「IgG4関連疾患の前方視治療研究」

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目的：梅原班では、下記の目的のために、前方視的治療研究を進めている。

IgG4 関連疾患の治療指針を確立する；本疾患にステロイド治療が有効な事は経験的に知られているが、初期投与量、漸減法、維持投与量などに関してはっきりしたエビデンスは無い。米国では、再発難治例に対する rituximab 投与の臨床試験が開始されようとしているが、それ以前に初期治療としてのステロイド治療のエビデンスを確立する事が先決である。

前方視臨床研究：「IgG4⁺MOLPS（IgG4 関連多臓器リンパ増殖症候群）のステロイド治療指針を決定するための第 II 相多施設共同前方視的治療研究」（UMIN :R000002820）
試験期間５年間、登録目標46例

倫理委員会承認および症例登録状況：
2012年１月末日現在、17施設（金沢医科大学、長岡赤十字病院、倉敷成人病センター、富山大学、西群馬病院、群馬県立がんセンター、札幌医科大学、諫早総合病院、長崎大学、筑波大学、神戸海星病院、福井大学、新潟大学、岡山大学、産業医科大学、長崎医療センター、三豊総合病院、以上承認順）で倫理委員会承認を得ている。５年間の試験期間のうち約３年が経過したが、予定登録ペースを上回る35例が既に登録されている。

まとめ：
各施設の諸先生方の御尽力により倫理委員会承認施設数も、登録症例数も着実に増えてきている。本邦発の IgG4 関連疾患の治療指針に関する、より質の高いエビデンスを確立するために前方視的臨床研究が重要である。本研究は今後も継続予定であり、参加施設の増加と、より積極的な症例登録を今後もお願いしたい。

【議事録】

Rituximabについて,Stoneが連続10例使っている。１例目Mayoでは、IgG4が下がらないことを再燃の根拠としている！

A:宜しくお願いします。

Q:後腹膜線維症。腎はいい。MDは再燃多い。臓器によって治癒がかわる可能性。

A:どこの臓器が多いとかはまだわからない。臓器別の議論は今から。現在は、経験的に使っている。

Q:ステロイドを使うタイミングは？症状(-)なら使わなくてもいいかも。再燃する病気であり、画像で悪化しても小波なら無視する。DX指針の次の一般の臨床医に対して何か示せ。

A:先ずは前方試験を。

「IgG4関連疾患の網羅的遺伝子発現解析」

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目　的

IgG4関連疾患の病態・病因解析を目的して、以下の２つの解析を進めてきた。
（１）患者末梢血リンパ球におけるトランスクリプトーム解析を行う。
（２）患者末梢血における血清プロテオミクス解析を行う。

材料と方法

（１） 健常人および患者の治療前後における末梢血リンパ球より全RNAをサンプルとして抽出した。DNAマイクロアレイ解析のプラットフォームとしては、Affymetrix社Human Gene 1.0 STアレイを利用した。解析ソフトウエアとしてはAgilent社GeneSpring version 11.0を利用し、遺伝子パスウエイデータベースにはIngenuity Pathways Analysis (IPA)を用いた。
（２） プロテオミクス解析には2次元電気泳動から発現差異のあるスポットを抽出してからLC-MS/MSを利用して同定を行った。

成　果

患者および健常人の発現パターンを比較して変動している遺伝子群を抽出した。このようにして得られた変動遺伝子群の機能をデータベース上で検索すると、免疫や炎症に関わる遺伝子群が多数含まれており、発症機序や病態との関わりが予想される。現在までに同定された疾患マーカーについて特許出願を行った（石垣靖人、友杉直久、正木康史、梅原久範：特願2010-194326「IgG4関連疾患マーカー及びその利用」）。さらにデータのバリデーションを進めて有用なマーカーの開拓につなげたいと考えている。

まとめ

今後は様々なデータセットとのデータの統合・比較を進めるとともに、発症の可能性や治療効果の判定に利用できるような遺伝子群の同定を進めていきたい。

【議事録】

Q:G4RDどういう人達に解析を
A:多くはMD like、リンパ増殖、複数臓器に渡る時は確診のもの

Q:個体差
A:個体差は大きい。この中でデータをとってくる。
Q:補正は？
A:大規模データによって補正をなくしていきたい。

「全ゲノム網羅的SNPを用いた自己免疫性膵炎の感受性遺伝子の解析」

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自己免疫性膵炎発症の背景には、遺伝と環境の両因子が関わっていると考えられる。しかし、残念なことに本疾患発症に影響を与える遺伝的要因は、いまだ明確にされていない。これまで我々は、疾患発症に寄与する多因子形質の遺伝子に HLA、Fc receptor-like 3 *(FCRL3)*遺伝子、cytotoxic T lymphocyte antigen *(CTLA4)*などを疾患感受性遺伝子として報告してきた。また、全染色体上に設けたマイクロサテライトマーカーを用いた相関解析から Potassium voltage-gated channel, shaker-related subfamily, member 3 (*KCNA3*) 遺伝子を疾患感受性候補遺伝子として報告した。更に最近、Affymetrix 社の GeneChip Human Mapping 500K Array Set (500,568 SNPs)を用いた相関解析を行い、$p < 1x10^{-5}$の有意差で、遺伝子内に2種類以上の有意差を示すSNPsを含む遺伝子を疾患感受性候補遺伝子として数十種類選択した。それらの中には機能的に興味ある遺伝子 *FCER2*(FC fragment of IgE, low affinity II, receptor for CD23)や *MIST* が観察された。FCER2はCD23とも呼ばれ、低親和性IgE受容体として、主に成熟B細胞、単球、濾胞樹状細胞に発現し、B細胞の活性化とIgE産生の制御に関与している。また、MISTはCLNKとも呼ばれ、T細胞およびB細胞抗原レセプター下流で免疫シグナリングを調節しているSLP-76と同じファミリーに属するアダプター分子であり、IgEレセプターを介したMAST細胞の脱顆粒反応や、サイトカイン刺激に伴う多様なシグナル伝達に関与している。このようにGWASを用いた解析により免疫学的に興味ある遺伝子が候補として挙げられたが、更に確証を得るには、サンプル数を増やし、一次試験で得た結果を別の集団で再現する確認試験、および他施設で行われた複数の研究結果を統合して分析するメタアナリシスを行う必要がある。また、感受性候補遺伝子の構造的相違が疾患に及ぼす影響を機能的に説明することが最も重要であると考えている。

【議事録】

Q:イントロンの機能に関しては？他疾患での報告は？
A:イントロンです。機能に関してはまだ。他疾患での報告はまだ。
Q:確認試験は？別の施設か？　　A:別の施設。
Q:自己免疫性膵炎について老人女性↑に多い。性差に対するgeneは？
A:今の後方試験では出ていない。
Q:高齢者に多い。Agingに対するgeneは？
A:いろいろ回復するgeneはあります。

「プロテオミクス解析による自己免疫性膵炎診断マーカーの探索」

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自己免疫性膵炎（AIP）を含むIgG4関連全身疾患は、高IgG4血症と病変腺組織中の著明なIgG4陽性形質細胞浸潤を特徴とする疾患である。血清IgG4はIgG4関連疾患の活動性指標として有用であるが、臓器特異性がない。膵病変の評価には、侵襲性の高い内視鏡下の造影検査などが必要であり、AIPの簡便な診断法の確立が望まれる。我々は、プロテオミクスを用い、IgG4関連全身疾患、特にAIPの新しい診断マーカーを探索した。

AIP患者（ステロイド治療前、治療後を含む）、アルコール性慢性膵炎患者、特発性膵炎患者および健常者の血清を用いた。ClinProtビーズ、MALDI-TOF/MS解析装置、および二次元電気泳動により解析を行った。

ClinProtシステムとMALDI-TOF/MSを用いたプロテオミクスでは、健常者とステロイド使用のないAIP患者群との比較で、AIP患者群で有意に上昇している2つのピーク（4963m/z、2560m/z）を認めた。但し、アルコール性慢性膵炎患者群でも上昇しており、疾患特異性に乏しかった。治療前後のAIP患者血清の比較では、治療後に有意に低下するピーク蛋白（5900m/z、3224m/z、2660m/zなど）、および治療後に有意に上昇するピーク蛋白（2953m/zなど）を認めた。また、二次元電気泳動法によるプロテオミクスでも治療により増減する多数の蛋白が認められ、そのうち3つの蛋白（Apolipoprotein E、Transthyretin、amyloid-P component）が同定された。これらはAIPの新しい診断マーカー候補であり、治療効果予測などに用いられる可能性があると考えられた。

【議事録】

Q:発症機序に対するアプローチ
A:微量なものを取る。多方に渡る為サンプルを集める事。
Q:ビーズを使ったやつについて。ビーズをかえることでデータはかわるか？
A:市販品です。性質がちがうとバラバラになる。
Q:タンパクごとにちがうとオーバーラップは？
A:ない。同定しやすいものから拾う。
Q:データがどのようにかわるのか？　A:はっきり比べてはいない。保存などが違うのか。

「IgG4 関連疾患に関わる自然免疫反応の解明」

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IgG4 関連疾患は血清 IgG4 の上昇と罹患臓器への IgG4 陽性形質細胞の浸潤を特色とする疾患である。IgG4 の産生には IL-4、IL-10、IL-13 などの Th2 サイトカインが関与することが知られているが、IgG4 産生に関わる自然免疫反応のメカニズムは不明である。Toll-like receptor (TLR)や NOD-like receptor (NLR)に代表される自然免疫反応の受容体は微生物由来抗原を認識し、抗体産生や Th 分化といった獲得免疫反応を誘導することから、TLR/NLR の活性化が IgG4 の産生に関与する可能性が考えられる。本研究において、我々は健常人末梢血から分離した単球を NOD2 ligand である Muramyl dipeptide (MDP)で刺激すると、B cell-activating factor (BAFF)の産生を介して、T 細胞非依存性に B 細胞からの IgG4 の産生を誘導することを見いだした。また、IgG4 関連疾患患者の末梢血単核球を TLR あるいは NLR ligands で刺激すると、IgG4 の産生が誘導されることを見出した。これらの結果から、IgG4 関連疾患患者の末梢血単球は TLR/NLR 経路の活性化により、BAFF シグナル伝達経路を介して、IgG4 の産生を促進することが示唆された。獲得免疫反応である IgG4 反応の誘導には自然免疫反応である TLR/NLR の活性化が必要であり、IgG4 関連疾患は自然免疫反応の異常を背景にして発症する可能性が示唆される。

【議事録】

Q:PDC type1 or 2?
A:type 1
Q:好中球が活性化すると type 2?
A:逆の結果になった。MDP で染めると少し染まる。
Q:微生物を想定？
A:最初はそうだった。内因性のものもありうる。
Q:自己免疫性膵炎で尿酸↑は稀？
A:3〜4 割で正常を少し超える人がいる。尿酸だけの刺激ではない。

平成23年度合同班会議出席者名簿

平成24年2月18日（土）
参加者51名（敬略略）

厚生労働科学研究難治性疾患克服研究事業研究奨励分野「新規疾患，IgG4 関連多臓器リンパ増殖性疾患（IgG4+MOLPS）の確立のための研究（梅原班）」

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ORIGINAL ARTICLE

Comprehensive diagnostic criteria for IgG4-related disease (IgG4-RD), 2011

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Abstract
Background IgG4-related disease (IgG4-RD) is a novel clinical disease entity characterized by elevated serum IgG4 concentration and tumefaction or tissue infiltration by IgG4+ plasma cells. Although IgG4-RD is not rare and is clinically important, its clinical diagnostic criteria have not been established. Comprehensive diagnostic criteria for IgG4-RD, including the involvement of various organs, are intended for the practical use of general physicians and nonspecialists.
Methods Two IgG4-RD study groups, the Umehara and Okazaki teams, were organized by the Ministry of Health, Labor and Welfare Japan. As IgG4-RD comprises a wide variety of diseases, these groups consist of physicians and researchers in various disciplines, including rheumatology, hematology, gastroenterology, nephrology, pulmonology, ophthalmology, odontology, pathology, statistics, and basic and molecular immunology throughout Japan, with 66 and 56 members of the Umehara and Okazaki teams, respectively. Collaborations of the two study groups involved

For the All Japan IgG4 team.

Professional collaborators of the All Japan G4 team are given in the Appendix.

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detailed analyses of clinical symptoms, laboratory results, and biopsy specimens of patients with IgG4-RD, resulting in the establishment of comprehensive diagnostic criteria for IgG4-RD.

Results Although many patients with IgG4-RD have lesions in several organs, either synchronously or metachronously, and the pathological features of each organ differ, consensus has been reached on two diagnostic criteria for IgG4RD: (1) serum IgG4 concentration >135 mg/dl, and (2) >40% of IgG+ plasma cells being IgG4+ and >10 cells/high powered field of biopsy sample. Although the comprehensive diagnostic criteria are not sufficiently sensitive for the diagnosis of type 1 IgG4-related autoimmune pancreatitis (IgG4-related AIP), they are adequately sensitive for IgG4-related Mikulicz's disease (MD) and kidney disease (KD). In addition, the comprehensive diagnostic criteria, combined with organ-specific diagnostic criteria, have increased the sensitivity of diagnosis to 100% for IgG4-related MD, KD, and AIP.

Conclusion Our comprehensive diagnostic criteria for IgG4-RD are practically useful for general physicians and nonspecialists.

Keywords IgG4-related disease · Criteria · Mikulicz's disease · Autoimmune pancreatitis · Interstitial nephritis

Abbreviations

IgG4-RD	IgG4-related disease
MD	Mikulicz's disease
AIP	Autoimmune pancreatitis
KD	Kidney disease
TIN	Tubulointerstitial nephritis
SS	Sjögren's syndrome
MHLW	Japan Ministry of Health, Labor and Welfare Japan; familial multifocal fibrosclerosis
RPF	Retroperitoneal fibrosis
TIN	Tubulointerstitial nephritis
MOLPS	Multiorgan lymphoproliferative syndrome
SIPS	Systemic IgG4 plasmacytic syndrome

Introduction

IgG4-related disease (IgG4-RD) is a new emerging disease entity of unknown etiology with multiorgan involvement [1]. IgG4-RD has been found to affect the pancreas, bile duct, lacrimal glands, salivary glands, central nervous system, thyroid, lungs, liver, gastrointestinal tract, kidney, prostate, retroperitoneum, arteries, lymph nodes, skin, and breast. Therefore, IgG4-RD includes a wide variety of diseases, including Mikulicz's disease (MD) [2, 3], autoimmune pancreatitis (AIP) [4], hypophysitis, Riedel

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thyroiditis [5], interstitial pneumonitis [6, 7], interstitial nephritis [8, 9], prostatitis, lymphadenopathy [10, 11], retroperitoneal fibrosis [12, 13], inflammatory aortic aneurysm [14], and inflammatory pseudotumor. Although IgG4-RD is not rare and is clinically important, its clinical diagnostic criteria have not yet been established. Two study groups where thus organized by the Ministry of Health, Labor and Welfare (MHLW) Japan. One group, the Umehara team, chaired by Professor Umehara of Kanazawa Medical University, is seeking to establish diagnostic criteria for IgG4-RD; the second group, the Okazaki team, chaired by Professor Okazaki of Kansai Medical University, is seeking to understand the etiology and pathogenesis of IgG4-RD. These groups consist of physicians and researchers in various fields, including rheumatology, hematology, gastroenterology, nephrology, pulmonology, ophthalmology, odontology, pathology, statistics, and basic and molecular immunology from all over Japan, with 66 and 56 members of the Umehara and Okazaki teams, respectively.

Background for establishing diagnostic criteria for IgG4-RD

General concepts of IgG4-RD

Although the two groups independently analyzed the clinical features and conditions of IgG4-RD, they collaborated closely, which resulted in the following consensus: (1) IgG4-RD can occur in various organs, including the central nervous system, salivary glands, thyroid gland, lungs, pancreas, biliary duct, liver, gastrointestinal tract, kidneys, prostate gland, retroperitoneum, and lymph nodes, with clinical symptoms depending on lesion location. (2) IgG4-RD mainly affects middle-aged to elderly men; its clinical symptoms are relatively mild, and the condition usually comes to clinical attention due to organ swelling or damage. (3) Many patients with IgG4-RD can be treated effectively by steroid therapy. (4) Although the infiltration of IgG4+ cells and increased serum concentrations of IgG4 are characteristic of IgG4-RD, the severity of fibrosis is dependent on the individual organs involved. The common characteristics of these conditions include elevated serum IgG4 concentrations and tissue infiltration by IgG4+ plasma cells, accompanied by tissue fibrosis and sclerosis [1].

Naming of IgG4-related disease

Many terms have been used to describe IgG4-RD, including IgG4-related sclerosing disease [15], IgG4-related autoimmune disease [16], systemic IgG4 plasmacytic syndrome (SIPS) [17], and IgG4-related multiorgan lymphoproliferative syndrome (IgG4-MOLPS) [3]". The members of the Umehara and Okazaki teams carefully examined reports using these different nomenclatures and concluded that they referred to the same condition, and the two teams finally agreed to use a uniform nomenclature—IgG4-related disease (IgG4-RD)—for several reasons: (1) Although infiltration of IgG4+ cells and increased serum concentrations of IgG4 are characteristic of IgG4-RD, the severity of fibrosis is dependent on the individual organs involved. For example, storiform fibrosis is characteristic of IgG4-related autoimmune pancreatitis (IgG4-related AIP), IgG4-related retroperitoneal fibrosis (IgG4-related RPF), and IgG4-related tubulointerstitial nephritis (IgG4-related TIN), but is very seldom found in patients with IgG4-related MD and IgG4-related lymphadenopathy. (2) Although many patients with this IgG4-RD have lesions in several organs, either synchronously or metachronously, other patients show involvement of a single organ. (3) As there have been several reports describing patients with IgG4-associated conditions concomitant with malignant tumors, such as pancreatic and salivary carcinomas [18–21] and ocular adnexal lymphoma [22, 23], using the term systemic may lead to an incorrect diagnosis of an IgG4-related condition in a patient with malignant tumors in other organs [24].

Prevalence of IgG4-RD

It is difficult to ascertain the number of patients with IgG4-RD because the awareness of this disease is low and its diagnostic criteria have not yet been established. The Umehara team attempted to estimate the number of individuals with IgG4-RD throughout Japan by using as an example Ishikawa Prefecture, which contains 1.16 million people with little population inflow/outflow. The incidence of this disease throughout Japan was estimated to be 0.28–1.08/100,000, with 336–1,300 patients newly diagnosed per year and approximately 6,700–26,000 patients who developed IgG4-RD over the past 20 years [1]. In contrast, the Okazaki team attempted to estimate the

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incidence of IgG4-RD through a network of Japanese researchers in an AIP study; they reported that 8,000 patients throughout Japan had IgG4-RD.

Proposal of comprehensive diagnostic criteria for IgG4-RD

Concept of comprehensive diagnostic criteria for IgG4-RD

IgG4-RD may occur, either synchronously or metachronously, in a variety of organs throughout the body, including the pancreas, bile duct, lacrimal gland, salivary gland, thyroid, lung, liver, gastrointestinal tract, kidney, and retroperitoneum [1]. As clinical symptoms and pathological features depend on lesion location, it is probably impossible to establish criteria that include all patients with IgG4-RD. Detailed diagnostic criteria are needed for the involvement of each organ, including clinical symptoms, serological and histological findings, and radiological images. To date, diagnostic criteria for IgG4-related MD [25] (Table 1), IgG4-related AIP type 1 [26] (Table 2), and IgG4-related kidney disease (KD) [27] (Table 3) have been established. However, these organ-specific criteria are not suitable for the diagnosis of patients with involvement of other organs. In addition, organ-specific criteria may not be familiar to general clinicians and specialists in diseases of those organs, although all clinicians should become aware of this new disease entity and its diagnosis. Therefore, comprehensive diagnostic criteria are necessary for practical use and to differentiate among malignancies.

Comprehensive diagnostic criteria for IgG4-RD

The comprehensive diagnostic criteria we have proposed for IgG4-RD (Table 4) consist of three parts: concept, diagnostic criteria, and explanatory notes. The concept clarifies the features characteristic of IgG4-RD, such as lesion location, symptoms, and prognosis. Diagnostic criteria are based on two major characteristics of IgG4-RD: increased serum concentrations of IgG4 and infiltration of IgG4+ cells. The cutoff value for serum IgG4 concentration, 135 mg/dl, was based on receiver operating characteristic (ROC) curves, and its validity was confirmed in patients with AIP [26, 28]. Although tissue biopsies are difficult to obtain from some organs, including the pancreas, retroperitoneum, and ocular cavity, histopathological examination is important. Because IgG4+ plasma cell infiltration has been reported in various diseases and clinical conditions, such as rheumatoid synovitis, inflammatory oral and skin lesions, and carcinomas with a peritumoral inflammatory response [29], pathological criteria should be rigorous. Histopathological findings of marked IgG4+ cell

Table 1 Diagnostic criteria for IgG4+ Mikulicz's disease [25] (approved by the Japanese Society for Sjögren's Syndrome, 2008)

1. Symmetrical swelling of at least two pairs of lachrymal, parotid, and submandibular glands continuing for more than 3 months;
and
2. Elevated serum IgG4 (>135 mg/dl);
or
3. Histopathological features including lymphocyte and IgG4+ plasma-cell infiltration (IgG4+ plasma cells/IgG+ plasma cells >50%) with typical tissue fibrosis or sclerosis
Differential diagnosis is necessary from other disorders, including sarcoidosis, Castleman's disease, Wegener's granulomatosis, lymphoma, and cancer. Although the diagnostic criteria for Sjögren's syndrome (SS) may also include some patients with IgG4+ Mikulicz's disease, the clinicopathological conditions of patients with typical SS and IgG4+ Mikulicz's disease are different

Table 2 Clinical diagnostic criteria for autoimmune pancreatitis in Japan (2006) [26]

1. Diffuse or segmental narrowing of the main pancreatic duct with irregular walls and diffuse or localized enlargement of the pancreas on imaging modalities, including abdominal ultrasound, computed tomography, and magnetic resonance imaging
2. High-serum F-globulin, IgG, or IgG4 concentration or the presence of autoantibodies, such as antinuclear antibodies and rheumatoid factor
3. Marked interlobular fibrosis and prominent infiltration of lymphocytes and plasma cells to the periductal area, occasionally accompanied by lymphoid follicles in the pancreas
For diagnosis, criterion 1 must be present, together with criterion 2 and/or 3
However, it is necessary to exclude malignant diseases such as pancreatic and biliary cancers

Table 3 Diagnostic criteria for IgG4-related kidney disease [27]

1. Presence of some kidney damage, as manifested by abnormal urinalysis or urine marker(s) or decreased kidney function with either elevated serum IgG or IgE or hypocomplementemia
2. Abnormal renal radiologic findings:
   a. Multiple low-density lesions on enhanced computed tomography
   b. Diffuse kidney enlargement
   c. Hypovascular solitary mass in the kidney
   d. Hypertrophic lesion of the renal pelvic wall without irregularities of the renal pelvic surface
3. Elevated serum IgG4 level (>135 mg/dl)
4. Histological findings in the kidney:
   a. Dense lymphoplasmacytic infiltration by >10 IgG4+ plasma cells/high power field (HPF) and/or IgG4+/IgG+ plasma cells >40%
   b. Characteristic (sclero-) fibrosis surrounding nests of lymphocytes and/or plasma cells
5. Histological findings in extra-renal organ(s):
   Dense lymphoplasmacytic infiltration by >10 IgG4+ plasma cells/HPF and/or IgG4+/IgG+ plasma cells >40%

Definite:	1 + 3 + 4 a, b
	2 + 3 + 4 a, b
	2 + 3 + 5
	1 + 3 + 4 a + 5
Probable:	1 + 4 a, b
	2 + 4 a, b
	2 + 5
	3 + 4 a, (b)
Possible:	1 + 3
	2 + 3
	1 + 4 a
	2 + 4 a

Appendix:

1. Clinically and histologically, the following diseases should be excluded: Wegener's granulomatosis, Churg–Strauss syndrome, extramedullary plasmacytoma
2. Radiologically, the following diseases should be excluded: malignant lymphoma, urinary tract carcinomas, renal infarction, and pyelonephritis (rarely, Wegener's granulomatosis, sarcoidosis and metastatic carcinoma)

infiltration [>10 cells/high power field (HPF)] and an IgG4+/IgG+ cell ratio >40% are diagnostic of IgG4-RD. Explanatory notes describe clinical characteristics of IgG4-RD specific to each organ, as well as blood tests and pathologic findings, responses to steroids, and differential diagnoses.

Algorithm for diagnosing IgG4-RD

A diagnostic algorithm for IgG4-RD, using comprehensive diagnostic criteria combined with organ-specific criteria, is shown in Fig. 1. A diagnosis of IgG4-RD is definitive in patients with: (1) organ enlargement, mass or nodular lesions, or organ dysfunction; (2) a serum IgG4 concentration >135 mg/dl; and (3) histopathological findings of >10 IgG4 cells/HPF and an IgG4+/IgG+ cell ratio >40% (category 1). A diagnosis of IgG4-RD is possible in patients who fulfill criteria (1) and (2), but with negative results on histopathology or without histopathologic examination (category 2 and 3), whereas a diagnosis of IgG4-RD is probable in patients with organ involvement (1) and fulfilled histopathologic criteria, but without increased serum IgG4 concentration (2) (category 4). Patients with organ symptoms without satisfying serologic or histopathologic criteria are considered unlikely to have IgG4-RD (category 5 and 6). For patients in categories 2–5, organ-specific criteria for IgG4-RD could be applied, such as those for AIP [26], MD [25], and KD [27] associated with IgG4. Patients who fulfill the organ-specific criteria for IgG4-RD have a definite diagnosis of this disease (category 7).

Validation of comprehensive diagnostic criteria in previous reports of patients with IgG4-RD

To validate the comprehensive diagnostic criteria, we applied them to patients described in two studies of IgG4-related MD [3, 30], two of IgG4-related KD [9, 27], and

Table 4 Comprehensive diagnostic criteria for IgG4-related disease, 2011

I. Concept

IgG4-related disease (IgG4-RD) shows organ enlargement or nodular/hyperplastic lesions in various organs concurrently or metachronously, due to marked infiltration of lymphocytes and IgG4+ plasma cells, as well as fibrosis of unknown etiology. IgG4-RD affects various organs, including the pancreas, bile duct, lacrimal gland, salivary gland, central nervous system, thyroid, lung, liver, gastrointestinal tract, kidney, prostate, retroperitoneum, arteries, lymph nodes, skin, and breast. Although many patients with IgG4-RD have lesions in several organs, either synchronously or metachronously, others show involvement of a single organ. Clinical symptoms vary depending on the affected organ, and some patients may experience serious complications, such as obstruction or compression symptoms due to organomegaly or hypertrophy, and organ dysfunction caused by cellular infiltration or fibrosis. Steroid therapy is often effective

II. [Comprehensive clinical diagnostic criteria for IgG4-RD]

1. Clinical examination showing characteristic diffuse/localized swelling or masses in single or multiple organs

2. Hematological examination shows elevated serum IgG4 concentrations(≥135 mg/dl)

3. Histopathologic examination shows:

(1) Marked lymphocyte and plasmacyte infiltration and fibrosis.

(2) Infiltration of IgG4+ plasma cells: ratio of IgG4+/IgG+ cells > 40% and >10 IgG4+ plasma cells/HPF

Definite: 1) + 2) + 3)

Probable: 1) + 3)

Possible: 1) + 2)

However, it is important to differentiate IgG4-RD from malignant tumors of each organ (e.g. cancer, lymphoma) and similar diseases (e.g. Sjögren's syndrome, primary sclerosing cholangitis, Castleman's disease, secondary retroperitoneal fibrosis, Wegener's granulomatosis, sarcoidosis, Churg–Strauss syndrome) by additional histopathological examination

Even when patients cannot be diagnosed using the CCD criteria, they may be diagnosed using organ-specific diagnostic criteria for IgG4RD

III. Explanatory notes

1. The comprehensive diagnostic criteria are the minimal consensus to aid general practitioners and other nonspecialist physicians in the clinical diagnosis of IgG4-RD. For each affected organ, organ-specific diagnostic criteria established for IgG4-related Mikulicz's disease, IgG4-related autoimmune pancreatitis, and IgG4-related kidney disease, should be used concurrently

2. Concept:

The difference from multifocal fibrosclerosis is unclear although these diseases may be IgG4-RD. Many patients show multiple organ involvement and are characterized as having systemic disease, whereas other patients show involvement of a single organ

(a) Autoimmune pancreatitis, type 1 (IgG4-related autoimmune pancreatitis): This disease is synonymous with IgG4-related sclerosing pancreatitis/lymphoplasmacytic sclerosing pancreatitis (LPSP). It can be diagnosed using the clinical diagnostic criteria for autoimmune pancreatitis established by the Ministry of Health, Labor and Welfare, Japan Pancreas Society, in 2006 [26]

(b) IgG4-related sclerosing cholangitis: This disease is characterized by sclerotic changes with diffuse or localized stenosis in the intrahepatic/extrahepatic bile duct and gallbladder. Circumferential wall thickening is observed at the site of stenosis, with similar changes in areas without stenosis. Obstructive jaundice often develops, making it important to differentiate this condition from tumors, such as cholangiocarcinoma and pancreatic cancer, and from primary sclerosing cholangitis. It is also necessary to exclude secondary sclerosing cholangitis as an apparent cause

(c) IgG4-related lacrimal, orbital, and salivary-gland lesions: This condition includes IgG4-related Mikulicz's disease characterized by symmetrical (sometimes unilateral) swelling of any of the lacrimal, parotid, submandibular, sublingual glands, and some minor salivary glands. Nodular/infiltrative lesions may also occur in orbital tissue other than the lacrimal glands. IgG4-related Mikulicz's disease can be diagnosed by the organ-specific diagnostic criteria for IgG4-related Mikulicz's disease established by the Sjögren's Syndrome Study Group of Japan in 2008 [25]

(d) IgG4-related central nervous system lesions: These lesions include infundibular hypophysitis, hypertrophic pachymeningitis, and intracerebral inflammatory pseudotumor

Table 4 continued

(e) IgG4-related respiratory lesions: These lesions occur primarily in the interstitium, such as bronchovascular bundles, interlobular septum, alveolar septum, and pleura. They are frequently accompanied by mediastinal and hilar lymphadenopathy, along with X-ray evidence of a mass or infiltration of the lung. Some patients have asthma-like symptoms. It is important to differentiate these lesions from malignant tumors, sarcoidosis, collagen diseases of the lung, and infection

(f) IgG4-related renal lesions: Abnormal imaging findings include diffuse renal enlargement, multifocal contrast defects of the renal parenchyma, renal mass lesions, and pelvic wall thickening. Renal histology shows mainly interstitial nephritis, but glomerular lesions (e.g., membranous nephropathy), may also be present. IgG4-related tubulointerstitial nephritis can be diagnosed using the organ-specific diagnostic criteria for IgG4-related kidney disease [27]

(g) IgG4-related retroperitoneal fibrosis/periarterial lesions: This disease is characterized by thickening of the abdominal aortic adventitia and periurethral soft tissue, often accompanied by hydronephrosis or mass lesions. Periarteritis may occur around the aorta or relatively large branches and is evident as arterial wall thickening on radiological imaging. Magnetic resonance imaging (MRI) and positron emission tomography (PET) have been shown to be helpful for diagnosing retroperitoneal fibrosis in addition to X-ray, which may include CT scan. Biopsy is often inconclusive, making it difficult to differentiate this condition from secondary retroperitoneal fibrosis due to malignant tumors or infectious diseases

(h) Other tumefactive lesions: Proliferation of IgG4+ plasma cells and lymphocytes may accompany fibrosis. Including some conventional inflammatory pseudotumors, these lesions have been reported in the brain, orbit, lung, breast, liver, pancreas, retroperitoneum, kidney, and lymph nodes

IV. Blood test findings

1. Polyclonal serum γ-globulin, IgG, and IgE are often elevated, and hypocomplementemia may occur

2. Elevated IgG4 can also be seen in other diseases (e.g., atopic dermatitis, pemphigus, asthma, and multicentric Castleman's disease) and is therefore not specific to IgG4-RD

3. On rare occasions, serum IgG4 concentration may be elevated in patients with malignant tumors. However, patients with >270 mg/dl IgG4 are unlikely to have pancreatic cancer

4. In patients with single-organ involvement and serum IgG4 concentration <135 mg/dl, the IgG4+/IgG+ ratio may be helpful in making a diagnosis

5. At present, the significance of elevated IgG4 in the pathogenesis/pathophysiology of IgG4-RD is unknown

V. Histopathological findings

1. Storiform or swirling fibrosis or obliterative phlebitis are characteristic of IgG4-RD and may be important in its diagnosis

2. Eosinophilic infiltration often occurs, along with infiltration of IgG4+ cells

3. Reactive infiltration of IgG4+ cells and fibrosis may also occur, such as at the periphery of pancreatic cancers

VI. Imaging studies

IgG4-RD may occur, either synchronously or metachronously, in a variety of organs throughout the body, including the pancreas, bile duct, lacrimal gland, salivary gland, thyroid, lung, liver, gastrointestinal tract, kidney, and retroperitoneum. MRI and fluorodeoxyglucose (FDG)-PET have been shown to be helpful for detecting multiorgan involvements

VII. Steroids

1. Patients with malignant lymphoma or paraneoplastic lesions can sometimes be improved by steroid administration. Therefore, steroid trials should be strictly avoided

2. Efforts should be made to collect tissue samples for diagnosis. However, patients having disease in organs difficult to biopsy, such as pancreas, retroperitoneum, and pituitary, and who respond to steroids may possibly have IgG4-RD

3. In accordance with the guidelines for treatment of autoimmune pancreatitis, patients should be started on 0.5–0.6 mg/kg per day of prednisolone. If patients do not respond to the initial steroid therapy, the diagnosis should be reviewed

VIII. Diseases to be excluded or differentiated

1. To exclude malignancies (e.g., cancer, lymphoma) in involved organs, it is essential to determine histopathologically whether malignant cells are present

2. Similar diseases (e.g., Sjögren's syndrome, primary sclerosing cholangitis, multicentric Castleman's disease, idiopathic retroperitoneal fibrosis, Wegener's granulomatosis, sarcoidosis, Churg–Strauss syndrome) are diagnosed using the diagnostic criteria for each disease

3. Multicentric Castleman's disease is a hyper-interleukin (IL)-6 syndrome and is not included among the IgG4-RDs, even if the diagnostic criteria for IgG4-RD are fulfilled

three of IgG4-related AIP [31] (Table 5). The sensitivity of these criteria were comparatively good for diagnosing IgG4-related MD (83 and 70%) and KD (87 and 85%). In contrast, patients with IgG4-related AIP could not be diagnosed by the comprehensive diagnostic criteria (0% for definite, nearly 70% for possible, and 10–30% for unlikely) because biopsies could not be obtained from most of these patients. Application of organ-specific criteria to undiagnosed patients increased the sensitivity of diagnosis to 100%, even for patients with IgG4-related AIP (Table 5).

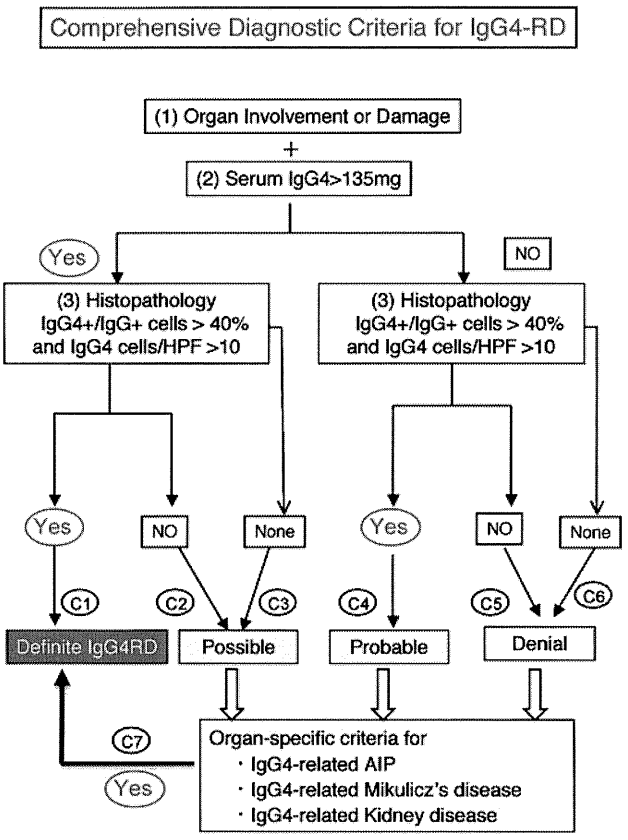

Fig. 1 Diagnostic algorithm performance for comprehensive diagnostic criteria for IgG4-related disease (IgG4-RD) using comprehensive diagnostic criteria combined with organ-specific criteria. A diagnosis of IgG4-RD is definitive in patients with (*1*) organ enlargement, mass or nodular lesions, or organ dysfunction, (*2*) a serum IgG4 concentration >135 mg/dl, and (*3*) histopathological findings of >10 IgG4+ cells/HPF and an IgG4+/IgG+ cell ratio >40% (*C1*). A diagnosis of IgG4-RD is possible in patients who fulfill criteria (*1*) and (*2*), but with negative results on histopathology or without histopathologic examination (*C2*, *C3*), whereas a diagnosis of IgG4-RD is probable in patients with (*1*) organ involvement and (*2*) fulfilled histopathologic criteria, but without increased serum IgG4 concentration (*C4*). Patients with organ symptoms without satisfying the serologic or histopathologic criteria are considered unlikely to have IgG4-RD (*C5*, *C6*). For patients in C2–C6, organ-specific criteria for IgG4-related autoimmune pancreatitis (AIP), IgG4-related Mikulicz's disease (MD), and IgG4-related kidney disease (KD). Patients who fulfill the organ-specific criteria have a definite diagnosis of IgG4-RD (*C7*)

Discussion

Although there is increased interest in IgG4-RD, awareness of it remains low and diagnostic criteria have not yet been published. Therefore, IgG4-RD has often been misdiagnosed as a malignant tumor, lymphoma, Sjögren's syndrome, or other diseases despite the effectiveness of steroid therapy. As IgG4-RD affects various organs, its clinical symptoms vary, and each patient with IgG4-RD may visit specialists addressing organ-specific lesions. Organ-specific criteria have been established for IgG4-related AIP [26], MD [25] and KD [27], but these criteria are not suitable for diagnosing patients with other involved organs, and they are not familiar to general clinicians and nonspecialists. Comprehensive diagnostic criteria are therefore needed for practical use by such physicians. Although it is difficult to obtain tissue biopsy samples from some organs, including the pancreas, retroperitoneum, and brain, histopathologic examination is highly important to exclude malignancies [18–21] and other types of disease [29]. Indeed, most patients with IgG4-related AIP could be diagnosed without biopsy. The comprehensive diagnostic criteria for IgG4-RD have relatively low sensitivity in patients with IgG4-related AIP because of a lack of biopsy samples but were sufficiently sensitive for IgG4-related MD and KD. Patients who could not be diagnosed by the comprehensive diagnostic criteria could be diagnosed by organ-specific criteria, indicating the complementarity of comprehensive diagnostic criteria and organ-specific criteria for IgG4-RD.

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Conflict of interest None.

Appendix

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Table 5 Sensitivity for diagnosis by comprehensive diagnostic criteria for IgG4-RD

Main organ	Definite	Probable	Possible	Denial	References
Mikulicz (64)	53 (83%)	4 (6%)	7 (11%)	0 (0%)	Masaki et al. [3]
+OS criteria		4/4	7/7		
Total	64 (100%)				
Mikulicz (40)	28 (70%)	0 (0%)	12 (30%)	0 (0%)	Yamamoto et al. [30]
+OS criteria			12/12		
Total	40/40 (100%)				
Kidney (23)[a]	20 (87%)	0 (0%)	0 (0%)	3 (13%)	Saeki et al. [9]
+OS criteria				3/3	
Total	23 (100%)				
Kidney (41)[a]	35 (85%)	0 (0%)	3 (7%)	3 (7%)	Kawano et al. [27]
+OS criteria			3/3	3/3	
Total	41/41 (100%)				
AIP (60)	0 (0%)	0 (0%)	41 (68%)	19 (32%)	Takuma et al. [32]
+OS criteria			41/41	19/19	
Total	60 (100%)				
AIP (54)	0 (0%)	0 (0%)	42 (78%)	12 (22%)	Okazaki et al. [31]
+OS criteria			42/42	12/12	
Total	54 (100%)				
AIP (90)	0 (0%)	3 (3%)	70 (78%)	9 (10%)	Fujiwara et al. [33]
+OS criteria		3/3	70/70	9/9	
Total	90 (100%)				

OS criteria organ-specific criteria

[a] 10 patients were included both in Refs. [9, 27]

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