与：モデルマウスを用いた検討. 第22回日本シェーグレン症候群学会, ブリーゼプラザ, 大阪, 2013年9月13-14日.

150. 水島伊知郎、山田和徳、松永貴弘、鈴木康倫、川村里佳、濱野良子、藤井博、松村正巳、川野充弘. IgG4関連腎臓病におけるマクロファージ、APRILの関与. 第56回日本腎臓学会学術総会. 東京. 2013年5月10-12日.
151. 佐伯敬子、川野充弘、水島伊知郎、和田庸子、中島衡、伊藤朋之、山崎肇、斉藤喬雄、成田一衛. ステロイド治療を行ったIgG4関連腎臓病の長期経過. 第56回日本腎臓学会学術総会. 東京. 2013年5月10-12日.
152. 山田和徳, 川上貴裕, 水島伊知郎, 鈴木康倫, 藤井博, 松村正巳, 能登原憲司, 川野充弘. IgG4関連腎臓病におけるAPRIL発現の検討. 第21回日本シェーグレン症候群学会. ウェスティン都ホテル京都,京都市, 2012年9月7−8日.
153. 水島伊知郎、山田和徳、川野充弘他. 腫大を伴う典型的なIgG4関連疾患病変における、日本の包括診断基準、国際病理診断Consensus statement基準の妥当性に関する検討. 第21回日本シェーグレン症候群学会. ウェスティン都ホテル京都. 2012年9月7-8日.
154. 川野充弘, 水島伊知郎, 佐伯敬子, 斉藤喬雄, IgG4関連腎臓病ワーキンググループ、IgG4関連腎臓病の免疫組織学的解析. 第55回日本腎臓学会学術集会. 横浜. 2012月6月1-3日.
155. 水島伊知郎, 金華恵, 藤井博, 山田和徳, 加藤隆志, 松村正巳, 川野充弘. IgG4関連腎疾患の特徴とステロイド治療前後の変化. 第56回日本リウマチ学会総会・学術総会. 東京. 2012年4月26-28日.
156. 山田和徳, 佐伯敬子, 川野充弘. IgG4関連皮膚疾患の臨床的・病理学的検討. 第56回日本リウマチ学会総会・学術集会. グランドプリンスホテル新高輪、東京. 2012年4月26-28日.
157. 水島伊知郎、山田和徳、松永貴弘、鈴木康倫、川村里佳、濱野良子、藤井博、松村正巳、川野充弘. 典型的なIgG4関連疾患病変における、IgG4陽性形質細胞数、IgG4/CD138陽性細胞比のCut off値に関する検討. 第57回日本リウマチ学会総会・学術集会. 京都. 2013年4月18-20日.
158. 佐伯敬子、川野充弘、水島伊知郎、山本元久、和田庸子、中島衡、伊藤朋之、山崎肇、高橋裕樹、斉藤喬雄、成田一衛. IgG4関連腎臓病43例の臨床経過. 第57回日本リウマチ学会総会・学術集会. 京都. 2013年4月18-20日.
159. Tanaka Y, Hirata S. Novel multi-biomarkers for estimating disease activity in rheumatoid arthritis. The 22nd International Rheumatology Symposium. Kyoto, Japan 平成25年4月
160. Tanaka Y. The Development of Anti-TNF Agents in Rheumatoid Arthritis. EAGOR2013, The 5th East Asian Group of Rheumatology (symposium). Seoul, Korea. 平成25年5月
161. Tanaka Y. A potential of human mesenchymal stem cells for the treatment of Rheumatoid Arthritis. The First ARISE WITH APLAR. Seoul, Korea. 平成25年9月
162. Tanaka Y. Certolizumab pegol and biologics for the treatment of rheumatic diseases. 12th International symposium on Sjögren's syndrome. Kyoto, Japan 平成25年10月
163. Tanaka Y, Emoto K, Tsujimoto M, Schlichting DE, Macias W. 12-week results of a phase 2b dose-ranging study of baricitinib, an oral JAK1/ JAK2 inhibitor in Japanese patients with rheumatoid arthritis on background methotrexate therapy. ACR 2013. San Diego, USA. 平成25年10月
164. Tanaka Y, Yamanaka Y, Ishiguro N, Miyasaka N, Kawana K, Kubo T, Kuroki A, Takeuchi T. Clinical remission after 52 weeks of treatment is a predictor of adalimumab-free disease control in patients with early rheumatoid arthritis: Hopeful 2 Study. ACR 2013. San Diego, USA. 平成25年10月
165. Shimizu Y, Yamamoto M, Yajima H, Tabeya T, Suzuki C, Naishiro Y, Takahashi H, Shinomura Y. Efficacy of early intervention for IgG4-related sialadenitis. The 12th International Symposium on Sjögren's Syndrome. Kyoto. 2013.10.10
166. 石垣靖人, 辰野貴則, 中村有香, 河南崇典, 中島章夫, 高田尊信, 正木康史, 梅原久範, 友杉直久：IgG4 関連疾患におけるトランスクリプトーム解析・日本薬学会・熊本・平成26年3月30日
167. Mastui S, Yamamoto H, Minamoto S, Waseda Y, Mishima M, Kubo K. Proposal for diagnostic criteria for IgG4-related respiratory disease. The 2nd International Symposium on

IgG4 -Related Diseases & Associated Conditions. Hawaii. 2014.2.16-19

168. Yamamoto H, Kubo K, Waseda Y, Matsui S, Ogura S, Hebisawa A, Sakai F, Miyashita T, Hata N, Masubuchi H, Shiraki A, Inoue M, Takagi T, Ishimatsu Y,Nakamoto K, Kurihara Y, Arakaki K, Terasaki Y : Clinico-Radioligic-Pathological Features In The Lung Involvement Of IGg4-Related Disease ATS San Francisco 2012.5.18-23
169. Matsui S, Yamamoto H, Waseda Y, Minamoto S, Inoue D, Mishima M, Kubo K, IgG4-related research group. : IgG4-related lung disease. The 17th Congress of APSR. Hong Kong. 2012.12. 14-16
170. 福島敏郎、立石一成、牛木淳人 、横山俊樹、漆畑一寿、山本 洋、花岡正幸、
171. 久保惠嗣：特徴的な尿道周囲病変を呈した IgG4 関連疾患の 1 女性例 第 131 回日本内科学会信越地方会 松本市 2012 年 10 月 27 日
172. 市山崇史、所弥生、牛木淳人、漆畑一寿、山本 洋、花岡正幸、小泉知展、吉澤明彦、本田孝行、久保惠嗣：高 γ グロブリン血症と間質性肺炎の契機に発見された IgG4 関連疾患の 1 例 第 202 回日本呼吸器学会関東地方会 東京都 2012 年 11 月 10 日
173. 後藤浩, 高比良雅之, 安積淳 IgG4 関連眼疾患の診断基準作成の試み. 第 31 回日本眼腫瘍学会, 高知市総合あんしんセンター, 2013 年 9 月 14 日.
174. Takahashi H, Usui Y, Mitsuhashi R, Yamakawa N, Sato-Otsubo A, Sato Y, Ogawa S, Arai A, Goto H. Genome-wide analysis of ocular adnexal lymphoproliferative disorders using high resolution single nucleotide polymorphism array. Annual meeting of Association for Research in Vision and Ophthalmology (ARVO), Washington state convention center, Seattle, USA. May 9, 2013.
175. 上田俊一郎, 臼井嘉彦, 木村圭介, 後藤浩. IgG4 関連眼疾患と眼窩 MALT リンパ腫における CD23 と CD25 による鑑別. 第 7 回 IgG4 研究会, 岡山国際交流センター, 2013 年 3 月 2 日.
176. 三橋良輔, 臼井嘉彦, 毛塚剛司, 後藤浩. 眼付属器リンパ増殖性疾患における制御性 T 細胞および Th 細胞の関与. 第 27 回日本眼窩疾患シンポジウム, 山形テルサ, 2012 年 11 月 3 日.
177. 後藤浩. IgG4 関連眼疾患分科会計画説明. 厚生労働科学研究費補助金(難治性疾患等克服研究事業) IgG4 関連疾患に関する調査研究. 平成 24 年度第 1 回班会議. 京都大学芝蘭会館, 2012 年 8 月 18 日
178. 上田俊一郎, 臼井嘉彦, 木村圭介, 後藤浩, 永井毅. 表面抗原の解析による眼窩リンパ増殖性疾患の診断. 第 6 回 IgG4 研究会, ホテル金沢, 2012 年 3 月 3 日.

[社会活動]

【医療従事者向け情報提供】

1. 神澤輝実：特別講演 "プライマリケア医が知って欲しい膵臓疾患"。北区医師会学術講演会、東京、2012.4.10
2. 神澤輝実：特別講義 "自己免疫性膵炎"。和歌山県立医科大学消化器内科、和歌山、2012.5.11
3. 神澤輝実：基調講演 "自己免疫性膵炎 Up-to-date"。第 9 回城北消化器病研究会、東京、2012.5.26
4. 神澤輝実：特別講演 "自己免疫性膵炎 Up-to-date"。第 41 回兵庫県内視鏡治療談話会、神戸、2012.6.13
5. 神澤輝実:「日本発の疾患概念「IgG4 関連疾患」に注目」Japan Medicine MONTHLY, 2013. 4. 25.
6. 川 茂幸：「自己免疫性膵炎と IgG4」第 29 回 日本胆膵病態・生理研究会（京都）2012.6.23
7. 川 茂幸：「自己免疫性膵炎と IgG4」いちょうの会（仙台）2012.7.6
8. 川 茂幸：「自己免疫性膵炎と IgG4」愛媛膵臓・代謝カンファレンス（愛媛）2012.9.22
9. 川 茂幸:「自己免疫性膵炎と IgG4」自己抗体と自己免疫, 東京, 2013. 2. 2
10. 梅原久範：「21 世紀 日本で見つかった新たな疾患概念-IgG4 関連疾患-」第 40 回和歌山内科臨床懇話会, （和歌山, ' 12.05）.
11. 梅原久範：「IgG4 関連疾患−日本からの発信」第 46 回近畿支部生涯教育講演会、（京都'12.6）
12. 梅原久範：「IgG4 関連疾患－日本からの発信」第 46 回日本内科学会近畿支部生涯教育講演会, （大阪, ' 12.06）.
13. 坪井洋人、飯塚麻菜、松尾直美、浅島弘充、近藤裕也、松本功、住田孝之：「シェーグレン症候群 VS IgG4 関連疾患：DNA アレイ解析」第 17 回シェーグレン症候群セミナー, 2012.5.19, 東京
14. 住田孝之:「シェーグレン症候群 VS IgG4 関連疾患」第 47 回日本内科学会北海道支

部生涯教育講演会, 2012.6.17, 札幌
15. 住田孝之：「シェーグレン症候群 VS IgG4 関連疾患」第 2 回兵庫・大阪シェーグレンフォーラム
16. 吉野　正:「炎症とリンパ腫」多摩アレルギー懇話会　2012. 11. 16, 京王プラザ.
17. 川野充弘, 笠島里美:「IgG4 関連動脈周囲炎」第 17 回血管病理研究会, 2012. 10. 26, 東京.
18. 鈴木康倫, 松永貴弘, 川村里佳, 浜野良子, 水島伊知郎, 藤井博, 山田和徳, 松村正巳, 川野充弘:「IgG4 陽性形質細胞浸潤を伴う間質性腎炎を呈した原発性シェーグレン症候群の 1 例」第 68 回中部日本糸球体腎炎談話会, 2012. 11. 17, 名古屋.
19. Mitsuhiro Kawano: "IgG4-related disease —Initial Discovery, Evolving Concepts, Up-to-date Knowledge, Role of APRIL—"Special Seminar, June 5, 2012, Geneva.
20. 川野充弘:「IgG4 関連疾患 2012　—腎病変の鑑別診断を中心に考える—」血圧管理を考える会, 2012.6.15, 新潟.
21. 川野充弘:「IgG4 関連疾患 2012　—腎病変を中心に—」第 16 回兵庫県腎疾患治療懇話会, 2012.7.20, 神戸.
22. 川野充弘:「IgG4 関連疾患 2012　—腎病変の鑑別診断を中心に—」第 45 回静岡腎セミナー,2012.9.15, 浜松.
23. 川野充弘:「IgG4 関連疾患 2012　—最近の話題を中心に—」福井膠原病関連疾患を考える会, 2012.12.7, 福井.
24. 川野充弘:「IgG4 関連疾患 2014 ー鑑別すべき疾患を中心にー」第一回富山膠原病研究会, 2014. 1. 30
25. 川野充弘:「腎臓からみた IgG4 関連疾患の世界」第 8 回北海道腎カンファレンス, 2013. 11. 15
26. 川野充弘:「身近にかくれている IgG4 関連疾患」福井県内科医会学術講演会, 2013. 5. 18
27. 田中良哉:「B 細胞標的治療薬」第 56 回日本リウマチ学会総会・学術集会（シンポジウム）, 2012.4, 東京
28. 田中良哉:「関節リウマチの薬物療法（生物学的製剤）」第 56 回日本リウマチ学会総会・学術集会（アニュアルコースレクチャー）, 2012.4, 東京
29. 田中良哉:「ステロイド治療抵抗性改善メカニズム」第 53 回日本神経学会学術大会（シンポジウム）, 2012.5, 東京
30. 田中良哉:「TNF 阻害薬を超える治療を考える」第 30 回日本骨代謝学会学術集会（教育講演）, 2012.7, 東京
31. 田中良哉:「キナーゼ阻害薬による関節リウマチ治療の進歩」第 30 回日本骨代謝学会学術集会（シンポジウム）, 2012.7, 東京
32. 高橋裕樹：特別講演「シェーグレン症候群とミクリッツ病」第 7 回山形アレルギー膠原病自己免疫疾患勉強会　山形大学医学部講堂（山形）2012/2/2
33. 高橋裕樹：特別講演「多彩な臓器病変を呈する全身性疾患-IgG4 関連疾患-」第 24 回北海道小児リウマチ性疾患研究会京王プラザホテル札幌（札幌）2012/2/25
34. 高橋裕樹：学術講演「札幌医大から発信する全身性疾患-IgG4 関連疾患-」平成 24 年度札幌医科大学医学部同窓会講演会　札幌プリンスホテル（札幌）2012/7/14
35. 高橋裕樹：「新しい全身性疾患-IgG4 関連疾患　発見物語」市立札幌病院院内研修会　市立札幌病院（札幌）2012/9/13

【患者・家族・一般市民向け情報提供】

1. 神澤輝実：読売新聞　医療ルネッサンス　"膵炎：診断難しい自己免疫性" 2012.4.4
2. 神澤輝実：ASAHI Medical 8 月号　"自己免疫性膵炎への対応"　26－28 ページ
3. 神澤輝実：週刊　医学界新聞　"日本発の新たな疾患概念　IgG4 関連疾患の潮流"　2012.11.12
4. 神澤輝実：日刊ゲンダイ "自己免疫性膵炎・IgG4 関連疾患" 2013.3.8
5. 神澤輝実：都政新報 "ひと：東京スピリット賞を受賞" 2013.3.12
6. 神澤輝実:「IgG4 関連疾患」読売新聞, 2013. 5. 23.
7. 神澤輝実:「自己免疫性膵炎の診療」ラジオ NIKKEI 医学講座, 2013. 9. 19.
8. 川 茂幸:「IgG4 関連疾患」ラジオ NIKKEI, 2013. 2. 4.
9. 田中良哉：第 52 回日本リウマチ友の会全国大会（特別医療講演）" リウマチ治療 現在　未来" 2012.5.27, 高松

【受賞】

神澤輝実：第 17 回東京スピリット賞(2013)

H. 知的財産権の出願・登録状況（予定を含む）

該当なし。

IgG4 関連疾患 診断基準

J Hepatobiliary Pancreat Sci (2012) 19:536–542
DOI 10.1007/s00534-012-0521-y

GUIDELINE

Clinical diagnostic criteria of IgG4-related sclerosing cholangitis 2012

Hirotaka Ohara · Kazuichi Okazaki · Hirohito Tsubouchi · Kazuo Inui · Shigeyuki Kawa · Terumi Kamisawa · Susumu Tazuma · Kazushige Uchida · Kenji Hirano · Hitoshi Yoshida · Takayoshi Nishino · Shigeru B. H. Ko · Nobumasa Mizuno · Hideaki Hamano · Atsushi Kanno · Kenji Notohara · Osamu Hasebe · Takahiro Nakazawa · Yasuni Nakanuma · Hajime Takikawa

Published online: 21 June 2012
© Japanese Society of Hepato-Biliary-Pancreatic Surgery and Springer 2012

Abstract
Background IgG4-sclerosing cholangitis (IgG4-SC) patients have an increased level of serum IgG4, dense infiltration of IgG4-positive plasma cells with extensive fibrosis in the bile duct wall, and a good response to steroid therapy. However, it is not easy to distinguish IgG4-SC from primary sclerosing cholangitis, pancreatic cancer, and cholangiocarcinoma on the basis of cholangiographic findings alone because various cholangiographic features of IgG4-SC are similar to those of the above progressive or malignant diseases.
Methods The Research Committee of IgG4-related Diseases and the Research Committee of Intractable Diseases of Liver and Biliary Tract in association with the Ministry of Health, Labor and Welfare, Japan and the Japan Biliary

This article is a secondary publication based on a study first reported in the JBA (Journal of Japan Biliary Association), 2012;26:59–63.

H. Ohara (✉)
Department of Community-based Medical Education, Nagoya City University Graduate School of Medical Sciences, 1 Kawasumi, Mizuho-cho, Mizuho-ku, Nagoya 467-8601, Japan
e-mail: hohara@med.nagoya-cu.ac.jp

K. Okazaki · K. Uchida
The Third Department of Internal Medicine, Kansai Medical University, Hirakata, Japan

H. Tsubouchi
Digestive and Lifestyle Diseases, Kagoshima University Graduate School of Medical and Dental Sciences, Kagoshima, Japan

K. Inui
Department of Internal Medicine, Second Teaching Hospital, Fujita Health University, Nagoya, Japan

S. Kawa
Center for Health, Safety and Environmental Management, Shinshu University, Matsumoto, Japan

T. Kamisawa
Internal Medicine, Tokyo Metropolitan Komagome Hospital, Tokyo, Japan

S. Tazuma
Department of General Medicine, Hiroshima University Graduate School of Medical Science, Programs of Applied Medicine, Clinical Pharmacotherapy, Hiroshima, Japan

K. Hirano
Department of Gastroenterology, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan

H. Yoshida
Division of Gastroenterology, Department of Medicine, Showa University School of Medicine, Tokyo, Japan

T. Nishino
Department of Gastroenterology, Tokyo Women's Medical University Yachiyo Medical Center, Tokyo, Japan

S. B. H. Ko
Department of Gastroenterology, Nagoya University Graduate School of Medicine, Nagoya, Japan

N. Mizuno
Department of Gastroenterology, Aichi Cancer Center Hospital, Nagoya, Japan

H. Hamano
Division of Medical Informatics, Department of Internal Medicine, Gastroenterology, Shinshu University Hospital, Matsumoto, Japan

A. Kanno
Division of Gastroenterology, Tohoku University Graduate School of Medicine, Sendai, Japan

Association have set up a working group consisting of researchers specializing in IgG4-SC, and established the new clinical diagnostic criteria of IgG4-SC 2012.
Results The diagnosis of IgG4-SC is based on the combination of the following 4 criteria: (1) characteristic biliary imaging findings, (2) elevation of serum IgG4 concentrations, (3) the coexistence of IgG4-related diseases except those of the biliary tract, and (4) characteristic histopathological features. Furthermore, the effectiveness of steroid therapy is an optional extra diagnostic criterion to confirm accurate diagnosis of IgG4-SC.
Conclusion These diagnostic criteria for IgG4-SC are useful in practice for general physicians and other nonspecialists.

Keywords IgG4 · Sclerosing cholangitis · Primary sclerosing cholangitis · Autoimmune pancreatitis · Cholangiocarcinoma

Introduction

IgG4-related sclerosing cholangitis (IgG4-SC) is a characteristic type of sclerosing cholangitis with an unknown pathogenic mechanism. IgG4-SC patients show increased levels of serum IgG4 [1] and dense infiltration of IgG4-positive plasma cells with extensive fibrosis in the bile duct wall [2]. IgG4-SC is frequently associated with autoimmune pancreatitis, and it shows a good response to steroid therapy [3–7]. Various cholangiographic features of IgG4-SC are similar to those of primary sclerosing cholangitis (PSC), pancreatic cancer, and cholangiocarcinoma [8, 9]. Therefore, it is not easy to discriminate IgG4-SC from these progressive or malignant diseases on the basis of cholangiographic findings alone [10, 11], and accurate diagnosis of IgG4-SC not associated with autoimmune pancreatitis is particularly difficult [12].

K. Notohara
Department of Pathology, Kurashiki Central Hospital, Kurashiki, Japan

O. Hasebe
Department of Gastroenterology, Nagano Municipal Hospital, Nagano, Japan

T. Nakazawa
Department of Gastroenterology and Metabolism, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan

Y. Nakanuma
Department of Human Pathology, Kanazawa University Graduate School of Medicine, Kanazawa, Japan

H. Takikawa
Department of Medicine, Teikyo University School of Medicine, Tokyo, Japan

Therefore, the Research Committee of IgG4-related Diseases (Chairman, Kazuichi Okazaki) and the Research Committee of Intractable Diseases of Liver and Biliary Tract (Chairman, Hirohito Tsubouchi) in association with the Ministry of Health, Labor, and Welfare of Japan, and the Japan Biliary Association (Chairman, Kazuo Inui) have set up a working group consisting of researchers specializing in IgG4-SC. After several meetings held on 15 October 2010, 1 February 2011, and 2 August 2011, and after the exchange of opinions via e-mail, this working group developed a tentative proposal for the clinical diagnostic criteria of IgG4-SC, including the clinical features of IgG4-SC, in order to avoid the misdiagnosis of PSC and malignant diseases. The open forum was held at the 47th Annual Meeting of the Japan Biliary Association on 17 September 2011, and the official announcement was made on the home page of the Japan Biliary Association, where extensive discussion of the tentative proposal can be found.

Disease concept of IgG4-SC

The working group analyzed the clinical features and conditions of IgG4-SC, resulting in the following disease concept of IgG4-SC.

IgG4-SC is a characteristic type of sclerosing cholangitis with an unknown pathogenic mechanism. IgG4-SC patients show increased levels of serum IgG4 [1] and dense infiltration of IgG4-positive plasma cells with extensive fibrosis in the bile duct wall [2]. Circular and symmetrical thickening of the bile duct wall is observed not only in the stenotic areas but also in the areas without stenosis that appear normal in the cholangiogram [13]. IgG4-SC is frequently associated with autoimmune pancreatitis [3–7]. IgG4-related dacryoadenitis/sialadenitis and IgG4-related retroperitoneal fibrosis are also occasionally observed in IgG4-SC [14–17]. However, some cases of IgG4-SC do not show any other organ involvement [12].

IgG4-SC is more common in elderly men. Obstructive jaundice is frequently observed in IgG4-SC. The clinical and radiological features of IgG4-SC are resolved by steroid therapy, though long-term prognosis of this disease is not clear [4–7].

The differential diagnosis of IgG4-SC from PSC and neoplastic lesions such as pancreatic or biliary cancers is very important. It is also necessary to rule out secondary sclerosing cholangitis caused by diseases with obvious pathogenesis.

The new clinical diagnostic criteria of IgG4-SC 2012

The working group established their final proposal for the new clinical diagnostic criteria of IgG4-SC 2012 (Table 1).

Table 1 Clinical diagnostic criteria of IgG4-related sclerosing cholangitis 2012

Diagnostic items
(1) Biliary tract imaging reveals diffuse or segmental narrowing of the intrahepatic and/or extrahepatic bile duct associated with the thickening of bile duct wall
(2) Hematological examination shows elevated serum IgG4 concentrations (≥135 mg/dl)
(3) Coexistence of autoimmune pancreatitis, IgG4-related dacryoadenitis/sialadenitis, or IgG4-related retroperitoneal fibrosis
(4) Histopathological examination shows:
a. Marked lymphocytic and plasmacyte infiltration and fibrosis
b. Infiltration of IgG4-positive plasma cells: >10 IgG4-positive plasma cells/HPF
c. Storiform fibrosis
d. Obliterative phlebitis
Option: effectiveness of steroid therapy
A specialized facility, in which detailed examinations such as endoscopic biliary biopsy and endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) can be administered, may include in its diagnosis the effectiveness of steroid therapy, once pancreatic or biliary cancers have been ruled out.
Diagnosis
Definite diagnosis
(1) + (3)
(1) + (2) + (4) a, b
(4) a, b, c
(4) a, b, d
Probable diagnosis
(1) + (2) + option
Possible diagnosis
(1) + (2)
It is necessary to exclude PSC, malignant diseases such as pancreatic or biliary cancers, and secondary sclerosing cholangitis caused by the diseases with obvious pathogenesis. When it is difficult to differentiate from malignant conditions, a patient must not be treated with facile steroid therapy but should be referred to a specialized medical facility

The diagnosis of IgG4-SC is based on the combination of the following 4 criteria: (1) characteristic biliary imaging findings, (2) elevation of serum IgG4 concentrations, (3) coexistence of IgG4-related diseases except those of the biliary tract, and (4) characteristic histopathological features. However, it is not easy to obtain sufficient biliary tract tissue to determine the characteristic histology of IgG4-SC by biopsy [[13], [18]]. Furthermore, the effectiveness of steroid therapy is an optional additional diagnostic criterion to confirm accurate diagnosis of IgG4-SC. The types of typical cholangiographic features are shown schematically [19]. The diseases to be discriminated from IgG4-SC and the necessary examinations for diagnosis are also described so that these diagnostic criteria can be used clinically [20].

Diagnostic imaging findings

Narrowing of the bile duct

Although magnetic resonance cholangiopancreatography provides useful information, the narrowing of the bile duct should be assessed by direct cholangiography such as endoscopic retrograde cholangiopancreatography or percutaneous transhepatic cholangiography.

IgG4-SC associated with autoimmune pancreatitis frequently shows a stricture of the lower common bile duct. This stricture might be caused by both the thickening of the bile duct and the effect of inflammation and/or edema of the pancreas [21].

Dilation after the confluent stricture is a characteristic feature of IgG4-SC. The typical cholangiographic findings of PSC, such as a band-like stricture, beaded appearance, pruned-tree appearance, and diverticulum-like outpouching are not observed in IgG4-SC (Fig. 1) [8].

The characteristic features of IgG4-SC can be classified into 4 types based on the regions of stricture as revealed by cholangiography and differential diagnosis (Fig. 2) [19]. Type 1 IgG4-SC shows stenosis only in the lower part of the common bile duct, and it should be differentiated from chronic pancreatitis, pancreatic cancer, and cholangiocarcinoma. The modalities useful for differential diagnosis are intraductal ultrasonography (IDUS) [13], endoscopic ultrasound-guided fine needle aspiration [22], and cytology and/or biopsy of the bile duct [13, 14]. Type 2 IgG4-SC, in

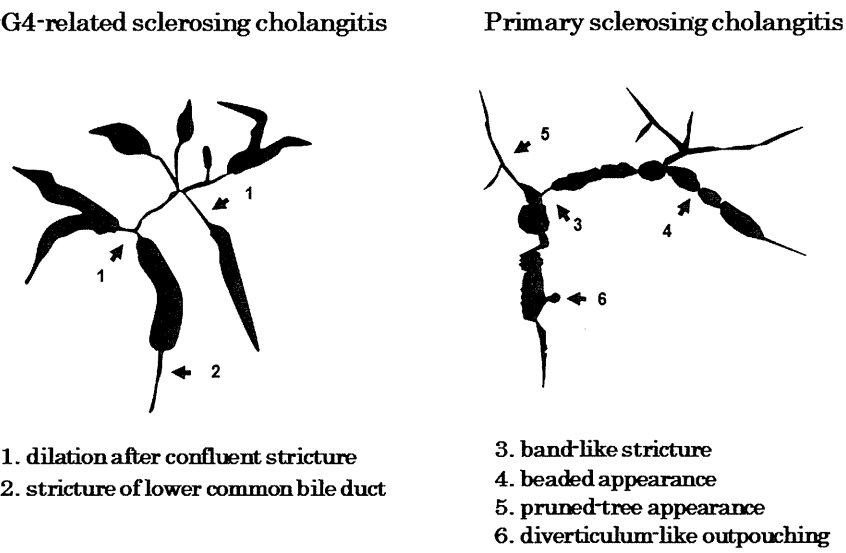


Fig. 1 The schematic comparison of cholangiographic findings between IgG4-related sclerosing cholangitis and primary sclerosing cholangitis. IgG4-related sclerosing cholangitis showing dilation after confluent stricture (>10 mm) and stricture of lower common bile duct. Primary sclerosing cholangitis showing band-like stricture (short stricture 1–2 mm), beaded appearance (short and annular stricture alternating with normal or minimally dilated segments), pruned-tree appearance (diminished arbolization of intrahepatic duct and pruning) and diverticulum-like outpouching (outpouchings resembling diverticula, often protruding between adjacent strictures)

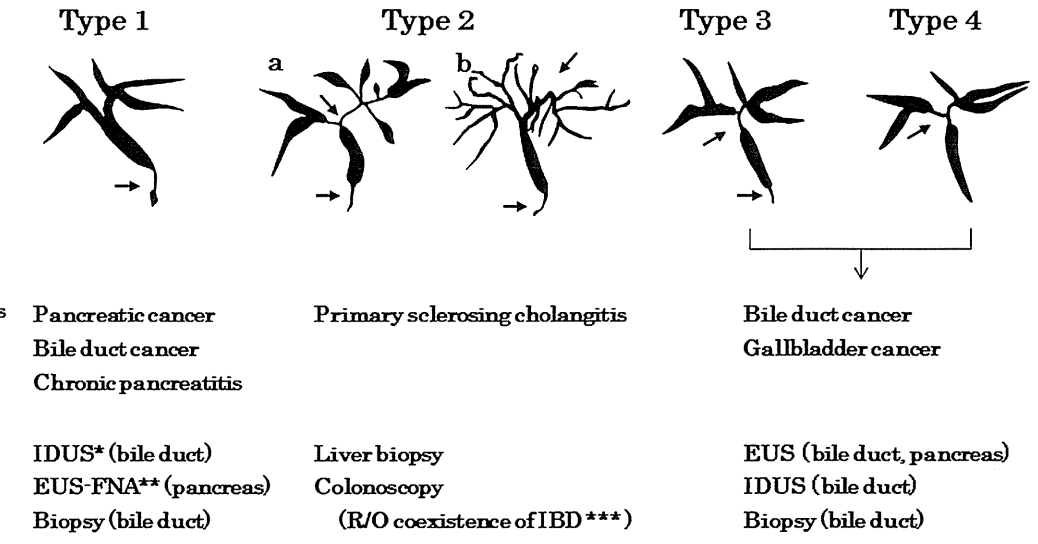


Fig. 2 The cholangiographic classification of IgG4-related sclerosing cholangitis and differential diagnosis. Stenosis is located only in the lower part of the common bile duct in type 1; stenosis is diffusely distributed in the intra- and extrahepatic bile ducts in type 2. Type 2 is further subdivided into 2 types: extended narrowing of the intrahepatic bile ducts with prestenotic dilation is widely distributed in type 2a; narrowing of the intrahepatic bile ducts without prestenotic dilation and reduced bile duct branches are widely distributed in type 2b. Stenosis is detected in both the hilar hepatic lesions and the lower part of the common bile ducts in type 3; and strictures of the bile duct are detected only in the hilar hepatic lesions in type 4. **IDUS* intraductal ultrasonography, ***EUS-FNA* endoscopic ultrasound-guided fine needle aspiration, ****IBD* inflammatory bowel disease

which stenosis is diffusely distributed throughout the intrahepatic and extrahepatic bile ducts, should be differentiated from PSC. Type 2 is subdivided into 2 further types: type 2a, with narrowing of the intrahepatic bile ducts with prestenotic dilation; and type 2b, with narrowing of the intrahepatic bile ducts without prestenotic dilation and

reduced bile duct branches, which is caused by marked lymphocytic and plasmacyte infiltration into the peripheral bile ducts. Type 3 IgG4-SC is characterized by stenosis in both the hilar hepatic lesions and the lower part of the common bile duct. Type 4 IgG4-SC shows strictures of the bile duct only in the hilar hepatic lesions. Cholangiographic findings of types 3 and 4 need to be discriminated from those of cholangiocarcinoma. The modalities useful for the differential diagnosis of types 3 and 4 are endoscopic ultrasonography (EUS), IDUS [13], and cytology and/or biopsy of the bile duct [13, 14]. Nevertheless, there are some IgG4-SC cases whose cholangiographic findings do not fit into any of the above 4 types.

Thickening of the bile duct

Abdominal ultrasonography (US) [23], abdominal computed tomography [24], abdominal magnetic resonance imaging, EUS, and IDUS show circular and symmetrical thickening of the bile duct wall, smooth outer and inner margins, and a homogenous internal echo [13]. These characteristic features are recognized not only in stenotic areas or occasionally in the gallbladder but also in areas without stenosis that appear normal on cholangiogram.

Hematological examination

Elevated level of serum IgG4 (135 mg/dl or higher, nephelometric method) is one of the diagnostic criteria for IgG4-SC [1]. Elevation of serum IgG4 levels is not necessarily specific to IgG4-SC because it is also observed in atopic dermatitis, pemphigus, asthma, etc.; in particular, elevated levels of serum IgG4 are also observed in some malignant cholangiopancreatic diseases (e.g., pancreatic cancer, cholangiocarcinoma) [25, 26].

Other organ involvement

IgG4-SC is frequently associated with autoimmune pancreatitis. It is particularly difficult to accurately diagnose IgG4-SC in cases not associated with autoimmune pancreatitis. Occasionally, IgG4-SC is associated with other systemic IgG4-related diseases, including IgG4-related symmetrical dacryoadenitis/sialadenitis and IgG4-related retroperitoneal fibrosis [14–17]. These associations are helpful in the correct diagnosis of IgG4-SC. Although IgG4-related dacryoadenitis/sialadenitis is basically characterized by symmetrical bilateral swelling, unilateral swelling can be included only if pathological diagnosis is made. Inflammatory bowel disease (IBD) is not usually an associated feature, unlike the frequent association of IBD with PSC [27, 28].

Pathological findings of bile ducts

In IgG4-SC, fibroinflammatory involvement is observed mainly in the submucosa of the bile duct wall, whereas the epithelium of the bile duct is intact [29]. However, slight injury and/or neutrophil infiltration are occasionally observed in IgG4-SC with associated secondary cholangitis. PSC should be excluded if inflammation is observed, particularly in the epithelium of the bile duct wall.

Cytological examination is commonly used for the diagnosis of cholangiocarcinoma. Endoscopic transpapillary bile duct biopsy is performed to rule out cholangiocarcinoma; however, it is not easy to obtain sufficient biliary tract tissue to study the characteristic histology of IgG4-SC biopsy specimens (e.g., storiform fibrosis, obliterative phlebitis) [13]. Liver biopsy is sometimes useful to diagnose IgG4-SC cases with intrahepatic bile duct strictures [30–32].

Exclusion of secondary sclerosing cholangitis

It is necessary to rule out the following features of secondary sclerosing cholangitis with obvious pathogenesis, including common bile duct stones, cholangiocarcinoma, trauma, previous operation on the biliary tract, congenital biliary anatomy, corrosive cholangitis, ischemic bile duct stenosis, AIDS-related cholangitis, and biliary injury caused by intra-arterial chemotherapy.

Effectiveness of steroid therapy

This optional diagnostic criterion should be applied only to the IgG4-SC cases in which the effect of steroid therapy can be evaluated by imaging modalities. Accordingly, clinical conditions or hematological findings cannot be evaluated by this method. It is sometimes difficult to obtain sufficient biopsy specimens from patients suffering from diseases of not only the biliary tract but also of other organs, such as the pancreas, lachrymal gland, salivary gland, and retroperitoneum. However, efforts should be made to collect enough tissue samples for diagnosis and steroid trials should be strictly avoided.

The effectiveness of steroid therapy should be cautiously evaluated because some malignant lesions may occasionally improve after steroid administration [33]. If neoplastic lesions cannot be clinically ruled out after

steroid therapy, it is advisable to perform re-evaluation to rule out malignant cholangiopancreatic diseases.

Conclusion

These IgG4-SC 2012 clinical diagnostic criteria, established by a working group consisting of researchers specializing in IgG4-SC, are thought to be useful practically for general physicians and nonspecialists. In the future, detailed investigation of IgG4-SC cases, improvement in diagnostic modalities, and basic research should be undertaken to evaluate the clinical features and pathogenic mechanism of IgG4-SC.

Appendix: members of the working group for the clinical diagnostic criteria of IgG4-SC

The Research Committee of IgG4-related Diseases in association with the Ministry of Health, Labor, and Welfare of Japan (Chairman, Kazuichi Okazaki): K. Okazaki, K. Inui, S. Kawa, T. Kamisawa, S. Tazuma, K. Uchida, K. Hirano, H. Yoshida, T. Nishino, S.B.H. Ko, N. Mizuno, H. Hamano, A. Kanno, K. Notohara, O. Hasebe, T. Nakazawa, and H. Ohara.

The Research Committee of Intractable Diseases of Liver and Biliary Tract in association with the Ministry of Health, Labor, and Welfare of Japan (Chairman, Hirohito Tsubouchi): H. Tsubouchi, S. Tazuma, Y. Nakanuma, and H. Takikawa.

The Japan Biliary Association (Chairman, Kazuo Inui): K. Inui.

This work was supported partially by the Research Program of Intractable Disease provided by the Ministry of Health, Labor, and Welfare of Japan.

References

1. Hamano H, Kawa S, Horiuchi A, Unno H, Furuya N, Akamatsu T, et al. High serum IgG4 concentrations in patients with sclerosing pancreatitis. N Engl J Med. 2001;344:732–8.
2. Zen Y, Harada K, Sasaki M, Sato Y, Tsuneyama K, Haratake J, et al. IgG4-related sclerosing cholangitis with and without hepatic inflammatory pseudotumor, and sclerosing pancreatitis-associated sclerosing cholangitis: do they belong to a spectrum of sclerosing pancreatitis? Am J Surg Pathol. 2004;28:1193–203.
3. Nakazawa T, Ohara H, Yamada T, Ando H, Sano H, Kajino S, et al. Atypical primary sclerosing cholangitis cases associated with unusual pancreatitis. Hepatogastroenterology. 2001;48:625–30.
4. Nakazawa T, Ohara H, Sano H, Ando T, Aoki S, Kobayashi S, et al. Clinical differences between primary sclerosing cholangitis and sclerosing cholangitis with autoimmune pancreatitis. Pancreas. 2005;30:20–5.
5. Nishino T, Toki F, Oyama H, Oi I, Kobayashi M, Takasaki K, et al. Biliary tract involvement in autoimmune pancreatitis. Pancreas. 2005;30:76–82.
6. Hirano K, Tada M, Isayama H, Yagioka H, Sasaki T, Kogure H, et al. Long-term prognosis of autoimmune pancreatitis with and without corticosteroid treatment. Gut. 2007;56:1719–24.
7. Ghazale A, Chari ST, Zhang L, Smyrk TC, Takahashi N, Levy MJ, et al. Immunoglobulin G4-associated cholangitis: clinical profile and response to therapy. Gastroenterology. 2008;134:706–15.
8. Nakazawa T, Ohara H, Sano H, Aoki S, Kobayashi S, Okamoto T, et al. Cholangiography can discriminate sclerosing cholangitis with autoimmune pancreatitis from primary sclerosing cholangitis. Gastrointest Endosc. 2004;60:937–44.
9. Nishino T, Oyama H, Hashimoto E, Toki F, Oi I, Kobayashi M, et al. Clinicopathological differentiation between sclerosing cholangitis with autoimmune pancreatitis and primary sclerosing cholangitis. J Gastroenterol. 2007;42:550–9.
10. Kalaitzakis E, Levy M, Kamisawa T, Johnson GJ, Baron TH, Topazian MD, et al. Endoscopic retrograde cholangiography does not reliably distinguish IgG4-associated cholangitis from primary sclerosing cholangitis or cholangiocarcinoma. Clin Gastroenterol Hepatol. 2011;9:800-3.e2.
11. Nakazawa T, Ando T, Hayashi K, Naitoh I, Okumura F, Miyabe K, et al. Diagnostic criteria for IgG4-related sclerosing cholangitis based on cholangiographic classification. J Gastroenterol. 2012;40:79–87.
12. Hamano H, Kawa S, Uehara T, Ochi Y, Takayama M, Komatsu K, et al. Immunoglobulin G4-related lymphoplasmacytic sclerosing cholangitis that mimics infiltrating hilar cholangiocarcinoma: part of a spectrum of autoimmune pancreatitis? Gastrointest Endosc. 2005;62:152–7.
13. Naitoh I, Nakazawa T, Ohara H, Andoh T, Hayashi K, Tanaka H, et al. Endoscopic transpapillary intraductal ultrasonography and biopsy in the diagnosis of IgG4-related sclerosing cholangitis. J Gastroenterol. 2009;44:1147–55.
14. Kamisawa T, Funata N, Hayashi Y, Eishi Y, Koike M, Tsuruta K, et al. A new clinicopathological entity of IgG4-related autoimmune disease. J Gastroenterol. 2003;38:982–4.
15. Ohara H, Nakazawa T, Sano H, Ando T, Okamoto T, Takada H, et al. Systemic extrapancreatic lesions associated with autoimmune pancreatitis. Pancreas. 2005;31:232–7.
16. Hamano H, Arakura N, Muraki T, Ozaki Y, Kiyosawa K, Kawa S. Prevalence and distribution of extrapancreatic lesions complicating autoimmune pancreatitis. J Gastroenterol. 2006;41:1197–205.
17. Naitoh I, Nakazawa T, Ohara H, Andoh T, Hayashi K, Tanaka H, et al. Clinical significance of extrapancreatic lesions in autoimmune pancreatitis. Pancreas. 2010;39:e1–5.
18. Kawakami H, Zen Y, Kuwatani M, Eto K, Haba S, Yamato H, et al. IgG4-related sclerosing cholangitis and autoimmune pancreatitis: histological assessment of biopsies from Vater's ampulla and the bile duct. J Gastroenterol Hepatol. 2010;25:1648–55.
19. Nakazawa T, Ohara H, Sano H, Ando T, Joh T. Schematic classification of sclerosing cholangitis with autoimmune pancreatitis by cholangiography. Pancreas. 2006;32:229.
20. Nakazawa T, Ando T, Hayashi K, Naitoh I, Ohara H, Joh T. Diagnostic procedures for IgG4-related sclerosing cholangitis. J Hepatobiliary Pancreat Sci. 2011;18:127–36.
21. Hirano K, Tada M, Isayama H, Yamamoto K, Mizuno S, Yagioka H, et al. Endoscopic evaluation of factors contributing to intrapancreatic biliary stricture in autoimmune pancreatitis. Gastrointest Endosc. 2010;71:85–90.

22. Mizuno N, Bhatia V, Hosoda W, Sawaki A, Hoki N, Hara K, et al. Histological diagnosis of autoimmune pancreatitis using EUS-guided trucut biopsy: a comparison study with EUS-FNA. J Gastroenterol. 2009;44:742–50.
23. Koyama R, Imamura T, Okuda C, Sakamoto N, Honjo H, Takeuchi K, et al. Ultrasonographic imaging of bile duct lesions in autoimmune pancreatitis. Pancreas. 2008;37:259–64.
24. Itoh S, Nagasaka T, Suzuki K, Satake H, Ota T, Naganawa N. Lymphoplasmacytic sclerosing cholangitis: assessment of clinical, CT, and pathological findings. Clin Radiol. 2009;64:1104–14.
25. Mendes FD, Jorgensen R, Keach J, Katzmann JA, Smyrk T, Donlinger J, et al. Elevated serum IgG4 concentration in patients with primary sclerosing cholangitis. Am J Gastroenterol. 2006; 101:2070–5.
26. Oseini AM, Chaiteerakij R, Shire AM, Ghazale A, Kaiya J, Moser CD, et al. Utility of serum immunoglobulin G4 in distinguishing immunoglobulin G4-associated cholangitis from cholangiocarcinoma. Hepatology. 2011;54:940–8.
27. Loftus EV Jr, Harewood GC, Loftus CG, Tremaine WJ, Harmsen WS, Zinsmeister AR, et al. PSC-IBD: a unique form of inflammatory bowel disease associated with primary sclerosing cholangitis. Gut. 2005;54:91–6.
28. Sano H, Nakazawa T, Ando T, Hayashi K, Naitoh I, Okumura F, Miyabe K, Yoshida M, Takahashi S, Ohara H, Joh T. Clinical characteristics of inflammatory bowel disease associated with primary sclerosing cholangitis. J Hepatobiliary Pancreat Sci. 2011;18:154–61.
29. Nakanuma Y, Zen Y. Pathology and immunopathology of immunoglobulin G4-related sclerosing cholangitis: The latest addition to the sclerosing cholangitis family. Hepatol Res. 2007; 37(Suppl 3):S478–86.
30. Umemura T, Zen Y, Hamano H, Kawa S, Nakanuma Y, Kiyosawa K, et al. Immunoglobin G4-hepatopathy: association of immunoglobin G4-bearing plasma cells in liver with autoimmune pancreatitis. Hepatology. 2007;46:463–71.
31. Deshpande V, Sainani NI, Chung RT, Pratt DS, Mentha G, Rubbia-Brandt L, et al. IgG4-associated cholangitis: a comparative histological and immunophenotypic study with primary sclerosing cholangitis on liver biopsy material. Mod Pathol. 2009;22:1287–95.
32. Naitoh I, Zen Y, Nakazawa T, Ando T, Hayashi K, Okumura F, et al. Small bile duct involvement in IgG4-related sclerosing cholangitis: liver biopsy and cholangiography correlation. J Gastroenterol. 2011;46:269–76.
33. Tomiyama T, Uchida K, Matsushita M, Ikeura T, Fukui T, Takaoka M, et al. Comparison of steroid pulse therapy and conventional oral steroid therapy as initial treatment for autoimmune pancreatitis. J Gastroenterol. 2011;46:696–704.

胆　道　26巻1号　59～63（2012）

＜報　　告＞

IgG4関連硬化性胆管炎臨床診断基準2012

厚生労働省IgG4関連全身硬化性疾患の診断法の確立と治療方法の開発に関する研究班
厚生労働省難治性の肝胆道疾患に関する調査研究班
日本胆道学会

IgG4関連硬化性胆管炎は，血中IgG4値の上昇，病変局所の線維化とIgG4陽性形質細胞の著しい浸潤などを特徴とする原因不明の硬化性胆管炎である．その多くは自己免疫性膵炎を合併し，ステロイド治療が奏功する比較的予後良好な疾患とされているが，胆管像からは，原発性硬化性胆管炎および胆管癌，膵癌などの腫瘍性病変との鑑別は容易ではない．特に，IgG4関連硬化性胆管炎単独で発症する症例ではその診断に難渋することが多い．

そこで厚生労働省IgG4関連全身硬化性疾患の診断法の確立と治療方法の開発に関する研究班，厚生労働省難治性の肝胆道疾患に関する調査研究班および日本胆道学会は，本症例を数多く経験している専門医からなる診断基準案作成のワーキンググループを組織した．そして，IgG4関連硬化性胆管炎の病態や臨床像を明らかにするとともに，原発性硬化性胆管炎や膵癌，胆管癌などの腫瘍性病変との鑑別を念頭に置いた本症の診断基準の策定を行った．

平成22年10月15日，平成23年2月1日および平成23年8月2日の3回の委員会と電子メールによる意見交換を重ね，本症の臨床診断基準試案をまとめた．この試案に対して平成23年9月17日宮崎で開催された第47回日本胆道学会学術集会において公聴会が開催された．この公聴会での論議を経て修正された臨床診断基準案が日本胆道学会ホームページに公開され，平成23年11月4日まで日本胆道学会の一般会員から広く意見をつのり，最終的に「IgG4関連硬化性胆管炎臨床診断基準2012」（表1）として報告するに至った．

「IgG4関連硬化性胆管炎臨床診断基準2012」では，まず疾患概念を明確にし，次に診断項目として1)胆管の特徴的な画像所見，2)高IgG4血症，3)胆管外のIgG4関連合併症の存在，4) 胆管壁の病理組織学的所見の4つの項目を掲げ，基本的にはこれらの組み合わせにより診断することが示されている．さらに本症では確定診断に必要な量の胆管組織を非観血的に得ることが容易ではないため，診断率の向上のためにステロイドによる治療効果がオプションの項目として採用された．また，代表的な胆管像を具体的にシェーマで示し，各タイプの胆管像を示す症例において，鑑別すべき疾患と追加すべき検査を明記して，実際の臨床現場で有用な診断基準になるよう配慮されている．

今回の「IgG4関連硬化性胆管炎臨床診断基準2012」は，現在までに数多くのIgG4関連硬化性胆管炎症例を経験してきた専門医により作成された実用的な診断基準であると考えられるが，今後の症例の蓄積，診断技術の発展および基礎的研究により本症の病態解明がさらに進展していくことが期待される．

IgG4関連硬化性胆管炎臨床診断基準作成ワーキンググループ
関西医科大学内科学第三講座　岡崎和一，信州大学総合健康安全センター　川　茂幸，藤田保健衛生大学坂文種報徳會病院消化器内科　乾　和郎，都立駒込病院内科　神澤輝実，広島大学総合内科・総合診療科　田妻　進，関西医科大学内科学第三講座　内田一茂，東京大学大学院消化器内科学　平野賢二，昭和大学医学部内科学講座消化器内科部門　吉田　仁，東京女子医科大学八千代医療センター消化器科　西野隆義，国立長寿医療研究センター・消化機能診療科　洪　繁，愛知県がんセンター中央病院消化器内科部　水野伸匡，信州大学医学部附属病院医療情報部　濱野英明，東北大学大学院消化器病態学　菅野　敦，倉敷中央病院病理検査科　能登原憲司，長野市民病院消化器内科　長谷部修，名古屋市立大学大学院消化器・代謝内科学　中沢貴宏，金沢大学大学院形態機能病理学　中沼安二，帝京大学内科　滝川　一，鹿児島大学大学院消化器疾患・生活習慣病学　坪内博仁，名古屋市立大学大学院地域医療教育学　大原弘隆（委員長）

表1　IgG4関連硬化性胆管炎臨床診断基準2012

厚生労働省IgG4関連全身硬化性疾患の診断法の確立と治療方法の開発に関する研究班
厚生労働省難治性の肝胆道疾患に関する調査研究班
日本胆道学会

【疾患概念】

IgG4関連硬化性胆管炎とは，血中IgG4値の上昇，病変局所の線維化とIgG4陽性形質細胞の著しい浸潤などを特徴とする原因不明の硬化性胆管炎である．狭窄部位では全周性の壁肥厚を認め，狭窄を認めない部位にも同様の変化がみられることが多い．自己免疫性膵炎を高率に合併し，硬化性唾液腺炎，後腹膜線維症などを合併する症例もあるが，単独で発症する場合もある．

臨床的特徴としては高齢の男性に好発し，閉塞性黄疸を発症することが多い．ステロイド治療に良好に反応して臨床徴候，画像所見などの改善を認めるが，長期予後は不明である．

本症の診断においては胆管癌や膵癌などの腫瘍性病変，および原発性硬化性胆管炎との鑑別が極めて重要である．また，原因が明らかな二次性硬化性胆管炎を除外する必要がある．

【臨床診断基準】

A. 診断項目

1. 胆道画像検査にて肝内・肝外胆管にびまん性，あるいは限局性の特徴的な狭窄像と壁肥厚を伴う硬化性病変を認める．
2. 血液学的に高IgG4血症（135mg/dl以上）を認める．
3. 自己免疫性膵炎，IgG4関連涙腺・唾液腺炎，IgG4関連後腹膜線維症のいずれかの合併を認める．
4. 胆管壁に以下の病理組織学的所見を認める．
   ①高度なリンパ球，形質細胞の浸潤と線維化
   ②強拡1視野あたり10個を超えるIgG4陽性形質細胞浸潤
   ③花筵状線維化（storiform fibrosis）
   ④閉塞性静脈炎（obliterative phlebitis）

オプション：ステロイド治療の効果

胆管生検や超音波内視鏡下穿刺吸引法（Endoscopic ultrasound-guided fine needle aspiration，EUS-FNA）を含む精密検査のできる専門施設においては，胆管癌や膵癌などの悪性腫瘍を除外後に，ステロイドによる治療効果を診断項目に含むことができる．

B. 診断

Ⅰ．確診　：1＋3，1＋2＋4①②，4①②③，4①②④
Ⅱ．準確診：1＋2＋オプション
Ⅲ．疑診　：1＋2

ただし，胆管癌や膵癌などの悪性疾患，原発性硬化性胆管炎や原因が明らかな二次性硬化性胆管炎を除外することが必要である．診断基準を満たさないが，臨床的にIgG4関連硬化性胆管炎が否定できない場合，安易にステロイド治療を行わずに専門施設に紹介することが重要である．

【解説】

1）画像診断

（1）胆管狭窄像

a. MRCPにて狭窄の存在診断はある程度可能であるが，基本的にはERCPや経皮経肝胆管造影などによる直接胆管造影が必要である．
b. 自己免疫性膵炎を合併する症例の多くは下部胆管の狭窄（stricture of lower common bile duct）を伴うが，胆管壁の肥厚と，膵の炎症と浮腫による影響の両方を加味して評価する必要がある．本症では，比較的長い狭窄とその上流の単純拡張（dilation after confluent stricture）が特徴的であり，原発性硬化性胆管炎に特徴的な長さ1-2mmの短い帯状狭窄（band-like stricture），狭窄と拡張を交互に繰り返す数珠状所見（beaded appearance），剪定したように肝内胆管分枝が減少している剪定状所見（pruned-tree appearance），憩室様突出（diverticulum-like outpouching）を認めることは少ない（図1）．
c. 鑑別すべき疾患を念頭におき胆管像は4型に分類される（図2）．

Type 1 は下部胆管のみに狭窄をきたし，膵癌や慢性膵炎による締め付けまたは下部胆管癌との鑑別を要する．管腔内超音波検査(Intraductal ultrasonography，IDUS)，EUS-FNA，細胞診，胆管生検などにより鑑別診断を行う必要がある．

Type2 は下部胆管のみならず，肝内胆管に狭窄が多発し，原発性硬化性胆管炎との鑑別を要する．Type2 はさらに上流胆管の単純拡張を伴う a と，肝内末梢胆管への強い炎症細胞浸潤により拡張を伴わない b に分類される．

Type3 は下部胆管と肝門部胆管に狭窄をきたし，Type4 では肝門部胆管のみに狭窄が認められ，いずれも胆管癌との鑑別を要する．超音波内視鏡検査(Endoscopic ultrasonography，EUS)，IDUS，細胞診，胆管生検などにより鑑別を行う．

なお，少数ながら上記 4 つの型に分類されない胆管像を呈する症例も存在し，今後検討していく必要がある．

(2) 胆管壁肥厚像

腹部超音波検査 (US)，腹部 CT 検査，腹部 MRI 検査，EUS，IDUS にて胆管狭窄部に全周性の壁肥厚所見を認め，内膜面，外膜面は平滑で内部は均一である．また，明らかな狭窄部以外の胆管壁，時には胆嚢壁にも広範に同様の肥厚所見を認めるのが特徴的である．

2) 血液検査

高 IgG4 血症とは 135mg/dl 以上が一つの基準である(測定方法：ネフェロメトリー法)．IgG4 高値は，アトピー性皮膚炎，天疱瘡，喘息など他疾患にも認められるため，本疾患に必ずしも特異的ではない．特に胆管癌，膵癌などの他の膵胆道の悪性疾患でも高値を呈する場合があるため注意を要する．

3) 胆管外病変

本症は自己免疫性膵炎を高率に合併するが，単独で発症する症例の診断は難しい．時に，左右対称性の硬化性涙腺・唾液腺炎，後腹膜線維症など全身に IgG4 関連疾患を合併することがあり，診断の参考となる．硬化性涙腺・唾液腺炎は原則的には左右対称性とするが，病理組織学的に IgG4 関連涙腺・唾液腺炎と診断されている場合は，片側性のものも含む．原発性硬化性胆管炎のように炎症性腸疾患を合併することはまれである．

4) 胆管の病理組織学的所見

胆管壁結合織に炎症の主座があり，上皮は正常であることが多い．しかし，本症に二次的な炎症を合併して，軽度の上皮障害や上皮を中心とする軽度の好中球浸潤を伴うこともある．炎症が上皮を主体とするものである場合には，原発性硬化性胆管炎との慎重な鑑別を要する．

一般的に，細胞診は胆管癌との鑑別に用いられる．経乳頭的胆管生検も胆管癌を除外するために施行されるが，通常 IgG4 関連硬化性胆管炎に特徴的な花筵状線維化や閉塞性静脈炎などの病理像を得ることは難しい．また，肝内の胆管に狭窄を認める症例では肝生検が診断に有効なことがある．

5) 除外すべき二次的硬化性胆管炎

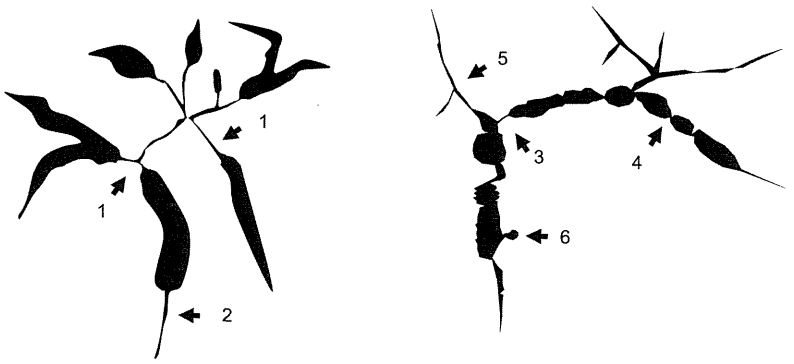
以下の原因などによる二次的硬化性胆管炎を除外する．

- 総胆管結石
- 胆管癌
- 外傷
- 胆道系手術
- 先天性胆道系異常
- 腐食性胆管炎
- 虚血性胆管狭窄
- AIDS 関連胆管炎
- 動注化学療法による胆管障害

6) オプション：ステロイド治療の効果

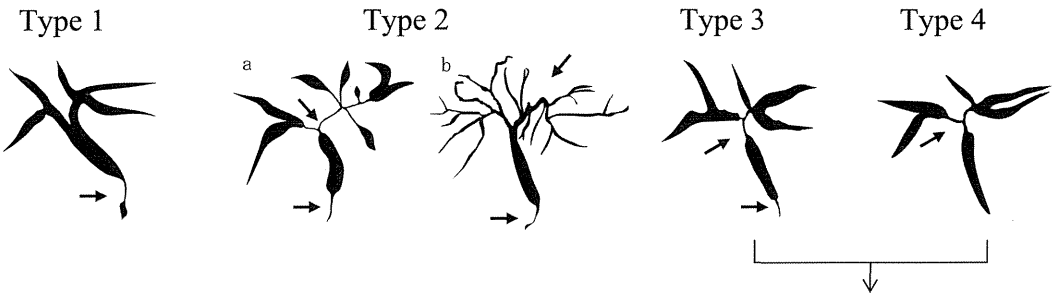
画像で評価可能な病変が対象であり，臨床症状や血液検査は評価の対象としない．胆管病変を含め，膵，涙腺，唾液腺，後腹膜などの胆管外病変でも組織診が難しいことがあるが，できる限り病理組織を採取するよう努力し，安易なステロイドトライアルは厳に慎むべきである．

ステロイド治療を行うときは，必ずその反応性を確認することが必要である．ステロイド治療の経過から腫瘍性病変が否定できない場合，膵胆道悪性腫瘍を念頭においた再評価を行う必要がある．また，一部の悪性腫瘍性病変でもステロイド投与により改善することがあるので注意を要する．



1.比較的長い狭窄とその上流の単純拡張
（dilation after confluent stricture）
2.下部胆管の狭窄
（stricture of lower common bile duct）
3.帯状狭窄（band-like stricture）
4.数珠状所見（beaded appearance）
5.剪定状所見（pruned-tree appearance）
6.憩室様突出（diverticulum-like outpouching）

図1　胆管像によるIgG4関連硬化性胆管炎と原発性硬化性胆管炎の比較



主な鑑別疾患	膵癌 胆管癌 慢性膵炎	原発性硬化性胆管炎	胆管癌 胆嚢癌
主な追加検査	IDUS*（胆管） EUS-FNA**（膵病変） 胆管生検	肝生検 下部消化管内視鏡検査 （炎症性腸疾患合併の検索）	EUS（胆管、膵） IDUS（胆管） 胆管生検

図2　IgG4関連硬化性胆管炎の胆管像の分類

*IDUS：Intraductal ultrasonography

**EUS-FNA：Endoscopic ultrasound-guided fine needle aspiration

Clinical diagnostic criteria of IgG4-related sclerosing cholangitis 2012

The Research Committee of IgG4-related Diseases provided by the Ministry of Health, Labor, and Welfare of Japan (chaired by Kazuichi Okazaki)
The Research Committee of Intractable Diseases of Liver and Biliary Tract provided by the Ministry of Health, Labor, and Welfare of Japan (chaired by Hirohito Tsubouchi)
The Japan Biliary Association (chaired by Kazuo Inui)

IgG4-related sclerosing cholangitis (IgG4-SC) is a characteristic sclerosing cholangitis showing the increased level of the serum IgG4, the dense infiltration of lymphocytes and IgG4-positive plasma cells with extensive fibrosis in the bile duct wall, and a good response to steroid therapy. IgG4-SC shows various cholangiographic features similar to those of primary sclerosing cholangitis (PSC), pancreatic cancer, and cholangiocarcinoma. Therefore, it is not easy to discriminate IgG4-SC from those progressive or malignant diseases on the basis of cholangiographic findings alone. The Research Committee of IgG4-related Diseases and the Research Committee of Intractable Diseases of Liver and Biliary Tract provided by the Ministry of Health, Labor, and Welfare of Japan, and the Japan Biliary Association organized a working group consisting of researchers specializing in IgG4-SC. This working group proposed the new clinical diagnostic criteria of IgG4-SC 2012 in order to avoid the misdiagnosis of PSC and malignant diseases as far as possible, after several meetings and the open forum on 17 September 2011 to discuss the tentative proposal.

Clinical Diagnostic Criteria of IgG4-SC

1. Biliary tract imaging studies showing diffuse or segmental narrowing of the intra and/or extra-hepatic bile duct associated with the thickening of bile duct wall.
2. Hematological examination shows elevated serum IgG4 concentrations (≥135mg/dl).
3. Coexistence of autoimmune pancreatitis, IgG4-related dacryoadenitis/sialoadenitis or IgG4-related retroperitoneal fibrosis.
4. Histopathologic examination shows:
   ①Marked lymphocytic and plasmacyte infiltration and fibrosis.
   ②Infiltration of IgG4-positive plasma cells: >10 IgG4-positive plasma cells/HPF
   ③Storiform fibrosis
   ④Obliterative phlebitis

Option: Effectiveness of steroid therapy

A specialized facility may include in its diagnosis the effectiveness of steroid therapy, once pancreatic or bile duct cancers have been ruled out.

Definite: 1 + 3, 1 + 2 + 4①②, 4①②③, 4①②④
Probable: 1 + 2 + Option
Possible: 1 + 2
It is necessary to exclude malignant diseases such as pancreatic or biliary cancers.

JJBA 2012; 26: 59—63

Members of working group for the clinical diagnostic criteria of IgG4-SC:
Kazuichi Okazaki (Kansai Medical University), Shigeyuki Kawa (Shinshu University), Kazuo Inui (Fujita Health University), Terumi Kamisawa (Tokyo Metropolitan Komagome Hospital), Susumu Tazuma (Hiroshima University), Kazushige Uchida (Kansai Medical University), Kenji Hirano (Tokyo University), Hitoshi Yoshida (Showa University), Takayoshi Nishino (Tokyo Women's Medical University), Shigeru Ko (National Center for Geriatrics and Gerontology), Nobumasa Mizuno (Aichi Cancer Center Hospital), Hideaki Hamano (Shinshu University), Atsushi Sugano (Tohoku University), Kenji Notohara (Kurashiki Central Hospital), Osamu Hasebe (Nagano Municipal Hospital), Takahiro Nakazawa (Nagoya City University), Yasuni Nakanuma (Kanazawa University), Hajime Takikawa (Teikyo University), Hirohito Tsubouchi (Kagoshima University), Hirotaka Ohara (Nagoya City University)

© 2012 Japan Biliary Association

Mod Rheumatol (2012) 22:1–14
DOI 10.1007/s10165-011-0508-6

REVIEW ARTICLE

A novel clinical entity, IgG4-related disease (IgG4RD): general concept and details

Hisanori Umehara · Kazuichi Okazaki · Yasufumi Masaki · Mitsuhiro Kawano · Motohisa Yamamoto · Takako Saeki · Shoko Matsui · Takayuki Sumida · Tsuneyo Mimori · Yoshiya Tanaka · Kazuo Tsubota · Tadashi Yoshino · Shigeyuki Kawa · Ritsuro Suzuki · Tsutomu Takegami · Naohisa Tomosugi · Nozomu Kurose · Yasuhito Ishigaki · Atsushi Azumi · Masaru Kojima · Shigeo Nakamura · Dai Inoue · The Research Program for Intractable Disease by Ministry of Health, Labor and Welfare (MHLW) Japan G4 team

Received: 17 May 2011 / Accepted: 28 July 2011 / Published online: 1 September 2011
© Japan College of Rheumatology 2011

Abstract IgG4-related disease (IgG4RD) is a novel clinical disease entity characterized by elevated serum IgG4 concentration and tumefaction or tissue infiltration by IgG4-positive plasma cells. IgG4RD may be present in a certain proportion of patients with a wide variety of diseases, including Mikulicz's disease, autoimmune pancreatitis, hypophysitis, Riedel thyroiditis, interstitial pneumonitis, interstitial nephritis, prostatitis, lymphadenopathy, retroperitoneal fibrosis, inflammatory aortic aneurysm, and inflammatory pseudotumor. Although IgG4RD forms a distinct, clinically independent disease category and is attracting strong attention as a new clinical entity, many questions and problems still remain to be elucidated, including its pathogenesis, the establishment of diagnostic criteria, and the role of IgG4. Here we describe the concept of IgG4RD and up-to-date information on this emerging disease entity.

H. Umehara and K. Okazaki contributed equally to this work.

Names of the collaborators of The Research Program for Intractable Disease by Ministry of Health, Labor and Welfare (MHLW) Japan G4 team are listed in Appendix.

H. Umehara (✉) · Y. Masaki
Division of Hematology and Immunology, Department of Internal Medicine, Kanazawa Medical University, 1-1 Daigaku, Uchinada-machi, Kahoku-gun, 920-0293 Ishikawa, Japan
e-mail: umehara@kanazawa-med.ac.jp

K. Okazaki
Division of Gastroenterology and Hepatology, The Third Department of Internal Medicine, Kansai Medical University, Osaka, Japan

M. Kawano
Division of Rheumatology, Department of Internal Medicine, Kanazawa University Graduate School of Medical Science, Ishikawa, Japan

M. Yamamoto
The First Department of Internal Medicine, Sapporo Medical University, Sapporo, Hokkaido, Japan

T. Saeki
Department of Internal Medicine, Nagaoka Red Cross Hospital, Niigata, Japan

S. Matsui
Health Administration Center, Sugitani Campus, University of Toyama, Toyama, Japan

T. Sumida
Department of Clinical Immunology, Doctoral Programs in Clinical Science, Graduate School of Comprehensive Human Science, University of Tuskuba, Ibaraki, Japan

T. Mimori
Department of Rheumatology and Clinical Immunology, Kyoto University Graduate School of Medicine, Kyoto, Japan

Y. Tanaka
First Department of Internal Medicine, School of Medicine, University of Occupational and Environmental Health, Fukuoka, Japan

K. Tsubota
Department of Ophthalmology, Keio University School of Medicine, Tokyo, Japan

Keywords IgG4-related diseases · Mikulicz's disease · Sjögren's syndrome · Autoimmune pancreatitis · Castleman's disease

Abbreviations

IgG4RD	IgG4-related disease
MD	Mikulicz's disease
SS	Sjögren's syndrome
MHLW Japan	Ministry of Health, Labor and Welfare Japan
LPSP	Lymphoplasmacytic sclerosing pancreatitis
AIP	Autoimmune pancreatitis
FMF	Familial multifocal fibrosclerosis
ANA	Anti-nuclear antibody

Introduction

In 1892, Dr. Johann von Mikulicz, also known as Jan Mikulicz-Radecki, published a paper describing a patient with symmetrical swelling of the lachrymal, parotid, and submandibular glands, with massive infiltration of these glands by mononuclear cells [1]. Following reports describing similar patients, this condition was called Mikulicz's disease (MD). In contrast, patients with similar symptoms, but with diseases such as leukemia, malignant lymphoma, and sarcoidosis, were reported to have Mikulicz's syndrome [2]. In 1930, Dr. Henrik Sjögren, an ophthalmologist, published a paper describing a woman with rheumatoid arthritis accompanied by keratoconjunctivitis sicca and severe swelling of the parotid glands, a condition that has been recognized as Sjögren's syndrome (SS) [3]. In 1953, Morgan and Castleman examined 18 patients with MD and concluded that this condition is one manifestation of SS [4]. Since then, MD has attracted very little interest in western countries. In Japan, however, there have been many patients with MD, such that differences between MD and SS have been clarified [5–7]. For example, their gender distribution is quite different, in that MD occurs in both men and women, whereas SS occurs mainly in women. Second, patients with MD have relatively mild xerostomia and xerophthalmia, despite significant enlargement of their lachrymal and salivary glands. Further, MD is accompanied by more complications, such as autoimmune pancreatitis (AIP). Patients with MD show a better response to glucocorticoid therapy than patients with SS. Finally, it has become clear that MD is related to elevated serum IgG4 concentrations and infiltration of IgG4-positive cells [5–9].

Following the description of a patient with chronic pancreatitis due to an autoimmune mechanism [10], lymphoplasmacytic sclerosing pancreatitis (LPSP) was found to be a characteristic histopathological finding in patients with AIP [11]. These findings led to the concept of AIP, which has characteristics similar to those of other autoimmune diseases, such as hypergammaglobulinemia, the

T. Yoshino
Department of Pathology,
Okayama University Graduate School of Medicine,
Dentistry and Pharmaceutical Sciences,
Okayama, Japan

S. Kawa
Center for Health, Safety and Environmental Management,
Shinshu University, Nagano, Japan

R. Suzuki
Department of HSCT Data Management and Biostatistics,
Graduate School of Medicine,
Nagoya University, Nagoya, Japan

T. Takegami
Division of Molecular Oncology and Virology,
Medical Research Institute, Kanazawa Medical University,
Ishikawa, Japan

N. Tomosugi
Department of Advanced Medicine, Medical Research Institute,
Kanazawa Medical University, Ishikawa, Japan

N. Kurose
Department of Pathology and Laboratory Medicine,
Kanazawa Medical University, Ishikawa, Japan

Y. Ishigaki
Division of Core Facility, Medical Research Institute,
Kanazawa Medical University, Ishikawa, Japan

A. Azumi
Ophthalmology Department, Kobe Kaisei Hospital,
Hyogo, Japan

M. Kojima
Department of Anatomic and Diagnostic Pathology,
Dokkyo University School of Medicine, Mibu, Japan

S. Nakamura
Department of Pathology and Laboratory Medicine,
Nagoya University Hospital, Nagoya, Japan

D. Inoue
Department of Radiology,
Kanazawa University Graduate
School of Medical Science,
Ishikawa, Japan

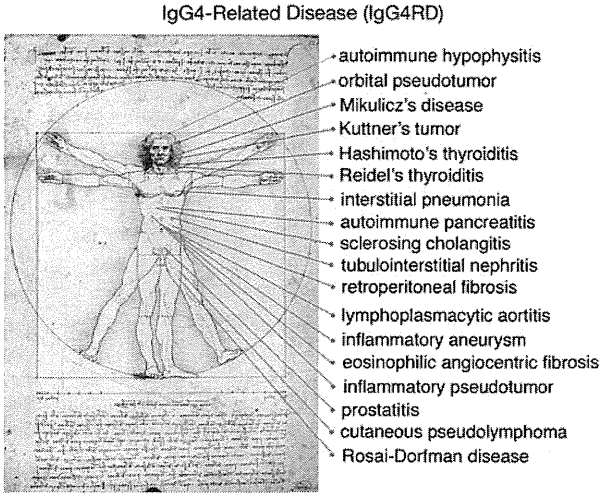


Fig. 1 IgG4-related conditions. Many diseases have been reported to be IgG4-related

presence of various autoantibodies, lymphocytic infiltration into pancreatic tissue, and good responsiveness to steroids [12]. Following a report showing elevated serum IgG4 concentrations in patients with AIP [13], the pancreatic research team of the Ministry of Health, Labor and Welfare Japan (MHLW Japan) showed that AIP was related to IgG4 [14].

IgG4-positive plasma cell infiltration has also been observed in patients with other conditions, including retroperitoneal and mediastinal fibrosis [15, 16], inflammatory pseudotumor of the lung and liver [17], Küttner tumor [18], and interstitial nephritis [19], indicating that these diseases and conditions collectively constitute a new disease concept, IgG4-related disease (Fig. 1). These findings have led to the organization of two study groups by MHLW Japan to analyze the condition of IgG4-related disease. These groups consist of doctors and researchers in various fields, including rheumatology, hematology, gastroenterology, nephrology, pulmonology, ophthalmology, odontology, pathology, statistics, and basic and molecular immunology, from all over Japan. One of these groups, chaired by Professor Umehara of Kanazawa Medical University, is seeking to establish diagnostic criteria for IgG4-related multi-organ lymphoproliferative syndrome (IgG4-MOLPS), whereas the second group, chaired by Professor Okazaki of Kasai Medical University, is seeking to understand the etiology and pathogenesis of IgG4-related systemic disease.

Unification of different nomenclatures for IgG4-related disease (IgG4RD)

The concept of IgG4RD arose when elevated serum IgG4 concentrations were first reported in patients with sclerosing pancreatitis [13]. Autoimmune pancreatitis (AIP) is also associated with a variety of extrapancreatic lesions, including sclerosing cholangitis, sclerosing sialadenitis, and dacryoadenitis, resulting in the concept of IgG4-related systemic disease [20], also called IgG4-related autoimmune disease [21] or IgG4-related sclerosing disease [15]. The finding of elevated serum IgG4 and IgG4-positive plasma cell infiltration in MD suggested that MD was a systemic disease, which was called systemic IgG4 plasmacytic syndrome (SIPS) [22]. Further, a comparison of patients with MD and those with typical SS resulted in the formulation of a new clinical entity, IgG4+MOLPS [23]. Although many reports from Japan and other countries have described IgG4-related conditions under different names (Table 1), these may refer to the same condition, familial multifocal fibrosclerosis (FMF). Indeed, retroperitoneal fibrosis (RPF), mediastinal fibrosis, sclerosing cholangitis, Riedel's thyroiditis, and pseudotumor of the orbit may all be different manifestations of a single disease [24].

Table 1 Nomenclatures of IgG-related conditions

IgG4-related autoimmune disease	Kamisawa [21]
IgG4-associated multifocal systemic fibrosis	van der Vliet [76]
IgG4-related systemic disease	Kamisawa [20]
IgG4-related sclerosing disease	Kamisawa [15]
Hyper-IgG4 disease	Neild [59]
IgG4-related disease (IgG4-RD)	Zen [77]
Systemic IgG4 plasmacytic syndrome (SIPS)	Yamamoto [22]
IgG4-related multi-organ lymphoproliferative syndrome (IgG4-MOLPS)	Masaki [29]
IgG4-associated disease	Geyer [78]

The name "IgG4-related sclerosing disease" is mainly based on the swelling of fibrous organs, such as the pancreas and retroperitoneum, whereas "SIPS" and "IgG4+MOLPS" are based on lymphoplasmacytic proliferation in glands and swollen lymph nodes without fibrosis. Although many patients with this condition (i.e., IgG4-related sclerosing disease, etc.) have lesions in several organs, either synchronously or metachronously, other patients show involvement of only a single organ. At this point, it is unclear whether the pathogenetic mechanism of this disease is systemic or whether it consists of manifestations in individual organs. In addition, several reports have described patients with IgG4-associated conditions concomitant with malignant tumors such as pancreatic [25, 26] and salivary [27] carcinomas, and ocular adnexal lymphoma [28]. Therefore, using the term 'systemic' may lead to an incorrect diagnosis of an IgG4-related condition in a patient with malignant

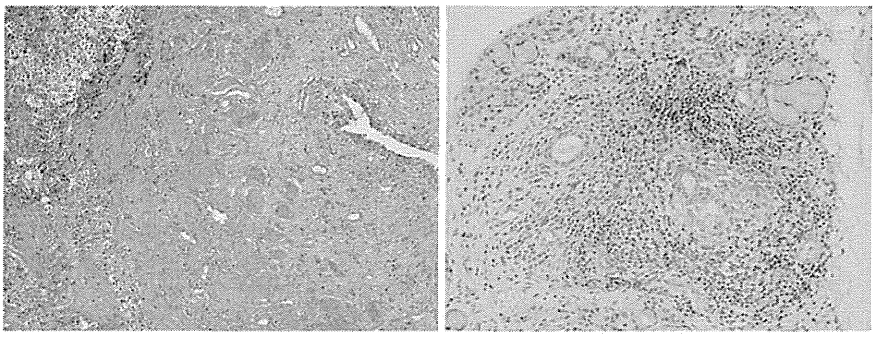


Fig. 2 Histopathology of IgG4-related disease (IgG4RD). IgG4RD is characterized histopathologically by the infiltration of IgG4-positive plasma cells and fibrosis. However, the severity of fibrosis is dependent on the individual organs involved. For example, storiform fibrosis and obliterative phlebitis are characteristic of retroperitoneal lesions, but are very seldom observed in salivary glands (×40)

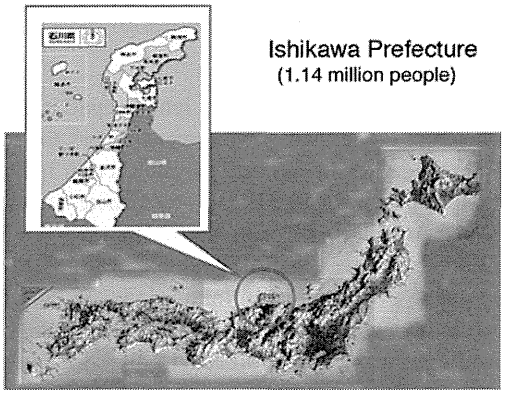
tumors in other organs. Based on these reasons, the members of the two MHLW Japan research teams agreed, at their second meeting in Kanazawa on February 11, 2010, to use the term "IgG4-related disease (IgG4RD)".

General concept of IgG4RD

After the unification of the disease name as IgG4RD, both MHLW Japan research teams have sought to determine its pathogenesis and to formulate diagnostic criteria. The two teams reached a consensus that IgG4RD 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, but that clinical symptoms depend on the location of the lesion. IgG4RD 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. Many patients with IgG4RD are treated effectively by steroid therapy. Although the infiltration of IgG4-positive cells and increased serum concentrations of IgG4 are characteristic of IgG4RD, the severity of fibrosis is dependent on the individual organs involved. For example, storiform fibrosis and obliterative phlebitis are characteristic of pancreatic, biliary tract, and retroperitoneal lesions, but are very seldom found in salivary glands or lymph nodes (Fig. 2).

Prevalence of IgG4RD

It is difficult to ascertain the number of patients with IgG4RD because its diagnostic criteria have not yet been established, the awareness of this disease is low, and its symptoms vary. An attempt was made to estimate the number of individuals with IgG4RD throughout Japan by using as an example Ishikawa Prefecture, which has a population of 1.14 million people with little population inflow/outflow (Fig. 3). In Ishikawa Prefecture, there are



	KMU	KUH	total
2003	2	2	4
2004	0	1	1
2005	1	3	4
2006	1	3	4
2007	1	4	5
2008	1	3	4
2009	1	6	7
	7	22	29

Fig. 3 Prevalence of patients with IgG4RD. An attempt was made to estimate the number of individuals with IgG4RD throughout Japan by using as an example Ishikawa Prefecture (population 1.14 million people) with little population inflow/outflow. If all new patients with IgG4RD visit Kanazawa Medical University Hospital (*KMU*) or Kanazawa University Hospital (*KUH*), the incidence of this disease throughout Japan would be 0.28–1.08/100,000 population, with 336–1,300 patients newly diagnosed per year. If life expectancy after diagnosis is 20 years, then approximately 6,700–26,000 patients in Japan would have developed IgG4RD over the past 20 years. The *numbers in the table* represent the numbers of patients who visited KMU or KUH each year