Yagishita N, Aratani S, Fujita H, Yamano Y, Nishioka K, Nakajima T. The role of E3 ubiquitin ligase Synoviolin in bone destruction of rheumatoid arthritis. 第58回日本リウマチ学会総会・学術集会, 2014年4月24日～26日,東京都（港区）.

H. 知的財産権の出願・登録状況（予定を含む）

1. 特許取得

特願2014-226719, 発明者：植田幸嗣, 石原誠人, 山野嘉久, 出願年月日：2014年11月7日、ヒトTリンパ好性ウイルス-1 (HTLV-1)関連脊髄症(HAM/TSP)の検査方法、及び検査用キット

特願2014-209669、発明者：山野嘉久、清野研一郎、武藤真人、出願年月日：2014年10月14日、γδT細胞の製造方法および医薬

特許取得：特許番号：第5552630号、登録日：2014年6月6日、出願番号：特願2008-274514、発明者：山野嘉久、新谷奈津美、出願年月日：2008年10月24日、HTLV-I関連脊髄症を治療または予防するための医薬、およびHTLV-I関連脊髄症の患者に対する抗体療法の効果を試験する方法

2. 実用新案登録

特記事項なし

3. その他

特記事項なし

図１　対象RP患者の発症年齢構成

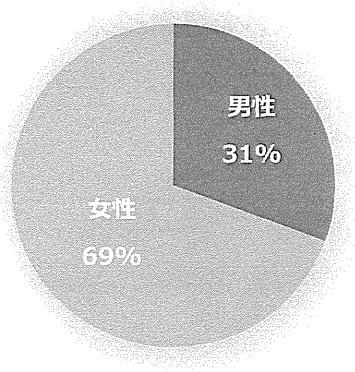



図２　対象RP患者の発症年齢構成

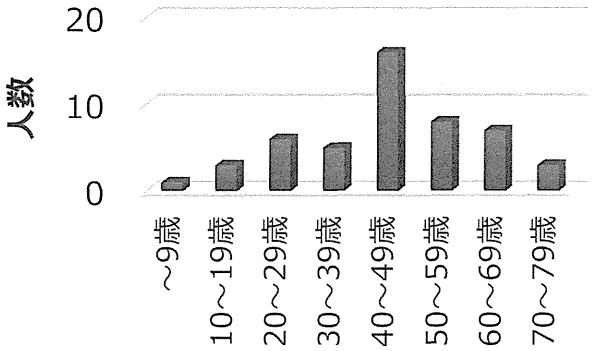



図３　対象RP患者の罹病期間

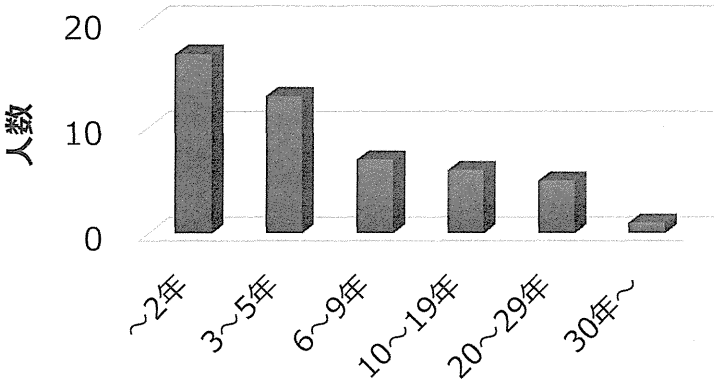
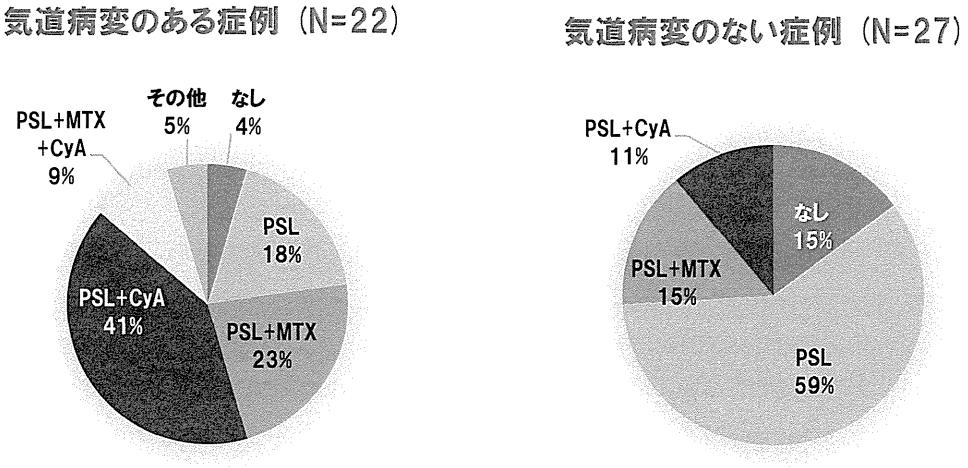
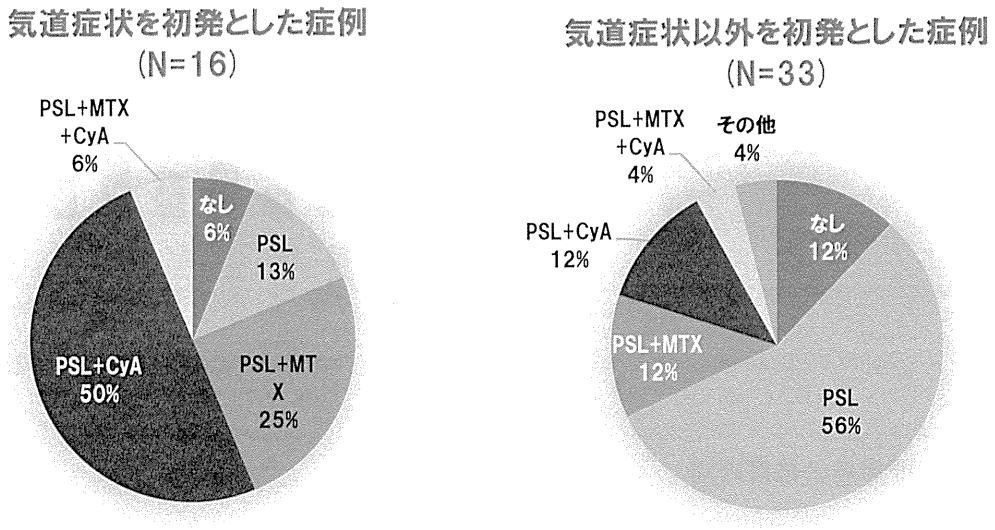



図４　気道病変の有無と現在の治療内容との関連




PSL=プレドニゾロン、MTX＝メトトレキサート、CyA=シクロスポリン

図５　初発症状としての気道症状の有無と現在の治療内容との関連




PSL=プレドニゾロン、MTX＝メトトレキサート、CyA=シクロスポリン

厚生労働科学研究費補助金 （難治性疾患政策研究事業）
分担研究報告書

# 再発性多発軟骨炎の診断と治療体系の確立
## －再発性多発軟骨炎における血清サイトカイン測定の意義－

研究分担者 清水 潤　聖マリアンナ医科大学免疫学・病害動物学

研究要旨： 再発性多発軟骨炎(relapsing polychondritis、以下 RP)は、全身の軟骨に炎症を来たしうる原因不明の難治性疾患である。本邦における患者数は 500 人程度と推察され、疫学・病態研究が端緒についたばかりであり、診断・治療指針は未確立である。

われわれは新規活動性指標の探索の一端として、RP患者血清の網羅的検討より血清sTREM-1レベルが有用であることを発見し報告した。昨年度は治療介入を見据えて、リンパ球機能より簡便な方法で評価しようと試みた。一般にヒトの自己免疫症候群は、細胞性免疫の抑制を要するTh1タイプの疾患と、自己抗体の上昇が顕著となる液性免疫が主体のTh2優勢タイプに2分される。この免疫所見をもとに治療方針を立てるためであるが、これにはこのタイプの規定には血中のサイトカインという物質の濃度を参考にする。RPの結果はTh1優勢タイプであった。

本年度はRP患者会の協力を得て、さらにサンプルを収集し上記所見の再検査を実施した。さらに同時に収集した、患者臨床情報との比較検討を試みた。その結果は、患者9症例のサンプルすべてのサイトカイン濃度が測定感度以下であった。患者臨床情報より、9症例ともに臨床的に寛解状態にあり、疾患活動性を示すものではないかと考えられた。

今後さらに症例を積み重ねTh1/Th17という自己免疫疾患における代表的な疾患パラメーターを解析し、治療指針確立の一助とすることを目的とする。

## A.研究目的

### i)研究の背景

**再発性多発軟骨炎の疫学調査**

再発性多発軟骨炎(relapsing polychondritis、以下 RP)は、原因不明で稀な難治性疾患である。本邦における疫学情報や病態研究は不十分であり、かつ診断・治療のための指針が作成されていない。その為、認知度が低く診断が見過ごされているケースも多く、気道軟骨病変などの臓器病変を伴う患者の予後は極めて不良であり、診断、治療法の確立が急務である。

我々は平成 21 年度厚生労働科学研究費補助金難治性疾患克服研究事業[課題名：再発性多発軟骨炎の診断と治療体系の確立]において、RP に対する患者実態・疫学調査(RP 239 症例)を行ない、本邦の患者実態として、本邦全体の患者数がおおよそ 500 人程度と推察されること、発症年齢は 3 歳より 97 歳まで多年齢層にわたり、平均は 52.7 歳であること、男性と女性の割合がほぼ同じであること、重症例となりやすい気道病変を持つ患者の割合が 50%程度になることを明らかにした。治療においては、気道病変はステロイド単独治療ではその病勢を抑えられないため、免疫抑制剤(メソトレキセート)が必要となることを発見した(文献 1)。

そこで現在免疫抑制剤を用いた臨床試験を計画しており、そのため新たな患者登録・追跡システムが必要となった。その際、適切でかつ正確な臨床検査データの収集と、疾患機序解明のための新規疾患パラメーターの開発が不可欠である。

**ii) 本年度研究の目的＝新規疾患パラメーターの開発の継続**

a) 単球性因子 TREM-1 （文献 1）

これまで RP 患者の疾患活動性は CRP や抗 type II コラーゲン抗体によって評価されており、急性期には多くの RP 患者で高値を認める。しかしながら、CRP が正常範囲内にある症例でも軟骨の破壊・線維化が進む例も多く、CRP では疾患活動性の評価が困難な面がある。また抗 type II コラーゲン抗体も疾患活動性との相関が報告されているが、陽性者は RP 患者の 30～50%にすぎず、感度・特異度もあまり高くないという報告もある。そこで、昨年度までに RP を検出する感度のよいマーカーを同定する目的で 28 種類のマーカー候補分子の中から、健常者と比較して RP 患者血清で有意に高値を示す分子を探索し、可溶性 TREM-1(sTREM-1)、インターフェロン $\gamma$、CCL4/MIP-1$\beta$、VEGF および MMP-3 を同定した。その中でも血清 sTREM-1 レベルは活動性 RP および非活動性 RP も区別することが可能であり、RP の疾患活動性マーカーとして優れていることを発見した。

b) 血清サイトカイン

ヒトの免疫機能は、自然免疫と獲得免疫にてなりたっており、上記 a)の TREM-1 は主に自然免疫の作用によるバイオマーカーである。さらに自然免疫に加えて獲得免疫の異常を研究することは治療効果を上昇させるために重要なことと考える。近年、様々なヒト免疫疾患において Th1 細胞および Th17 細胞という獲得免疫の主要な細胞に異常がみられることが報告されている。昨年度はこの細胞群の維持に必須であるサイトカインの血中濃度を測定した。

獲得免疫の要である T 細胞は、生体の局所にあわせた機能の発揮のため、網内系においていくつかのサブセットに分化する。Th1 細胞/Th2 細胞/Th17 細胞は、代表的な炎症惹起性のサブセットと考えられており、それぞれ細胞内寄生菌排除、抗体産生による細胞外寄生菌排除、真菌排除を任務とすると考えられている。その任務を遂行するにあたって必要となるのがサイトカインである。Th1 細胞/Th2 細胞/Th17 細胞は、それぞれ IL-12、IL-4、IL-23 というサイトカインを要する。炎症を惹起するためにそれぞれのリンパ球が分泌する物質もサイトカインであり、IFN$\gamma$、IL-4、IL-17 によって適切な免疫反応を起こすことによって外敵を排除する。

ヒト免疫疾患ではこれらのサイトカインが異常に分泌される状態と考えられている。代表的な疾患は Th1 細胞/Th2 細胞/Th17 細胞の異常の順で、関節リウマチ/SLE/炎症性腸疾患とされている（文献 2～5）。この疾患概念にてすべての免疫疾患において、おおよその治療指針が考えられている。

25 年度は疾患および健常者血清中の IFN$\gamma$、IL-12、IL-17 および IL-23 濃度を観察し、生体内での T 細胞分化誘導環境を検討した。

対象は RP6 例、健常者 8 例、疾患コントロールとしてベーチェット病 4 例。それぞれのキットを用い測定した。

RP において Th1 細胞が産生する IFN$\gamma$ の上昇、Th1 細胞の維持に重要な IL-12 の低下がみられ、Th1 細胞の過剰な活性化とそのネガティブフィードバックが考察された（図 1)。

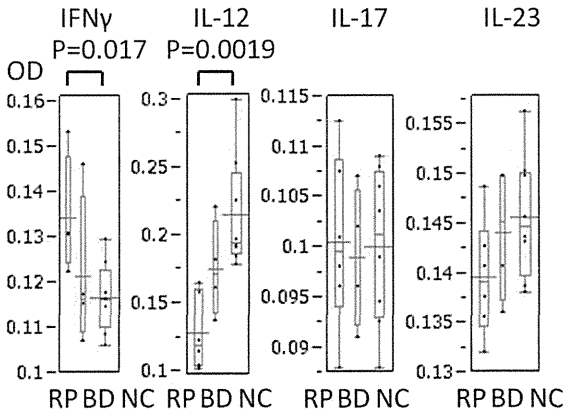


図1　RP、ベーチェット病（BD；疾患コントロール）、健常者（NC）の血中Th1/Th17細胞関連サイトカイン濃度

さらにそのIFNγ濃度はIL-23濃度と正相関（P=0.028）を示した（図2）。IL-23がその活性に重要に関与するTh17細胞もTh1細胞機能を介して、二次的にRPの病態形成に関わることが示唆される。

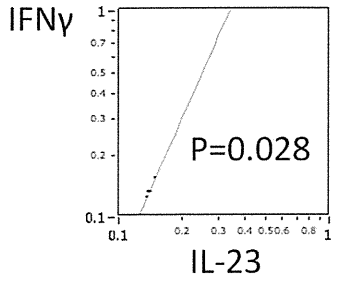



図2　RPにおける血中サイトカイン濃度の相関検討

**iii) 期待される研究成果**

①RP の病態・病勢を的確に反映する、簡便な検査法の確立。

②RP に有効性が高いと考えられるメソトレキセート（MTX）治療の前向き研究における評価方法の確立。

③情報収集の多元化による、患者訴えの綿密な収集。

## B. 平成 26 年度研究結果

**i) RP 患者会**

RP の患者会は平成 24 年 10 月に前身の「患者支援の会」を引き継ぐ形で発足した。以後、患者会総会の開催に合わせて、特に血清や血球の組織バンクへの登録につき支援をお願いしてきた。今回の解析サンプルについても平成 26 年 6 月開催の総会の開催時にご協力いただいた検体 9 検体である。性別は男性 3 症例、女性 6 症例。平均年齢は 46.9±15.6（SD）才であった。同時に臨床情報もご提供いただいたが、9 症例中 PSL、MTX の投薬を受けているものがそれぞれ 5 症例および 2 症例であり、全員が外来通院中。気道病変を認めるものが 2 症例で、寛解中と考えられる症例が 3 症例あった。

**ii) J-RARE**

これは希少疾患を対象とした、患者自身が健康情報や医療情報を入力する患者情報登録サイト（患者レジストリ）である。本研究班は厚生労働科学研究費補助金難治性疾患克服研究事業「患者支援団体等が主体的に難病研究支援を実施するための体制構築に向けた研究（JPA 研究班）」とともに上記患者主体レジストリ立ち上げを目指してきたが、平成 25 年 9 月 26 日より運営を開始した。現在登録を進めている段階であり、今後さらに研究をすすめる必要がある。しかしながらその理念からは上記 i)のような患者基本情報だけではなく、患者・医師間のリアルタイム連結による、臨床サンプルの収集を可能にする。

**iii) RP 血清中 Th1/Th17 細胞関連サイトカイン濃度の検討**

血清 IFNγ 濃度の測定のみ実施したが、今回の検討では 9 症例すべてが測定感度以下という結果であった。

疾患の活動性を示すものと考えている。

## C. 倫理面への配慮

**i) 臨床試験の実施について**

臨床検体の収集に際しては、本学の生命倫理委員会で承認された（承認番号：第 1625 号）同意書を用いて、不利益や危険性の排除などに関するインフォームドコンセントを行った。また検体は、提供者を特定できないように個人情報管理者が連結不可能匿名化により番号化し、

患者の人権擁護に努めた。

**ii) 被験者の同意取得方法**

患者が研究に参加を希望する際、被験者（あるいは法定代理人）から文書による同意を取得した。同意取得に当たっては、臨床試験審査委員会の承認を受けた同意説明文書を用いて、担当医師から研究の目的、方法、プライバシーに関する遵守事項、同意しない場合でも不利益を受けないこと、同意した場合でも随時これを撤回できること、被験者の人権保護など必要な事項について被験者（あるいは法定代理人）に十分説明し、被験者の自由意思による同意を文書で得ることとした。

**iii) 中止・脱落基準**

研究に同意した患者が自由意思で撤回を希望した場合は、この患者を対象とした研究を中止することとした。

**iv) 生体試料提供者の人権擁護について**

患者の生体試料の一部を用いて研究を実施する場合は、研究機関の生命倫理委員会の許可と指導のもとに、研究代表者の責任において秘密保持を厳守する予定である。被験者からの同意取得の後に収集された試料は、個人情報管理者により、まず連結可能匿名化の方法によって試料番号が付与され、研究実施者は匿名化（番号化）された試料のみを受け取るため、提供者を特定できない。また、いかなる研究成果の公表においても個人名およびそれを想起させることのないように留意することとした。

## D. 結語

今回の結果からは、血清サイトカイン濃度はRP重症度判定に応用できる可能性が示唆された。さらにTh2細胞/Th17細胞関連のサイトカイン濃度も検討し、病態・病勢の機序についても研究をすすめる。

## E. 健康危険情報

特記事項なし。

## F. 文献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3) Shimizu J, Takai K, Fujiwara N et al (2012) Excessive CD4+ T cells co-expressing interleukin-17 and interferon-$\gamma$ in patients with Behçet's disease. Clin Exp Immunol 168:68-74
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## G. 知的財産権の出願、登録状況

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。

# Ⅲ．研究成果の発表に関する一覧表

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 |
|---|---|---|---|---|---|
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| Oka H, Yamano Y, Shimizu J, Yudoh K, Suzuki N. | A large-scale survey of patients with relapsing polychondritis in Japan. | Inflammation and Regeneration | 34(3) | 149-156 | 2014 |
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| Suzuki N, Shimizu J, Oka H, Yamano Y, Yudoh K. | Cardiac Involvement of Relapsing Polychondritis in Japan | | 投稿中. | | |

# Ⅳ. 研究成果の刊行物・別刷

# Cardiac Involvement of Relapsing Polychondritis in Japan;

# An Epidemiological Study

by

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Key index terms: Relapsing polychondritis, Epidemiology, Coronary heart disease, Valvular heart disease, Aortic lesions

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Conflict of Interest: None

Short running footline: Cardiac involvement of RP in Japan

Relapsing polychondritis (RP) is a relatively rare disease, exhibiting swelling of the ear, destruction of the nose, fever, and arthritis often accompanying autoimmune reactions [1]. Tracheobroncheal involvement was potentially lethal through the occlusion [2]. Cardiac complications of RP begin to attract increasing attention because it is the second most frequent cause of mortality in this disease [3, 4, 5].

We conducted large scale epidemiological study in Japan [2] and revealed the high mortality rate in RP patients with cardiac involvement. We reanalyzed the data in view of cardiac involvement in patients with RP.

A Multi-institutional study survey of Japanese major medical facilities was conducted from July to December 2009 [2, 6]. All subjects being sent the questionnaire were informed of the purpose of the study and the responses would be kept confidential. All the authors reviewed the questionnaire.

We obtained responses from 121 facilities and clinical information of 239 RP patients was accumulated. The average age of onset diagnosis was 52.7 years old (range, 3~97) and the male-to-female ratio was 1.1:1 (127 males, 112 females) [2].

Biopsies were performed in 228 patients (95.4 %) and histological confirmation of RP was obtained in 138 patients (57.7 %). Auricular and nasal chondritis were shown in 187 patients (78.2 %) and 94 patients (39.3 %), respectively, during follow-up. One hundred and twenty patients (50 %) showed airway involvement. Forty nine patients (20.5 %) suffered from upper airway collapse and 42 patients (17.6 %) underwent tracheotomy.

Among 239 RP patients, 17 cases (7.1 %) developed cardiac

involvement. Mean age of onset of RP with cardiac involvement was 64.6 years old, suggesting that cardiac involvement developed later than other patient group. The ratio of men to women was 3.25 to 1 and thus men predominantly developed cardiac symptoms. RP patients with cardiac involvement were diagnosed with the diagnostic criterion [7], accompanying the histological confirmation (all, auricular chondritis) in 8 patients (53 % of the 15 patients who had histological examinations). When cardiovascular symptom is the first symptom appeared in the RP patients, even though such patients are not prevalent, it is hard to reach final diagnosis of RP. Thus, it is possible that prevalent rate of cardiovascular symptoms is underestimated in Japan. In the literatures, cardiac involvement was reported to be 6 to 23 % in patients with RP, almost comparable with that of Japan [5].

Differential diagnosis of cardiovascular complications of RP, from such symptoms of atherosclerosis/aging origin was not completely clear from this type of epidemiological studies.

Japanese RP patients developed myocardial infarction/angina pectoris (5 cases out of 239 cases, 2.1 %), valvular heart disease (5 cases, 2.1 %; mitral regurgitation (MR) 3 cases; aortic regurgitation (AR) 2 cases) and aortic aneurysm/aortitis (3 cases, 1.7 %). It has been reported that MR and AR—attributable to progressive dilation of the aortic root of the ascending aorta rather than to inflammation of the valve leaflet—occur in about 2–6% of the patients [5, 8]. 2.1 % of the patients showed coronary artery diseases in this Japanese study. The underlying mechanism is uncertain, although vasculitis may account for a few cases.

Our survey revealed that RP death rate in Japan was 9 % [2]. When we focused on RP with cardiac involvement, 6 cases had died out of 17 cases; accordingly the death rate was 35 %. Three deaths were caused by valvular heart disease. The remaining two patients were myocardial infarction and severe cardiac failure. A patient died suddenly from uncertain causes. Even though complete heart block, aortic valve rupture and acute aortic insufficiency have been reported as fatal cardiovascular complications [5, 8], we did not obtain such information in this Japanese study.

In order to make more accurate and easier diagnosis of RP, we have to establish assay systems which measure RP specific and RP associated disease markers. We are going to study whether serum soluble triggering receptor expressed on myeloid cells 1 (sTREM1) levels become one of RP associated markers [9].

Further studies are needed to disclose the entire clinical pictures of RP patients with cardiac involvement [10]. In addition, conventional treatment, such as steroid and immunosuppressant, which had been administered on a vast majority of the patients, was not fully satisfactory. Establishment of a new therapeutic strategy for cardiac symptoms in patients with RP is awaited.

In conclusion, 7.1 % of Japanese patients with RP developed relatively severe cardiac involvement and cardiac involvement appeared to be a major determinant of disease severity in patients with RP in Japan as well.

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Original Article

# A large-scale survey of patients with relapsing polychondritis in Japan

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**Relapsing polychondritis (RP) is a multisystem disorder characterized by recurrent inflammation and destruction of cartilage. The aim of this study is to assess the clinical characteristics of patients with RP in Japan, which remain unclear.**

**A survey was sent to 395 experienced clinicians who worked in Japanese major institutions. The questionnaire was designed to assess patients' profiles, clinical features, diagnosis, treatments and present complications. The response rate was 30.6% and 239 RP patient data were collected.**

**The average age of onset diagnosis was 52.7 years (range, 3-97) and the male-to-female ratio was 1.1:1. Clinical features of patients with RP in Japan were similar to previous studies. Airway and cardiac involvement, both of which were potentially serious complications of RP, were observed in 119 (49.8%) and 17 patients (7.1 %), respectively. Four patients (1.7%) had myelodysplasia. In addition to oral prednisolone (91.6%), patients received methotrexate (19.7%), cyclophosphamide (12.6%) and cyclosporine (8.4%) with clinical response rates of 64.0%, 66.7% and 73.7%, respectively.**

**42 patients (17.6%) required and underwent tracheotomy, including 12 patients (5.0%) who were treated with prednisolone only. 22 patients (9.2%) underwent stent placement and/or tracheotomy. The overall mortality rate was 9.0% (22 patients) and respiratory failure and pulmonary infection were the leading causes of death in patients with RP.**

**Airway involvement of RP was fundamentally progressive and required frequent clinical checks and appropriate intervention with administration of both prednisolone and immunosuppressant. Cardiac involvement of RP was less common in Japan as compared with that in Western countries.**

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## Introduction

Relapsing polychondritis (RP) is an uncommon inflammatory disorder of unknown etiology that affects the cartilage of ear, nose, peripheral joints, and respiratory tract[1-4]. Other proteoglycan-rich tissues such as eye, inner ear, heart, blood vessels, and kidneys are also involved[1-4]. When the visceral is affected by inflammation, RP is a potentially lethal disease.

The epidemiological studies of this disease have been conducted in Caucasian population[4]. The incidence of RP in Rochester, Minnesota is estimated to be 3.5 cases per million populations per year[5]. It seems to occur with equal frequency in all racial groups, but there are very few data available on non-Caucasian populations. Several case series with a decade of RP patient data have been reported from South/North India[6, 7] and Singapore[8].

In 2012, RP Disease Activity Index (RPDAI), a preliminary score for assessing disease activity, was developed by worldwide specialists[9]. Nonetheless, even now, physicians treat patients with RP on the basis of largely empirical evidence because of the lack of large-scale survey and clinical guidelines for the management of patients.

Here, we conducted a survey of 239 patients with RP to outline the current epidemiology, clinical manifestations, management and long-term outcome of RP in Japan.

## Subjects and Methods

A Multi-institutional study survey of Japanese major medical facilities was conducted from July to December 2009. All subjects who were sent the questionnaire were informed of the purpose of the study and the responses would be kept confidential. All the authors reviewed the questionnaire.

We performed preliminary survey of clinical experience to treat patients with RP in 1894 Japanese medical facilities on July 1st, 2009, using a surveillance definition as follows: larger bed sizes (+200 or university hospitals) and adequate functions for RP treatments (providing services with eye-throat-nose, respiratory, chest surgery, dermatology, neurology and rheumatology divisions). We also reviewed recent Japanese clinical reports and research articles of RP using web accessible medical literature databases made by US National Library of Medicine, Japan Medical Abstracts Society and Japan University hospital Medical Information Network, and sent the initial survey questionnaire to the authors. Then, a main survey was sent to the 395 physicians who have returned a mail to us that the physicians have been treating or treated at least one patient with RP on August 14th, 2009. The patient data of the survey questionnaire were collected anonymously. This survey was approved by the ethics committee of St. Marianna University School of Medicine.

Table 1 Summary of Japan RP Questionnaire

| |
|---|
| a. Patients' profile |
| Sex, onset age, follow-up years and diagnostic delay |
| b. Clinical features |
| Primary and follow-up |
| c. Laboratory findings |
| Laboratory tests, image analysis and histopathologic features |
| d. Treatment |
| Non-steroidal anti-inflammatory, prednisolone, immunosuppressants, antibiotics and surgical intervention |
| e. Prognosis and complications |
| Tracheal collapse, tracheotomy, vulvar surgery and death |

The questionnaire consisted of 5 sections to assess patients' (a) profiles, (b) clinical features, (c) diagnosis, (d) treatments and (e) present complications. It was summarized in Table 1. We asked the physicians to give us the most current laboratory findings with respiratory function except the titers of anti-type II collagen antibody and pathological findings.

## Results

The survey response rate was 30.6% (121 of 395 surveyed physicians) and 239 RP patient data were collected.

## Patients' profiles

Patient characteristics in McAdam series[10] and current survey were summarized in Table 2. The male-to-female ratio was 1.13:1 (127 males and 112 females). Uni-modal age distribution of disease onset is indicated in Fig.1. The average age at onset was 52.7 years with a range from 3 to 97 and the average disease duration was 5.3 years with a range from 1 to 33. The ratios of patients whose disease duration was shorter than 2 and 5 years were 25 and 65 % of whole patients, respectively. We suggested that the time to diagnosis was not so long because a large part of patients had relatively short duration of disease. Older people

Table 2 Characteristics of patients with RP in McAdam series10) and current survey

| | McAdam (n=159) | | Current survey (n=239) | |
|---|---|---|---|---|
| Profile<br>Male-female ratio<br>Mean age<br>Mean age of disease onset<br>Disease duration (yr) | 83:76<br>44 | | 127:112<br>57 (range 6-104)<br>53 (range 3-97)<br>5.3 (range 1-33) | |
| Clinical features (%) | Onset | Follow-up | Onset | Follow-up |
| External ear | 26 | 89 | 57 | 78 |
| Internal ear | 6.4 | 46 | 3.8 | 27 |
| Nasal cartilage | 13 | 72 | 2,1 | 39 |
| Airway<br>laryngo<br>tracheobronchial | 14 | 56 | 17 | 50<br>20<br>41 |
| Eye<br>conjunctivitis<br>scleritis<br>uveitis | 14 | 65 | 9.2 | 46<br>15<br>26<br>11 |
| Arthritis | 23 | 81 | 6.2 | 39 |
| Skin | | 17 | | 13 |
| Cardiovascular | | 24 | | 7.1 |
| Neurological | | | 2.9 | 9.6 |
| Renal | | | | 6.7 |
| Myelodysplasia | | | | 1.7 |

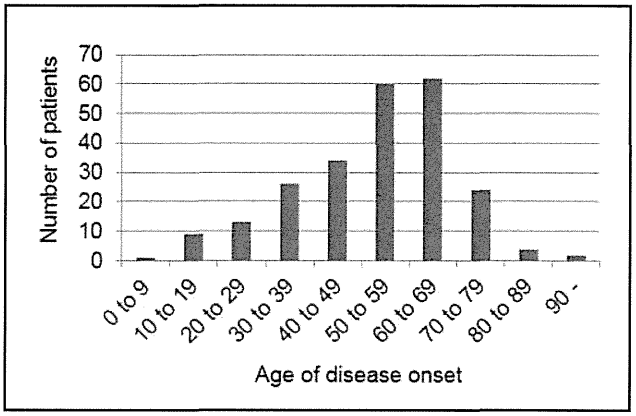


Fig.1 Age distribution of disease onset in patients with RP
The mean age at onset of disease was 52.7 years old with a range from 3 to 97 years old. Older people (more than 51 years old) tend to develop RP rather than younger people (0-20 years old).

(more than 51 years old) tend to develop RP rather than younger people (0-20 years old).

## Clinical features

Initial lesions and symptoms in patients with RP varied considerably. Auricular chondritis was shown in 137 patients (57.3%) and is the earliest and most frequent manifestation. 41 patients (17.2%) developed respiratory symptoms as an initial manifestation which included hoarseness, persistent cough, dyspnea, wheezing and inspiratory stridor caused by the inflammation of laryngeal, tracheal and bronchial cartilages.

Ocular symptoms (22 patients, 9.2%), arthritis (15 patients, 6.2%), inner ear disorder (9 patients, 3.8%), neurological symptoms (7 patients, 2.9%) and nasal chondritis (5 patients, 2.1%) were recognized in relatively small numbers of patients at the onset of disease.

The prevalence and severity of the disease symptoms increased during follow-up (Table 2).

Ninety-seven patients (40.6%), 47 patients (19.7%) and 119 patients (49.8%) showed tracheal lesion, laryngeal lesion and laryngotracheal involvement, respectively. Forty-nine patients (20.5%) suffered from upper airway collapse and 42 patients (17.6%) required tracheotomy. 22 patients (9.2%) underwent stent placement and 12 patients (5.0%) received nasal continuous positive airway pressure because of their tracheobronchomalacia.

Auricular and nasal chondritis were seen in 187 patients (78.2%) and 94 patients (39.3%), respectively. Saddle nose deformity after the nasal chondritis was observed in 76 patients (31.8%).

Otitis media complications with vestibular dysfunction were observed in 64 patients (26.8%). Prolonged inflammation in inner ear and vasculitis of internal auditory artery[2] caused hearing loss (52 patients, 21.8%) and the vestibular dysfunction (39 patients, 16.3%) such as dizziness, ataxia, nausea and vomiting.

Joint, skin and eye involvement were observed in 92 (38.5%), 32 (13.4%), and 109 (45.6%) patients, respectively. The arthritis was mainly asymmetric, migratory and non-erosive.

Dermatologic manifestations included the purpura, papules, macules, vesicles, bullae, chronic dermatitis and nodules. Ocular symptoms included recurrent episcleritis, conjunctivitis, keratitis, uveitis, proptosis, periorbital edema, tarsitis and extra-ocular muscle palsy.

Neurologic and renal involvements were observed in 23 patients (9.6%) and 16 patients (6.7%), respectively. Cardiovascular involvement, including aortic insufficiency, myocarditis, pericarditis, paroxysmal atrial tachycardia, heart block and vasculitis, was observed in 17 patients (7.1%).

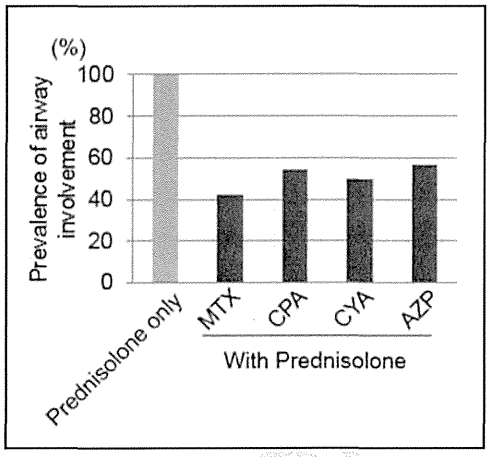


Fig.2 Effects of immunosuppressants to the airway involvement of RP patients

Prevalence rates of airway involvement in patients with RP were 100, 42.6, 50.0 and 57.0% in treatment with steroid only, steroid with MTX, CPA, CYA and AZP, respectively, with and/or after each treatment.

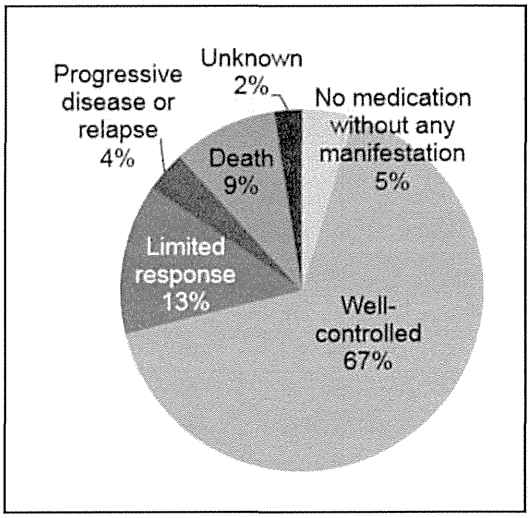


Fig.3 Summary of prognostic outcome in patients with RP in this survey

Medication was discontinued without any manifestation in 11 patients (4.6%). 159 patients (66.5%) were well controlled and, in total, 71.1% of patients in our cohort responded to the treatments. 32 patients (13.4%) showed limited response and 9 patients (3.8%) suffered from progressive disease or relapse. 22 patients (9.0%) died.

## Laboratory findings

Most of patients with RP showed the elevation of erythrocyte sedimentation rate (ESR, 68.2%) and C-reactive protein (CRP, 86.2%). Urinalysis was usually normal. Although the data were not routinely available, matrix metalloprotease (MMP)-3 and antibody to type II collagen were found in 20.1% and 13.8% of patients, respectively.

Conventional radiograph showed changes in larynx, trachea, surrounding soft tissues and bronchi. In two cases, respiratory tract involvement was assessed by laryngoscopy. Endobronchial ultrasonography revealed fragmentation and edema of tracheobronchial cartilage in two patients[11]. 3 dimensional-CT scan was performed in 61 patients (25.5%) and conventional CT was conducted in 30 patients (12.6%).

Biopsies were performed in 228 patients (95.4%) and 138 patients (60.5% of patients who underwent biopsy) were diagnosed with histological confirmation of RP.

## Treatments

Main treatment for RP patients even with airway involvement remains medical management. In the medication history profile, non-steroidal anti-inflammatory drugs were administered alone for 8 patients (3.3%) who had mild auricular or nasal chondritis. 219 patients (91.6%) had received at least one course of prednisolone through oral administration (204 patients, 85.4% of all patients), intravenous infusion (17 patients, 7.1%) and pulse therapy (40 patients, 16.7%). Low daily dose of prednisolone was administered in the majority of patients. Minocycline hydrochloride was used in 8 patients with RP but its effect remained unclear.

Immunosuppressants which were used against the chronic progression of RP included methotrexate (MTX, n=47), cyclophosphamide (CPA, n=30), cyclosporin A (CYA, n=20) and azathioprine (AZP, n=22). MTX, CPA, and CYA elicited considerable effects on clinical outcomes in 64.0%, 66.7%, and 73.7% of patients, respectively. MTX was added as an adjuvant treatment in refractory RP patients who required higher maintenance doses of prednisolone to reduce the overall steroid requirement. 3 patients were maintained with MTX alone. AZP was less effective than other agents and the rate was estimated as fewer than 40%. Tacrolims was used in 3 patients and ameliorated manifestations in one patient.

Of those 47 patients with the combined therapy of steroid with MTX, 20 patients (42.6%) had some respiratory symptoms and did not require any surgical intervention (Fig.2). In contrast, all 12 patients (5.0% of all patients)