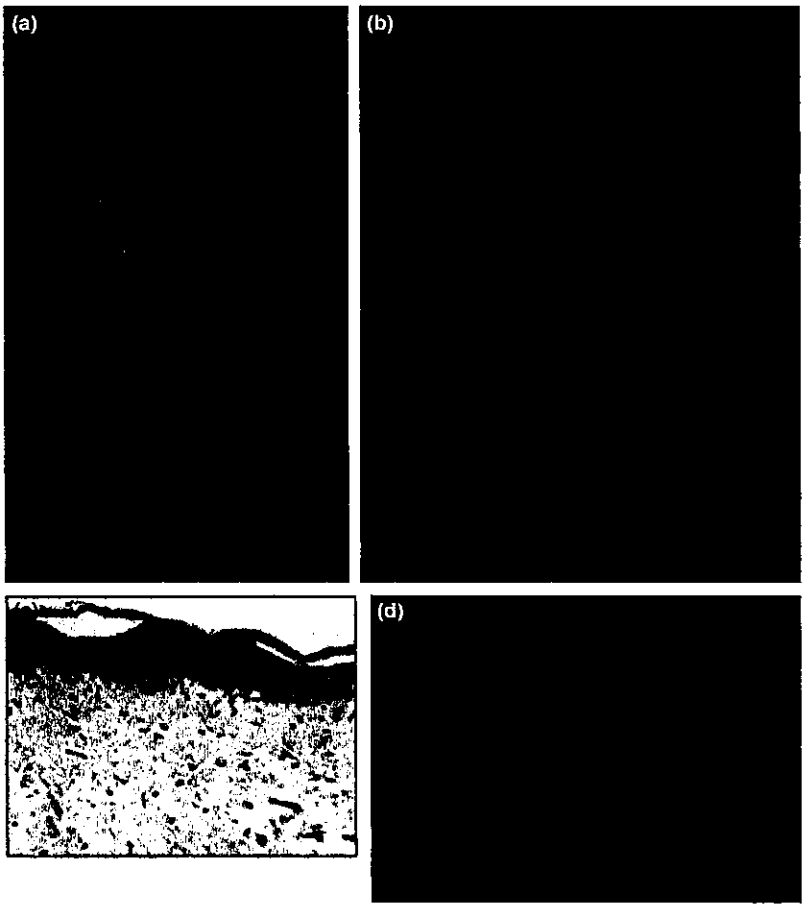

Fig. 1 The patient's clinical presentation. (a) Facial erythema and (b) scattered erythematous lesions on the trunk can be seen. (c) Histopathological findings reveal vacuolar degeneration of basal keratinocytes (Hematoxylin and eosin staining ×200). (d) ^{18}F-fluorodeoxyglucose positron emission tomography computed tomography (FDG-PET-CT) shows abnormal FDG accumulation in the left ovary.

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Differential clinical features of patients with clinically amyopathic dermatomyositis who have circulating anti-MDA5 autoantibodies with or without myositis-associated autoantibodies

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ABSTRACT

Background: Anti-melanoma differentiation-associated gene 5 (MDA5) autoantibodies have been identified as myositis-specific autoantibodies that are often associated with clinically amyopathic dermatomyositis (CADM) and a poor prognosis due to rapidly progressive interstitial lung disease (RP-ILD) in East Asian patients. Besides anti-MDA5 autoantibodies, patients with CADM may have myositis-associated autoantibodies (MAAs), which characterize other connective tissue diseases such as rheumatoid arthritis and Sjögren's syndrome. However, the clinical significance of the coexistence of anti-MDA5 autoantibodies and MAAs in patients with CADM remains unclear.

Methods: We retrospectively analyzed 24 patients with CADM who had anti-MDA5 autoantibodies. Their clinical phenotypes including laboratory test results, high-resolution lung computed tomography data, response to therapy, and prognosis were compared between those who were positive and negative for MAAs, such as antinuclear antibody (ANA), anti-cyclic citrullinated peptide (CCP), anti-SSA, and anti-SSB antibodies.

Results: Among 24 patients, 9 (37.5%) additionally had at least one of the MAAs examined in this study: 1 patient was positive for ANA, 5 for anti-CCP, 5 for either anti-SSA or anti-SSB, 1 for anti-cardiolipin, and 1 for anti-Scl-70. Although all anti-MDA5-positive patients with CADM had ILD, the MAA-positive patients showed a lower risk of developing RP-ILD ($p = 0.03$), a more favorable response to combination therapy of corticosteroids and immunosuppressive agents, and a lower mortality rate than patients with no MAAs ($p = 0.03$).

Conclusions: Our data suggest that anti-MDA5-positive patients with CADM who also have MAAs have a better prognosis than those without MAAs; thus, anti-MDA5 autoantibodies by themselves may not be strong predictors of worse clinical outcomes in patients with CADM. Coexistent MAAs could be biomarkers for a favorable prognosis in anti-MDA5-positive patients with CADM.

1. Introduction

Dermatomyositis (DM), defined by hallmark cutaneous manifestations and skeletal muscle weakness resulting from a characteristic pattern of autoimmune myositis, has a heterogeneous clinical presentation. Myositis-specific autoantibodies are found in approximately 60% of patients with myositis and are strongly associated with distinct clinical phenotypes [1]. For example, autoantibodies to histidyl transfer RNA synthetase (Jo-1) or aminoacyl tRNA synthetase are associated with a clinical phenotype termed "antisynthetase syndrome," which consists of myopathy, fever, interstitial lung disease (ILD), Raynaud's phenomenon, nonerosive arthritis, and mechanic's hands [2]. Anti-TIF1-γ-positive patients with DM have an increased risk for an associated internal malignancy. Further, anti-Mi-2 autoantibodies are

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Japan College of Rheumatology MODERN RHEUMATOLOGY

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REVIEW ARTICLE

OPEN ACCESS Check for updates

Japan College of Rheumatology guideline for the use of methotrexate in patients with rheumatoid arthritis

Hideto Kameda[a], Takao Fujii[b], Ayako Nakajima[c], Ryuji Koike[d], Akira Sagawa[e], Katsuaki Kanbe[f], Tetsuya Tomita[g], Masayoshi Harigai[h] and Yasuo Suzuki[i]: Japan College of Rheumatology subcommittee on the guideline for the use of methotrexate in patients with rheumatoid arthritis

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ABSTRACT

Methotrexate (MTX), the anchor drug in the current treatment strategy for rheumatoid arthritis (RA), was first approved for treatment of RA in Japan in 1999 at the recommended dose of 6–8 mg/week; it was approved as first-line drug with the maximum dose of 16 mg/week in February 2011. However, more than half of Japanese patients with RA are unable to tolerate a dose of 16 mg/week of MTX. Moreover, some serious adverse events during the treatment with MTX, such as pneumocystis pneumonia (PCP) and lymphoproliferative disorders (LPD) have been observed much more frequently in Japan than in other countries. Therefore, this article, an abridged English translation summarizing the 2016 update of the Japan College of Rheumatology (JCR) guideline for the use of MTX in Japanese patients with RA, is not intended to be valid for global use; however, it is helpful for the Japanese community of rheumatology and its understanding might be useful to the global community of rheumatology.

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Guideline; Japan College of Rheumatology; methotrexate; rheumatoid arthritis

Introduction

Methotrexate (MTX) is the anchor drug in current treatment strategy for rheumatoid arthritis (RA) [1,2]. In Japan, MTX was first approved for refractory RA in adults in 1999 at the recommended dose of 6–8 mg/week. In February 2011, MTX was approved for adult RA with the maximum dose up to 16 mg/week, and as first-line conventional synthetic disease-modifying anti-rheumatic drug (csDMARD). The Japan College of Rheumatology (JCR) subcommittee on the guideline for the use of MTX in patients with RA published the first Japanese version of the guideline in 2011 and updated it in 2016. Since the adverse events during the treatment with MTX in Japan are rather serious and unique, such as pneumocystis pneumonia (PCP) and lymphoproliferative disorders (LPD), and its maximum dose is limited, it is important to publish the guideline in English for better understanding of the use of MTX for RA in Japan. This article is an abridged English translation summarizing the 2016 update of the JCR guideline for the use of MTX in Japanese patients with RA with a minimal update, and it is not intended to be valid for global use.

Indications, contraindications, and precautions

The paradigm of 'Treat to Target (T2T)' [1], in which long-term health-related quality of life is maximized by estimating disease activity and adjusting the therapy accordingly until reaching the target, has been widely accepted, and the first-line use of MTX as the anchor drug for the treatment of RA has been recommended [2]. The evidences from clinical trials on Japanese patients with poorly prognostic RA treated with first-line MTX therapy have been accumulated [3,4]. Therefore, MTX should be considered as the first choice among csDMARDs to maintain a balance between risk factors associated with MTX treatment, such as advanced age and comorbidities and benefits obtained by prompt control of disease activity (Table 1). In addition, MTX should be used as far as possible in patients who are likely to develop a functional disorder or its progression despite optimal dose of other csDMARDs for 2–3 months.

Contraindications for MTX include severe hematological and lymphatic disorders, namely, myelodysplasia, aplastic anemia, pure red cell aplasia, LPD within recent 5 years, and severe leukopenia or thrombocytopenia (white blood

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Transforming Growth Factor-β and Interleukin-10 Synergistically Regulate Humoral Immunity *via* Modulating Metabolic Signals

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Inhibitory cytokines, such as transforming growth factor-β (TGF-β) and interleukin-10 (IL-10), are humoral factors involved in the suppressive function of regulatory T cells and play critical roles in maintaining immune homeostasis. However, TGF-β and IL-10 also have pleiotropic effects and induce humoral immune responses depending on conditions, and thus their therapeutic application to autoimmune diseases remains limited. Here, we show that a combination of TGF-β and IL-10, but not single cytokine, is required to suppress B cell activation induced by toll-like receptor (TLR) stimulation. In *in vivo* analyses, the simultaneous presence of TGF-β and IL-10 effectively suppressed TLR-mediated antigen-specific immune responses and ameliorated pathologies in imiquimod (TLR7 agonist)-induced lupus model and lupus-prone MRL/*lpr* mice. Intriguingly, TGF-β and IL-10 synergistically modulated transcriptional programs and suppressed cellular energetics of both glycolysis and oxidative phosphorylation *via* inhibition of the mammalian target of rapamycin complex 1 (mTORC1)/S6 kinase 1 (S6K1) pathway in TLR-stimulated B cells. On the other hand, enhancement of mTOR signaling and mitochondrial biosynthesis in TLR-stimulated B cells counteracted the synergistic inhibitory effects. The inhibitory cytokine synergy of TGF-β and IL-10 *via* suppression of energy metabolism was also observed in human TLR-stimulated B cells. There is increasing evidence supporting the importance of adequate metabolic signals in various immune cells to exert their immune function. In this study, we have shown that a previously unrecognized synergy of inhibitory cytokines regulates systemic humoral immune responses *via* modulating immunometabolism in B cells. Our findings indicate that inhibition of B cell metabolism mediated by two synergistic cytokines contributes to the induction of immune tolerance and could be a new therapeutic strategy for autoimmune diseases such as systemic lupus erythematosus.

Keywords: humoral immunity, systemic lupus erythematosus, cytokine synergy, transforming growth factor-β, interleukin-10, B cells, immunometabolism

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LETTERS

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Reduction of CD83 expression on B cells and the genetic basis for rheumatoid arthritis: comment on the article by Thalayasingam et al

To the Editor:

In a recent article in *Arthritis & Rheumatology*, Thalayasingam et al (1) reported that the 6p23 locus, associated with rheumatoid arthritis (RA), has a B cell–specific expression quantitative trait locus (eQTL) effect on CD83. The B cell–specific eQTL effect at this locus is robust and has also been reported by others (2), and it presumably contributes to the pathogenesis of RA by decreasing the expression of CD83 on B cells. We sought to determine the basis for the B cell–specific eQTL effect and to further elucidate the mechanism by which it contributes to RA pathogenesis.

Publicly available epigenomic data showed that rs12529514, the lead single-nucleotide polymorphism (SNP) from RA genome-wide association studies (3), resides near a DNase hypersensitivity site in B cells (4) (Figure 1A). Furthermore, NF-κB induces the expression of CD83 (5), and rs74405933, which is in tight linkage disequilibrium with rs12529514 ($r^2 = 1.00$ in Asians), alters an NF-κB binding motif. Thus, the B cell–specific eQTL effect may be due to a change in the binding of NF-κB to this locus in B cells.

CD83 regulates the development of murine B cells (5). We therefore hypothesized that CD83 expression might influence the development of human B cells, and we examined the relationship between this haplotype and peripheral blood B cells in healthy subjects from our data set (2,6). Individuals with the RA risk SNP had an increased frequency of CD27−IgD− double-negative B cells (Figure 1B), a subset that is increased in the peripheral blood of RA patients and thought to be pathogenic (6–8). Thus, the rs12529514 risk haplotype, by reducing the expression of CD83 on B cells, may induce changes in B cell differentiation and skew the B cell compartment toward a phenotype similar to that observed in RA.

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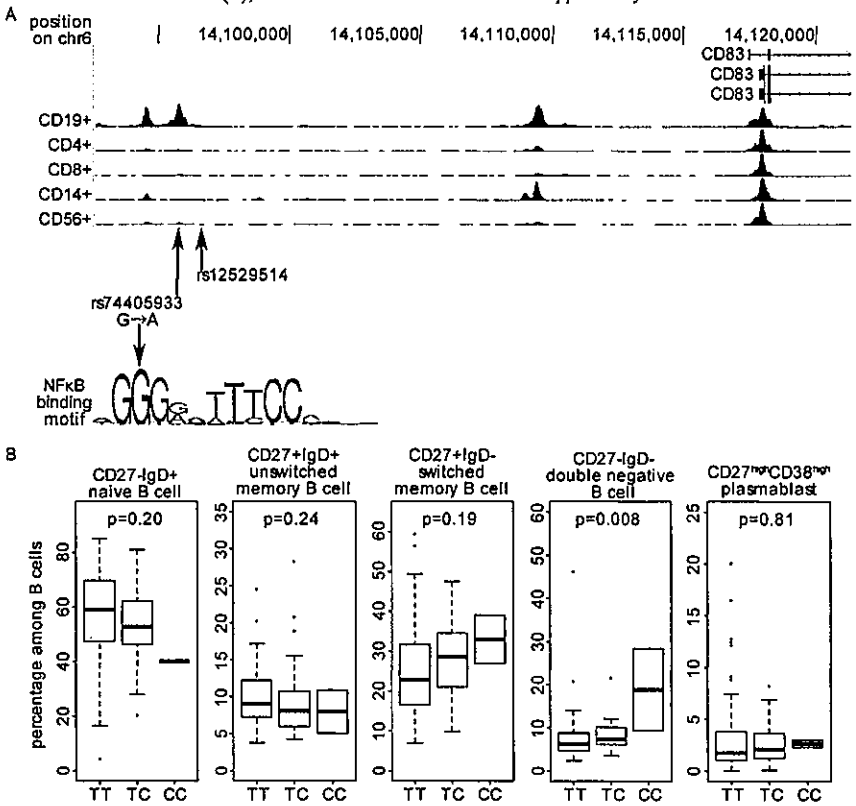

Figure 1. The rs12529514 rheumatoid arthritis risk haplotype and B cells. **A,** Data from the Roadmap Epigenomics Project (4), indicating that rs12529514 resides near a DNase hypersensitivity site in B cells and alters an NF-κB binding site close by. **B,** Flow cytometric analysis of peripheral blood from 106 healthy donors (6). Plots indicate the frequencies of B cell subsets by rs12529514 genotype. Cell subset frequency was normalized by inverse normal transformation, and linear regression was used to assess the effect of rs12529514 genotype on cell subset frequency. Data are presented as box plots, where the boxes represent the interquartile range, the lines within the boxes represent the median, and the lines outside the boxes represent values within 1.5 times the interquartile range. Circles indicate outliers.

HLA-DRB1 Shared Epitope Alleles and Disease Activity Are Correlated with Reduced T Cell Receptor Repertoire Diversity in CD4+ T Cells in Rheumatoid Arthritis

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ABSTRACT. ***Objective.*** Shared epitope (SE) alleles are the most significant genetic susceptibility locus in rheumatoid arthritis (RA); however, their target populations in CD4+ T cells are not well elucidated. We analyzed the association between SE alleles and the T cell receptor (TCR) repertoire diversity of naive and memory CD4+ T cells using next-generation sequencing (NGS).

Methods. The TCR beta chains in naive and memory CD4+ T cells from the peripheral blood of 22 patients with RA and 18 age- and sex-matched healthy donors (HD) were analyzed by NGS. The Renyi entropy was used to evaluate TCR repertoire diversity and its correlations with SE alleles and other variables were examined. Serum cytokine levels were measured by multiplex ELISA.

Results. The TCR repertoire diversity in memory CD4+ T cells was reduced in SE allele-positive patients with RA compared with HD, and showed a significant negative correlation with the SE allele dosage in RA. The TCR repertoire diversity of naive and memory T cells was also negatively correlated with disease activity, and the SE allele dosage and disease activity were independently associated with reduced TCR repertoire diversity. TCR repertoire diversity showed a significant positive correlation with the serum interleukin 2 levels.

Conclusion. SE alleles and disease activity were negatively correlated with the TCR repertoire diversity of CD4+ T cells in RA. Considering the pivotal role of CD4+ T cells in RA, restoring the altered TCR repertoire diversity will provide a potential RA therapeutic target. (First Release April 15 2018; J Rheumatol 2018;45:905–14; doi:10.3899/jrheum.170909)

Key Indexing Terms:
RHEUMATOID ARTHRITIS T LYMPHOCYTES HLA ANTIGENS
CYTOKINES NEXT-GENERATION SEQUENCING

Rheumatoid arthritis (RA) is characterized by chronic synovitis and joint deformity, and the pathogenesis of RA is based on genetic risks and environmental factors[1]. HLA-DRB1 risk alleles are the most significant genetic susceptibility locus in RA, and these alleles share consensus sequences in the third hypervariable region of the HLA-DRB1 chain, p70-74 (shared epitope; SE)[1,2]. Structural analysis provided the molecular basis of the SE hypothesis,

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SCIENTIFIC REPORTS

OPEN

Egr2-independent, Klf1-mediated induction of PD-L1 in CD4$^+$T cells

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Programmed death ligand 1 (PD-L1)-mediated induction of immune tolerance has been vigorously investigated in autoimmunity and anti-tumor immunity. However, details of the mechanism by which PD-L1 is induced in CD4$^+$T cells are unknown. Here, we revealed the potential function of Klf1 and Egr2-mediated induction of PD-L1 in CD4$^+$T cells. We focused on the molecules specifically expressed in CD4$^+$CD25$^-$LAG3$^+$ regulatory T cells (LAG3$^+$ Tregs) highly express of PD-L1 and transcription factor Egr2. Although ectopic expression of Egr2 induced PD-L1, a deficiency of Egr2 did not affect its expression, indicating the involvement of another PD-L1 induction mechanism. Comprehensive gene expression analysis of LAG3$^+$Tregs and *in silico* binding predictions revealed that Krüppel-like factor 1 (Klf1) is a candidate inducer of the PD-L1 gene (*Cd274*). Klf1 is a transcription factor that promotes β-globin synthesis in erythroid progenitors, and its role in immunological homeostasis is unknown. Ectopic expression of Klf1 induced PD-L1 in CD4$^+$T cells through activation of the PI3K-mTOR signaling pathway, independent of STATs signaling and Egr2 expression. Our findings indicate that Klf1 and Egr2 are modulators of PD-L1-mediated immune suppression in CD4$^+$T cells and might provide new insights into therapeutic targets for autoimmune diseases and malignancies.

The pathological bases of autoimmune diseases such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) have gradually been elucidated[1,2]. Vigorous analyses of cytokines and inhibitory cell surface molecules of immune cells have led to novel treatment methods. Tumor necrosis factor-α (TNF-α) inhibitors, antibodies against the interleukin-6 (IL-6) receptor and cytotoxic T lymphocyte associated protein-4 (CTLA-4) immunoglobulin (Ig) fusion protein have been widely used in the clinic[3]. In inflammatory conditions, T cell responses are regulated both positively and negatively by cell surface molecules. CD28/CD80 (B7-1), CD28/CD86 (B7-2), inducible costimulator (ICOS) and its ligand ICOSL stimulate immune responses. In contrast, immune responses are inhibited by binding of CTLA4/CD80, CTLA4/CD86 and lymphocyte activation gene 3 (LAG3)/MHC class II[4]. Recently, a B7 family co-inhibitory molecule, Programmed death-ligand 1 (PD-L1, encoded by *Cd274*), belonging to the CD28 receptor family[5], has become a subject of active investigation. Engagement of PD-1 by PD-L1 or PD-L2 transduces a signal that inhibits T-cell proliferation, cytokine production, and cytolytic function. PD-L1 and PD-L2 have marked structural similarities, but they display different expression patterns. Although the expression of PD-L2 is restricted to activated dendritic cells and macrophages[6], PD-L1 is expressed by activated CD4$^+$ T cells, CD8$^+$ T cells, natural killer cells, activated monocytes, myelocytes and CD4$^-$CD8$^-$ (double negative: DN) T cells in the thymus. PD-L1 is also expressed in non-hematopoietic organs such as heart, lung, spleen, thymus and kidney[7]. High expression of PD-L1 has been observed in various tumors including lung cancer and pancreatic cancer[7].

Whereas PD-L1 is induced by stimulation of the T cell receptor (TCR)[8], CD4$^+$ regulatory T cells (Tregs) constitutively express PD-L1 in the steady state[9,10]. Tregs play a major role in maintaining immune tolerance and are divided into two types: those emerging from the thymus and those induced in the periphery. CD4$^+$CD25$^+$ Tregs (CD25$^+$ Tregs) mainly emerge from the thymus and express the transcription factor forkhead protein 3 (Foxp3) as a master regulator gene (*Foxp3*)[11]. CD25$^+$ Tregs inhibit effector cell proliferation and cytokine production[8,12] and directly suppress B cell activation via PD-L1[13]. Immunological homeostasis is thought to be maintained by

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Altered gene expression profiles of histone lysine methyltransferases and demethylases in rheumatoid arthritis synovial fibroblasts

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Key words: rheumatoid arthritis, synovial fibroblast, histone lysine methylation, histone lysine methyltransferase, histone lysine demethylase

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ABSTRACT

Objective. *Aberrant histone lysine methylation (HKM) has been reported in rheumatoid arthritis (RA) synovial fibroblasts (SFs). As histone lysine methyltransferases (HKMTs) and demethylases (HKDMs) regulate HKM, these enzymes are believed to be dysregulated in RASFs. The aim of this study is to clarify whether gene expressions of HKMTs and HKDMs are altered in RASFs.*

Methods. *SFs were isolated from synovial tissues obtained from RA or osteoarthritis (OA) patients during total knee joint replacement. The mRNA levels of 34 HKMTs and 22 HKDMs were examined after stimulation with tumour necrosis factor α (TNF-α) in RASFs and OASFs.*

Results. *The gene expression of the 12 HKMTs, including MLL1, MLL3, SUV39H1, SUV39H2, PRDM2, EZH2, SETD2, NSD2, NSD3, SMYD4, DOT1, and PR-set7, that catalyse the methylation of H3K4, H3K9, H3K27, H3K36, H3K79, or H4K20 was higher after TNFα stimulation in RASFs vs. OASFs. The gene expression of the 4 HKDMs, including FBXL10, NO66, JMJD2D, and FBXL11, that catalyse the methylation of H3K4, H3K9, or H3K36 was higher after TNFα stimulation in RASFs vs. OASFs.*

Conclusion. *The study findings suggest that the HKM-modifying enzymes are involved in the alteration of HKM, which results in changes in the gene expression of RASFs.*

Introduction

Rheumatoid arthritis (RA) is an autoimmune disease characterised by chronic inflammation that results in progressive joint destruction and is difficult to treat effectively (1). RA synovial fibroblasts (SFs), which are also called fibroblast-like synoviocytes (FLS), maintain an activated and aggressive phenotype and play a central role in the aetiology of RA (2). Recent advances have revealed that epigenetic changes are associated with the pathogenesis of RA (3, 4). Epigenetic mechanisms, such as histone modifications, determine chromatin structure and consequently influence gene transcription without any change in the DNA sequence itself (5). We recently reported that compared with osteoarthritis (OA) SFs, RASFs exhibit altered profiles of histone lysine methylation (HKM), including trimethylation of lysine 4 at histone H3 (H3K4me3) and H3K27me3, in some of the genes of the matrix metalloproteinases that are known to be key pathogenic matrix-degrading enzymes (6, 7). OA is an age-related joint degenerative disease that results in pain and disability of the affected joints (8). However, little is currently known about the mechanisms involved in the dysregulation of HKM in RASFs.

HKM is catalysed by histone lysine methyltransferases (HKMTs) or histone lysine demethylases (HKDMs), which methylate or demethylate particular lysine residues in the histone tails, respectively (9). Methylation of H3K4, H3K36, and H3K79 is associated with gene activation, whereas methylation of H3K9, H3K27, and H4K20 is associated with gene repression (10). Our current study investigated the gene expression of HKMTs and HKDMs in RASFs in order to address whether the HKM-modifying enzymes are involved in the dysregulation of HKM.

Materials and methods

Patients and the isolation of SFs

Human synovial tissues were obtained from 7 RA and 7 OA patients during total knee joint replacement at the Saitama Medical University Hospital as previously described (6, 11). All of the RA patients fulfilled the 1987 American College of Rheumatology revised criteria for the diagnosis of RA. This study was approved by the Ethics Committee of Saitama Medical University. Written informed consent was obtained from every patient and all samples were rendered anonymous. After digestion of the synovial tissues, cultured cells (SFs) from passages 4 through 8 were used for the following experiments.

Treatment of SFs with tumour necrosis factor α (TNF-α)

SFs were stimulated with 10 ng/ml recombinant human TNF-α (Peprotech, Rocky Hill, NJ, USA) and cultured for the designated times prior to the quantitative RT-PCR analysis.

Urinary levels of the leukocyte surface molecule CD11b associate with glomerular inflammation in lupus nephritis

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Noninvasive biomarkers of disease activity are needed to monitor response to therapy and predict disease recurrence in patients with glomerulonephritis. The leukocyte surface markers integrin Mac-1 and CD16b have been implicated in the pathogenesis of lupus nephritis (LN). Mac-1 comprises a unique α subunit (CD11b) complexed with a common β2 subunit, which are released along with CD16b from specific leukocyte subsets under inflammatory conditions including glomerulonephritis. We investigated the association of urinary CD11b and CD16b with histopathological activity in 272 patients with biopsy-proven glomerular diseases, including 118 with LN. Urine CD11b and CD16b were measured via enzyme-linked immunosorbent assay. Urinary levels of both markers were increased in LN, but only urinary CD11b was correlated with the number of glomerular leukocytes and with overall histopathological activity. In a subset of patients with samples available from the time of biopsy and subsequent clinical remission of LN, urinary levels of CD11b decreased with successful glucocorticoid treatment. Receiver-operating characteristic curve analysis demonstrated that urinary CD11b was superior to CD16b, the scavenger receptor CD163, and monocyte chemotactic protein-1 for the prediction of proliferative LN. In anti-mouse nephrotoxic serum glomerulonephritis, urinary CD11b correlated with histologic damage and decreased with corticosteroid treatment. *In vitro*, CD11b levels were decreased on activated mouse neutrophils displaying Fcγ receptor clustering and transendothelial migration, suggesting that leukocyte activation and transmigration are required for CD11b shedding in urine. Together, our results suggest that urinary CD11b may be a useful biomarker to estimate histopathological activity, particularly glomerular leukocyte accumulation, in LN.

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KEYWORDS: glomerulonephritis; inflammation; kidney biopsy; lupus; macrophages

Lupus nephritis (LN) is a complication affecting the prognosis of patients with systemic lupus erythematosus (SLE), a representative type III allergy caused by immune complexes (ICs).[1,2] Histopathological images of kidney samples can be used to assess the classification of LN as well as its activity and prognosis;[3–5] however, there are undiagnosed cases in which invasive biopsies cannot be performed, such as in patients whose general body condition is poor or aged[6] or in developing nations with insufficient medical abilities.[7] Moreover, frequent invasive examinations should be avoided for monitoring patient conditions to identify the inflammatory period, determine treatment results, and predict disease recurrence. Therefore, a diagnostic test to evaluate kidney diseases using fluids such as blood and urine (biomarkers) would have a high clinical value for early diagnosis and patient monitoring to improve patient prognoses.[8,9]

Immunological mechanisms are indispensable for the onset and progress of LN; in particular, neutrophils and macrophages play a central role in acute glomerular inflammation.[10–12] Their detection in kidneys from patients with LN is associated with disease activation and poor renal prognosis.[10,13] Mac-1, which is composed of a unique α subunit (αm; CD11b) complexed to a common β2 subunit (CD18) on neutrophils and macrophages,[14] and glycosylphosphatidylinositol-anchored CD16b (Fcγ receptor [FcγR] IIIB), a low-affinity receptor for aggregated IgG or IgG-containing ICs primarily on neutrophils,[15] has been shown to support various immunological functions on the IC-deposited glomerular

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RESEARCH ARTICLE

Renal protective effect of antiplatelet therapy in antiphospholipid antibody-positive lupus nephritis patients without antiphospholipid syndrome

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Abstract

Objective

We sought to evaluate the effect of antiplatelet therapy in addition to conventional immunosuppressive therapy for lupus nephritis (LN) patients positive for antiphospholipid antibodies (aPL) without definite antiphospholipid syndrome (APS).

Methods

Patients with biopsy-proven LN class III or IV were retrospectively evaluated. We selected patients positive for anticardiolipin antibody (aCL) or lupus anticoagulant (LA) who did not meet the criteria for a diagnosis of APS. The patients were divided into two subgroups according to whether antiplatelet therapy was received. The cumulative complete renal response (CR) rate, relapse-free rate, and change in estimated glomerular filtration rate (eGFR) over 3 years after induction therapy were calculated.

Results

We identified 17 patients who received antiplatelet therapy and 21 who did not. Baseline clinicopathological characteristics and immunosuppressive therapy did not show a significant difference between the two groups except for a higher incidence of LN class IV in the treatment group ($p = 0.03$). There was no difference in cumulative CR rate, relapse-free rate, or eGFR change between these subgroups. However, when data on LA-positive patients were assessed, an improvement in eGFR was found ($p = 0.04$) in patients receiving antiplatelet treatment.

Conclusion

Addition of anti-platelet therapy was associated with an improvement of eGFR in LA-positive patients with LN class III or IV.

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ORIGINAL ARTICLE

Hemodynamic heterogeneity of connective tissue disease patients with borderline mean pulmonary artery pressure and its distinctive characters from those with normal pulmonary artery pressure: a retrospective study

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Abstract
To clarify whether patients with connective tissue disease (CTD)-associated borderline mean pulmonary artery pressure (mPAP) have distinctive hemodynamic characteristics from those with normal mPAP and whether pathogenesis is as heterogeneous as manifest pulmonary hypertension (PH). Seventy-five CTD patients who underwent right heart catheterization (RHC) from 2008 through 2016 were retrospectively analyzed. We compared between-group differences in clinical and hemodynamic findings: normal mPAP ($n = 35$), borderline mPAP ($n = 15$), and PH ($n = 25$). A therapeutic intervention trial based on RHC results was performed in nine patients. The values of tricuspid regurgitation pressure gradient (TRPG) in patients with borderline mPAP were comparable at rest but became higher after exercise compared to those with a normal mPAP ($P = 0.01$). Pulmonary artery wedge pressure in patients with borderline mPAP was higher than in those with normal mPAP ($P < 0.0001$) and comparable to those with PH. Each of the three patients was treated for pre-capillary and post-capillary disease and two for interstitial lung disease (ILD). During the mean follow-up period of 40 months, mPAP or TRPG normalized in all patients treated for pre-capillary and post-capillary disease. One patient with severe ILD developed to PH and died from it. CTD patients with borderline mPAP, the underlining pathogenesis of which is heterogeneous as PH, have distinctive hemodynamic characteristics from those with normal mPAP. Whether a specific treatment targeting the inflammatory process or local hemodynamics may alter the clinical course to PH is a topic for future research.

Keywords Borderline mean pulmonary artery pressure · Connective tissue diseases · Left heart disease · Pulmonary arterial hypertension

Introduction

Pulmonary hypertension (PH) is defined as a mean pulmonary artery pressure (PAP) ≥ 25 mmHg, measured by right heart catheterization (RHC) at rest [1]. PH is a severe and fatal complication of connective tissue diseases (CTDs), such as systemic sclerosis (SSc) [2]. Early identification of PH is associated with improved long-term survival in patients with CTD-associated PH (CTD-PH) [3, 4].

Borderline mean PAP (mPAP), defined by values of 21–24 mmHg, may comprise a transition phase from a normal pulmonary hemodynamic condition to pulmonary arterial hypertension (PAH), with this range of pressures possibly being representative of the early stage of PAH [5, 6]. Though early

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CONCISE REPORT

A positive direct Coombs' test in the absence of hemolytic anemia predicts high disease activity and poor renal response in systemic lupus erythematosus

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We determined the clinical utility of the direct Coombs' test in the absence of hemolytic anemia as an indicator of disease activity and therapeutic response in systemic lupus erythematosus (SLE). SLE patients without hemolytic anemia who visited our hospital from January 2016 to November 2016 were retrospectively evaluated with a direct Coombs' test. Clinical features, including SLE disease activity index (SLEDAI), treatment and laboratory findings were analyzed. For patients with lupus nephritis, we additionally evaluated the cumulative complete renal response rate over one year after induction therapy. Among 182 patients evaluated, 10 (5.8%) patients had a positive direct Coombs' test in the absence of hemolytic anemia. They had a higher SLEDAI ($p < 0.01$), higher circulating immune complex levels ($p = 0.01$), higher anti-DNA titers ($p < 0.01$) and a lower complete renal response rate ($p = 0.03$) compared with those who were negative. Multivariate analysis indicated that SLEDAI was an independent factor correlated with the direct Coombs' test without hemolytic anemia (odds ratio 2.4, 95% confidence interval 1.66–4.98, $p < 0.01$). A positive direct Coombs' test in the absence of hemolytic anemia may therefore represent a useful biomarker for assessing disease activity and therapeutic response. *Lupus* (2018) **0**, 1–5.

Key words: Systemic lupus erythematosus; Coombs' test; biomarker; SLEDAI

Introduction

Abnormalities in immune complex production and elimination are fundamental in the pathogenesis of systemic lupus erythematosus (SLE).[1] Besides the Fcγ receptors of monocytes, macrophages and neutrophils, complement binding receptor type 1 (CR1) also takes part in the binding, transport and endocytosis of complement binding immune complex.[2] CR1 is differentially expressed on erythrocytes, eosinophils, monocytes, dendritic cells and kidney podocytes.[3] Among other cells, erythrocytes play a pivotal role in contributing to the clearance of immune complex from the circulation by binding immune complex to CR1. The direct Coombs' test detects both anti-erythrocyte antibody binding to the surface of erythrocytes and immune complex binding to CR1 on erythrocytes.[4] Binding of anti-erythrocyte antibody to erythrocytes is a hallmark of autoimmune hemolytic anemia; however, immune complex binding to CR1 is not associated with hemolysis. The direct Coombs' test in the absence of hemolytic anemia has been newly included in the Systemic Lupus Erythematosus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) 2012 criteria for SLE.[5] Since erythrocyte CR1 contributes to the clearance of circulating immune complex,[4] a positive direct Coombs' test in the absence of hemolytic anemia may indicate excessive immune complex production. In this study, we determined the clinical significance of a positive direct Coombs' test in the absence of hemolytic anemia, focusing on disease activity and therapeutic response of lupus nephritis, in a Japanese SLE population.

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ORIGINAL RESEARCH

Anti-IL-10 antibody in systemic lupus erythematosus

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Purpose: IL-10 is a cytokine known to inhibit inflammatory cytokines. To determine its role in the pathogenesis of systemic lupus erythematosus (SLE), the presence of anti-IL-10 antibody is required to be examined. Although antibodies against cytokines are known to be present in SLE, no studies have determined the role of IL-10, particularly in Japanese patients. We assayed anti-IL-10 antibody in SLE and examined the clinical significance.

Patients and methods: We performed a retrospective study of 80 Japanese patients with SLE. Sixteen scleroderma patients, 19 rheumatoid arthritis (RA) patients, 23 Behcet's disease patients, and 23 healthy subjects were selected as control groups. Clinical information was abstracted from medical records. Anti-IL-10 antibody level was determined with an ELISA.

Results: With the cutoff established as serum absorbance +2 SDs (OD 0.729) in healthy subjects, we defined any sample above this cutoff as anti-IL-10 antibody-positive. Fourteen patients with SLE (17.5%) were found to be anti-IL-10 antibody positive. Absorbance was significantly higher in serum from patients with SLE and RA than in healthy individuals. In SLE, patients with low complement values were significantly more common in the antibody-positive group. Serum IgG levels were significantly higher in the antibody-positive group. In multivariable analysis, high level of serum IgG is associated with anti-IL-10 antibody positive.

Conclusion: The present study found that anti-IL-10 antibody is present in SLE and related to clinical parameters. These results suggest that the presence of anti-IL-10 antibody was associated with high level of serum IgG, but is not associated with disease activity in patients with SLE.

Keywords: anti-IL-10 antibody, IL-10, systemic lupus erythematosus, autoantibody

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by the production of antinuclear and other autoantibodies. Moreover, previous studies[1–4] demonstrate that cytokines contribute to various manifestations of SLE.

IL-10 is a cytokine known to inhibit inflammatory cytokines.[5–7] In an SLE mouse model, IL-10 has been reported to inhibit nephritis, arthritis, and neurological symptoms. Therefore, low levels of IL-10 may be associated with active SLE.[8,9] On the contrary, some studies report high levels of IL-10 in SLE patients.[10–13] This may be attributed not only to enhanced production of IL-10 but also to the positive feedback of anti-IL-10 antibodies or the effect of anti-IL-10 receptor antibodies.

Low levels of IL-10 suggest decreased production of IL-10 and the presence of anti-IL-10 antibody. Antibodies against cytokines have been shown to be involved

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BRIEF REPORT

Mycophenolate mofetil treatment with or without a calcineurin inhibitor in resistant inflammatory myopathy

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Abstract
To evaluate the efficacy and tolerability of mycophenolate mofetil (MMF) with or without calcineurin inhibitors (CNIs) in patients with inflammatory myopathy taking prednisolone, but refractory to conventional immunosuppressive therapy. The records of patients with inflammatory myopathy who had previously failed treatment with at least one immunosuppressant were retrospectively evaluated. We selected patients treated with MMF and divided them into two groups depending on whether or not there was concomitant use of CNIs. We investigated the efficacy by changes in creatine kinase (CK) levels, forced vital capacity (%FVC), prednisolone dose, and high-resolution computed tomography (HRCT) findings. Interstitial lung disease (ILD) progression was defined by more than 10% decline of %FVC from baseline. We identified 19 patients on MMF treatment. There were seven (36.8%) patients on MMF and CNIs, including five on cyclosporine and two on tacrolimus. At baseline, no significant difference was seen in the prevalence of ILD between patients taking or not taking CNIs (85.7% vs. 75.0%, $P = 0.68$). Improvement in CK was seen in patients treated with CNIs ($P = 0.04$) but not in those without ($P = 0.39$). No significant improvement in %FVC and HRCT findings were found in patients with ILD in either group, and there were no differences in death or ILD progression. The combination of CNIs and MMF might be more effective for decreasing CK levels than MMF alone. Neither treatment arm had a beneficial effect on ILD over a variable observation period.

Keywords Dermatomyositis · Drug therapy · Inflammatory myopathy/CO · Interstitial lung disease · Mycophenolate mofetil · Polymyositis · Tacrolimus

Introduction

Idiopathic inflammatory myopathies (IIMs) are a group of heterogeneous, systemic rheumatic diseases that include adult polymyositis (PM) and adult dermatomyositis (DM) [1]. Glucocorticoids are the standard first-line therapy for patients with PM/DM, but approximately 50% of patients fail to respond when the glucocorticoids were tapered. Patients refractory to glucocorticoid therapy have been treated with a variety of immunosuppressants, most commonly methotrexate (MTX), azathioprine (AZA), intravenous immunoglobulin (IVIg), and calcineurin inhibitors (CNIs), including cyclosporine A (CsA) and tacrolimus (TAC) [2]. Mycophenolate mofetil (MMF) is an immunosuppressant widely used in organ transplantation and currently used for autoimmune conditions, mostly systemic lupus erythematosus (SLE) [3]. Recently, combination therapy with MMF and TAC showed significant efficacy in lupus nephritis in a 6-month trial [4]. Although MMF has been found efficacious in connective tissue disease-associated interstitial lung disease (CTD-ILD) [5] and refractory myositis [6–10], the efficacy of combination therapy with MMF and TAC in PM/DM or myositis-associated ILD has not been elucidated.

Here, we analyzed the efficacy and tolerability of MMF with or without CNIs in patients with inflammatory myopathy on prednisolone (PSL) refractory to conventional immunosuppressive therapy.

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[ORIGINAL ARTICLE]

Hydroxychloroquine Improves the Disease Activity and Allows the Reduction of the Corticosteroid Dose Regardless of Background Treatment in Japanese Patients with Systemic Lupus Erythematosus

Hironari Hanaoka, Harunobu Iida, Tomofumi Kiyokawa,
Yukiko Takakuwa and Kimito Kawahata

Abstract:

Objective Hydroxychloroquine (HCQ) was not approved in Japan until 2015, and its therapeutic potential has not been explored in depth. We evaluated the additional therapeutic effect of HCQ in Japanese patients with systemic lupus erythematosus (SLE) on maintenance therapy.

Methods Patients with SLE who visited our hospital from 2015 to 2016 and were taking prednisolone (PSL) at <20 mg/day were retrospectively evaluated. All patients were divided into three groups according to their maintenance treatment regimen: PSL + immunosuppressant, PSL alone, and no treatment. We compared the changes in the SLE disease activity index (SLEDAI), PSL dose, and cumulative flare rate between patients who were and were not treated with HCQ.

Results Among the 165 patients evaluated, 35 (21.2%) were treated with HCQ. The mean period of observation did not differ markedly between patients who did and did not receive HCQ (p=0.3). The SLEDAI and PSL dose were significantly reduced in patients who received HCQ, regardless of their background treatment regimen. The cumulative flare rate was lower in patients who received HCQ than in those who did not in the PSL + immunosuppressant and no maintenance treatment groups (p=0.03 and 0.05, respectively).

Conclusion The addition of HCQ reduced the disease activity and allowed PSL dose reduction, regardless of background treatment, in Japanese patients with SLE.

Key words: systemic lupus erythematosus, hydroxychloroquine, SLEDAI

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Introduction

Hydroxychloroquine (HCQ) is an antimalarial drug that is recommended for patients with systemic lupus erythematosus (SLE) because of its beneficial effect on decreasing the risk of flares (1), diabetes mellitus (2), thrombotic events (3, 4), and dyslipidaemia (5). HCQ also reportedly reduces damage accrual (6) and improves the survival (7).

Many investigators have recently examined the association between the blood HCQ concentration and the clinical outcome (8-11). According to Mok et al., an increased concentration of HCQ is associated with a reduced number of flares in patients in clinical remission (8). Yeon et al. examined factors related to the blood HCQ concentration in SLE patients and concluded that taking an additional immunosuppressant other than a corticosteroid is associated with increased HCQ concentrations (9). Therefore, the therapeutic effect of HCQ may differ depending on the background treatment.

Given that HCQ was not approved in Japan until 2015, its therapeutic potential remains poorly understood in the Japanese population. In one study, a randomized trial showed that the mean cutaneous lupus erythematosus disease area and severity index (CLASI) were significantly improved in the HCQ group compared with the placebo group among

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SCIENTIFIC REPORTS

OPEN

Interleukin-23 as a therapeutic target for inflammatory myopathy

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Current treatments of polymyositis and dermatomyositis (PM/DM) depend on non-specific immunosuppressants. This study was performed to elucidate the role of interleukin (IL)-23, as their possible therapeutic target. As was reported earlier in PM/DM patients, serum IL-23 levels were elevated in mice with C protein induced-myositis (CIM), a murine model of PM. IL-23 was expressed by macrophages in the PM/DM and CIM muscles and by dendritic cells and macrophages in the lymph nodes from the CIM mice. It was also expressed by macrophages in the chemically injured muscles, but not those recruited into the muscles by footpad injection of Freund's complete adjuvant, demonstrating that IL-23 production should be associated with muscle damage. Genetic deletion of IL-23 as well as preventive and therapeutic administration of blocking antibodies against IL-23p19 subunit suppressed CIM. When lymph node cells from the CIM mice were transferred adoptively into naive wild type or IL-23p19 deficient recipient mice, both recipients developed myositis equally. Thus, elevated IL-23 should promote dendritic cells and macrophages to activate the autoaggressive T cells. Our findings suggest that IL-23 should mediate positive feedback loop from the muscle damage to the T cell activation and be a promising therapeutic target for autoimmune myositis.

Polymyositis (PM) is a chronic inflammatory myopathy that impairs muscle functions to restrict daily activities of the affected patients. Because its precise pathogenesis remains unclear, the standard treatment depends on non-specific immunosuppressants including glucocorticoids and other immunosuppressive agents. Patients under these agents often suffer from their adverse effects and occasionally fail to respond for complete control of the disease activities[1].

Activated cytotoxic CD8 + T cells, which circulate systemically in patients with PM, play a crucial role in its pathogenesis[2,3]. However, magnetic resonance imaging of the PM muscles demonstrates a patchy pattern consisting of the inflamed and intact muscles. This involvement bias implies that not only autoreactive CD8 + T cells but also local conditioning of the muscles should be required for the myositis development. In C protein-induced myositis (CIM), a murine model of PM[4], muscle injury is mediated by C protein-reactive CD8 + T cells[5]. In addition, the activated T cells could induce transferred myositis only in the muscles where the local innate immunity was activated with footpad injection of Freund's complete adjuvant (CFA)[6]. We thus proposed "seed and soil" model of autoimmunity; "seed" stands for the autoreactive T cells while "soil" for the target tissues. Both have to be activated for the development of autoimmune myositis.

Our previous report disclosed that recruited macrophages into the muscle in response to the footpad CFA injection could not develop myositis on their own, but are responsible for "soil" activation by producing Interleukin (IL)-1 and tumor-necrosis factor alpha[6]. However, these cytokines are also expressed by muscle fibers during homeostatic regeneration[7] and unpromising as therapeutic targets for PM/ dermatomyositis (DM) in clinical settings[8]. Thus, as a therapeutic target of PM/DM, we should explore specific molecules expressed in the damaged muscles.

It was reported that IL-23 was higher in sera from PM/DM patients than in those from healthy donors[9,10], and expressed by macrophages and dendritic cells in the PM/DM muscles[11]. Although these facts indicate its pathological contribution to PM/DM, little has been known about its roles in inflammatory myopathy.

IL-23 is a member of IL-12 cytokine family[12,13] and consists of IL-23 subunit p19 (IL-23p19) and IL-12 subunit p40 (IL-12p40). The IL-23R and IL-12Rβ1 subunits comprise the IL-23 receptor complex and bind to IL-23p19 and IL-12p40, respectively[14]. IL-23 is produced primarily by activated macrophages and dendritic cells (DCs). It expands Th17 cells and maintains their phenotype such as their cytokine production including IL-17A, which is

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LETTER Open Access

Early achievement of deep remission predicts low incidence of renal flare in lupus nephritis class III or IV

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Recommendations for lupus nephritis (LN) management specify that the therapeutic target should be a complete renal response (CR) [1], defined as a urine protein:Cr ratio (UPCR) of 0.5 g/gCr (50 mg/mmol) and normal or near-normal renal function. Earlier studies suggested that patients who achieved CR experienced fewer renal flares than those who achieved partial remission, defined as a 50% reduction of proteinuria [2]. Among patients who achieved CR (less than 0.50 g/gCr of UPCR), however, the renal outcome of those who achieved a value below the normal UPCR limit of 0.15 g/gCr was unclear. We recently reported that an early renal response may predict a good renal or systemic outcome [3, 4]. In this study, we investigated whether it is beneficial to achieve deep remission early by evaluating flare rate, Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI), cumulative glucocorticoid dose, and eGFR level.

We retrospectively assessed 69 patients with biopsy-proven LN class III or IV who achieved CR in our hospital. We divided them into two groups based on whether deep remission was achieved, defined as less than 0.15 g/gCr UPCR, and compared cumulative flare rates [1], defined as estimated glomerular filtration rate (eGFR) decreasing by ≥ 10%, active urine sediment, or increasing UPCR > 1.0 g/gCr after achieving CR. Furthermore, we analyzed the additional effect of early achievement of CR, defined as CR within 3 months after induction therapy. Clinical characteristics between the two groups were compared using the non-parametric Mann-Whitney *U*-test. Frequencies of clinicopathological characteristics were compared using the Chi-square test. Cumulative flare free rates were calculated using the Kaplan-Meier method, and differences between the two groups were tested with a log-rank test. To identify independent parameters that predict CR at 3 years, we performed multivariate analysis.

During the 3-year period, 55 of 69 CR patients achieved deep remission while 14 did not. Among clinical features at baseline, the proportion of females was significantly higher among patients with deep remission ($p = 0.01$; Table 1).

We found a significantly higher flare-free rate among patients who achieved deep remission compared with those who did not ($p = 0.001$; Fig. 1a). For patients with deep remission, those with early CR had a higher flare-free rate than those without ($p = 0.04$) (Fig. 1b), but significant difference was found in those with non-deep remission (Fig. 1c). Multivariate analysis to predict sustained CR indicated that early achievement of deep remission was an independent factor (odds ratio 3.62, 95% confidence interval 1.1–18.9, $p = 0.05$). Regarding SDI, cumulative glucocorticoid dose, and eGFR level at year 3, patients with early deep remission had the most favorable result compared to the other groups (Fig. 2).

In this study, we found that achieving early and deep remission predicts a good renal outcome in patients with LN class III or IV. Since renal flare predicts a worse prognosis [5], determining the method of treatment to ensure long-term maintenance of CR is challenging. Our results suggest that deep remission might be a more beneficial therapeutic goal than that of the EULAR/ERA-EDTA recommendations regarding the prevention of renal flare. A future multi-center, prospective study is required to confirm our findings.

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REVIEW ARTICLE

Clinical practice guidance for juvenile idiopathic arthritis (JIA) 2018

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ABSTRACT

Juvenile idiopathic arthritis (JIA) is the most common disease in pediatric rheumatism. There is no specific symptom or examination finding for JIA, and the diagnosis is made by exclusion and differentiation. Because non-pediatric rheumatologists are sometimes involved in medical care, 'proposal for JIA guidance on diagnosis and treatment for primary care pediatricians and non-pediatric rheumatologists' was first published in 2007. In these 10 years, a number of new findings on pathophysiology and treatment of JIA have been published; therefore, we propose this guidance of 2018th edition aiming at updating and standardization of JIA medical care in Japan. This edition included the management of uveitis, macrophage activation syndrome, infectious diseases before and during treatment. Moreover, details of biologics are also described. Although this guidance is tailored to adaptation of examinations and drugs, we do not purpose to limit the physicians' discretion in clinical practice. This guidance should be viewed as recommendations and be individualized according to the condition of the patient. We hope that medical care for JIA will advance and more patients will get benefit based on this guidance. Then, further revisions are needed due to changes in future conditions.

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KEYWORDS
Juvenile idiopathic arthritis; clinical practice guidance; algorism of treatment; macrophage activation syndrome; uveitis; biologics

1. General considerations and classification of pediatric patients with chronic arthritis

Juvenile idiopathic arthritis (JIA) is defined as chronic arthritis of unknown etiology beginning before the 16th birthday and persisting for at least 6 weeks when other known conditions are excluded.

The current classification of JIA was proposed by the Pediatric Standing Committee of the International League of Associations for Rheumatology (ILAR) [1], which published an initial revision in 1997 [2] and subsequently a second revision in 2001 [3]. This classification includes seven categories of JIA (Table 1) which mainly fall into two types according to the differences in clinical symptoms and pathophysiology, namely systemic arthritis (systemic JIA) and the other six JIA categories. The latter consist of oligoarthritis, rheumatoid factor-negative polyarthritis, rheumatoid factor-positive polyarthritis, psoriatic arthritis, enthesitis-related arthritis, and undifferentiated arthritis, and are often considered as 'articular-type JIA' in clinical practice in Japan. We therefore use this term in this guide. Within systemic arthritis, we can clearly differentiate a form where only arthritis remains after systemic inflammation subsides (fever, eruption, hepatosplenomegaly, serositis, etc.) from articular-type JIA. Here, we will use the term 'systemic arthritis with active arthritis (and without active systemic features)' in the present guide, according to the '2011 American College of Rheumatology Recommendations for the Treatment of Juvenile Idiopathic Arthritis' [4].

Recently, the term 'spondyloarthritis (SpA)' has been widely used in children. The main manifestations of this disease are axial arthritis (such as spondylitis and sacroiliitis), peripheral arthritis, and enthesitis of tendons and ligaments [5]. This is an umbrella disease which includes ankylosing spondylitis [6], psoriatic arthritis [7], arthritis of inflammatory bowel disease and reactive arthritis. Enthesitis-related arthritis, psoriatic arthritis, children with some undifferentiated arthritis in JIA categories are equivalent to SpA [5]. Because the categories which are excluded from the JIA classification (e.g. arthritis of inflammatory bowel disease) could be also diagnosed using SpA criteria,

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Relapsing polychondritis patients were divided into three subgroups: patients with respiratory involvement (R subgroup), patients with auricular involvement (A subgroup), and overlapping patients with both involvements (O subgroup), and each group had distinctive clinical characteristics

Jun Shimizu, MD, PhD, Yoshihisa Yamano, MD, PhD, Kimito Kawahata, MD, PhD, Noboru Suzuki, MD, PhD*

Abstract

Relapsing polychondritis (RP) is a multisystem disorder of cartilaginous tissues. Previously, we found that patients with respiratory involvement and patients with auricular involvement were mutually exclusive in the RP cohort, which suggests a strong inverse relationship between respiratory and auricular involvement. Here, we examined the clinical manifestation patterns in a subgroup of patients with respiratory involvement (R subgroup) and a subgroup of patients with auricular involvement (A subgroup) and investigated the clinical and laboratory characteristics of each subgroup.

There were 47 patients (19.7%) and 118 patients (49.4%) allocated to the R and A subgroups, respectively. Saddle nose deformity and a progressive disease course were observed frequently in the R subgroup. Arthritis, conjunctivitis, and CNS involvement were observed frequently in the A subgroup.

The remaining RP patients formed a third subgroup of patients that had both respiratory involvement and auricular involvement. We designated this subgroup as the O (overlap) subgroup, and 75 patients (31.4%) were allocated to the O subgroup. Disease duration in the O subgroup (5.70±0.64 years) was significantly longer than that in the A subgroup (4.12±0.45 years) and relatively longer than that in the R subgroup (4.80±0.63 years).

We found that cardiovascular involvement was more predominant in the O subgroup than in the R and A subgroups. Higher concentrations of serum matrix metalloproteinase (MMP)3 were observed in the O subgroup than in the R and A subgroups.

We measured serum MMP3 concentrations in another patient cohort including 22 newly recruited RP patients. MMP3 concentrations were significantly higher in the O subgroup (n=10) than those in the R subgroup (n=6) and A subgroup (n=10).

RP patients in the R and A subgroups had different characteristics from each other, and the overlap of respiratory and auricular involvement was an important prognostic factor in patients with RP. Cardiovascular involvement was not observed in the R subgroup in RP patients. The current study may provide insights into the classification and treatment of RP.

Abbreviations: A = auricular involvement, CNS = central nervous system, MDS = myelodysplastic syndrome, MMP3 = matrix metalloproteinase-3, O = overlap, R = respiratory involvement, RP = relapsing polychondritis.

Keywords: auricular involvement, cardiovascular involvement, inflammation, relapsing polychondritis, respiratory involvement

1. Introduction

Relapsing polychondritis (RP) is a multisystem disorder characterized by recurrent inflammation and degeneration of cartilaginous tissues such as the ear, nose, joint, and respiratory tract.[1] RP may affect other proteoglycan rich organs such as the eye, inner ear, heart, blood vessels, and kidney.[1]

We conducted an epidemiological survey of 239 RP patients and collected clinical information.[2] We reported that respiratory failure with pulmonary infection was a major cause of death in patients with RP.[2] Although the incidence was lower than that in a Caucasian study,[3] central nervous system (CNS) involvement,[4] and cardiovascular system involvement[5] were important prognostic factors in Japan. Cardiovascular involvement frequently occurred with CNS, auricular, and kidney involvement.[5]

Francès et al[6] reported that a relatively large number of French RP patients (36.5%) had chronic dermatitis, and these patients suffered frequently from hematological disorders (12.0%), especially myelodysplastic syndrome (MDS, 11.0%) and connective tissue diseases (11.0%).

Our previous study showed that 32 RP patients (13.8%) developed cutaneous manifestations and 5 patients (2.1%) had MDS.[7] All 5 patients with MDS had cutaneous manifestations.

Recently, the same French group reported that, using a cluster analysis, 142 RP patents were characterized by three different

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ORIGINAL ARTICLE

The findings of musculoskeletal ultrasonography on primary Sjögren's syndrome patients in childhood with articular manifestations and the impact of anti-cyclic citrullinated peptide antibody

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ABSTRACT

Objective: We researched the findings of musculoskeletal ultrasound sonography (MSUS) on primary Sjogren's syndrome in childhood (pSS-C) with articular manifestations. The correlation of rheumatoid factor (RF) and anti-cyclic citrullinated peptide antibody (ACPA) were investigated to evaluate the usefulness of MSUS on their articular prognosis.

Method: The objective patients are pSS-C cases who visited our hospital complaining joint pain and/or joint swelling and for whom MSUS was performed.

Result: Eight patients included 6 female and 2 male, 5 RF-positive patients and 3 ACPA- positive patients. The mean age of onset was 11.1 ± 3.0 years (352 physical joint findings and 284 MSUS findings. The number of joints found clinical articular manifestations was 58/352 joints, and arthritis detected by MSUS was 30/284 joints). In multivariate analysis, the odds ratio of clinical articular manifestations was significant high in RF-positivity (2.9, 95%CI 1.5–6.2). The odds ratio of arthritis detected by MSUS in ACPA-positivity was significant high (3.7, 95%CI 1.5–11.6), although odds ratio in RF-positivity had no statistical significance and a similar trend was seen in odds ratios of subclinical arthritis (4.9, 95%CI 1.6–18.0).

Conclusion: It was indicated that MSUS is useful for pSS-C. ACPA-positive pSS-C patients have arthritis and subclinical arthritis more frequently than ACPA-negative patients.

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Anti-cyclic citrullinated peptide antibody; juvenile idiopathic arthritis; primary Sjogren's syndrome; childhood; musculoskeletal ultrasonography

Introduction

Sjogren's syndrome is an autoimmune disease presenting chronic inflammation of exocrine tissue including salivary glands and lacrimal glands. The patients of Sjogren's syndrome present xerophthalmia and xerostomia as a disease progression. Additionally, ~40% of patients with primary Sjogren's syndrome (pSS) have extra-glandular manifestations [1], and articular manifestations are common extra-glandular manifestations of pSS [2]. A few patients develop their first symptom in childhood and the rate of pSS in childhood (pSS-C) is reported to be 17.5% in all pSS patients[3]. Generally, sicca symptoms become apparent after the long course of inflammation on exocrine tissue and are seldom seen in patients with pSS-C (35.0%) [3]. Therefore, systemic symptoms including fever, rash, fatigue and the articular symptoms are observed more frequently among pSS-C than pSS in adults. Some patients with pSS-C complain arthralgia and/or arthritis as their first manifestation and we often need to distinguish them from juvenile idiopathic arthritis (JIA) or other rheumatic diseases.

Musculoskeletal ultrasound sonography (MSUS) is a noninvasive examination of joint and used for evaluation of musculoskeletal tissue in various rheumatic diseases. Particularly a number of studies have addressed that MSUS with power Doppler (PD) is useful to detect active arthritis in patients with rheumatoid arthritis and juvenile idiopathic arthritis (JIA). It is identified that MSUS examination could evaluate even subclinical arthritis [4–11]. However, there are few studies on MSUS findings of pSS that was investigated only in adult patients [12,13].

Rheumatoid factor (RF) and anti-cyclic citrullinated peptide antibody (ACPA) are the items of the 2010 ACR/EULAR classification criteria for rheumatoid arthritis (RA) [14]. ACPA is also detected in 48% of RF-positive polyarthritis patients of juvenile idiopathic arthritis (RF + pJIA) [15]. ACPA is regarded as a risk factor for early progression of the joints destruction both in RA and RF + pJIA[16]. RF is detected in 36–74% [17,18] and ACPA is also detected in 3–10% [19–23] of pSS patients, despite the absence of RA or JIA. It has been reported that RF-positive pSS patients presented an increased prevalence of systemic complications including articular manifestations [2,24]. On the other hand, the studies on the correlation between SS and ACPA addressed that the prevalence of synovitis did not differ in pSS between patients with and without ACPA [21,22]. Moreover, ACPA in pSS is reported to have no association

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Soluble CD163, a unique biomarker to evaluate the disease activity, exhibits macrophage activation in systemic juvenile idiopathic arthritis

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ABSTRACT

This study aims to investigate the clinical significance of serum soluble CD163 (sCD163) levels as a predictor of the disease activity of systemic juvenile idiopathic arthritis (s-JIA). In this study, we examined 63 patients with s-JIA, four with Epstein-Barr virus-induced hemophagocytic lymphohistiocytosis (EBV-HLH), and seven with Kawasaki disease (KD), along with 14 healthy controls. We quantified serum cytokine levels (sCD163, neopterin, IL-18, IL-6) by enzyme-linked immunosorbent assay and compared the results with the clinical features of s-JIA. Serum sCD163 levels were significantly elevated in patients with s-JIA associated macrophage activation syndrome (MAS) and EBV-HLH compared to those in patients with acute-phase s-JIA and KD. In addition, serum sCD163 levels profoundly increased with the progress of MAS and correlated positively with the disease activity of s-JIA, even in patients receiving tocilizumab. Furthermore, serum sCD163 levels significantly decreased in the inactive phase compared to those in the active phase and normalized in remission. The correlation between macrophage activation and serum sCD163 levels might be a unique indicator of the disease activity and a potential diagnostic laboratory criterion for clinical remission in patients with s-JIA, including those receiving tocilizumab.

1. Introduction

Systemic juvenile idiopathic arthritis (s-JIA) is characterized by chronic arthritis accompanied by high spiking fever and other systemic symptoms, including salmon-pink evanescent rash, hepatosplenomegaly, lymphadenopathy, and serositis [1]. A recent study investigating the pathophysiology of s-JIA revealed that s-JIA is an auto-inflammatory condition [2]. It is possible that the aberrant induction of proinflammatory cytokines such as IL-6, IL-1β, and IL-18 could be involved in the pathogenesis of s-JIA and might also correlate with the disease activity and secondary complications [2]. Furthermore, inadequate downregulation of the immune activation could be another crucial pathological mechanism of s-JIA [2–4].

The macrophage lineage is categorized into two different subsets: the classical M1 macrophages and the alternatively activated M2 macrophages. While M1 macrophages comprise the proinflammatory subset, M2 macrophages resolve inflammatory responses, perform scavenger functions, and promote tissue remodeling and repair [5]. In addition, M2 macrophages play a role as hemophagocytic macrophages in macrophage activation syndrome (MAS) [6], and resolve inflammatory responses in the pathogenesis of s-JIA [3].

The hemoglobin-haptoglobin scavenger receptor CD163 is a monocyte/macrophage-restricted 130-kDa transmembrane protein of the cysteine-rich scavenger receptor family [7,8]. The CD163 expression identifies M2 macrophages undergoing differentiation through the alternative pathway related to enhanced phagocytic activity [9]. Upon appropriate activation of the cells, the extracellular portion of CD163 is shed from the cell surface in the form of soluble CD163 (sCD163). Previously, extensive expansion of $CD163^+$ macrophages has been reported in the bone marrow of a patient with MAS [6].

Reportedly, the serum sCD163 levels are a valuable diagnostic marker in hemophagocytic syndromes and MAS [10,11]. We have previously reported that serum sCD163 levels remained elevated even in the inactive phase of s-JIA [4]. However, the kinetics of the serum sCD163 levels from the active phase to remission in s-JIA remains unclear. Furthermore, recent research has revealed that the expression of inflammatory proteins such as C-reactive protein (CRP) is modified by the treatment of IL-6 blocking in s-JIA [12]; however, whether sCD163

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BRIEF REPORT

Validation of Classification Criteria of Macrophage Activation Syndrome in Japanese Patients With Systemic Juvenile Idiopathic Arthritis

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Objective. To validate whether the 2016 American College of Rheumatology/European League Against Rheumatism classification criteria of macrophage activation syndrome (MAS) complicating systemic juvenile idiopathic arthritis (JIA) is practical in the real world.

Methods. A combination of expert consensus and analysis of real patient data was conducted by a panel of 15 pediatric rheumatologists. A total of 65 profiles comprised 18 patients with systemic JIA–associated MAS and 47 patients with active systemic JIA without evidence of MAS. From these profiles, 10 patient data points for full-blown MAS, 11 patient data points for MAS onset, and 47 patient data points for acute systemic JIA without MAS were evaluated.

Results. Evaluation of the classification criteria to discriminate full-blown MAS from acute systemic JIA without MAS showed a sensitivity of 1.000 and specificity of 1.000 at the time of full-blown MAS. Sensitivity was 0.636 and specificity was 1.000 at the time of MAS onset. The number of measurement items that fulfilled the criteria increased in full-blown MAS compared to that at MAS onset. At MAS onset, the positive rates of patients who met the criteria for platelet counts and triglycerides were low, whereas those for aspartate aminotransferase were relatively high. At full-blown MAS, the number of patients who met the criteria for each measurement item increased.

Conclusion. The classification criteria for MAS complicating systemic JIA had a very high diagnostic performance. However, the diagnostic sensitivity for MAS onset was relatively low. For the early diagnosis of MAS in systemic JIA, the dynamics of laboratory values during the course of MAS should be further investigated.

Introduction

Macrophage activation syndrome (MAS) is a severe complication of systemic juvenile idiopathic arthritis (JIA), which is clinically characterized by fever, hepatosplenomegaly, lymphadenopathy, depression of all 3 blood cell lines, deranged liver function, intravascular coagulation, and central nervous system dysfunction (1). MAS is a potentially life-threatening disease, and thus, a timely and prompt diagnosis is essential to initiate life-saving treatment. However, it can be difficult to distinguish MAS from systemic JIA flares, sepsis, or other secondary hemophagocytic lymphohistiocytosis. Differentiation of MAS from these conditions is essential for the selection of an appropriate therapeutic intervention in a timely

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Transient natural killer cell dysfunction associated with interleukin-18 overproduction in systemic juvenile idiopathic arthritis

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Key words interleukin-18, macrophage activation syndrome, systemic juvenile idiopathic arthritis.

There is accumulating evidence for a key role of interleukin (IL)-18 as a driver of systemic juvenile idiopathic arthritis (s-JIA) and its life-threating complication, macrophage activation syndrome (MAS).[1] IL-18 is the most effective factor for regulating natural killer (NK) cell activity. Although it augments the cytolytic activity of NK cells, exposure to high IL-18 concentration induces NK cell death.[2] NK cell dysfunction is a characteristic feature of MAS. Although a defect in the IL-18 receptor β phosphorylation has been proposed,[3] the exact mechanism remains unclear. To test the hypothesis that exposure to high IL-18 concentration, as a consequence of its overproduction in s-JIA, induces NK cell exhaustion and secondary transient NK cell dysfunction, we monitored changes in serum IL-18 from the active phase to remission in s-JIA patients and assessed NK cell activation in response to recombinant IL-18.

Four s-JIA patients and 10 healthy controls (HC) were enrolled. The clinical characteristics of the s-JIA patients are listed in Table S1. This study was approved by the institutional review board of Kanazawa University, and informed consent was obtained from all the participants. Whole blood was cultured for 2 h at 37°C with or without IL-18. Recombinant human IL-18 (MBL, Nagoya, Japan) was used at indicated concentrations in all *in vitro* cell culture experiments. Monoclonal antibodies to CD56 and CD69 were purchased from BD Biosciences (Franklin Lakes, NJ, USA) and Beckman Coulter (Brea, CA, USA), respectively. Cells were analyzed using FACSCalibur and CellQuest Pro (both from BD Biosciences). NK cell activation was assessed according to mean fluorescence intensity (MFI) of surface CD69 expression on $CD56^+$ NK cells. Serum IL-18 was measured using a commercial enzyme-linked immunosorbent assay (MBL, Nagoya, Japan). Correlations were expressed using Spearman's rank order correlation coefficient. $P < 0.05$ was considered to be statistically significant.

As shown in Figures S1 and S2, NK cells from HC were activated by IL-18 in a dose-dependent manner, whereas NK cell activation by IL-18 was impaired in active s-JIA patients. NK cell activation by IL-18 was impaired in all four active s-JIA patients. Next, we assessed the change in MFI of CD69 expression on $CD56^+$ NK cells, after stimulation with 10 ng/mL IL-18, defined as ΔMFI10. ΔMFI10 recovered in all four s-JIA patients as serum IL-18 decreased in the inactive phase (Fig. 1). There was a significant negative correlation between ΔMFI10 and serum IL-18 ($r = -0.9098$, $P < 0001$; Fig. S3), although the extent of recovery of NK cell response to IL-18 varied between the four s-JIA patients.

Decreased NK cytotoxic activity is associated with decreased perforin expression on NK cells in some s-JIA patients,[4] but most s-JIA patients have a defect in NK cytotoxic activity, indicating the involvement of secondary effectors. IL-18 has been shown to play a key role in the pathogenesis of both s-JIA and MAS.[1] Recently, this was illustrated by the persistently elevated IL-18 and recurrent MAS in patients with gain-of-function mutations in the NLRC4 inflammasome.[5]

In the present study, NK cell activation by IL-18 was impaired in patients with active s-JIA. Furthermore, NK cell activation was restored by exogenous IL-18 stimulation in patients with s-JIA in whom serum IL-18 was decreased after starting treatment. Furthermore, NK cell activation by IL-18 stimulation

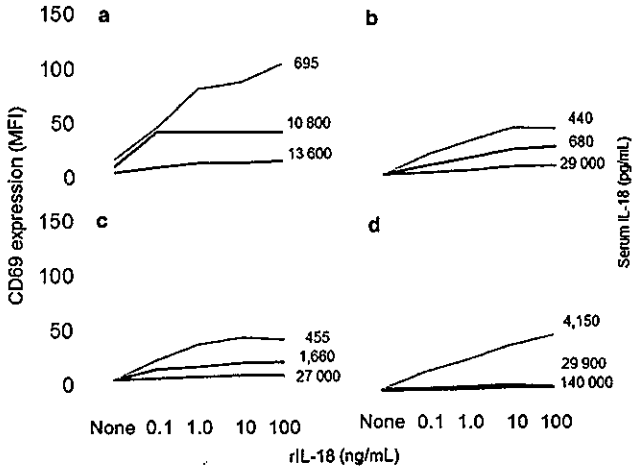

Fig. 1 Change in mean fluorescence intensity (MFI) of CD69 expression on $CD56^+$ natural killer (NK) cells after stimulation with 10 ng/mL interleukin (IL)-18 in patients (a) 1, (b) 2, (c) 3 and (d) 4 with systemic juvenile idiopathic arthritis (s-JIA). Blue line, active phase of s-JIA; red and green lines, inactive phase of s-JIA at several weeks and several months after starting treatments. rIL-18, recombinant IL-18.

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RESEARCH ARTICLE

Role of selected polymorphisms in determining muscle fiber composition in Japanese men and women

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Kumagai H, Tobina T, Ichinoseki-Sekine N, Kakigi R, Tsuzuki T, Zempo H, Shiose K, Yoshimura E, Kumahara H, Ayabe M, Higaki Y, Yamada R, Kobayashi H, Kiyonaga A, Naito H, Tanaka H, Fuku N. Role of selected polymorphisms in determining muscle fiber composition in Japanese men and women. *J Appl Physiol* 124: 1377–1384, 2018. First published January 18, 2018; doi:10.1152/japplphysiol.00953.2017.—Genetic polymorphisms and sex differences are suggested to affect muscle fiber composition; however, no study has investigated the effects of genetic polymorphisms on muscle fiber composition with respect to sex differences. Therefore, the present study examined the effects of genetic polymorphisms on muscle fiber composition with respect to sex differences in the Japanese population. The present study included 211 healthy Japanese individuals (102 men and 109 women). Muscle biopsies were obtained from the vastus lateralis to determine the proportion of myosin heavy chain (MHC) isoforms (MHC-I, MHC-IIa, and MHC-IIx). Moreover, we analyzed polymorphisms in α-actinin-3 gene (*ACTN3*; rs1815739), angiotensin-converting enzyme gene (*ACE*; rs4341), hypoxia-inducible factor 1 α gene (rs11549465), vascular endothelial growth factor receptor 2 gene (rs1870377), and angiotensin II receptor, type 2 gene (rs11091046), by TaqMan single-nucleotide polymorphism genotyping assays. The proportion of MHC-I was 9.8% lower in men than in women, whereas the proportion of MHC-IIa and MHC-IIx was higher in men than in women (5.0 and 4.6%, respectively). Men with the *ACTN3* RR + RX genotype had a 4.8% higher proportion of MHC-IIx than those with the *ACTN3* XX genotype. Moreover, men with the *ACE* ID + DD genotype had a 4.7% higher proportion of MHC-I than those with the *ACE* II genotype. Furthermore, a combined genotype of *ACTN3* R577X and *ACE* insertion/deletion (I/D) was significantly correlated with the proportion of MHC-I ($r = -0.23$) and MHC-IIx ($r = 0.27$) in men. In contrast, no significant correlation was observed between the examined polymorphisms and muscle fiber composition in women. These results suggest that the *ACTN3* R577X and *ACE* I/D polymorphisms independently affect the proportion of human skeletal muscle fibers MHC-I and MHC-IIx in men but not in women.

NEW & NOTEWORTHY In men, the RR + RX genotype of the α-actinin-3 gene (*ACTN3*) R577X polymorphism was associated with a higher proportion of myosin heavy chain (MHC)-IIx. The ID + DD genotype of the angiotensin-converting enzyme gene (*ACE*) insertion/deletion (I/D) polymorphism, in contrast to a previous finding, was associated with a higher proportion of MHC-I in men. In addition, the combined genotype of these polymorphisms was correlated with the proportion of MHC-I and MHC-IIx in men. Thus *ACTN3* R577X and *ACE* I/D polymorphisms influence the muscle fiber composition in Japanese men.

ACE; ACTN3; myosin heavy chain isoform; polymorphism; sex difference

INTRODUCTION

Human skeletal muscles are composed of two main fiber types, namely, types I and II; type II muscle fibers are further divided into subgroups IIa and IIx (8). Type I fibers show high resistance to fatigue and are suitable for endurance performance, type IIa fibers are suitable for medium-term anaerobic exercise, and type IIx fibers are suitable for short bursts of strength and speed (5, 14). Type I fibers contain high levels of oxidative enzymes and low levels of glycolytic enzymes, whereas type IIx fibers contain high levels of glycolytic enzymes and low levels of oxidative enzymes; in contrast, the properties of type IIa fibers are intermediate to those of types I and IIx fibers (11). Simoneau and Bouchard (38) reported large, interindividual differences in the fiber-type composition of human skeletal muscle (i.e., 15–85% type I fibers, 5–77% type IIa, 0–44% type IIx) in healthy individuals. This variation in the composition of skeletal muscle fibers partly explains the marked difference in the physical performance of individuals, such as endurance running performance (32, 49), and occur-

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In silico study of medical decision-making for rare diseases: heterogeneity of decision-makers in a population improves overall benefit

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ABSTRACT

Background. Medical decision-making is difficult when information is limited due to its rareness. For example, there are two treatment options for patients affected by a rare disease with high lethality. The information about both treatment effects is unavailable or very limited. Patients are inclined to accept one of the interventions rather than waiting for death, but they are reluctant to be assigned the inferior one. While a single patient selects one treatment that seems better based on the limited information, he or she loses the chance to select the other treatment, which may be the better option. This is the so-called dilemma between exploitation (enjoying the benefits of using current knowledge) and exploration (taking the risk to obtain new knowledge). In clinical settings, the statistical advice for individual patients seems to be the maximum expected success rate or something equivalent and patients' selections tend to be homogeneous, which does not solve the dilemma. In this study, our aim is to investigate the effects of the heterogeneity of decision-makers in the decision process.

Methods. Here, we proposed a decision strategy that introduced the heterogeneity of decision-makers by considering patients' self-decisions where the patients' heterogeneous attitudes towards the treatment are integrated into the probabilistic utility function based on the Beta Bayesian posterior. Based on the context of two-armed bandit treatment options with limited information, we compared the overall success rate of treatment between our heterogeneous decision strategy and a homogeneous decision strategy that is defined to select the treatment with the largest posterior mean.

Results. The heterogeneity of decision-makers in a population improved the overall benefit of treatment under some conditions.

Discussion. In clinical settings, there exists heterogeneity of decision-making among patients. Our study investigated a targeting strategy by respecting the self-decision of all individuals and found that the heterogeneity of decision-making can improve the overall benefit under some conditions. In addition, this outperformance may suggest that heterogeneity of decision-making is of importance to human beings. Besides the ethical merit, our findings provide meaningful ideas for better strategies towards decision-making dilemmas in clinical settings for rare diseases or cases where only limited information is available. Furthermore, it is suggested to investigate the effects of heterogeneity of decision-making in other fashions, such as genetic heterogeneity and phenotypic heterogeneity.

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ORIGINAL ARTICLE

Disease activity, treatment and long-term prognosis of adult juvenile idiopathic arthritis patients compared with rheumatoid arthritis patients

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ABSTRACT

Objective: To evaluate the difference between adult juvenile idiopathic arthritis (JIA, starting at <16 years) and rheumatoid arthritis (RA).

Methods: Data on 128 adult JIA patients were from the National Database of Rheumatic Diseases in Japan (NinJa), 2014, divided into 4 groups by period of disease onset (Group 1: 2000–2013, $n=32$; Group 2: 1981–1999, $n=32$; Group 3: 1966–1980, $n=31$; Group 4: ~1965, $n=33$). Disease activity, treatment and long-term prognosis of adult JIA patients were compared with RA patients matched for sex- and disease duration in each era.

Results: In Groups 1 and 2, adult JIA patients had significantly lower clinical disease activity indices (CDAI) (Group 1: adult JIA 1.5 [0.4–6.9]-vs-RA 5.3 [2.5–10.3], $p=.001$, Group 2: 2.6 [0.6–9.0]-vs-6.9 [3.5–11.0], $p=.001$, shown as median [quartile range], p-value, respectively), and had higher CDAI remission rates than RA patients (Group 1: 54.8%-vs-28.2%, $p=.002$, Group 2: 51.7%-vs-17.0%, $p<.001$). More adult JIA than RA patients in Group 1 used biologics (62.5%-vs-24.7%, $p<.001$). However, there were no adult JIA-vs-RA differences in joint destruction and physical function in any group.

Conclusions: Adult rheumatologists must recognize that adult JIA patients are different from RA patients even when disease duration is the same.

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KEYWORDS
Transition; adult Juvenile idiopathic arthritis (JIA); rheumatoid arthritis (RA)

Introduction

Juvenile idiopathic arthritis (JIA) is the most common form of arthritis in children. JIA is of unknown aetiology, beginning before the 16th birthday and persisting for at least 6 weeks [1]. Recently, treatment of JIA has been improved by employing biological therapies, as in rheumatoid arthritis (RA). Advances in pediatric medicine have resulted in increased numbers of adult patients who had childhood-onset chronic disease [2]. However, long-term follow-up data in other countries showed that JIA is still ongoing in 34–50% of JIA patients after they reach adulthood [3,4]. Therefore, a seamless transition in medical care from adolescence to adulthood (i.e. transitional care) is important [5,6]. However, adult rheumatologists who take over the care of adult JIA patients commonly have little knowledge of the pathogenesis, treatment and characteristics of JIA [7]. Moreover, it is unclear whether adult JIA patients should be treated similarly to RA patients [8]. To provide appropriate medical care, we should establish evidence-based management strategies for adult JIA.

In the pre-biologics era, only one study comparing the prognosis of JIA and RA has been published [9]. That study, which dealt with disease subtypes and the presence of antibody, indicated that oligoarticular JIA had the best outcome according to radiographic changes, whereas seropositive RA had the worst [9]. However, little evidence is available with regard to the difference in prognosis between adult JIA and RA in the biologics era. Although the long-term prognosis of JIA still requires elucidation, to the best of our knowledge, there are no large databases on adult JIA patients in Japan which could be explored for this purpose. For this reason, here we extracted data on adult JIA patients (defined as onset at <16 years of age) who were registered in the RA database as 'oligoarticular JIA (oligoarthritis) or polyarticular JIA (polyarthritis)'. We then compared their current status and prognosis with RA patients (defined as starting at ≧16 years of age) who had the same disease duration.

The National Database of Rheumatic Diseases in Japan (NinJa) was established in 2002 to reveal trends and problems associated with RA [10]. Nationwide, attending physicians in multiple centres register patients diagnosed with RA in this database, which includes disease activity, drug use, physical function, joint outcome and other data which are collected annually. Adult JIA patients (oligoarthritis or

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Review Article

Proposal for the development of biologics in pediatric rheumatology

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Abstract In order to assess the development, approval and early introduction into clinical practice of biologics in the pediatric field, we herein describe the current status of the development to approval of biologics as anti-rheumatic agents for children in Japan, discuss the present problems and provide a proposal for the future. It has become apparent that the duration of the review period required for the preparation of clinical trials and Pharmaceuticals and Medical Devices Agency approval is clearly reduced compared with the past. Thus, it was speculated that a rate-limiting step in the process from development to approval was the duration of clinical trials from start to end. Hence, we focused on the following key words with regard to promotion of the development of biologics and their early practical use: "registry", "centralization", and "global cooperation", all of which are related to the reduction of duration of a clinical trial. In conclusion, to reduce the duration of a clinical trial, it is essential to complete a world-scale registry system by developing the registry system established by the Pediatric Rheumatology Association of Japan. The next step is then to carefully plan to participate in the international network using the world-scale registry system, and develop global cooperative trials in which we can ensure a sufficient number of entries from Japan.

Key words biologic, centralization, international cooperation, pediatric rheumatology, registry.

Rheumatic diseases in childhood are regarded as incurable even now, and their pathogenesis has not been clarified. These are serious diseases that fulfill the following four conditions: (i) the pathogenesis has not been clarified; (ii) the therapeutic method has not been established; (iii) they are rare; and (iv) they need long-term medical treatment. Pediatric rheumatic diseases are systemic inflammatory diseases involving autoinflammation and autoimmunization, and their medication and treatment have dramatically advanced due to marked progress in diagnostic technology in inflammatory science and rheumatology. Therefore, favorable outcomes in the inflammatory state are expected without carrying over organ failure to adulthood if the principles of early diagnosis and early therapeutic intervention are maintained, and it is not too much to say that the advent of biologics facilitated this improvement. In the pediatric rheumatology field, four biologics (tocilizumab, etanercept, adalimumab and palivizumab) were approved in Japan by June 2017. In particular, new approval for pediatric indications for tocilizumab, etanercept and adalimumab – anti-rheumatic agents – has greatly changed medical treatment in the pediatric rheumatology field, by which many clinicians have realized that treatment has changed from care to cure.[1]

In this article, to assess the development, approval and early introduction into clinical practice of biologics in the pediatric field, we herein describe the current status of the development to approval of biologics as anti-rheumatic agents for children in Japan, discuss the present problems and provide a proposal for the future.

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Positioning of biologics as anti-rheumatic agents for children in Japan

In the early first decade of the 2000s, the major treatment for systemic-onset juvenile idiopathic arthritis (JIA) was steroid, and that for polyarticular JIA was methotrexate (MTX).[2] It was recognized, however, that 30–40% of pediatric patients did not respond to these treatments, nor did their symptoms easily resolve.[1]

Recently, indications for the use of biologics have been described according to guidelines for initial treatment[3,4] and guidelines for the use of biological preparations.[5–7] Namely,

II. 主要疾患の診断・治療の進歩　特発性炎症性筋疾患(多発筋炎・皮膚筋炎)

成人特発性炎症性筋疾患

五野貴久　　桑名正隆

Adult idiopathic inflammatory myopathies (polymyositis/dermatomyositis)

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Abstract

Idiopathic inflammatory myopathies (IIMs) are one of the skeletomuscular disorders, caused by aberrant autoimmunity against the muscles. Adult IIMs are classified into the following four groups: dermatomyositis (DM), amyopathic DM, polymyositis (PM)/immune-medaited necrotizing myopathy and inclusion body myositis, based on the European League Against Rheumatism/American College of Rheumatology Classification Criteria. Patients with PM/DM often have complications such as arthritis, cardiomyopathy, interstitial lung disease and malignancy. The measurement of myositis-specific autoantibodies (MSAs) is highly useful for predicting the occurrence of those complications associated with PM/DM, treatment response and prognosis. Therefore, physicias should determine the therapeutic strategy for PM/DM, taking the finding regarding MSAs into account.

Key words: dermatomyositis, polymyositis, myositis-specific autoantibody

はじめに

特発性炎症性筋疾患(idiopathic inflammatory myopathies: IIMs)は，文字通り特発性(原因不明で発病する)に筋肉に炎症が生じる疾患である．原因不明といっても，自己抗体の存在をはじめとした自己免疫の応答異常が病態に関わっていることは明らかとなっている．自己の免疫担当細胞が筋肉を攻撃し，筋炎が生じた結果，患者は筋痛や筋力低下を自覚し，日常生活動作に支障を来す．時にIIMsの患者では，筋肉以外の皮膚，関節，心臓，肺にも炎症が生じ得る．

本稿では，IIMsの中でも，皮膚筋炎(dermatomyositis: DM)や多発性筋炎(polymyositis: PM)に焦点を当て，診断と治療を中心に近年のIIMsの診療状況を紹介する．

1. 診　　断

PM/DMを診断する上で，1975年に提唱されたBohan & Peterの基準(表1)が国際的に広く用いられてきた[1]．このBohan & Peter基準は，皮疹の有無でPMとDMを分けており，シンプルで明解な基準である．しかし，本基準の問題点として，筋病理による正確な評価なしでは，筋ジストロフィーなどのIIMs以外の筋症をPMと誤診してしまうといった疾患特異

日本医科大学大学院医学研究科 アレルギー膠原病内科学分野

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実地医療に役立つ膠原病の診断・臓器障害の Pearls and Myths

炎症性筋疾患と自己抗体

桑名正隆
日本医科大学リウマチ・膠原病内科／くわな・まさたか

はじめに

多発性筋炎 polymyositis（PM）/皮膚筋炎 dermatomyositis（DM）は炎症性筋疾患の特発性病態に分類される．これら疾患は骨格筋の障害だけでなく，肺，皮膚など全身諸臓器の病変を伴い，臨床症状は患者ごとにきわめて多彩である．従来，抗 Jo-1 抗体が日常診療で測定できる唯一の PM/DM 関連自己抗体であったが，新規自己抗体が次々に同定され，それらが比較的均質な臨床病型と相関することが明らかにされた．これら自己抗体の多くが保険診療で測定できるようになり，診断，臓器障害や予後の予測，治療方針の決定に役立っている．本稿では PM/DM 診療に有用な自己抗体の活用法を概説する．

筋炎スペクトラムの多様性

これまで特発性炎症性筋疾患は成人 PM，成人 DM，小児筋炎，悪性腫瘍関連筋炎 cancer-associated myositis（CAM），膠原病関連筋炎（オーバーラップ症候群），封入体筋炎に分類されてきた（図 1）[1]．しかし，典型的な DM 皮疹があっても筋症状を欠く例が古くから指摘されており，臨床的に筋障害のない DM（clinically amyopathic DM：CADM）という疾患概念が提唱された．CADM の呼称に対し，筋炎の明確な場合を古典的 DM（classic DM：CDM）と呼ぶ．一方，筋病理の観点から PM，DM，封入体筋炎に加えて，炎症性細胞浸潤に乏しい免疫介在性壊死性筋症 immune-mediated necrotizing myopathy（IMNM）という概念が広く受け

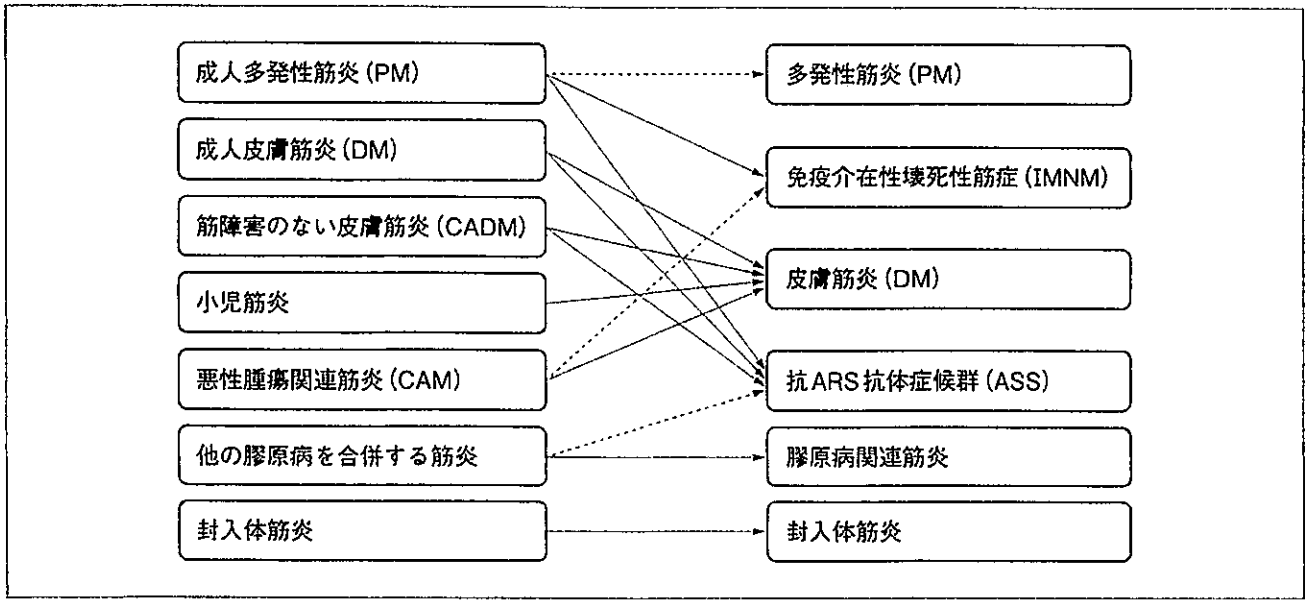

図 1　筋炎スペクトラムの臨床分類の変遷

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ANCA関連血管炎；専門領域の視点から

診療科によるANCA関連血管炎治療に対する考え方の相違について

Difference of real world treatment for ANCA-associated vasculitis among clinical departments

藤井隆夫[1]　野澤和久[2]　高崎芳成[2]

Key words：ANCA関連血管炎，ガイドライン，進行性腎障害，アンケート調査

はじめに

顕微鏡的多発血管炎(microscopic polyangiitis: MPA)と多発血管炎性肉芽腫症(granulomatosis with polyangiitis: GPA)は多臓器障害を起こす難病であるため，その診療には膠原病内科，腎臓内科，呼吸器内科，循環器内科，神経内科，耳鼻咽喉科，眼科など多科が関わるケースが多い．そして，その関係科間の連携が重要である．現在まで，複数の研究班で抗好中球細胞質抗体(ANCA)関連血管炎(ANCA-associated vasculitides: AAV)に関する診療ガイドラインが作成され，日常診療に利用されてきた．すなわち，血管炎症候群の診療ガイドライン(循環器病の診断と治療に関するガイドライン，Japanese Circulation Society，2008)[1]，AAVの診療ガイドライン(2014改訂版，厚労省研究班)[2]，エビデンスに基づく進行性腎障害診療ガイドライン(2014，厚労省研究班)[3]などが策定されている．しかし，それぞれ異なる診療科の医師を中心として作成されたものであるため，同じAAVに対する治療推奨が異なっているケースも見受けられた．その結果，日常臨床においても治療方針を他科とディスカッションする際に意見が食い違うことが経験される．筆者らは，厚生労働省難治性血管炎に対する調査研究班(横断協力分科会)に属し，AAVの診療ガイドラインを広めるとともに，標準化するための努力を行ってきた．

その一環として，膠原病内科，腎臓内科，呼吸器内科の医師を対象として，これら過去のガイドラインに対する医師へのアンケート調査を2015年に行った．この結果は，昨年出版されたAAVの診療ガイドライン2017[4]にも一部掲載されているが，本稿ではそのアンケート調査の結果を中心に紹介したい．

1. 研究方法

AAVの診療機会が多い日本リウマチ学会(925人)，日本呼吸器学会(631人)，日本腎臓学会(399人)の評議員(代議員)にメールを送付

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特集

クリニックで診る
小児膠原病・炎症性疾患 5

Key words
自己免疫性外分泌腺症
乾燥自覚症状
診断の手引き
新生児ループス

小児期のSjögren症候群の診断と外来フォローのポイント

富板美奈子*

小児期のSjögren症候群（Sjögren's syndrome：SS）は乾燥自覚症状を訴えることがほとんどなく，見逃されている例が多い．突然重要臓器障害をきたす例や，個人差は大きいが外分泌腺腺障害は進行するので早期診断と慎重な経過フォローが必要である．「小児期シェーグレン症候群診断の手引き」と，「小児期シェーグレン症候群診療の手引き」をもとに，クリニックでの小児期SSの診断とフォローについて，概説する．

はじめに—小児期のSjögren症候群

Sjögren症候群（Sjögren's syndrome：SS）は，涙腺・唾液腺を主とした外分泌腺の障害を特徴とする，全身の自己免疫性の炎症性疾患である．自己免疫性外分泌腺症（autoimmune exocrinopathy）ともいわれるが，外分泌腺のみでなく全身のさまざまな臓器に障害が起こり得る．

小児期のSSはまれといわれてきたが，1995年の日本小児リウマチ研究会による全国1,290の小児科常勤医がいる病院を対象とした小児膠原病疫学調査では5番目[1]，2016年の厚生労働科学研究班の小児科学会専門医教育認定施設における調査においては4番目に多い疾患として位置している[2]．患者の数の多い疾患は，若年性特発性関節炎（juvenile idiopathic arthritis：JIA），全身性エリテマトーデス（systemic erythematosus：SLE），若年性皮膚筋炎（juvenile dermatomyositis：JDM）の順で，この3つの疾患の位置は不動であり，1995年の調査では，4番目は混合性結合組織病（mixed connective tissue disease：MCTD）であった．

武井は，小児慢性特定疾患調査研究（小慢）に登録された患者データを解析して報告しているが，1999～2004年に登録された患者数は，全国で138名であった[3]．小児の人口10万人あたり0.53となるが，実際の登録患者の分布には著しい地域差がみられた．北海道・東北地方0.38，関東地方0.84，東海地方0.27，北陸地方0，近畿地方0.77，中国地方0.31，四国地方0.12，九州・沖縄地方0.24であり，症例登録数0の都道府県が20あった．この分布は当時の小児リウマチ専門医の分布とほぼ一致しており，小児リウマチ専門医の数が多い地方は患者登録数が多い．このことから，小児期のSS患者は診断されていない例が多くあることが予測される．

小児期SSを適切に診断するために，日本シェーグレン症候群学会と日本小児リウマチ学会は合同でワーキンググループ（WG）を立ち

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II. 主要疾患の診断・治療の進歩 シェーグレン症候群

小児期シェーグレン症候群

冨板美奈子

Sjögren's syndrome in pediatric age

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Abstract

Sjögren's syndrome (SS) is a systemic inflammatory disease with exocrinopathy characterized by xerostomia and xerophthalmia. It is thought to be rare in children, however, in Japan, it is the 4th major disease among the pediatric rheumatic diseases. Most pediatric patients with SS do not complain about sicca symptoms, which is the reason for under diagnosis of SS in this age group. The Japanese Society of Sjögren's Syndrome and the Pediatric Rheumatology Association in Japan made "The guidance for diagnosis of SS in children" together. Pediatric patients who have either symptoms or laboratory findings which suspect SS should be examined for immunological abnormality and damage of lacrimal glands and salivary glands. After those examinations, according to the scoring system, the patients will be classified into definite SS, probable SS, possible SS, needs follow-up or possibly non-SS. We should follow-up the patients with SS for a long time, because in those patients, extra-glandular manifestations will happen suddenly and glandular involvements progress gradually.

Key words: extra-glandular manifestations, recurrent swelling of the parotid gland, the guidance for diagnosis of SS in children

はじめに

Sjögren 症候群(Sjögren's syndrome: SS)は，涙腺・唾液腺を主とした全身の外分泌腺の障害を特徴とした全身の炎症性疾患である．患者の多くは自己抗体を産生することから，自己免疫疾患と考えられている．

SS は中年女性に多い疾患と考えられてきたが，小児のリウマチ性疾患の疫学調査を行うと，直近 2 回の調査では[1,2]，いずれも若年性特発性関節炎(juvenile idiopathic arthritis: JIA)，全身性エリテマトーデス(systemic lupus erythematosus: SLE)，若年性皮膚筋炎(juvenile dermatomyositis: JDM)に次いで 4 番目に多い疾患であり，患者数は 3 位の JDM とそれほど差はなかった．また，平成 10～16 年の小児慢性特定疾患調査研究事業で登録された小児 SS 患者の分布をみると，症例登録数 0 の県が 20 あるなど，登録症例数の地域差が著しかった[3]．この地域差は当時の小児リウマチ専門医(小児

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4 小児のシェーグレン症候群

Essential Points!

- 1999年の厚生省診断基準を満たした小児の一次性Sjögren症候群（SS）の病像をまとめると，発症年齢は小児期全体にわたっており，女児に多い．発熱，皮膚症状，耳下腺腫脹が初発症状として多い．血液検査では成人と同様，抗核抗体（ANA），IgG高値，リウマトイド因子（RF），抗SS-A/Ro抗体，抗SS-B/La抗体を認める．外分泌腺組織への細胞浸潤とFas/Fas Lを介したアポトーシスが認められる．唾液腺シンチグラフィの異常は認められるが，分泌量低下まで至る例は30%程度であり，眼科検査の異常を認める例はさらに少ない．腺外臓器障害は約半数で認められる．10年以上の長期経過ではほとんどの症例において何らかの乾燥自覚症状が出現するが，他覚症状と必ずしも一致しない．新たな腺外症状・臓器障害は半数で出現した．長期経過で他の膠原病を合併してくる例は14%程度あり，注意を要する．
- 新生児ループス（NLE）は，膠原病母体からの移行抗体により児に全身性エリテマトーデス（SLE）様の皮疹，先天性心ブロック（CHB）などが出現するものである．NLE発症のリスクは抗SS-A/Ro抗体のなかでもSS-A/Ro抗原の52 kDa蛋白の特定のアミノ酸を認識する抗体陽性例に高いが，胎児側の因子として特定のHLAも指摘されている．最も問題となるCHBは妊娠16～28週に発症することが多く，この時期は慎重に胎児エコーで経過を観察し，徐脈がみられた場合には母体にフッ化ステロイドを投与する．CHBの長期予後では拡張型心筋症が問題となる．

1 小児Sjögren症候群の病態

SSは，「自己免疫性外分泌腺症」ともいわれるように，涙腺・唾液腺を主とした外分泌腺の自己免疫性の炎症による障害を特徴とする全身疾患である[1]．SSは一般に「眼・口の乾く中年女性に多い疾患」と考えられている．眼や口の乾きを訴えて病院を受診する小児はほとんどいないため，小児ではまれと思われている．しかし，「眼や口の乾き」は，「自己免疫性外分泌腺症」の結果として生じるものである．そこで，「自己免疫」と「外分泌腺障害」を中心病態としてSSを考えて検索すると，小児でもこれらを認める患者が少なからず存在する[2,3]．

1995年に日本小児リウマチ研究会により行われた，100床以上で小児科常勤医のいる1,290病院を対象とした全国調査では，若年性特発性関節炎（juvenile idiopathic arthritis：JIA）1,606人，全身性エリテマトーデス（systemic lupus erythematosus：SLE）906人，若年性皮膚筋炎（juvenile dermatomyositis：JDM）/多発性筋炎320人，混合性結合組織病（mixed connective tissue disease：MCTD）93人，一次性・二次性SS 70人であった[5]．小児慢性特定疾患治療研究事業（小慢）に1998～2004年に新規登録された患者数から計算すると，小児のSSの有病率は小児人口10万人あたり0.53人であったが[6]，小慢制度では無治療の症例は登録できないことと，二次性SSは合併膠原病での登録が多くなるため，実際の患者はさらに多いことが推測されていた[7]．2016年の厚生労働科学研究「若年性特発性関節炎を主とした小児リウマチ性疾患の診断基準・重症度分類の標準化とエビデンスに基づいた診療ガイドラインの策定に関する研究」班が，小児科中核病院519施設に行ったアンケート調査（平成28年10月，回収473施設，回収率91.1%）によると，これらの病院で診療されている小児期発症SSは273名（有病率1.25/10万人）であり，小慢データより増加している[8]．しかし，地域別にみると症例数が0の県もあり，いまだ診断されていない症例が多いものと推測される．

1）臨床像

千葉大学医学部附属病院小児科における一次性SS症例を中心に小児のSSの臨床像をまとめる．

1989～2010年に受診し，1999厚生省基準を満たすSSと診断した患者は46名であった．うち，初診から1年以内に他の膠原病と診断されない患者（一次性SS）は28例．初診時あるいは初診から1年以内に他の膠原病の合併と診断した例（二次性SS）は18例であり，合併する膠原病はSLEが最も多かった．

他の膠原病を合併した症例は病像が一次性SSとは異なるため，以下は一次性SSについて述べる．

① 発症年齢・性差

一次性SS患者の推定される発症年齢を図1に示す．発症年齢は，SSに起因すると思われる何らかの症状が初めて現れた年齢とした．たとえば反復性耳下腺腫脹が症状である症例では，最初に耳下腺腫脹がみられた年齢を発症年齢と推定した．平均は10.1±3.9歳であったが，図1に示すように発症年齢は小児期のすべてにわたっている．男女比は1：8であり，成人同様，女児に多かった．

② 発症から初診時までに認められた症状

初診時までに認められた症状を表1に示す．発熱，皮膚症状，耳下腺腫脹が多い症状であり，口腔症状，眼症状を認めた例は多くない．耳下腺腫脹は，過去の文献でも小児期のSSの初発症状として報告が多い[3,4]．流行性耳下腺炎は出席停止扱いの伝染病となっているため，耳下腺腫脹を繰り返す児は学童期になると流行性耳下腺炎かどうかの抗体を調べることが多い．このときにIgG，抗核抗体（anti-nuclear antibody：ANA），リウマトイド因子（rheumatoid factor：RF），抗SS-A/Ro抗体をチェックすると，SSのスクリーニングが可能となる．初診時までに腺症状を認めた例は耳下腺腫脹11例とがま腫1例の計12例（42.9%）であり，表1のように，多くの症例が発熱，皮膚症状，関節痛など非特異的な腺外症状で発症していることが，小児期SSを診断するうえで重要な点である．また，血小板減少性紫斑病，無菌性髄膜炎などの重篤な腺外臓器の障害で発症してくる例もあることに注意を要する．

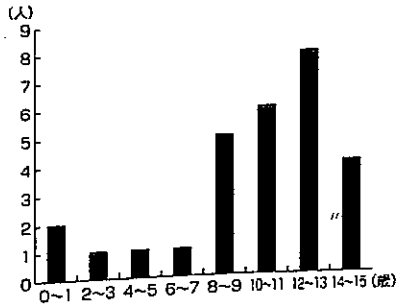

図1 発症推定年齢の分布

表1 初診時までにみられた症状

腺症状	乾燥自覚症状	0
	耳下腺腫脹	11
	がま腫	1
腺外症状	発熱	9
	皮疹	9
	関節症状	6
	リンパ節腫脹	2
	倦怠感	2
	ぶどう膜炎	1
	無菌性髄膜炎	1
	朝のこわばり	1
	出血傾向	1
	レイノー現象	1
	甲状腺腫	1
その他	検査で偶然	3

③ 血液検査所見

血液検査では，IgG高値，ANA陽性，RF陽性，抗SS-A/Ro抗体，抗SS-B/La抗体が成人とほぼ同様の頻度で認められる（図2）．ポリクローナルなB細胞の活性化を反映して，抗RNP抗体，抗DNA抗体が陽性になる例もあるが，これらの患者ではSLEやMCTDの発症を常に考慮して経過をみる必要がある．RFは3桁の高値となる例も珍しくないが，関節症状とは相関しない．

M3ムスカリン作動性アセチルコリン受容体（M3 muscarinic acetylcholine receptor：M3R）に対する抗体は，小児SSでは陽性者が多くみられ[9]，当科症例では24例中13例が陽性であった．Maenoら[10]がα-フォドリンに対する抗体はKobayashiら[9]，小児のSS患者には疾患特異的に，早期から出現すると報告している．

④ 外分泌腺障害

図3に各検査の陽性率を示す．

Ⅲ 小児期シェーグレン症候群 診断の手引き

・日本シェーグレン症候群学会，日本小児リウマチ学会合同のワーキンググループで，「小児期シェーグレン症候群 診断の手引き」を作成した．
・SSを示唆する臨床症状，検査所見を有する患者を診察したら，SSの可能性を考慮しつつ，鑑別診断，除外診断を進める．
・SSが疑わしければ，SSに特徴的な血液検査，外分泌腺の障害の検査を行う．
・それぞれの検査をスコアリングして診断し，SSらしさを分類する．

1 診断の手引き作成の経緯

第3章でも述べたように，小児期SSは診断されない例が多い．また，成人のSSのデータを基にした既存の診断基準・分類基準では，約1/4が診断されない．そこで，日本シェーグレン症候群学会と日本小児リウマチ学会は合同のワーキンググループ（WG）を立ち上げ，小児期SSの診断の手引きを作成した[1]．日本シェーグレン症候群学会からは関連する診療科（内科，眼科，耳鼻咽喉科，歯科口腔外科）の医師各1名，日本小児リウマチ学会からは全国8つの主な小児リウマチ専門施設から小児リウマチ専門医が参加した．小児科施設から集積した症例のデータから，診断の参考となる症状，合併症，検査所見などをまとめ，診断手順を作成した．両学会の理事会，運営委員会の承認のもと，2015年の小児慢性特定疾病対策事業の改訂に合わせ公表した．

2 診断スコア設定の経緯

本手引きでは特徴的な血液検査所見，外分泌腺の障害をそれぞれスコアリングし，両者を合わせて診断する．1999年の厚生省シェーグレン症候群改訂診断基準（厚生省改訂基準）[2]，2012年の米国リウマチ学会分類基準（ACR分類基準）[3]，ACR/EULAR分類基準[4]では，自己抗体が陰性でも唾液腺障害，涙腺障害の両方があれば，診断が可能となっている．しかし，小児では涙腺機能の低下を認める例が非常に少ないため，本手引きでは血液検査と外分泌腺異常（唾液腺，涙腺のいずれか）の組み合わせで診断することとした．

また，スコアの設定は，以下のように行った．

1）血液検査

①抗SS-A/Ro抗体，抗SS-B/La抗体：厚生省診断基準，ACR分類基準で，どちらかが陽性で1項目陽性とカウント．

②RF陽性：ACR分類基準で，③と合わせて，1項目陽性とカウント．

136 Sjögren 症候群

Sjögren's syndrome

富板美奈子*

Key Words：自己免疫性外分泌腺症，腺外臓器障害，反復性耳下腺腫脹

定　義：Sjögren 症候群（Sjögren's syndrome：SS）は，全身性の自己免疫性炎症性疾患である。自己免疫性外分泌腺症（autoimmune-exocrinopathy）ともいわれ，涙腺および耳下腺を主とした全身の外分泌腺の障害を特徴とするが，さまざまな全身症状，腺外臓器障害を伴う全身性疾患である。患者の多くは種々の自己抗体を有する。

中年女性に好発する眼と口の乾く病気，というイメージが一般的であるが，小児でもまれではなく，わが国の小児膠原病では，若年性特発性関節炎，全身性エリテマトーデス，若年性皮膚筋炎についで多い。小児患者は乾燥症状を訴えることはほとんどなく，不明熱や関節症状，あるいは反復性耳下腺腫脹が主訴であることが多い。

病態生理：病態の基本は，全身の外分泌腺の炎症および自己免疫反応による障害である。

なんらかの遺伝的素因をもつ個体の外分泌腺が，外的因子により傷害を受けると，局所で自己抗原の表出，サイトカイン産生，炎症性細胞の浸潤が生じ，自己免疫反応が成立する。炎症性細胞が産生するサイトカインや細胞間のシグナル伝達により新たな細胞浸潤，B 細胞からの自己抗体産生が起こり，炎症は慢性化する。

腺組織の障害の機序は主として腺細胞・導管上皮細胞のアポトーシスである。また，regeneration gene product（Reg）に対する自己抗体による唾液腺上皮の再生の阻害や，抗 M3 ムスカリン作動性アセチルコリンレセプター抗体，水チャンネル分子のアクアポリン 5 の分布異常による分泌機能の障害も報告されている。

SS では多彩な全身症状，腺外臓器障害を認める。B 細胞のポリクローナルな活性化によりγグロブリンの異常高値が起こり，高γグロブリン性紫斑や過粘稠度症候群をきたす。また，種々の自己抗体が産生され，自己免疫による溶血性貧血や血小板減少症，免疫複合体による血管炎も生じる。慢性炎症によるサイトカイン産生異常は発熱や全身倦怠感などをもたらす。外分泌腺以外の臓器にも炎症細胞浸潤が生じ，間質性肺炎や間質性腎炎を起こす。

臨床症状・経過・予後：小児では，乾燥症状を訴える患者は少なく，初診時までにみられる症状は，発熱，関節痛，皮疹などの膠原病を疑わせるような非特異的な腺外症状，反復性耳下腺腫脹が多い。倦怠感などの不定愁訴もみられる。また，血小板減少，溶血性貧血などの血液障害，無菌性髄膜炎，間質性腎炎など重篤な腺外臓器障害が契機となって診断される例もある。

発症年齢は小児期のほぼ全体にわたる。男女比はおおよそ 1：8 で女児が多い。

長期観察例では，半数が腺外臓器障害・症状を新たに発症し，10 年以上の経過で，ほぼ全例で眼や口腔のなんらかの乾燥症状がみられる。

10 年以上経過観察した成人症例 43 例のまとめで

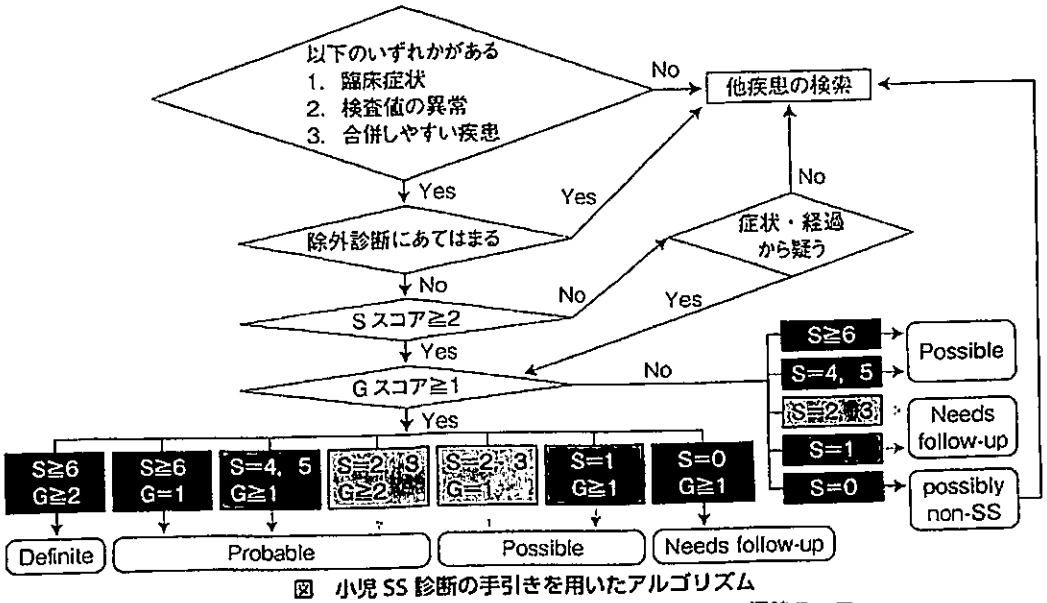

図　小児 SS 診断の手引きを用いたアルゴリズム

S スコア：血清スコア，G スコア：唾液腺スコアあるいは涙腺スコア

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C 膠原病

1 エリテマトーデス（LE）

ESSENTIAL POINTS

- 小児期のエリテマトーデス（LE）は，全身性エリテマトーデス（SLE）の病型が多い．
- 小児 SLE では初発症状として半数以上の症例で蝶形紅斑を認める．
- 小児 SLE は疾患活動性が高く，合併症の検索と初期治療が重要である．

どんな病気か？　日常診療で遭遇する頻度は？

「エリテマトーデス［紅斑性狼瘡（lupus erythematosus: LE）］」は，顔面に狼の噛み跡（lupus）のような侵食性・破壊性紅斑（erythema）を呈する疾患を指す言葉として用いられています．LE には，多彩な免疫異常による全身症状を呈する全身性エリテマトーデス（systemic LE: SLE），症状が皮膚のみに限局し全身症状を欠く皮膚限局性エリテマトーデス（cutaneous-limited LE: CLE），軽度の全身症状を認めるが SLE 分類基準を満たさない症例があります．小児では SLE の病型が多く認められます．

SLE は自己免疫疾患の 1 つです．①自己反応性 B 細胞による自己抗体の産生と自己反応性 T 細胞への抗原提示，②自己抗体と抗原により形成された免疫複合体の組織への沈着と補体の活性化，③自己反応性 T 細胞の組織浸潤と産生されるサイトカインによる自己反応性 B 細胞の活性化などの機序により全身の臓器障害が起こります．発熱，皮膚・粘膜症状，腎炎，神経・精神症状，血球減少に伴う症状，関節炎などを経過中に認めます．詳しい病因は未だに不明で，遺伝的素因と環境要因が関与しているといわれています．わが国での小児 SLE の有病率は 4.70 人 / 小児人口 10 万人（平成 12 年厚労科研報告書）と推定されています．

どのように診断をつけるか？　そのポイントは？

LE は疾患特異的な皮疹で診断し，SLE 分類基準に沿った全身症状の評価により病型を決定します．LE の特異的皮疹は皮疹の経過から急性型，亜急性型，慢性型に分類さ