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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＜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
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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

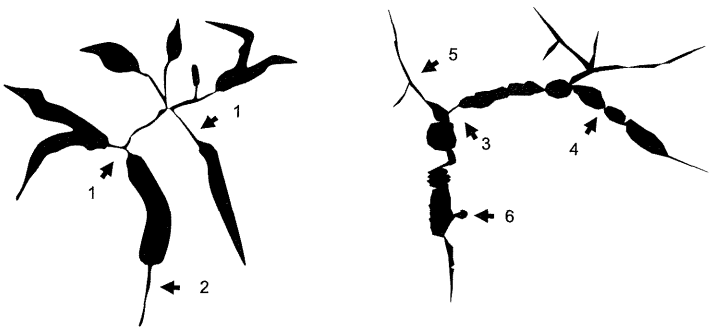
以下の原因などによる二次的硬化性胆管炎を除外する．

- ・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

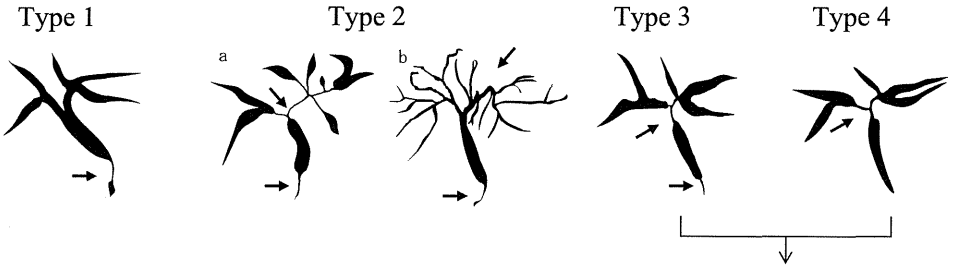
画像で評価可能な病変が対象であり，臨床症状や血液検査は評価の対象としない．胆管病変を含め，膵，涙腺，唾液腺，後腹膜などの胆管外病変でも組織診が難しいことがあるが，できる限り病理組織を採取するよう努力し，安易なステロイドトライアルは厳に慎むべきである．

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



	Type 1	Type 2	Type 3	Type 4
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.

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SPEICIAL ARTICLE

Proposal for diagnostic criteria for IgG4-related kidney disease

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Abstract
Background IgG4-related disease has attracted wide attention recently. It is characterized by a high level of serum IgG4 and dense infiltration of IgG4-positive plasma cells into multiple organs, with the kidney being one representative target. Although several sets of diagnostic criteria for autoimmune pancreatitis (AIP) are available and renal lesion is recognized as an extra-pancreatic manifestation of AIP, it is difficult to differentiate IgG4-related tubulointerstitial nephritis (TIN) without AIP from other types of TIN. To clarify the entity of IgG4-related kidney disease (IgG4-RKD) and support in-depth studies, the Japanese Society of Nephrology has established a working group to prepare diagnostic criteria for IgG4-RKD.
Method The working group analyzed 41 patients with IgG4-RKD, and collected the following data to devise a diagnostic algorithm and diagnostic criteria for IgG4-RKD: clinical features including extra-renal organ involvement, urinalysis and serological features including serum IgG4

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levels, imaging findings demonstrated by computed tomography (CT), renal histology with IgG4 immunostaining, and response to steroid therapy.

Results The conditions for criteria are as follows. (1) Presence of some kidney damage, as manifested by abnormal urinalysis or urine marker(s) and/or decreased kidney function with either elevated serum IgG level, hypocomplementemia, or elevated serum IgE level. (2) Kidney imaging studies showing abnormal renal imaging findings, i.e., multiple low density lesions on enhanced CT, diffuse kidney enlargement, hypovascular solitary mass in the kidney, and hypertrophic lesion of the renal pelvic wall without irregularity of the renal pelvic surface. (3) Serum IgG4 level exceeding 135 mg/dl. (4) Renal histology showing two abnormal findings: (a) dense lymphoplasmacytic infiltration with infiltrating IgG4-positive plasma cells >10/high power field (HPF) and/or ratio of IgG4-positive plasma cells/IgG positive plasma cells >40%. (b) Characteristic 'storiform' fibrosis surrounding nests of lymphocytes and/or plasma cells. (5) Extra-renal histology showing dense lymphoplasmacytic infiltration with infiltrating IgG4-positive plasma cells >10/HPF and/or ratio of IgG4-positive plasma cells/IgG-positive plasma cells >40%. The diagnosis is classified into 3 stages of definite, probable and possible according to the combinations of the above conditions. Thirty-nine cases (95.1%) were diagnosed with IgG4-RKD according to the criteria.

Conclusion The provisional criteria and algorithm appear to be useful for clarifying the entity of IgG4-RKD and seeking underlying IgG4-RKD cases; however, further experience is needed to confirm the validity of these criteria.

Keywords IgG4-related kidney disease · Diagnostic criteria · IgG4 · Tubulointerstitial nephritis

Introduction

After the recognition of autoimmune pancreatitis (AIP) as an IgG4-related disease [1], similar lesions in other organs have attracted much attention. IgG4-related kidney disease (IgG4-RKD) was first reported as a complication or an extrapancreatic manifestation of AIP in 2004 [2, 3]. In the early reported cases, the development of renal dysfunction and/or proteinuria during the clinical course of AIP was the clue to the presence of renal involvement, and renal biopsy revealed tubulointerstitial nephritis (TIN) and fibrosis with dense infiltration of IgG4-positive plasma cells [2–4]. Thereafter, incidentally-detected IgG4-RKD cases in the course of close examination of AIP [5–7] or chronic sclerosing sialadenitis and dacryoadenitis [8] using enhanced computed tomography (CT) have been additionally accumulated. Recently, IgG4-RKD without AIP or chronic sclerosing sialadenitis and dacryoadenitis has also been reported [9–11].

Against this background of detection of IgG4-RKD with the kidney being the first recognized organ of IgG4-related disease [9–11], demand for practical diagnostic criteria for IgG4-RKD has been growing. To meet this demand and spread recognition of IgG4-RKD among nephrologists and other clinical practitioners, we organized a working group in the Japanese Society of Nephrology (JSN) consisting of specialists in clinical nephrology, renal pathology, clinical immunology and rheumatology. This report describes our proposal for a diagnostic algorithm and the diagnostic criteria for IgG4-RKD prepared by this working group.

Methods

Patients

Between 2004 and 2011, we identified 41 patients with IgG4-RKD in Kanazawa University Hospital, Nagaoka Red Cross Hospital, Niigata University Hospital, Sapporo Medical University Hospital, and Fukuoka University Hospital. Nine patients [3 Churg–Strauss syndrome; 2 IgG4-RKD without TIN with decreased renal function; 1 Sjögren's syndrome (SS) with TIN; 1 minimal change nephrotic syndrome; 1 allergic disease with hypocomplementemia; 1 relapsing polychondritis] were selected as a negative control. Written informed consent for all data and samples was obtained from each patient. The diagnosis of IgG4-RKD was made principally based on the histologic and immunohistochemical findings of the kidney or other organs with the support of a comprehensive analysis of the clinical picture including elevated serum IgG4 levels, and final clinical judgment was left to the observers at each hospital who had sufficient experience in IgG4-related disease and clinical nephrology. This study was approved by each institutional ethics board and ethics board of the JSN. The research was conducted in compliance with the Declaration of Helsinki.

Clinical features

The clinical picture including symptoms resulting from other organ involvement such as the pancreas, lacrimal and salivary glands, or lungs was noted. Diagnostic clues to IgG4-RKD were carefully evaluated, and important items were extracted. Serum IgG, IgG4, IgE, and complement levels were collected from the clinical data file. Serum creatinine (Cr) levels and any abnormalities of urinalysis including proteinuria and hematuria before corticosteroid therapy were noted in all cases. Urine *N*-acetyl-β-D-glucosaminidase and urine β_2-microglobulin levels were also noted if available.

Imaging

CT was the most recommended radiographic imaging method for IgG4-RKD. In general, contrast-enhanced CT was needed to make the correct diagnosis; however, the use of contrast medium required careful judgment in patients with impaired renal function. Without enhancement, diffuse enlargement of the kidney inconsistent with the degree of renal function was noted. Other modalities including gallium scintigraphy, magnetic resonance imaging, and fluorodeoxyglucose positron emission tomography were additionally used to identify renal lesions.

Histology and immunostaining

Renal histology was available in 28 patients. Bouin's fluid-fixed or formalin-fixed and paraffin-embedded renal specimens of patients with IgG4-RKD were analyzed, and the degree of lymphoplasmacytic infiltration in the interstitium, degree of fibrosis, eosinophilic infiltration, and glomerular lesions were recorded. In immunostaining, immunofluorescence was performed against IgG, IgA, IgM, C3, C1q, and fibrinogen. Immunostaining was performed using mouse monoclonal antibody against human IgG4 (Zymed Laboratories, San Francisco, CA, USA, or The Binding Site, Birmingham, UK), anti-human IgG (Dako, Glostrup, Denmark), and/or anti-human CD138 (AbD Serotec, Oxford, UK).

Diagnostic algorithm and criteria

We first analyzed 41 cases of IgG4-RKD, the preliminary diagnosis of which was made based on the clinical decision of observers who had sufficient experience with IgG4-related disease including AIP. To select the most sensitive and specific test for the diagnosis of IgG4-RKD, we referred to the revised clinical diagnostic criteria for AIP proposed by Okazaki et al. [12] and Mayo Clinic criteria for AIP proposed by Chari et al. [13]. On the basis of these analyses, a diagnostic algorithm and criteria were prepared.

Results

Clinical features

Table 1 summarizes clinical and histological characteristics of the 41 patients. The mean age of the 41 patients was 63.7 years (range 27–83). The ratio of male to female patients was 30:11. Eight patients without preceding IgG4-related disease were suspected to have renal disease because of decreased kidney function ($n = 4$), radiographic abnormalities ($n = 2$) and/or urinary abnormalities ($n = 1$). The remaining one patient was detected after close examination of highly suspected elderly-onset lupus with elevated serum IgG, hypocomplementemia, and polyarthritis without urinary abnormalities. In contrast, 33 patients were diagnosed as having IgG4-RKD during the clinical course of IgG4-related disease. Of these, 20 patients were incidentally detected when systemic examination for IgG4-related disease was performed through radiographic examination. Thirteen patients were suspected of having renal disease because of newly noted renal dysfunction.

Serological features

The mean serum IgG level was 3467 mg/dl (range 1480–9470 mg/dl), and 37 patients (90.2%) had elevated serum IgG level. In 21 patients (51.2%), serum IgG levels exceeded 3000 mg/dl. The mean serum IgG4 level was 991.2 mg/dl (range 152–2940 mg/dl), and all patients had elevated serum IgG4 levels. Hypocomplementemia was detected in 22 patients (53.7%), 16 of whom had low C3, C4, and CH50 levels. Two patients had both low C3 and CH50 levels, one had both low C3 and C4 levels, one had low C3 levels only, and two had low C4 levels only. Serum IgE level was evaluated in 33 patients. Mean serum IgE level was 754.3 U/ml (range 3–3960 U/ml), and 26 patients (78.8%) had elevated serum IgE levels. Mean serum Cr level was 1.7 mg/dl, and 24 patients had elevated serum Cr levels (serum Cr $\geq$ 1.0 mg/dl).

Imaging

Contrast-enhanced CT was performed in 29 patients. Twelve of 41 patients had no remarkable CT findings. In 10 of these, use of contrast enhancement was withheld because of decreased renal function. The remaining two patients had no remarkable CT findings despite the use of contrast enhancement. Multiple low-density lesions on enhanced CT were the most common radiologic finding in IgG4-RKD, and 19 patients (46.3%) showed this feature (Fig. 1a). When decreased renal function existed and administration of contrast medium was deemed inadvisable, diffuse bilateral renal swelling was another feature ($n = 2$) (Fig. 1b). The third characteristic radiologic finding of IgG4-RKD was diffuse thickening of the renal pelvis wall with smooth intraluminal surface, and this finding was sometimes detected in patients with IgG4-related disease without obvious clinical symptoms (Fig. 1d). This radiologic finding was usually pointed out incidentally during the close systemic evaluation of IgG4-related disease patients, and 6 patients had this type of pelvic lesion. A hypovascular solitary nodule of the renal parenchyma was

Table 1 Clinical and pathological characteristics of 41 patients

Characteristics	The number of cases[a] (%)
Age (years)	63.7 ± 12.3
Male sex [no. (%)]	30 (73.2)
Patients with preceding IgG4-RD [no. (%)]	33 (80.5)
Clue to detect IgG4-RKD with preceding IgG4-RD [no./total no. (%)]	
Incidentally detected during systemic examination for IgG4-RD	20/33 (60.6)
Newly noted renal dysfunction	13/33 (39.4)
Clue to detect IgG4-RKD without preceding IgG4-RD [no./total no. (%)]	
Decreased kidney function	4/8 (50.0)
Radiographic abnormalities	2/8 (25.0)
Urinary abnormalities	1/8 (12.5)
Urinalysis and serological features	
Proteinuria [no./total no. (%)]	
3+	1/36 (2.8)
2+	6/36 (16.7)
1+	11/36 (30.6)
±	3/36 (8.3)
Hematuria [no./total no. (%)]	
3+	1/36 (2.8)
2+	2/36 (5.6)
1+	9/36 (25.0)
±	3/36 (8.3)
Elevated serum creatinine [no./total no. (%)]	24/41 (58.5)
Serum creatinine level (mg/dl)	1.7 ± 1.5
Elevated serum IgG [no./total no. (%)]	37/41 (90.2)
Serum IgG level (mg/dl)	3467.4 ± 1658.2
Serum IgG levels exceeding 3000 mg/dl [no./total no. (%)]	21/41 (51.2)
Hypocomplementemia [no./total no. (%)]	22/41 (53.7)
Elevated serum IgE [no./total no. (%)]	26/33 (78.8)
Serum IgE level (U/ml)	754.3 ± 876.8
Elevated serum IgG4 [no./total no. (%)]	41/41 (100.0)
Serum IgG4 level (mg/dl)	991.2 ± 604.9
Imaging (CT)	
Contrast medium used [no./total no. (%)]	29/41 (70.7)
Multiple low-density lesions on enhanced CT [no./total no. (%)]	19/29 (65.5)
Diffuse bilateral renal swelling on enhanced CT [no./total no. (%)]	1/29 (3.4)
Diffuse bilateral renal swelling without enhanced CT [no./total no. (%)]	2/12 (16.7)
Diffuse thickening of the renal pelvis wall [no./total no. (%)]	6/41 (14.6)
Hypovascular solitary nodule [no./total no. (%)]	1/29 (3.4)
Histology	
Patients with tubulointerstitial lesions [no./total biopsied no. (%)]	28/28 (100.0)
Patients with glomerular lesions [no./total biopsied no. (%)]	11/28 (39.3)
Other organ involvement [no. (%)]	
Pancreas	13 (31.7)
Salivary gland	29 (70.7)
Lacrimal gland	12 (29.3)
Lung	12 (29.3)
Lymph node	17 (42.5)
Retroperitoneum	4 (9.8)
Prostate	3 (7.3)
Periaortic area	2 (4.9)
Breast, liver, nerve, thyroid gland, peritoneum, bile duct, or joint[b]	1 (2.4)

IgG4-RD IgG4-related disease; *IgG4-RKD* IgG4-related kidney disease; *no.* numbers

[a] Plus-minus values are mean ± SD

[b] The number of each organ involvement is the same

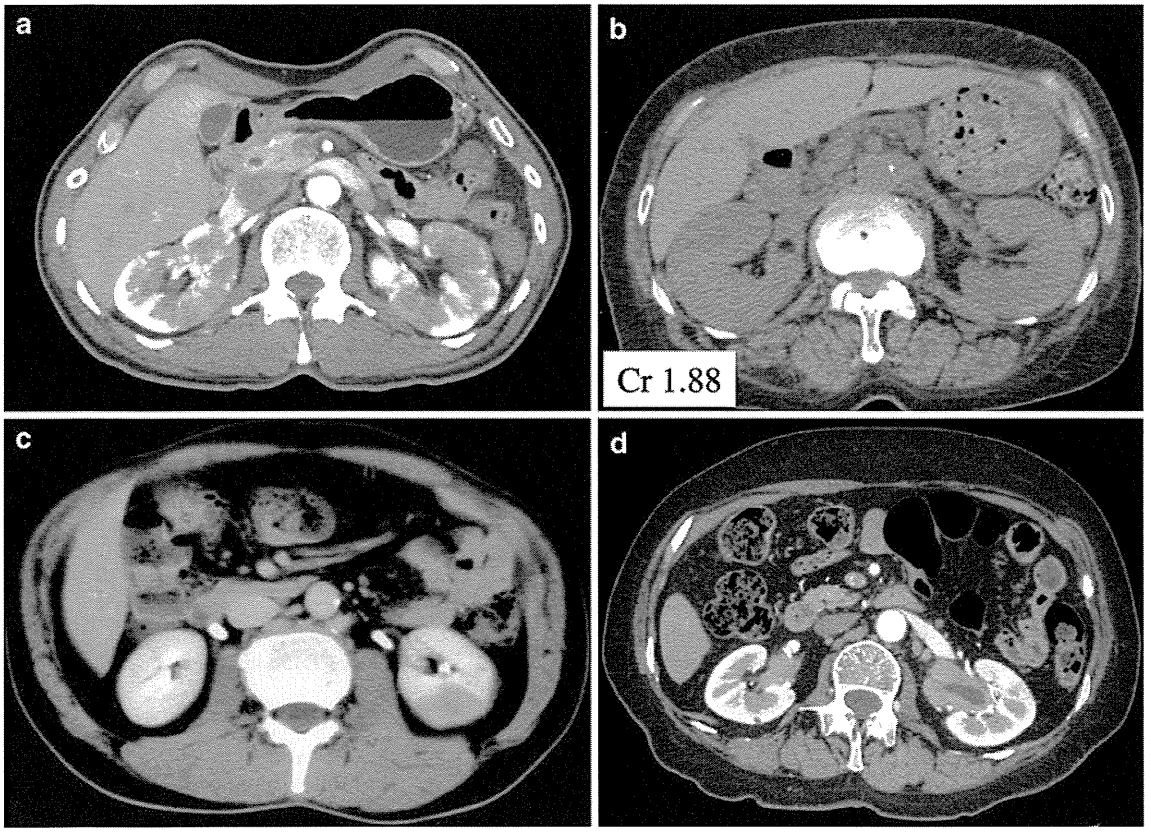

Fig. 1 Characteristic renal computed tomography (CT) imaging. **a** Multiple low-density lesions on enhanced CT. **b** Diffuse bilateral renal swelling. **c** A hypovascular solitary nodule. **d** Diffuse thickening of the renal pelvis wall with smooth intra-luminal surface

very rarely diagnosed as an IgG4-related kidney lesion, with only one such case detected in this study (Fig. 1c). Another patient had unilateral renal swelling probably because of a unilateral renal mass, but decreased renal function prevented more detailed analysis using contrast-enhanced CT.

Histology and immunostaining

A renal biopsy was performed in 28 of 37 patients (75.7%) with renal parenchymal lesions. Dense lymphoplasmacytic infiltration with fibrosis in the interstitium was found in 27 patients (Fig. 2a), and without fibrosis in one patient. Interstitial fibrosis surrounding nests of lymphocytes was characteristic and resembled the 'storiform' shape in AIP [14, 15], and also termed 'bird's eye' pattern [16] (Fig. 2b). Of these, marked IgG4-positive plasma cell infiltration was confirmed immunohistochemically in all patients (Fig. 2c, d). On the other hand, glomerular lesions were not specific, although they were found in 11 patients [3 membranous nephropathy (MN), 2 Henoch-Schönlein purpura nephritis, 2 IgA nephropathy, 2 focal and segmental endocapillary proliferative glomerulonephritis, 1 membranoproliferative glomerulonephritis, 1 mesangial proliferative glomerulonephritis]. Five patients who showed only diffuse pelvic wall thickening radiologically were excluded from the renal histological examination.

Other organ involvement

Other organ involvement was detected in 39 of 41 patients (95.1%). The average number of affected organs was 3.4 (range 1–8), and the distribution was shown in Fig. 3. The most frequently involved organ was the salivary gland, with 29 of 41 patients (70.7%) affected. Lymph node swelling was also frequently noted (17 of 41 patients; 42.5%). Thirteen patients (31.7%) had AIP, 12 (29.3%) had dacryoadenitis, 12 (29.3%) had lung lesion, 4 (9.8%) had retroperitoneal fibrosis, 3 (7.3%) had prostate lesion, and 2 (4.9%) had periaortic lesion. Breast, liver, nerve, thyroid gland, peritoneum, bile duct, or joint lesion was detected in one patient each. Eleven patients had both chronic sclerosing sialadenitis and dacryoadenitis.

Response to steroid therapy

Thirty-eight patients were treated with corticosteroid, 35 of whom had a favorable response to steroid therapy. One patient eventually required maintenance hemodialysis in spite of corticosteroid therapy. In the remaining two

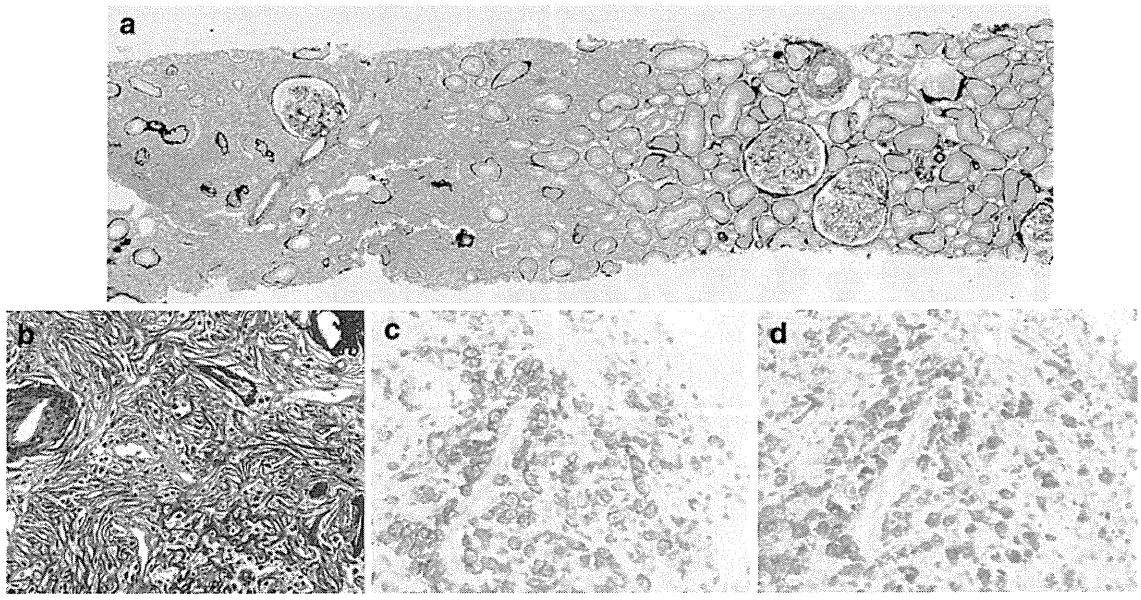

Fig. 2 Representative light microscopic histology. **a** Dense lymphoplasmacytic infiltration with fibrosis in the interstitium with clear border between affected and unaffected areas. **b** Typical fibrosis. **c**, **d** CD138 and IgG4 stain shows that >40% of plasma cells are IgG4-positive (**a** Periodic acid-Schiff stain ×40, **b** PAM-Masson's trichrome stain ×100, **c** CD138 immunostain ×400, **d** IgG4 immunostain ×400)

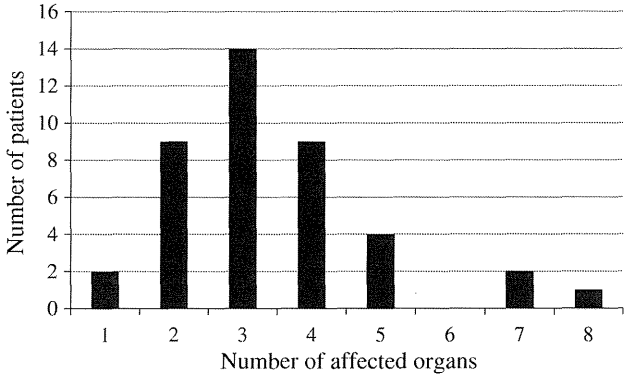

Fig. 3 Frequency distribution of the number of affected organs. The mean number of affected organs was 3.4

patients, reduction of serum Cr was not achieved probably because of a delay in the initiation of steroid treatment.

Diagnostic algorithm

Based on the analysis results of the diagnostic processes of these 41 cases and previously reported cases, our working group prepared a diagnostic algorithm of IgG4-RKD (Fig. 4; Table 2). Forty of 41 patients (97.6%) had either abnormal urinalysis or urine marker(s), abnormal radiologic findings, or decreased kidney function. Either elevated serum IgG level, hypocomplementemia, or elevated serum IgE level was detected in 40 of 41 patients (97.6%). In four patients with normal serum IgG level, three had increased serum IgE levels without hypocomplementemia. Therefore, the presence of some kidney damage, as manifested by abnormal urinalysis or urine marker(s), abnormal radiologic findings, or decreased kidney function, with either elevated serum IgG level, hypocomplementemia, or elevated serum IgE level was selected to be the first step to suspect the diagnosis of IgG4-RKD. However, as these features are shared with systemic lupus erythematosus, cryoglobulinemia, or vasculitis including Wegener's granulomatosis and Churg–Strauss syndrome, exclusion criteria were inserted in the next step. The third step was chosen to confirm an elevated serum IgG4 level, and the following step consisted of two complementary components: radiologic and histopathologic examinations. If renal pathology was not available, a careful differential diagnosis to rule out malignant lymphoma, urinary tract carcinomas, renal infarction, pyelonephritis, Wegener's granulomatosis [17, 18], sarcoidosis [19] and metastatic carcinoma was necessary, and non-renal histological finding with infiltrating IgG4-positive plasma cells >10/high power field (HPF) or IgG4/IgG >40% was necessary to support the radiologic findings. As the pathologic examination part, the following characteristic renal pathological findings of IgG4-RKD were listed: (a) marked lymphoplasmacytic infiltration, accompanied by >10 infiltrating IgG4-positive plasma cells/HPF and/or a ratio of IgG4/IgG-positive plasma cells >40%, (b) characteristic fibrosis surrounding several infiltrating cells, (c) other useful findings for the differential diagnosis [positive findings: lesions extending into the renal capsule, eosinophil infiltration, well-defined regional lesion distribution, marked fibrosis, negative findings: (necrotizing) angiitis,

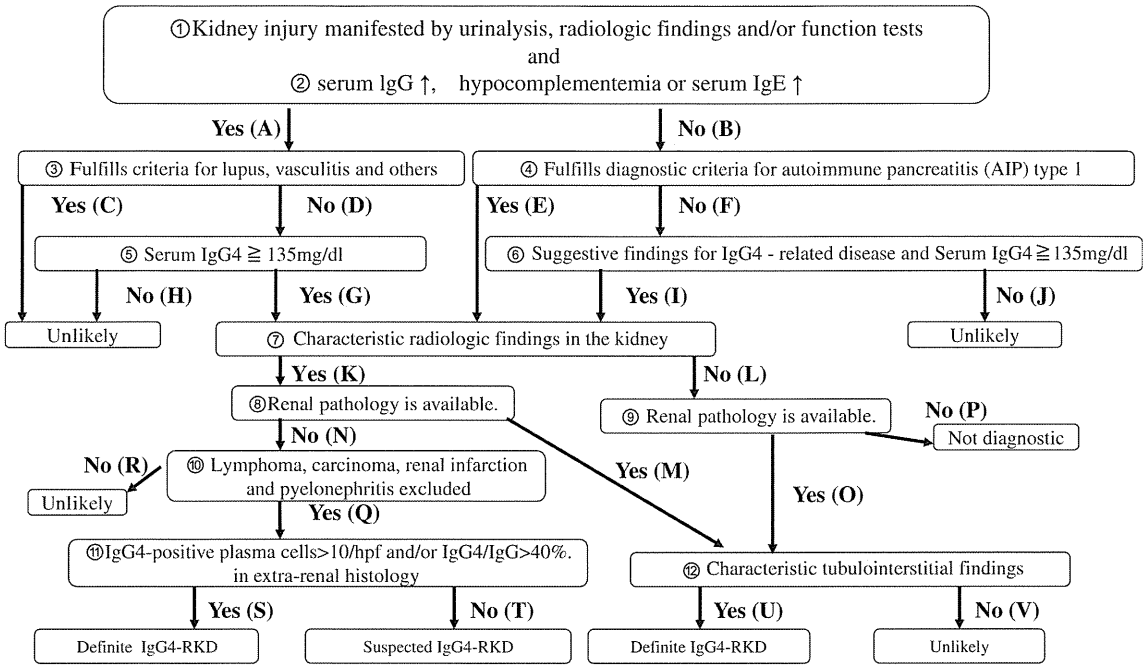

Fig. 4 Diagnostic algorithm for IgG4-related kidney disease (IgG4-RKD). Table 2 is a supplement of Fig. 4

granulomatous lesion, neutrophil infiltration, advanced tubulitis]. Since about 80% of patients were diagnosed as having IgG4-RKD during the close examination of IgG4-related disease other than IgG4-RKD, an alternative pathway was inserted in the algorithm. Then, the performance of the diagnostic algorithm procedure was tested on these 41 patients with IgG4-RKD (Fig. 5). In this way, 38 of 41 patients (92.7%) were diagnosed with definite IgG4-RKD, two with suspected IgG4-RKD. In contrast, none of the negative control patients were diagnosed with IgG4-RKD.

Diagnostic criteria

On the basis of the result of diagnostic algorithm procedure and referring to several diagnostic criteria for AIP, we propose criteria for diagnosis of IgG4-RKD (Table 3). Using the proposed criteria, 39 of 41 patients (95.1%) were diagnosed with definite, one with probable, and one with possible IgG4-RKD.

Discussion

IgG4-RKD is a new clinical entity in the field of nephrology, unrecognized before 2004, when the notion gradually emerged of it being an extrapancreatic manifestation of AIP [2–11, 20–25]. This disease has many features helping to distinguish it from other types of TIN radiographically [26–30] and pathologically [11, 21], and early detection provides the best chance for preservation of renal function because of its good responsiveness to corticosteroid therapy [2–11]. However, any delay in treatment increases the risk of kidney failure [31]. This prompted us to prepare by consensus a set of diagnostic criteria for IgG4-RKD.

To prepare diagnostic criteria, characteristic radiologic findings are a very important component because these are usually the first recognized distinctive features of this disease, while rarely being seen in other tubulointerstitial nephritides [26–30]. Of these, the most common radiologic finding was multiple low-density lesions on enhanced CT [26–30], with 46.3% showing this type of abnormality in our study. Takahashi et al. [26] found 9 patients with bilateral multiple renal lesions, which could be included in the same category as our multiple low-density lesions, in 14 renal involvement cases. If the presence of decreased renal function precludes use of contrast-enhanced CT, bilateral diffuse kidney enlargement in plain CT is another feature. In addition, very rarely, a hypovascular solitary mass in the kidney was also detected [30, 32]; with this type of CT finding, malignancy must be ruled out. The fourth radiologic finding was hypertrophic lesion of the renal pelvic wall without irregularity of the renal pelvic surface, with urinary tract carcinoma being the most important condition to consider in the differential diagnosis [26, 28–30].

Hypergammaglobulinemia or elevated serum IgG levels, hypocomplementemia, and elevated serum IgE levels are all frequently observed serologic features of IgG4-RKD [2–11]. In our series as well we confirmed that 90.2% had

Table 2 Diagnostic algorithm for IgG4-related kidney disease (IgG4-RKD)—Supplement to Figure 4

1. This diagnostic algorithm for IgG4-RKD covers renal parenchymal lesions and renal pelvic lesions
2. ① Kidney injury is recognized by proteinuria, hematuria, and elevated *N*-acetyl-β-D-glucosaminidase, β_2-microglobulin and/or α_1-microglobulin excretions in urinalysis
3. ② At least one of 3 abnormalities (elevated serum IgG, hypocomplementemia and elevated serum IgE) is necessary
4. ③ The following diseases: systemic lupus erythematosus, systemic vasculitis (Churg–Strauss syndrome and Wegener's granulomatosis), and cryoglobulinemia should be excluded. However, even if the patient fulfills the classification criteria of lupus or vasculitis, this may not be sufficient to completely rule out IgG4-related disease, and measurement of serum IgG4 level is recommended in atypical cases
5. ④ Autoimmune pancreatitis is diagnosed according to the previously proposed diagnostic criteria
6. ⑥ Systemic lesion(s) other than AIP suggesting IgG4-related disease are listed as follows:

   Biliary lesion (sclerosing cholangitis)

   Pulmonary lesion (interstitial pneumonia, pseudotumor)

   Retroperitoneal lesion (retroperitoneal fibrosis)

   (peri-)Arterial lesion (inflammatory aortic aneurysm)

   Lymph node lesion (hilar lymph node swelling, mediastinal lymph node swelling)

   Lacrimal and salivary gland lesion (Mikulicz's disease, chronic sclerosing dacryoadenitis and sialadenitis)

   Hepatic lesion (pseudotumor of the liver)
7. ⑦ Characteristic renal radiologic findings of IgG4-related kidney disease are listed as follows: (in general, contrast-enhanced CT is needed to make the correct diagnosis. However, the use of contrast medium requires careful judgment in patients with impaired renal function)
   a. Multiple low-density lesions on enhanced CT
   b. Diffuse kidney enlargement
   c. Hypovascular solitary mass in the kidney
   d. Hypertrophic lesion of renal pelvic wall without irregularity of the renal pelvic surface
8. ⑩ Malignant lymphoma, urinary tract carcinomas, renal infarction and pyelonephritis sometime have similar and confusing radiologic findings, and their exclusion is necessary. In particular, misdiagnosis of malignancy as IgG4-related disease must be avoided

   (rarely, Wegener's granulomatosis, sarcoidosis and metastatic carcinoma have similar radiologic findings)
9. ⑫ Characteristic tubulointerstitial findings of IgG4-related kidney disease are listed as follows:
   a. Marked lymphoplasmacytic infiltration, which must be accompanied by >10 infiltrating IgG4-positive plasma cells/high power field and/or a ratio of IgG4/IgG-positive plasma cells $>40\%$
   b. Characteristic 'storiform' fibrosis surrounding infiltrating cells
   c. Other useful findings for differential diagnosis:
      1. Positive findings: lesions extending into the renal capsule, eosinophil infiltration, well-defined regional lesion distribution, marked fibrosis
      2. Negative findings: (necrotizing) angiitis, granulomatous lesion, neutrophil infiltration, advanced tubulitis

Circled numbers correspond to those in Fig. 4

increased serum IgG levels, 53.7% hypocomplementemia, and 78.8% increased serum IgE levels. In addition, decreased renal function was detected 58.5%. Therefore, we considered that the presence of kidney damage, as manifested by abnormal urinalysis or urine marker(s) or decreased function, in combination with either elevated serum IgG level, hypocomplementemia, or elevated serum IgE level could obviate the need for characteristic radiographic renal findings.

Although elevated serum IgG4 level is a useful marker of IgG4-related disease including AIP, not all patients with AIP manifest it. In fact, 8–23% of AIP patients are thought to have normal serum IgG4 levels in Japanese patients [33–35]. In contrast, our criteria do not consider the presence of IgG4-RKD with a normal serum IgG4 level because we found that all our patients with IgG4-RKD had elevated serum IgG4 levels, and considered that the presence of a normal serum IgG4 patient might lead to misdiagnosis. In fact, recent studies [36–38] have shown that only the characteristic histologic finding of marked IgG4-positive plasma cell infiltration is not specific for IgG4-related disease but is also seen in other diseases such as vasculitis and Castleman's disease. However, a case report with IgG4-related inflammatory pseudotumor of the kidney with normal serum IgG4 level is available [32], and this represents one of the limitations of our criteria.

Chari et al. [13] considered histologic criteria to be the gold standard for the diagnosis of AIP. In addition to the immunohistochemical findings obtained by IgG4 staining, distinguishing fibrosis called 'storiform fibrosis' and obliterative phlebitis are also very important for the diagnosis of type 1 AIP [14, 15]. Interestingly, we identified that the same kind of fibrosis was detected in the involved

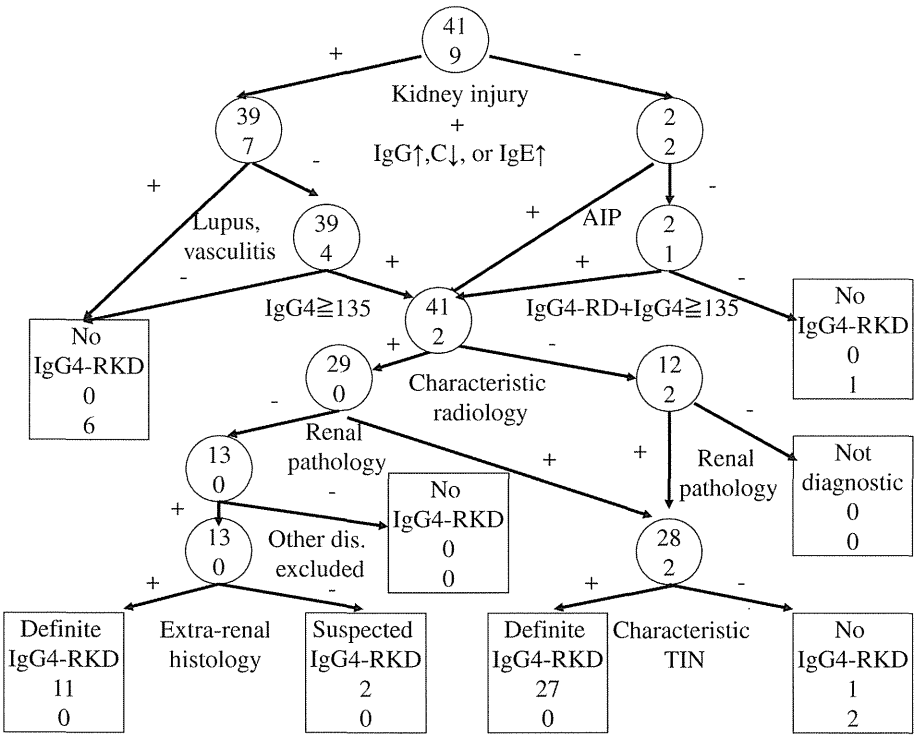

Fig. 5 Diagnostic algorithm performance for IgG4-related kidney disease (IgG4-RKD). This figure shows the results of performance of diagnostic algorithm for IgG4-RKD using 41 patients with IgG4-RKD and 9 patients as a negative control. *Upper number* in each *circle* or *box* shows the number of IgG4-RKD, and *lower number* shows that of the negative control. *Each box* shows the number of final diagnosis with IgG4-RKD or non-IgG4-RKD. Using this algorithm, 38 of 41 patients (92.7%) were diagnosed with definite IgG4-RKD, while none of the negative control patients were diagnosed with IgG4-RKD

kidney and in a previous study found that this characteristic fibrosis was very useful in distinguishing IgG4-RKD from other tubulointerstitial nephritides [16]. In contrast, obliterative phlebitis was not detected in any renal biopsy specimens in this study (data not shown). Therefore, lymphoplasmacytic TIN with fibrosis and prominent IgG4-positive plasma cells seems to be a representative histopathologic feature of IgG4-RKD.

Several kinds of glomerular lesions have been reported that overlap with those of typical lymphoplasmacytic TIN [11, 23, 24]. The most frequently reported lesion is membranous nephropathy (MN), and three patients had this type of glomerulopathy in this study. In addition, 8 other patients had various glomerular lesions other than MN. Although the significance of glomerular lesions in IgG4-RKD is unclear now, careful attention should be paid to glomerular lesions in cases of IgG4-RKD.

One of the important differential diagnoses in daily clinical practice is SS with TIN. Some investigators still consider that Mikulicz's disease and SS are the same disease because they have common clinical features such as hypergammaglobulinemia, salivary gland enlargement or dry symptoms. However, Mikulicz's disease rarely has positive serum anti-SSA/Ro or SSB/La antibodies as seen in SS [39, 40], and has gradually been accepted as a representative IgG4-related disease. On the other hand, patients with SS seldom have elevated serum IgG4 levels. Moreover, although both diseases have similar TIN in renal histology, IgG4 immunostaining is very useful to differentiate between them [39, 40]. Hence, IgG4-RKD is unlikely to be confused with SS.

Considering the above-mentioned features of IgG4-RKD and referring to several sets of previously established diagnostic criteria for AIP [12, 13, 41, 42], we prepared diagnostic criteria for IgG4-RKD. In the diagnostic procedure of AIP, pancreatic imaging, serology, and histology have been regarded as important factors by Japanese researchers [12]. In addition, Chari et al. [13] added other organ involvement and response to steroid therapy as useful findings in making the diagnosis of AIP. Application of the approach of AIP to IgG4-RKD based on renal imaging, serology, and histology appears reasonable and are similarly useful. In addition, if renal pathology is not available, histological findings of an extra-renal sample with abundant infiltrating IgG4-positive plasma cells ($>$ 10/HPF and/or IgG4/IgG $>$ 40%) with characteristic radiographic findings of kidneys seem to be sufficient to make a definite diagnosis. Responsiveness to corticosteroid therapy was not very useful in the diagnosis of IgG4-RKD because idiopathic TIN is in general responsive to it.

On the basis of this analysis of 41 patients with IgG4-RKD, we proposed a diagnostic algorithm (Fig. 4) and a set of diagnostic criteria (Table 3). Using this algorithm, 92.7% of patients were diagnosed with definite IgG4-RKD, and using these diagnostic criteria, 95.1% of them were diagnosed with definite IgG4-RKD.

A merit of our diagnostic algorithm and our set of diagnostic criteria in daily clinical practice is that it

Table 3 Diagnostic criteria for IgG4-related kidney disease (IgG4-RKD)

1. Presence of some kidney damage, as manifested by abnormal urinalysis or urine marker(s) or decreased kidney function with either elevated serum IgG level, hypocomplementemia, or elevated serum IgE level
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 renal pelvic wall without irregularity of the renal pelvic surface
3. Elevated serum IgG4 level (IgG4 $\geq$ 135 mg/dl)
4. Histologic findings in the kidney
   a. Dense lymphoplasmacytic infiltration with infiltrating IgG4-positive plasma cells $>$10/high power field (HPF) and/or IgG4/IgG-positive plasma cells $>$40%
   b. Characteristic fibrosis surrounding nests of lymphocytes and/or plasma cells
5. Histologic findings in extra-renal organ(s):
   Dense lymphoplasmacytic infiltration with infiltrating IgG4-positive plasma cells $>$10/HPF and/or IgG4/IgG-positive plasma cells $>$40% in extra-renal organ(s)

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)
3. Cases with suspected disease according to the diagnostic algorithm (Fig. 4) are classified into probable or possible IgG4-RKD according to these criteria

provides nephrologists and other clinical practitioners with the opportunity to identify patients with kidney-restricted IgG4-related disease among those with miscellaneous tubulointerstitial nephritides. In this study, only two patients (4.9%) had no extra-renal manifestations of IgG-related disease. Similarly, Zen and Nakanuma [43] showed that all the kidney lesions that they experienced were associated with extrarenal IgG4-related disease. These results can be interpreted in two ways; either kidney-restricted IgG4-related disease is very rare or it is often overlooked because of poor recognition. Our diagnostic algorithm and set of diagnostic criteria for IgG4-RKD may also provide a promising approach to elucidate this issue.

In contrast, decreased renal function associated with IgG4-related disease does not necessarily mean renal involvement by IgG4-related disease. We experienced two cases of IgG4-related disease with elevated serum Cr levels, the renal histology of which turned out to be nephrosclerosis in one case and diabetic nephropathy in the other case (data not shown). Other such diagnostic pitfalls will surely be recognized with the accumulation of greater numbers of cases in various populations. Because of the existence of such cases the diagnosis of IgG4-RKD must rely on characteristic radiographic findings or histopathologic findings.

In summary, we proposed the first diagnostic algorithm and a set of diagnostic criteria for IgG4-RKD. Prospective studies are required to access the sensitivity and specificity of these methods and to identify patients undiagnosed with IgG4-RKD among the patients with idiopathic TIN and other renal diseases.

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Conflict of interest The authors have declared that no conflict of interest exists.

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