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GUIDELINE

Clinical diagnostic criteria of IgG4-related sclerosing cholangitis 2012

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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

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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].

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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

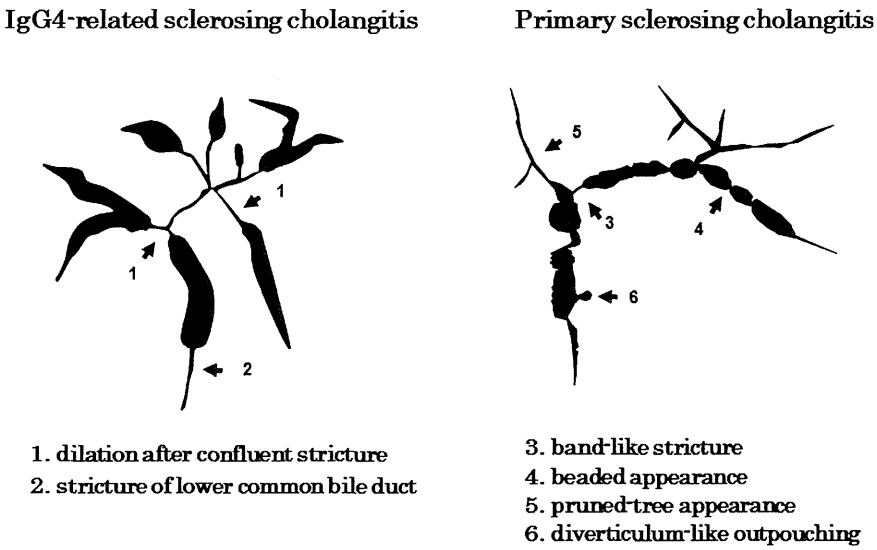

Fig. 1 The schematic comparison of cholangiographic findings between IgG4-related sclerosing cholangitis and primary sclerosing cholangitis. IgG4-related sclerosing cholangitis showing dilation after confluent stricture (>10 mm) and stricture of lower common bile duct. Primary sclerosing cholangitis 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)

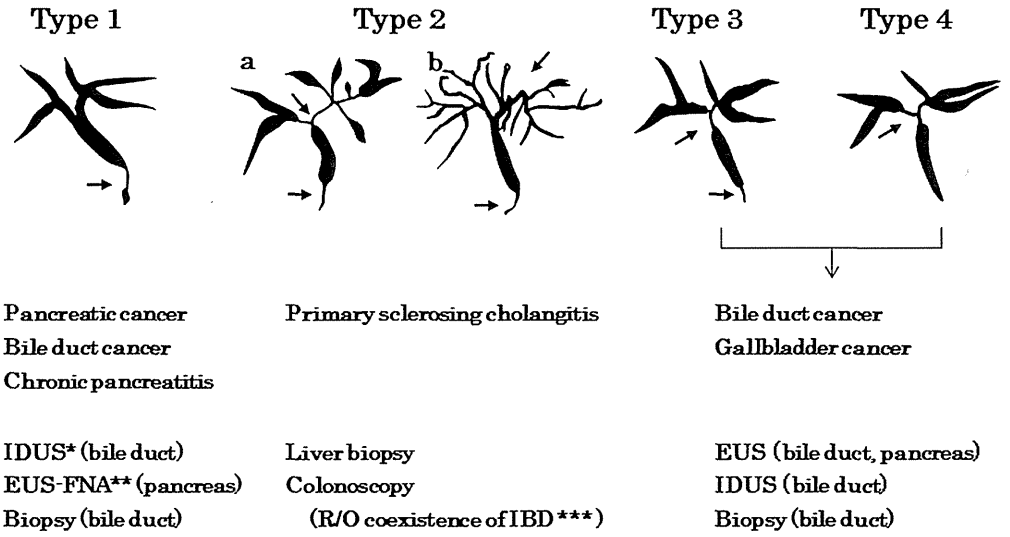

Fig. 2 The cholangiographic classification of IgG4-related sclerosing cholangitis and differential diagnosis. Stenosis is located only in the lower part of the common bile duct in type 1; stenosis is diffusely distributed in the intra- and extrahepatic bile ducts in type 2. Type 2 is further subdivided 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.

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IgG4 関連疾患包括診断基準 2011

厚生労働省難治性疾患克服研究事業　奨励研究分野
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[1)]
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班[2)]

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表1．厚生労働省難治性疾患対策事業「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」（岡崎班），「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）合同包括診断基準2011作成ワーキンググループ

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1．はじめに　～包括診断基準作成と寄稿の経緯～

IgG4関連疾患（IgG4-related disease：IgG4-RD）は，2001年のHamanoらによる自己免疫性膵炎での高IgG4血症（*N Eng J Med*）の報告を契機として[1]，わが国より発信された新しい疾患概念といえる．本疾患は，膵，肝胆，涙腺・唾液腺，後腹膜腔など全身臓器の腫大や肥厚と血中IgG4高値に加え，病理組織学的に著しいIgG4形質細胞浸潤，線維化，閉塞性静脈炎などを認める特異な疾患群と考えられている[2~9]．しかしながら，自己免疫性膵炎，硬化性胆管炎，後腹膜線維症などでは，著しい線維化を認める一方で，涙腺・唾液腺病変における線維化は比較的軽度であり，またリンパ節病変では線維化や閉塞性静脈炎を認めず，臨床病理所見は臓器により多少異なる．そのため，自己免疫性膵炎の研究からは，Kamisawaらによる「IgG4-related autoimmune disease」(2003年)[4]，「IgG4-related sclerosing disease」[5]（2006年）が，Mikulicz病の研究からはYamamotoら[6]による「IgG4-related plasmacytic disease」「Systemic IgG4-related plasmacytic syndrome（SIPS）」(2006年）やMasakiら[7]による「IgG4-multiorgan lymphoproliferative syndrome（MOLPS）」(2009年）などが，主にわが国の研究者から各専門臓器病変の立場から種々の概念・疾患名が提唱されてきた．原因は不明であるが，臨床的には，癌や悪性リンパ腫などの悪性腫瘍や類似の周辺疾患との鑑別が重要であり，ステロイドの有効なことが多い．

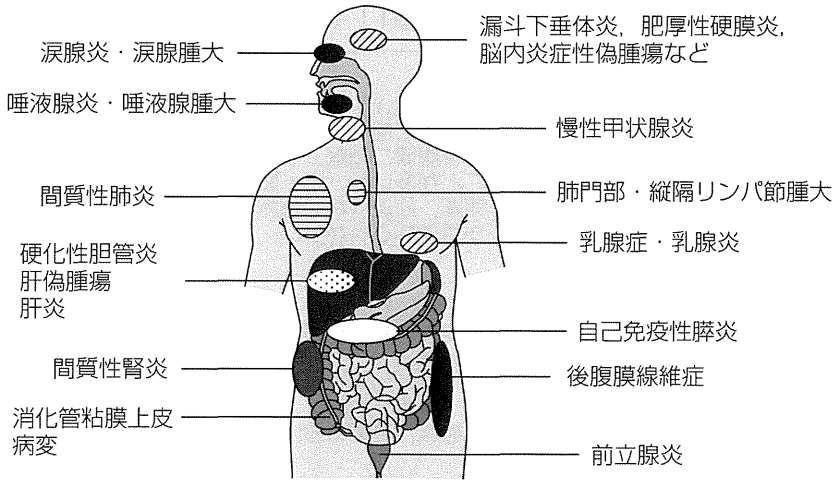

図 1. IgG4 関連疾患の各臓器病変（文献 38 より一部改変）

以上を背景に，本症の疾患概念と診断・治療法の確立にむけ，平成 21 年に厚生労働省難治性疾患克服研究事業の奨励研究分野として，全身性線維硬化性疾患の立場から「IgG4 関連全身硬化性疾患の診断法の確立と治療法の開発に関する研究」班（研究代表者　岡崎和一）[2]とリンパ増殖症の立場から「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」班（研究代表者　梅原久範）[3]が組織された．両研究班はそれぞれ独自で病態解明にむけた研究を行うとともに，連携協力して平成 22 年度には病名を「IgG4 関連疾患（IgG4-related disease : IgG4-RD）」[8]に統一することを提案し，その後の国際シンポジウム（「International IgG4-RD symposium」（ボストン，2011 年 10 月）においてもこの疾患名称が採用された．さらに，診断法の確立を目的として診断基準作成のための共同ワーキンググループ（表 1）を組織し，平成 23 年度には世界に先駆けてIgG4 関連疾患包括診断基準として「Comprehensive Diagnostic Criteria for IgG4-related disease, 2011」[9]を提唱した．

本稿は，この疾患の概念と包括診断基準を用いた診断法を広くわが国の臨床医にも知っていただくことを目的として，Modern Rheumatology 誌編集長のProf. Tsuneyo Mimoriの承諾のもと両研究班が合同で寄稿するものである．

2. IgG4 関連疾患の概念

病理組織学的にはリンパ球とIgG4 陽性形質細胞の著しい浸潤と線維化を特徴とし，臨床的には高IgG4 血症，高IgG，特に抗核抗体などを認めるとともに，同時性あるいは異時性に全身諸臓器の腫大や結節・肥厚性病変などを認める原因不明の疾患である．比較的高齢者に多い[2,3]．罹患臓器としては中枢神経系[10~12]，涙腺・唾液腺（硬化性唾液腺炎，Mikulicz病）[6,7]，甲状腺[13~16]，肺[17~19]，膵臓（自己免疫性膵炎）[1,4,5,20,21]，胆管（硬化性胆管炎）[4,5,20~23]，肝臓[24]，消化管[25~27]，腎臓[28,29]，前立腺[30]，後腹膜腔[2~9,20,21]，リンパ節[2~9]，動脈[31~34]，皮膚[35]，乳腺[36,37]などの報告がある[38]（図 1）．多巣性線維硬化症（multifocal fibrosclerosis）[39]との異同は不明であるが，本症である可能性がある．予後は不明であるが，臨床的には各臓器病変により異なった症状を呈し，肝・胆・膵病変における閉塞性黄疸，後腹膜病変における水腎症，肺病変における呼吸器症状など，時に重篤な合併症を伴うことがある．本疾患は，高IgG4 血症や臨床・病理組織所見などより総合的に診断できることが多いが，各臓器の悪性腫

表 2. IgG4 関連疾患包括診断基準 2011（厚生労働省　岡崎班・梅原班）

【概念】

IgG4 関連疾患とは，リンパ球とIgG4 陽性形質細胞の著しい浸潤と線維化により，同時性あるいは異時性に全身諸臓器の腫大や結節・肥厚性病変などを認める原因不明の疾患である．罹患臓器としては膵臓，胆管，涙腺・唾液腺，中枢神経系，甲状腺，肺，肝臓，消化管，腎臓，前立腺，後腹膜，動脈，リンパ節，皮膚，乳腺などが知られている．病変が複数臓器におよび全身疾患としての特徴を有することが多いが，単一臓器病変の場合もある．臨床的には各臓器病変により異なった症状を呈し，臓器腫大，肥厚による閉塞，圧迫症状や細胞浸潤，線維化に伴う臓器機能不全など時に重篤な合併症を伴うことがある．治療にはステロイドが有効なことが多い．

【臨床診断基準】

1．臨床的に単一または複数臓器に特徴的なびまん性あるいは限局性腫大，腫瘤，結節，肥厚性病変を認める．

2．血液学的に高IgG4 血症（135 mg/dl以上）を認める．

3．病理組織学的に以下の 2 つを認める．

①組織所見：著明なリンパ球，形質細胞の浸潤と線維化を認める．

②IgG4 陽性形質細胞浸潤：

IgG4/IgG陽性細胞比 40% 以上，且つIgG4 陽性形質細胞が 10/HPFを超える．

上記のうち，1）＋2）＋3）を満たすものを確定診断群（definite），1）＋3）を満たすものを準確診群（probable），1）＋2）のみをみたすものを疑診群（possible）とする．

但し，できる限り組織診断を加えて，各臓器の悪性腫瘍（癌，悪性リンパ腫など）や類似疾患（Sjogren症候群，原発性硬化性胆管炎，Castleman病，二次性後腹膜線維症，Wegener肉芽腫，サルコイドーシス，Churg-Strauss症候群など）と鑑別することが重要である．

本基準により確診できない場合にも，各臓器の診断基準により診断が可能である．

【解説】

Ⅰ）本診断基準は，一般臨床医や疾患該当臓器が専門外の医師でも，臨床的にIgG4 関連疾患を包括して診断できることをめざしたミニマムコンセンサスであり，各臓器病変に関しては，より専門的な臓器病変の診断基準を併用することが望ましい．

Ⅱ）概念：

多巣性線維硬化症（multifocal fibrosclerosis）との異同は不明であるが，本症である可能性がある．IgG4 関連疾患を疑う病態には以下のようなものがある．多くの症例では複数臓器に病変が及び全身疾患としての特徴を有するが，単一臓器病変の場合もある．

①自己免疫性膵炎（1 型）

IgG4 関連の自己免疫性膵炎（autoimmune pancreatitis：AIP）あるいはリンパ形質細胞浸潤の著しい硬化性膵炎（lymphoplasmacytic sclerosing pancreatitis：LPSP）と同義である．AIPの国際コンセンサス基準（International Consensus Diagnostic Criteria (ICDC) for AIP）や自己免疫性膵炎臨床診断基準 2011（日本膵臓学会・厚生労働省難治性膵疾患調査研究班，2011 年）により診断できる．

②IgG4 関連硬化性胆管炎

肝内・肝外胆管や胆嚢にびまん性あるいは限局性の特徴的な狭窄を伴う硬化性変化を示す．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．臨床的特徴としては閉塞性黄疸を発症することが多く，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．

③IgG4 関連涙腺・眼窩および唾液腺病変

IgG4 関連Mikulicz病を含み，対称性（時に片側性）の涙腺，耳下腺，顎下腺，舌下腺，小唾液腺の一部のいずれかの腫脹が特徴である．涙腺以外の眼窩組織にも結節性浸潤性に病変を生じることがある．IgG4 関連Mikulicz病は臓器診断基準（IgG4 関連Mikulicz病の診断基準，日本シェーグレン症候群研究会，2008 年）により診断できる．

④IgG4 関連中枢神経系病変

漏斗下垂体炎，肥厚性硬膜炎，脳内炎症性偽腫瘍などが知られている．

表2. 続き

⑤IgG4 関連呼吸器病変

主に気管支血管束，小葉間隔壁・肺胞隔壁などの間質および胸膜に病変を認める．縦隔・肺門リンパ節腫大を高率に伴い，肺野の腫瘤影や浸潤影を認めることもある．症例によっては喘息様症状を伴う．悪性腫瘍，サルコイドーシス，膠原病肺，感染症との鑑別が重要である．

⑥IgG4 関連腎臓病

画像上特徴的な異常所見（びまん性腎腫大，腎実質の多発性造影不良域，腎腫瘤，腎盂壁肥厚病変）を認めることが多い．腎組織は間質性腎炎が主体であるが糸球体病変（膜性腎症など）を伴う場合もある．

⑦IgG4 関連後腹膜線維症/動脈周囲病変

腹部大動脈外膜や尿管の周囲軟部組織の肥厚が特徴的で水腎症や腫瘤を形成することもある．動脈周囲炎は大動脈や比較的大きな分枝に病変を生じ，画像上動脈壁の肥厚として認識される．生検困難例も多く，その場合には悪性疾患や感染症などによる二次性後腹膜線維症との鑑別が問題となる．

⑧その他の腫瘤性病変

IgG4 陽性形質細胞やリンパ球の増殖を主体とし，線維化を伴う場合もある．従来の炎症性偽腫瘍の一部を含め，脳，眼窩内，肺，乳腺，肝，膵，後腹膜，腎，リンパ節などでの報告がある．

Ⅲ）血液所見

①ポリクローナルな血清γグロブリンの上昇，血清IgG，IgEの上昇を認めることが多く，低補体血症を認めることがある．

②血清IgG4 高値は，他疾患（アトピー性皮膚炎，天疱瘡，気管支喘息，多中心性Castleman病など）にも認められるため，本疾患に必ずしも特異的ではない．

③血清IgG4 は悪性腫瘍でも稀に上昇を認める．ただし，カットオフ値の 2 倍以上では膵癌の可能性が低いとの報告がある．

④単一臓器病変では血清IgG4 が 135 mg/dl未満でもIgG4/IgG比が診断の参考になることがある．

⑤今のところ，病因・病態生理におけるIgG4 の意義は不明である．

Ⅳ）病理組織所見

①臓器によっては，花筵様線維化（storiform fibrosis）あるいは渦巻き様線維化（swirling fibrosis），閉塞性静脈炎(obliterative phlebitis）が特徴的な病理像であり，この疾患を診断する上で重要な所見である．

②IgG4 陽性形質細胞以外に好酸球の浸潤もしばしばみられる．

③膵癌などの周辺にも反応性にIgG4 陽性形質細胞の浸潤や線維化を認めることがある．

Ⅴ）ステロイド

①悪性リンパ腫や腫瘍随伴病変もステロイド投与により，時に改善する可能性があり，安易なステロイドトライアルは厳に慎むべきである．

②診断はできる限り病理組織を採取する努力をすべきである．ただし，膵，後腹膜，脳下垂体病変など組織診の難しい臓器に限っては，ステロイド効果のある場合，本疾患の可能性もある．

③初期使用量は自己免疫性膵炎のガイドラインに準じてprednisolone 0.5 ～ 0.6 mg/kg/dayが推奨される．初回治療でのステロイド無効例は診断を見直すべきである．

Ⅵ）除外あるいは鑑別すべき疾患

①各臓器の悪性腫瘍（癌，悪性リンパ腫など）は病理組織で悪性細胞の有無を確認することが必須である．

②類似疾患（Sjogren症候群，原発性硬化性胆管炎，多中心性Castleman病，特発性後腹膜線維症，Wegener肉芽腫，サルコイドーシス，Churg-Strauss症候群など）の診断は各疾患の診断法や診断基準にもとづいて診断する．

③多中心性Castleman病はhyper IL-6 syndromeであり，診断基準を満たしていてもIgG4 関連疾患には含まれない．

瘍(癌，悪性リンパ腫など)や類似疾患(Sjogren症候群，原発性硬化性胆管炎(Primary sclerosing cholangitis：PSC)，Castleman病など)を除外することが必要である[9]．ステロイド治療の有効なことが多いため，膵，後腹膜，脳下垂体病変など組織診の難しい臓器では，ステロイド効果を認める場合，本症の可能性も考えられるが，感染症における病状悪化や悪性リンパ腫における縮小効果などステロイドによる病態の修飾もあるので，安易なステロイドトライアルは厳に慎むべきである[9]．

3. 各臓器病変の特徴と診断法の現状

1) 自己免疫性膵炎（1型）[1,20,21,40]

IgG4関連の自己免疫性膵炎(autoimmune pancreatitis：AIP）あるいはリンパ形質細胞浸潤の著しい硬化性膵炎（lymphoplasmacytic sclerosing pancreatitis：LPSP)と同義である．AIPの国際コンセンサス基準（International Consensus Diagnostic Criteria（ICDC）for AIP)[40]や自己免疫性膵炎臨床診断基準2011（日本膵臓学会・厚生労働省難治性膵疾患調査研究班，2011年)[21]により診断できる．

2) IgG4関連硬化性胆管炎[21,23]

肝内・肝外胆管や胆嚢にびまん性あるいは限局性の特徴的な狭窄を伴う硬化性変化を示す．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．臨床的特徴としては閉塞性黄疸を発症することが多く，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．

3) IgG4関連涙腺・眼窩および唾液腺病変[5,16]

IgG4関連Mikulicz病を含み，対称性（時に片側性）の涙腺，耳下腺，顎下腺，舌下腺，小唾液腺の一部のいずれかの腫脹が特徴である．涙腺以外の眼窩組織にも結節性浸潤性に病変を生じることがある．IgG4関連Mikulicz病は臓器診断基準（IgG4関連Mikulicz病の診断基準，日本シェーグレン症候群研究会，2008年）により診断できる．

4) IgG4関連中枢神経系病変[10~12]

漏斗下垂体炎，肥厚性硬膜炎，脳内炎症性偽腫瘍などが知られている．

5) IgG4関連呼吸器病変[24~28]

主に気管支血管束，小葉間隔壁・肺胞隔壁などの間質および胸膜に病変を認める．縦隔・肺門リンパ節腫大を高率に伴い，肺野の腫瘤影や浸潤影を認めることもある．症例によっては喘息様症状を伴う．悪性腫瘍，サルコイドーシス，膠原病肺，感染症との鑑別が重要である．

6) IgG4関連腎臓病[26,27,33,34,41]

画像上特徴的な異常所見（びまん性腎腫大，腎実質の多発性造影不良域，腎腫瘤，腎盂壁肥厚病変）を認めることが多い．腎組織は間質性腎炎が主体であるが糸球体病変(膜性腎症など)を伴う場合もある．腎臓学会との連携により「IgG4関連腎臓病診断基準」[41]が制定された．

7) IgG4関連後腹膜線維症/動脈周囲病変[36~39]

腹部大動脈外膜や尿管の周囲軟部組織の肥厚が特徴的で水腎症や腫瘤を形成することもある．動脈周囲炎は大動脈や比較的大きな分枝に病変を生じ，画像上動脈壁の肥厚として認識される．生検困難例も多く，その場合には悪性疾患や感染症などによる二次性後腹膜線維症との鑑別が問題となる．

8) その他の腫瘤性病変[2~9]

IgG4陽性形質細胞やリンパ球の増殖を主体とし，線維化を伴う場合もある．従来の炎症性偽腫瘍の一部を含め，脳，眼窩内，肺，乳腺，肝，膵，後腹膜，腎，リンパ節などでの報告がある．

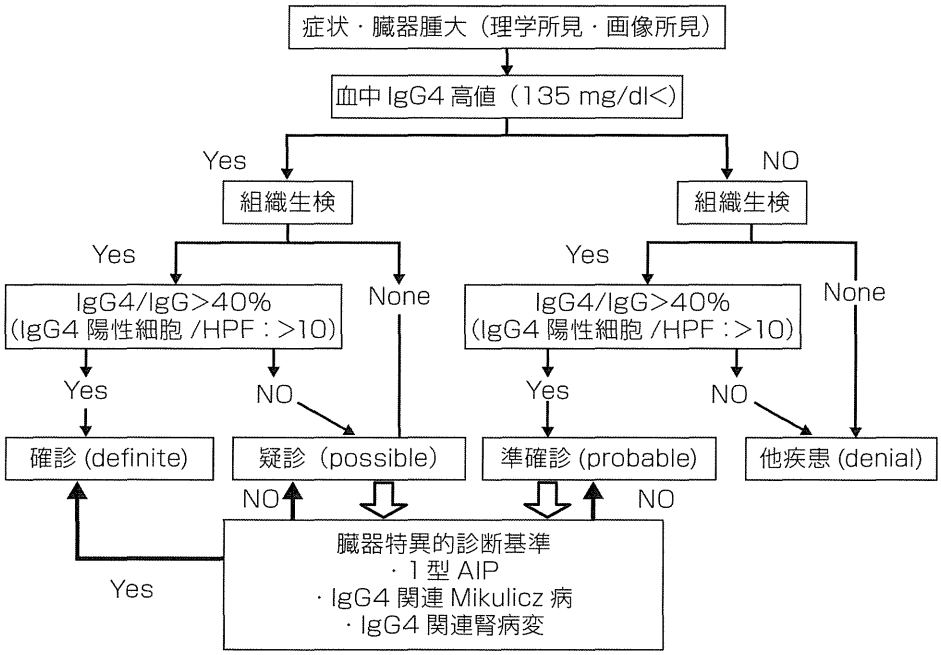

図 2. IgG4 関連疾患の診断アルゴリズム（文献 9 より一部改変）
臨床的にIgG4 関連疾患を疑う臨床症状や臓器腫大を認めると，血中IgG4 を測定し，可能な限り病理検査を行う．抱括診断基準で疑診あるいは準確診にとどまる場合でも，各臓器診断基準を併用することにより，診断を確定できる可能性がある．

4. IgG4関連疾患包括診断基準2011[9]（表2）

本包括診断基準の基本コンセプトは，①各臓器病変の専門医以外の臨床医でも使用できる，②各臓器の診断基準と併用できることを前提とする，③出来るだけ簡潔化する，④鑑別に最も重要な悪性腫瘍を除外するために病理組織所見を重視する，⑤ステロイドの診断的治療は推奨しない，である．診断項目は臨床的所見，血液所見，病理組織所見の 3 項目よりなる．すなわち（1）臨床的に単一または複数臓器に特徴的なびまん性あるいは限局性腫大，腫瘤，結節，肥厚性病変を認めること，（2）血液学的に高IgG4 血症（135 mg/dl以上）を認めること，（3）病理組織学的に，①組織所見：著明なリンパ球，形質細胞の浸潤と線維化を認める．②IgG4 陽性形質細胞浸潤：IgG4/IgG陽性細胞比 40% 以上，且つIgG4 陽性形質細胞が 10/HPFを超えること，が提案されている．これらの診断項目の組み合わせにより，確定診断群（definite），準確診群（probable），疑診群（possible）と診断する提案がなされている．

血液所見では，単一臓器病変では血清IgG4 が 135 mg/dl未満でもIgG4/IgG比が診断の参考になることがある．またIgG4 高値以外にはポリクローナルな血清γグロブリンの上昇，血清IgG，IgEの上昇を認めることが多く，低補体血症を認めることがある．しかしながら，血清IgG4 高値は，他疾患（アトピー性皮膚炎，天疱瘡，気管支喘息，多中心性Castleman病など）にも認められるため，本疾患に必ずしも特異的ではなく，今のところ，病因・病態生理におけるIgG4 の意義は不明である．また，血清IgG4 は悪性腫瘍でも稀に上昇を認めるが，カットオフ値の 2 倍以上では膵癌の可能性が低いとの報告がある．

病理組織所見では，臓器によっては，花筵様線維化（storiform fibrosis）あるいは渦巻き様線

維化(swirling fibrosis)，閉塞性静脈炎(obliterative phlebitis)が特徴的な病理像であり，この疾患を診断する上で重要な所見である．またIgG4陽性形質細胞以外に好酸球の浸潤もしばしばみられる．注意すべきは，膵癌などの周辺にも反応性にIgG4陽性形質細胞の浸潤や線維化を認めることがあり非特異的反応所見の存在に留意する必要がある．

除外すべき疾患として，各臓器の悪性腫瘍(癌，悪性リンパ腫など）では病理組織で悪性細胞の有無を確認することが必須である．また類似疾患(Sjogren症候群，原発性硬化性胆管炎，多中心性Castleman病[42]，特発性後腹膜線維症，Wegener肉芽腫，サルコイドーシス，Churg-Strauss症候群[43]など）の診断は各疾患の診断法や診断基準にもとづいて診断することが重要である．多中心性Castleman病はhyper IL-6 syndromeであり，現状では診断基準を満たしていてもIgG4関連疾患には含まれない[9]．

また，膵，後腹膜，脳下垂体病変など組織診の難しい臓器に限っては，ステロイド効果のある場合，本疾患の可能性も示唆されるため，自己免疫性膵炎の国際診断基準や新しく改訂された自己免疫性膵炎臨床診断基準2011のようにステロイド効果を診断基準に含むものもある．しかしながら，悪性リンパ腫や腫瘍随伴病変もステロイド投与により，時に改善する可能性があるため，安易なステロイドトライアルは厳に慎むべきであり，包括診断基準では採用されていない[9]．そのため，診断にはできる限り病理組織を採取する努力をする必要がある[9]．

5. 本包括診断基準を用いた診断アルゴリズム[9]（図2）

本包括診断基準は上記の基本コンセプトに基づいており，病理組織を重視することやステロイドの診断的治療が推奨されていないため，臨床的に生検材料の得られにくい臓器病変における診断感度は必ずしも高くはない．そのため，準確診群（probable）や疑診群（possible）では，すでに作成あるいは今後作成される各臓器診断基準との併用が推奨されており，最終的には臓器により確診と準確診あるいは疑診病変の混在することもある．

6. おわりに

近年注目されている新規疾患概念である「IgG4関連疾患」の概念にもとづいた包括診断基準について述べた．

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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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