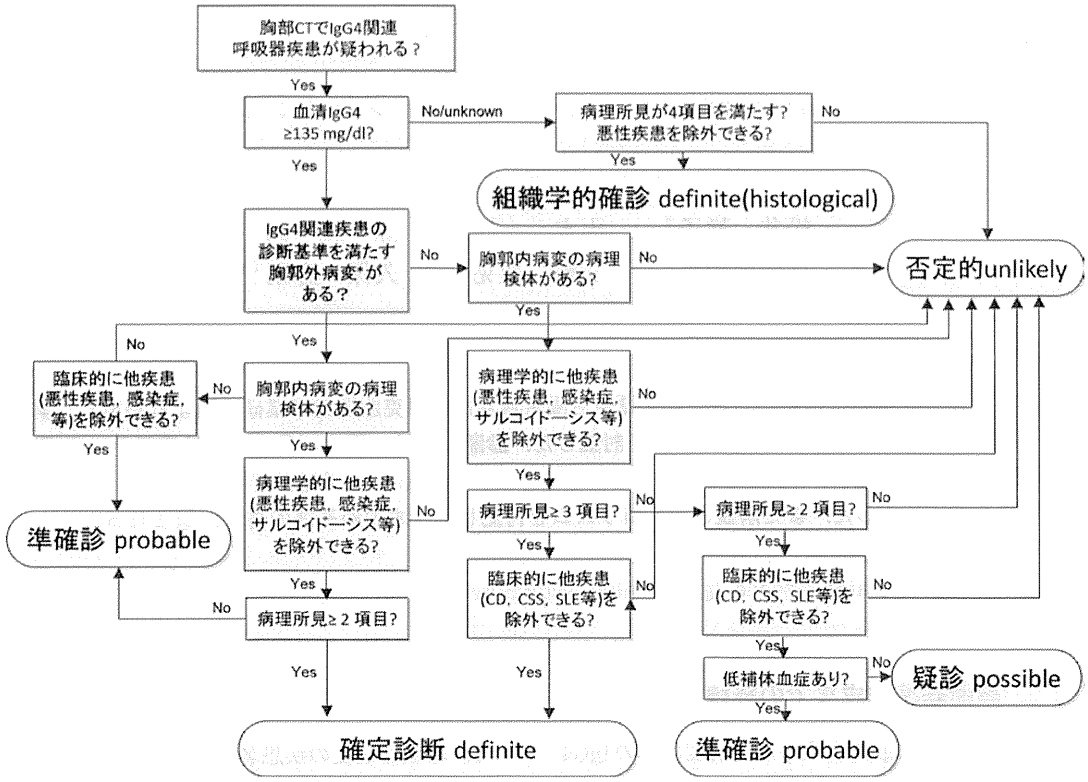

図1 診断のアルゴリズム．CD：Castleman disease（plasma cell type），CSS：Churg-Strauss syndrome，SLE：systemic lupus erythematosus．*硬化性涙腺炎・唾液腺炎，自己免疫性膵炎，IgG4 関連硬化性胆管炎，IgG4 関連腎臓病，後腹膜線維症．

表1 IgG4 関連呼吸器疾患診断基準

A．診断基準

1. 画像所見上，下記の所見のいずれかを含む胸郭内病変を認める
   肺門縦隔リンパ節腫大，気管支壁/気管支血管束の肥厚
   小葉間隔壁の肥厚，結節影，浸潤影，胸膜病変
2. 血清 IgG4 高値（135 mg/dl 以上）を認める
3. 病理所見上，呼吸器の組織において以下の①～④の所見を認める
   a：3 項目以上，b：2 項目
   ①気管支血管束周囲，小葉間隔壁，胸膜などの広義間質への著明なリンパ球，形質細胞の浸潤
   ②IgG4/IgG 陽性細胞比＞40%，かつ IgG4 陽性細胞＞10 cells/HPF
   ③閉塞性静脈炎，もしくは閉塞性動脈炎
   ④浸潤細胞周囲の特徴的な線維化*
4. 胸郭外臓器にて，IgG4 関連疾患の診断基準を満たす病変# がある

〈参考所見〉低補体血症

*自己免疫性膵炎診断基準の花筵状線維化に準ずる線維化所見

#硬化性涙腺炎・唾液腺炎，自己免疫性膵炎，IgG4 関連硬化性胆管炎，IgG4 関連腎臓病，後腹膜線維症

B．診　　断

1. 確定診断（definite）：1＋2＋3a，1＋2＋3b＋4
   組織学的確定診断［definite（histological）］：1＋3-①～④すべて
2. 準確診（probable）：1＋2＋4，1＋2＋3b＋参考所見
3. 疑診（possible）：1＋2＋3b

C．鑑別診断

Castleman 病（plasma cell type），膠原病関連肺疾患，granulomatosis with polyangiitis（Wegener 肉芽腫症），eosinophilic granulomatosis with polyangitiis（Churg-Strauss 症候群），サルコイドーシス，呼吸器感染症，Rosai-Dorfman 病，inflammatory myofibroblastic tumor，悪性リンパ腫，肺癌　など

表 2 付記：IgG4 関連呼吸器疾患診断基準の解説

1. 画像所見 ・肺門・縦隔リンパ節腫大や気管支壁/気管支血管束の肥厚は頻度の高い所見である ・小葉間間質や胸膜を含む，いわゆる広義間質に病変を認める ・胸郭内の結節性，腫瘤性陰影や浸潤影として認められることがある ・画像所見は非特異的であるので，感染症や悪性疾患など鑑別診断に掲げた疾患を除外する必要がある
2. 臨床所見・検査所見 ・アレルギー性鼻炎や気管支喘息などのアレルギー症状の既往や合併を伴うことがある ・高 IgG 血症，高 IgE 血症を伴うことが多いが，血清 IgA および IgM が同時に上昇することはまれである ・抗核抗体陽性，リウマチ因子陽性，低補体血症を認めることがある ・白血球増加や CRP 上昇などの炎症所見は認めないか，もしくは軽度異常にとどまる
3. 病理所見 ・気管支血管束周囲の間質，小葉間隔壁，胸膜および連続する肺胞隔壁などの広義間質に，リンパ球，形質細胞の浸潤を伴う線維化巣を認める ・線維化の典型は「花筵状線維化」であり，リンパ球・形質細胞の浸潤を伴う紡錘形細胞の増生からなる．その方向性は無秩序で時に渦巻き状を呈する ・著明な細胞浸潤と線維化のため，肺胞腔を埋めるような腫瘤性病変が形成されることがある ・好酸球浸潤が散見されるが，好中球浸潤や肉芽腫は通常認めない ・病理診断には，外科的生検材料が望ましい
4. 胸郭外臓器病変 ・胸郭外臓器病変は，確立された臓器別診断基準を満たす病変（膵臓，胆管，腎臓），あるいは病理所見にて著明なリンパ球・IgG4 陽性形質細胞浸潤と線維化を伴い特徴的な臨床・画像所見を示す病変（涙腺・唾液腺，後腹膜）である

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Abstract

Diagnostic criteria for IgG4-related respiratory disease

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The diagnostic criteria for IgG4-related respiratory disease were proposed by the Subcommittee of Respiratory Disease of IgG4-related Disease supported by the Health and Labor Sciences Research Grants for the Study of Intractable Diseases from the Ministry of Health, Labour and Welfare, Japan. The criteria include the following 4 conditions: 1) image findings, 2) blood test findings, 3) pathological findings, and 4) presence of extra-thoracic organ lesions, and are classified in three stages of definite, probable, and possible according to combinations of the above conditions. Also, we added a commentary and algorithm to the diagnostic criteria. The criteria were presented in the symposium of the 54th Annual Meeting of the Japanese Respiratory Society (2014) and discussed by members of the respiratory society. The diagnostic criteria and algorithm will be useful for clarifying the entity of IgG4-related respiratory disease.

REVIEW

OPEN

IgG4-related kidney disease – an update

Mitsuhiro Kawano[a] *and Takako Saeki*[b]

Purpose of review
IgG4-related disease (IgG4-RD) is a recently recognized systemic inflammatory disorder that can affect most organs/tissues such as sarcoidosis. The kidney is a frequently affected organ with tubulointerstitial nephritis (TIN), the representative lesion of IgG4-RD. This review focuses on the latest knowledge of IgG4-related kidney disease (IgG4-RKD).

Recent findings
A wide range of renal manifestations of IgG4-RD, that is TIN, membranous glomerulonephritis (MGN) and other glomerular lesions, and pyelitis, are collectively referred to as IgG4-RKD. Clinically, decreased renal function, or characteristic imaging findings such as multiple low-density lesions on contrast-enhanced computed tomography or diffuse thickening of the renal pelvic wall, are typical presenting features. Although a rapid response to corticosteroid therapy is a very important feature of IgG4-TIN, in cases in which renal function is moderately to severely decreased before therapy, only partial recovery of renal function is obtained.

Summary
TIN with characteristic imaging findings is a typical manifestation of IgG4-RKD in the interstitium, while MGN is a representative manifestation of the glomerular lesions. Although IgG4 is a central feature of IgG4-RD, the recent discovery of IgG4-negative IgG4-RD raises questions about the causative role of the IgG4 molecule in this context.

Keywords
IgG4, IgG4-related disease, membranous glomerulonephritis, tubulointerstitial nephritis

INTRODUCTION

IgG4-related disease (IgG4-RD), a recently recognized systemic inflammatory disorder, generally presents as a mass-forming lesion, or lesions, or organ enlargement [1,2]. Clinical symptoms are diverse depending on the combination of organs affected, but most patients have only mild or no symptoms. The most important feature is marked IgG4-positive plasma cell (IgG4+PC) infiltration in affected organs [3,4]. In addition, it has common histopathological features: dense lymphoplasmacytic infiltrates, storiform fibrosis and obliterative phlebitis [4]. Lacrimal and salivary glands, pancreas, kidneys and aorta/retroperitoneum are frequently affected organs. Patients often have multiple organ involvement simultaneously and sometimes metachronously, and spontaneous regression has been observed. Target organs are summarized in Table 1 [5–14,15▪].

The kidney is a representative organ, and the various renal lesions are collectively referred to as IgG4-related kidney disease (IgG4-RKD) [16–18]. Tubulointerstitial nephritis (TIN) is a typical lesion of the renal parenchyma, named IgG4-related TIN (IgG4-TIN), and renal pyelitis is typical of the renal pelvis [5]. IgG4-related retroperitoneal fibrosis can also induce renal insufficiency through hydronephrosis.

CLINICAL AND LABORATORY FEATURES OF IgG4-RELATED KIDNEY DISEASE

Patients with IgG4-RKD present at an average age of 65 years, and 73–87% are men [16–18]. Two major clinical presentations are well recognized: unexplained renal dysfunction and imaging

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Curr Opin Nephrol Hypertens 2015, 24:193–201

DOI:10.1097/MNH.0000000000000102

KEY POINTS

- IgG4-RD is a systemic inflammatory disorder that typically shows mass-forming lesions in various combinations that can involve almost every organ.
- IgG4-RKD is characterized by IgG4-positive plasma cell-rich tubulointerstitial nephritis with different degrees of fibrosis intermingled from area to area.
- A typical glomerular lesion of IgG4-RKD is membranous glomerulonephritis with IgG4-dominant glomerular basement membrane deposits without anti-M-type phospholipase A2 receptor antibody.
- A condition that closely mimics IgG4-RD may uncommonly develop even in the absence of IgG4-positive plasma cells.

abnormality. In one study, about half of all patients were suspected of having IgG4-RKD because of renal dysfunction, with renal lesions detected in the remaining patients during the course of imaging evaluation for IgG4-RD [18]. In another study, 77% of patients presented with acute or progressive renal failure requiring renal biopsy [17]. In both studies, more than 80% of patients had other organ involvement.

Elevated serum IgG level and hypocomplementaemia are characteristic features of IgG4-RKD. Although hypocomplementaemia is a distinct feature of IgG4-RD, a relatively low proportion of patients actually have it. Muraki *et al.* [19] evaluated serum complement levels in 44 patients with autoimmune pancreatitis (AIP) and found that only 17% of them had a CH50 of less than 30 U/ml. In contrast, it seems to be more frequent if the kidney is involved, with more than 50% of patients having hypocomplementaemia [17,18]. In cases with IgG4-RKD with hypocomplementaemia, both C3 and C4 are extremely low, resembling the active stage of systemic lupus erythematosus (SLE). In addition, complement might become a biomarker to monitor the recurrence of IgG4-TIN [20▪▪,21]. Saeki *et al.* [20▪▪] followed serum complement levels in 14 patients with IgG4-RKD and found that three again showed a decrease at the time of relapse. Hyper IgG-aemia is also prominent in many cases, and serum IgG levels exceeded 3000 mg/dl in 50% of patients in our IgG4-RKD series [18]. Increased serum levels of IgE and eosinophilia are other features possibly related to the allergic predisposition of this disease [16–18].

Elevated serum IgG4 levels are the most important serological finding in IgG4-RKD [1–3]. Although about 20–30% of patients with IgG4-RD have normal serum IgG4 levels, in two studies more than 90% of patients with IgG4-RKD had increased serum IgG4 levels [17,18]. Serum levels of IgG4

Table 1. Representative organ manifestations in IgG4-related disease

A. Organs adopted at the 1st international symposium in Boston in 2011	
Pancreas	Lymphoplasmacytic sclerosing pancreatitis
Eye/orbit/lacrimal glands	Dacryoadenitis/orbital inflammation/pseudotumour
Salivary glands	Sialadenitis/Mikulicz disease/Kuttner's tumour
Aorta/arteries	Aortitis/periaortitis/arteritis
Mediastinum/retroperitoneum/mesentery	Mediastinitis/retroperitoneal fibrosis/mesenteritis
Kidney	Tubulointerstitial nephritis/renal pyelitis
Pachymeninges/hypophysis/thyroid	Pachymeningitis/hypophysitis/Riedel thyroiditis
Lung	Lung disease/inflammatory pseudotumor
Pleura/pericardium	Pleuritis/pericarditis
Breast	Mastitis
Bile ducts/gall bladder/liver	Sclerosing cholangitis/cholecystitis/hepatopathy
Prostate	Prostatitis
Skin	Skin disease/pseudolymphoma
Lymph node	Lymphadenopathy
B. Organs newly recognized after the Boston meeting	
Nerve	Infraorbital nerve swelling
Paranasal sinus	Chronic rhinosinusitis
Testis/paratestis	Paratesticular pseudotumour
Ureter	Ureteritis
Urethra	Urethritis
Urinary bladder	Interstitial cystitis

dramatically decrease after successful corticosteroid therapy, but show re-elevation without apparent relapse in about half of the patients during maintenance steroid therapy [20▪▪].

Although neither proteinuria nor haematuria is usually detected in IgG4-TIN, many patients with coexistent glomerular lesions have proteinuria or haematuria, or both, and patients with membranous glomerulonephritis (MGN) may show even nephrotic levels of proteinuria. In contrast to drug-induced acute TIN, IgG4-TIN is usually not accompanied by urinary excretion of many white blood cells (WBCs) or WBC casts. This finding probably mirrors a very mild tubulitis, a histopathological feature of IgG4-TIN.

Serum C-reactive protein levels are usually normal, with this being a useful marker to distinguish IgG4-RD from anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis or Castleman's disease.

IMAGING FEATURES OF IgG4-RELATED KIDNEY DISEASE

A distinguishing feature of IgG4-TIN is its characteristic imaging findings frequently observed on computed tomography (CT) [18,22,23]. Contrast-enhanced CT is most useful in delineating the characteristics and distribution of the renal lesions. Multiple or solitary, round or wedge-shaped, parenchymal low-density lesions are common on CT [22,23]. Generally, solitary lesions are very rare, but if encountered, the suspicion of malignant tumour is high and often leads to nephrectomy [24]. In some cases, the lesions are well defined on contrast-enhanced CT, but can be ill defined in others, and in the latter, 'diffuse patchy involvement' is a more suitable description in extreme cases (Fig. 1). In addition, mass-like lesions protruding beyond the surface of the kidney, suggestive of tumour progression, may be detected in some cases (Fig. 1). Corresponding to the rim-like lesion of type 1 AIP, a rim-like lesion of the kidney is occasionally seen along a part of the renal capsule (Fig. 1) [22,23]. In addition to parenchymal lesions, renal pelvic lesions are sometimes encountered as a diffuse thickening of the renal pelvis wall with smooth intraluminal surface during systemic evaluation of IgG4-RD by CT [18,22,23].

Recently, MRI has become a useful imaging method to detect IgG4-RKD from a very early stage [23,25]. A typical finding of such lesions is hypointensity on T2-weighted images. Moreover, using diffusion-weighted imaging, a study showed that sensitivity was 100% in an analysis of 20 patients with presumptive IgG4-RKD (14 with contrast enhancement; six without) [25]. Therefore, if impaired renal function contraindicates the use of contrast-enhanced CT, MRI might be a promising alternative.

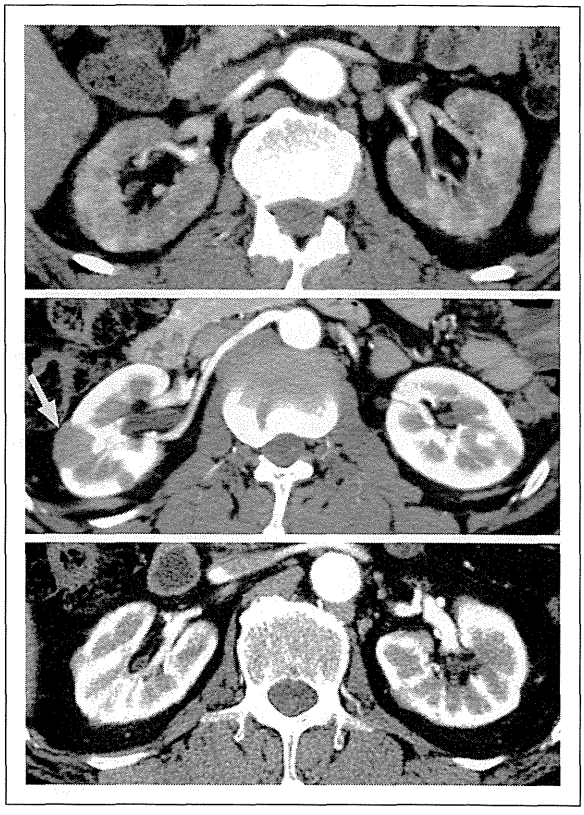

FIGURE 1. A variety of patterns of multiple low-density lesions on contrast-enhanced computed tomography (CT). Upper: Contrast-enhanced CT scan shows bilateral diffuse patchy involvement. Middle: Contrast-enhanced CT scan shows multiple parenchymal low-density lesions including mass-like lesions protruding beyond the surface of the kidney (arrow). Lower: Contrast-enhanced CT scan shows a rim-like lesion of the kidney.

FDG-PET [26,27] and gallium scintigraphy [28,29] are other imaging modalities sometimes employed. They are used mainly for whole body screening to determine the extent of the systemic organ involvement by IgG4-RD.

HISTOPATHOLOGICAL FEATURES OF IgG4-RELATED KIDNEY DISEASE: TUBULOINTERSTITIAL LESIONS

Plasma cell rich TIN with fibrosis and sometimes numerous infiltrating eosinophils are typical pathological findings of IgG4-RKD (Fig. 2) [4,30–32]. Histologic findings are mandatory for the definite diagnosis of IgG4-RKD. However, several situations such as inaccessible regional lesion distribution (e.g.

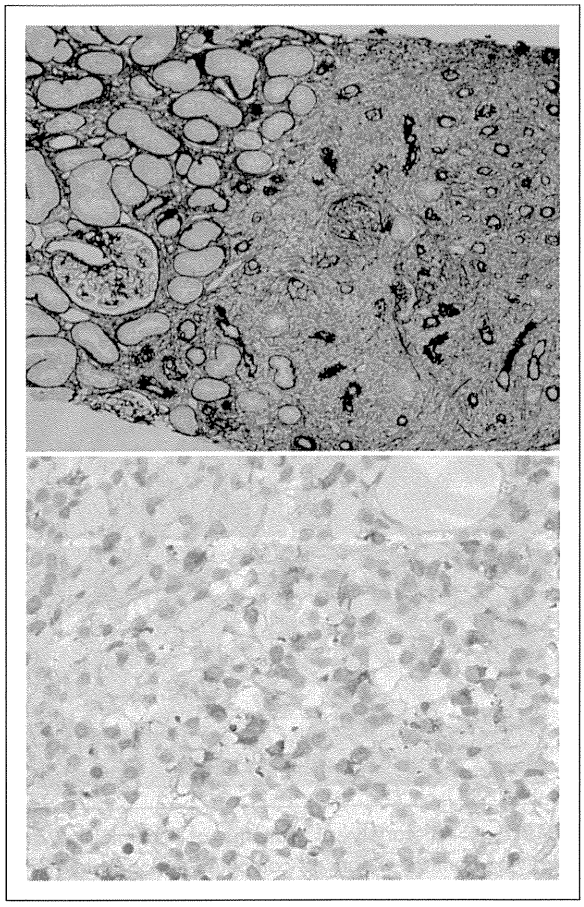

FIGURE 2. Typical histological features of IgG4-related tubulointerstitial nephritis. Upper: Histopathological examination in a patient with IgG4-related kidney disease (IgG4-RKD) shows plasma cell rich tubulointerstitial nephritis with different stages of fibrosis intermingled within different areas (periodic acid-methenamine-silver staining x100). Lower: Immunostaining for IgG4 shows many IgG4-positive plasma cells in the area of inflammation just outside the renal capsule, probably corresponding to the rim-like lesion of the kidney noted on imaging study (x400).

lesions distributed in only the upper pole of the kidney) hamper histologic examination of the kidney. In such cases, histologic findings from other organs could support typical renal imaging findings and clinical features of IgG4-RKD to allow the diagnosis of IgG4-RKD. Although Sjögren's syndrome sometimes shows plasma cell rich TIN, IgG4 immunostaining clearly differentiates these two diseases. Usually, more than 10 infiltrating IgG4 and plasma cells per high-power field or at least 40% of the ratio of IgG4 and plasma cells to IgG and plasma cells are employed as the cutoff values. However, the specificity of IgG4 immunostaining is not high because ANCA-associated vasculitis, particularly eosinophilic granulomatosis with polyangiitis [33–35] and granulomatosis with polyangiitis (GPA) [36], sometimes show lymphoplasmacytic infiltrates with copious IgG4 and plasma cells in the interstitium. Moreover, serum IgG4 levels have been reported to be sometimes elevated in such cases. Therefore, special caution is needed to differentiate IgG4-RD from ANCA-associated vasculitis. Elevated serum CRP levels and a partial response to corticosteroid therapy seem to be helpful in differentiating these diseases.

Similarly, Houghton and Troxell [37] reported that an abundance of IgG4 and plasma cells in the renal interstitium is not specific for IgG4-TIN but found in some patients with necrotizing glomerulonephritis, diabetic nephropathy, lupus nephritis, MGN and idiopathic TIN. Therefore, it must be kept in mind that IgG4 and plasma cell infiltration is a necessary, but not specific, finding for the diagnosis of IgG4-TIN.

Another important pathological feature is fibrosis [4,16–18,31,32]. At least some portion of the fibrosis shows a storiform pattern, namely a swirling fibrosis. Tubular atrophy with thickened tubular basement membrane (TBM) and disappearance of tubules are prominent in the lesions. In IgG4-TIN, fibrosis is generally more severe than that in other types of TIN, with the degree of fibrosis differing from area to area. Several studies have tried to define the stages of the fibrosis according to its degree, and one study showed that different stages of fibrosis are intermingled within different areas of the needle-biopsied specimens of the same case [38].

The specific distribution of renal parenchyma lesions is another distinctive feature of this disease. First, the margin between affected and unaffected portions is very clearly demarcated, with this finding thought to correspond to the imaging feature of multiple low-density lesions [16,18,32]. Second, lymphoplasmacytic cell infiltration into and beyond the renal capsule is a unique feature of this disease, reflected by the rim-like lesion of the kidney noted on CT (Fig. 2) [32,38].

Granuloma formation and fibrinoid necrosis of the artery have never been reported in IgG4-RKD [17,18], although only one case of IgG4-related renal arteritis without fibrinoid necrosis has been described [39]. Neutrophil infiltration is also very rare, so that the presence of these lesions is a useful clue to rule out IgG4-RKD [18].

Immunoglobulin and complement deposition in the TBM and interstitium has been documented by immunofluorescence microscopy [17,30–32]. Raissian *et al.* [17] showed that granular immune complex deposits composed of IgG and C3 in the TBM were detected in more than 80% of IgG4-TIN. C1q was also stained in a small number of cases. In a

subclass analysis, Yamaguchi *et al.* [31] analysed five cases by immunofluorescence microscopy and found that all cases had IgG1 and IgG4 deposition in the TBM and interstitium. In addition, IgG3 deposits were found in three cases, C3 in three, and C1q in two.

GLOMERULAR LESIONS

Although a variety of glomerular diseases have been reported to be associated with IgG4-RD, MGN is the most common (about 7%), having a specific significance [40–42,43▪▪,44–46]. MGN is classified into primary and secondary forms according to the presence or absence of an obvious cause. Anti-M-type phospholipase A2 receptor antibody, which is an important marker of primary MGN, is usually negative in IgG4-related MGN [43▪▪,47]. Granular deposits of IgG and C3 along the glomerular capillary walls, seen by immunofluorescence microscopy, are a typical feature. Interestingly, in the analyses of glomerular basement membrane (GBM) deposited IgG subclasses, IgG4 is the most dominant subclass in the great majority of patients and is usually accompanied by lower amounts of other IgG subclasses (Table 2) [40–42,43▪▪,44–46]. In contrast to primary MGN, granular C1q deposits are sometimes prominent, and some but not all cases have coexistent TBM deposits (Table 2). MGN is sometimes associated with IgG4-TIN, but some patients with MGN and IgG4-RD but without IgG4-TIN have also been reported [41,42,43▪▪,44]. MGN usually occurs simultaneously with IgG4-RD or becomes apparent during the course of already diagnosed IgG4-RD, but can precede IgG4-RD [45].

The response to corticosteroid therapy may differ between IgG4-related MGN and other organ lesions [46], and in some cases, proteinuria persists despite rapid disappearance of other IgG4-RD associated signs. As both MGN [48] and IgG4-RD [49,50] are thought to be associated with enhanced T helper type 2 (Th2) responses, a common pathogenetic role of Th2 responses is speculated.

Other glomerular lesions are classified into two subgroups according to the presence/absence of a predominance of Th2 responses. The association of Henoch–Schönlein purpura nephritis [51,52] or minimal change nephrotic syndrome [53], several cases of both of which have been published or presented, represent the former. The latter includes IgA nephropathy [35], membranoproliferative glomerulonephritis [54] and endocapillary proliferative glomerulonephritis [55].

TREATMENT OF IgG4-RELATED KIDNEY DISEASE

A good and rapid response to corticosteroid therapy is a very important feature of IgG4-RD [1,2], and this has sometimes been used to confirm the diagnosis of type 1 AIP [56]. Steroid is the first-line therapy, and the administration of 0.6 mg/kg/day or 30 or 40 mg/day of prednisolone is recommended as the initial dose to induce remission in type 1 AIP [57,58]. The initial dose is continued for 2–4 weeks, and then tapered gradually (5 mg every 1–2 weeks) to a maintenance dose (5–10 mg/day). If the disease is refractory or frequently recurrent, addition of immunosuppressants such as azathioprine or rituximab is recommended [59,60▪▪].

Table 2. Immunoglobulin subclasses deposited on the glomerular basement membrane in IgG4-related membranous glomerulonephritis

	IgG1	IgG2	IgG3	IgG4	C3	C1q	TBM deposits	TIN with IgG4 and PC	References
83/M	2+	1+	–	2+	1+	–	IgG, IgG4, C3	Yes	Saeki *et al.* [40]
68/M	NA	NA	NA	+*	+*	NA	IgG, IgG4	No	Palmisano *et al.* [41]
54/M	±	–	3+	1+~2+	±	3+	–	No	Cravedi *et al.* [42]
67/F	–	3+	–	1+	1+	-	C3	Yes	Alexander *et al.* [43▪▪]
67/M	±	±	–	3+	2+	–	–	Yes	Alexander *et al.* [43▪▪]
75/M	NA	NA	NA	+*	–	–	–	Yes	Alexander *et al.* [43▪▪]
53/M	±	1+	1+	3+	2+	–	–	No	Alexander *et al.* [43▪▪]
34/M	–	–	1+	2+	2+	±	± (focal)	No	Alexander *et al.* [43▪▪]
55/M	+*	NA	NA	+*	+*	NA	NA	No	Kanda *et al.* [44]
59/M	2+	1+	1+	2+	1+	–	–	(Only imaging)	Wada *et al.* [45]
69/M	NA	NA	NA	+*	–	+*	–	Yes	Miyata *et al.* [46]
80/M	NA	NA	NA	+*	+*	+*	NA	Yes	Miyata *et al.* [46]

IgG4 +PC, IgG4-positive plasma cells; NA, not available; TBM, tubular basement membrane; TIN, tubulointerstitial nephritis.
'+*' indicates that intensity information is not available in the references.

Although in the vast majority of IgG4-TIN cases prompt recovery of renal function is achieved within 1 month of corticosteroid administration, in cases in which the eGFR has already decreased to less than 60 before treatment, only partial recovery of renal function is obtained (mostly in the first month and plateauing thereafter) [20▪▪]. The reasons for this can be explained through longitudinal pathological and imaging studies.

In histopathological examination, a re-biopsy study revealed that localized severe fibrosis became obvious in some parts after long-term corticosteroid maintenance therapy, although only minor abnormalities were seen in other parts [61].

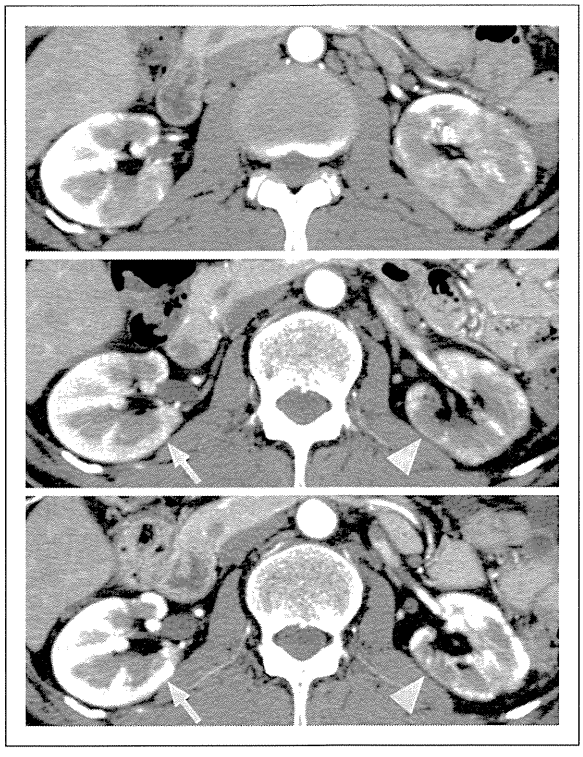

FIGURE 3. Longitudinal changes of imaging findings during corticosteroid therapy. Upper: Contrast-enhanced computed tomography (CT) scan before corticosteroid therapy shows multiple low-density lesions in the bilateral kidneys in a patient with IgG4-RKD. Middle: Two months after starting steroid therapy, contrast-enhanced CT scan shows complete recovery and disappearance of low-density lesions without atrophy in some areas of the kidney (arrow), while atrophic scarring starts to appear in other areas (arrowhead). Lower: Six years after therapy and still under steroid maintenance therapy, the area that showed early recovery maintains its normal appearance without atrophy (arrow), but the area where atrophic scarring started to appear shows progressive scarring with decreased enhancement (arrowhead) on contrast-enhanced CT scan.

In a longitudinal imaging study, contrast enhancement of the renal cortex recovered after therapy in almost all patients with multiple low-density lesions [20▪▪]. In particular, some areas of the kidney showed complete recovery and disappearance of low-density lesions without atrophy even with long-term administration of the maintenance dose of steroid (Fig. 3). In contrast, other areas of the kidney in the same patient developed atrophic scarring with decreased enhancement persisting (Fig. 3) [61]. This observation is very important because it implies that some areas of the kidney have reversible involvement and others irreversible involvement in the same patient, suggesting that the degree of fibrosis differs in individual parts of the kidney, and that a threshold of fibrosis exists, which when exceeded may push an area in the direction of irreversible fibrotic scarring. These findings might explain the reason for the early rapid but only partial recovery of renal function noted after steroid therapy.

IS IgG4-RELATED DISEASE AN AUTOIMMUNE DISEASE?

There is controversy as to whether IgG4-RD is an autoimmune disease or not [1]. IgG4-related pancreatitis has been called AIP because Yoshida *et al.* [62], who proposed its concept, considered it to be an autoimmune disease on the grounds of hypergammaglobulinaemia, autoantibody seropositivity, frequent association with Sjögren's syndrome and primary biliary cirrhosis (PBC), and good responsiveness to corticosteroid therapy. However, more recently, greater experience has clarified that the diseases associated with it are not Sjögren's syndrome and PBC, but rather IgG4-related dacryoadenitis and sialadenitis and IgG4-related sclerosing cholangitis [63]. In contrast, the association of IgG4-RD with Sjögren's syndrome is very rare, despite Sjögren's syndrome being sometimes accompanied by other autoimmune diseases [64]. Next, many patients with IgG4-RD have been shown to have antinuclear antibodies (ANA) or rheumatoid factor. However, in more than half of patients with ANA, low titres (<x80) were present and most patients did not have disease-specific autoantibodies [47,63]. Therefore, some researchers have concluded that IgG4-RD might not be an autoimmune disease after all, but rather an allergic one. However, Mattoo *et al.* [65▪▪] recently showed that several single plasmablast-derived antibody clones established from patients with active IgG4-RD could react with autoantigens in the cytosole of Hep-2 cells. Therefore, further studies are needed to clarify whether disease-specific autoantibodies exist or not in IgG4-RD.

Table 3. IgG4-negative IgG4-related kidney disease

Pt no.	Age/sex	Allergy	Histological findings	IgG4 IHC (cells/HPF)	Renal CT findings	IgG/IgG4 (mg/dl)	C3/C4 (mg/dl)	sCr (mg/dl)	Eo (/μl)	IgE(IU/ml)	Extrarenal lesions	Steroid response	References
1	56/M	none	pTIN, MGN	IgG4/IgG <2%	mLDL	4193/7.5	25/1	2.75	782	547	Sa, AIP, LN	Good	Makiishi *et al.* [66▪]
2	74/M	AR, BA, EP	pTIN	infrequent (<10)	mLDL	5593/20	40/1	0.71	1475	352	Sa, AIP, Lu, P, LN	Good	Hara *et al.* [67▪▪]

AIP, autoimmune pancreatitis; AR, allergic rhinitis; BA, bronchial asthma; Eo, eosinophil; EP, eosinophilic pneumonia; HPF, high power field; IHC, immunohistochemistry; LN, lymphadenitis; Lu, lung lesion; MGN, membranous glomerulonephritis; mLDL, multiple low-density lesions; P, prostatitis; pTIN, plasma cell rich tubulointerstitial nephritis; Sa, sialadenitis; sCr, serum creatinine.

IgG4-NEGATIVE IgG4-RELATED DISEASE

Recently, two cases of IgG4-negative IgG4-RD were reported [66▪,67▪]. These patients both showed typical clinical, imaging and histopathological features of IgG4-RD, despite the absence of any IgG4 involvement, that is with normal serum IgG4 levels and very few IgG4 and plasma cell infiltrates in the affected organs (Table 3). Interestingly, the favourable clinical course with a good response to corticosteroid seen in these patients resembles that in patients with IgG4-RD. Moreover, these two patients had biopsy-proven plasma cell rich TIN very similar to IgG4-TIN. Hart *et al.* [68] also showed three patients with type 1 AIP histologically but without serum or tissue IgG4 abnormalities. Thus, these cases suggest that a condition that closely mimics IgG4-RD may develop even in the absence of IgG4 and plasma cells.

CONCLUSION

TIN with characteristic imaging findings is a typical manifestation of IgG4-RD in the kidney. MGN can be a manifestation of IgG4-RD, although a variety of glomerular diseases are known to accompany IgG4-TIN. Although IgG4 is a key molecule and abundantly present in both the serum and tissues in this disease, it is unknown whether IgG4 *per se* plays a crucial role in inducing multiple systemic lesions or is only a bystander. Analysis of many more cases, including ones with IgG4-negative IgG4-RD, with longer-term follow-up will be needed to define more precisely the role played by IgG4 in this disease.

Acknowledgements

We would like to thank Mr. John Gelblum for his critical reading of the manuscript.

Financial support and sponsorship

This work was supported by Health and Labour Sciences Research Grants for the Study of Intractable Diseases from the Ministry of Health, Labour and Welfare, Japan.

Conflicts of interest

None.

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Human Pathology (2014) 45, 793–801

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Original contribution

Immunoglobulin class switching to IgG4 in Warthin tumor and analysis of serum IgG4 levels and IgG4-positive plasma cells in the tumor☆

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Received 10 June 2013; revised 14 November 2013; accepted 22 November 2013

Keywords:
Warthin tumor;
IgG4-related disease;
Class-switch recombination

Summary We previously reported a case of immunoglobulin (Ig)G4-related immune inflammation in Warthin tumor. Increased serum IgG4 levels and tissue infiltration of IgG4-positive plasma cells are characteristics of IgG4-related disease (IgG4-RD), a newly emerging clinicopathological entity. However, the relationship between IgG4-RD and Warthin tumor remains to be elucidated. We aimed to investigate the involvement of systemic and local IgG4 production and class-switch recombination in Warthin tumor. We examined serum IgG4 levels and also analyzed the involvement of IgG4-positive plasma cells in Warthin tumors (18 cases) compared with those of pleomorphic adenomas (19 cases) as controls. Furthermore, in specimens of Warthin tumors (3 cases), pleomorphic adenomas (2 cases), and IgG4-RDs (2 cases), we examined messenger RNA expression of activation-induced cytidine deaminase, IgG4 germline transcripts and productive IgG4 by reverse transcription polymerase chain reaction. Serum IgG4 levels were increased in 5 of 18 Warthin tumors and not in any of the 19 pleomorphic adenomas. Infiltration of IgG4-positive plasma cells was detected in 4 Warthin tumors and none in the pleomorphic adenomas. Moreover, activation-induced cytidine deaminase, IgG4 germline transcripts, and productive IgG4 messenger RNA were found to be expressed in 2 of 3 Warthin tumors as well as IgG4-RDs by reverse transcription polymerase chain reaction, but not in pleomorphic adenomas. In conclusion, immunoglobulin class switching to IgG4 may be involved in the pathogenesis of Warthin tumor, and it is possible that certain inflammatory background with an immune reaction is involved in the pathogenesis of Warthin tumor.

☆ Disclosures: No funding sources and support and no conflict of interest.
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0046-8177/$ – see front matter © 2014 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.humpath.2013.11.012

1. Introduction

Warthin tumor is the second most common benign neoplasm of the salivary glands, which was initially reported in 1929 by the pathologist Aldred Scott Warthin, and it is predominantly located in the parotid gland [1]. The term *Warthin tumor* was used as a synonym for lymphomatous papilliferum cistoadenoma and for cystadenolymphoma and adenolymphoma. Warthin tumor presents peculiar pathophysiologic characteristics. Although the epithelial component is generally believed to represent the neoplastic proliferation of salivary ducts, Honda et al [2] showed, using HUMARA (human androgen receptor gene) analysis, that the epithelial component of Warthin tumor was a polyclonal population, which indicates that Warthin tumor is a nonneoplastic lesion.

Previous studies have shown that immune and inflammatory reactions [3] and lymphocytic infiltration [4] may occur in Warthin tumor, although whether and how B-cell immunity is related to the formation of the lymphoid component remains to be fully elucidated. Recently, we and others reported cases that revealed the infiltration of immunoglobulin (Ig)G4-positive plasma cells in Warthin tumor, which implied the possible relationship with IgG4-related disease (IgG4-RD) [5,6].

IgG4-RD is a systemic inflammatory disease distinguished by tissue infiltration of IgG4-positive plasma cells and elevated serum IgG4 levels. T helper type 2 (Th2) cell responses are predominantly activated at affected sites [7,8]. Tissue messenger RNA (mRNA) expression of Th2 cytokines, including interleukin (IL)-4, IL-5, IL-10, and IL-13, is substantially increased compared with that in classic autoimmune conditions [7,8], and it is considered that Th2 cytokines play an important role to induce class switch [9,10]. IgG4-RDs are most frequently reported in the pancreatic and hepatobiliary systems; however, they can also affect the salivary glands [11,12].

In this study, we aimed to investigate the involvement of systemic and local IgG4 production and class-switch recombination in Warthin tumor. We measured serum IgG4 levels as well as examined the involvement of IgG4-positive plasma cells immunohistochemically in Warthin tumors. Furthermore, we examined the immune mechanisms involved in Warthin tumor, focusing on class-switch recombination to IgG4.

2. Materials and methods

2.1. Patients and materials

We obtained 18 specimens from patients with Warthin tumor (18 men; age, 42-76 years) and 19 from patients with pleomorphic adenoma (11 men and 8 women; age, 34-83 years) who had been diagnosed at the Division of Otolaryngology at Kanazawa University Hospital. Patients treated between 2000 and 2012 whose serum and surgically resected samples were available were selected by an electronic medical record system review. The diagnosis was made on the basis of clinical data and pathological findings. All cases underwent surgical resection on the basis of clinical diagnosis of salivary gland tumors. Specimens showed histologic findings corresponding to those of tumors. Informed consent was obtained from all patients in accordance with our institutional guidelines.

2.2. Laboratory data

The serum samples were collected from patients at first presentation and stored at −80°C until further processing. Serum immunoglobulins (IgG, IgG4, and IgE) were measured routinely.

2.3. Histologic examinations and immunohistochemistry for IgG and IgG4

Surgically resected specimens of salivary glands were used for immunohistochemical analysis of IgG and IgG4 expression. Three-micrometer-thick sections were prepared from each block of tissue embedded in paraffin. Deparaffinized sections were treated with 3% hydrogen peroxide for 10 minutes to inactivate endogenous peroxidase activity. The sections were incubated with protein blocker (Dako, Glostrup, Denmark) for 20 minutes and incubated at 4°C overnight with rabbit antihuman IgG (dilution 1:5000; Dako) and mouse antihuman antibodies for IgG4 (dilution 1:2000; Life technologies, Grand Island, NY). The sections were washed 3 times with phosphate-buffered saline (pH 7.2), after which they were exposed to Envision^{+} secondary antibody (Dako) for 30 minutes. The reaction products were developed by immersing the sections in a 3,3′-diaminobenzidine tetrahydrochloride solution. The sections were counterstained with hematoxylin. IgG- or IgG4-positive plasma cells were counted at 5 different high-power fields (HPFs; ×400) with intense inflammation. The proportion (percentage) of IgG4-positive plasma cells/IgG-positive plasma cells was calculated in each case.

2.4. Reverse transcription polymerase chain reaction

Total RNA was extracted from frozen sections in cases of Warthin tumor (3 cases), pleomorphic adenoma (2 cases), and 1 of IgG4-RDs, IgG4-related sialadenitis (2 cases), using the RNeasy Mini Kit (QIAGEN, Valencia, CA). Lanes 1 to 5 of Fig. 1 are relevant to cases 1, 3, 2, 21, and 29, respectively. We performed reverse transcription polymerase chain reaction (RT-PCR) for activation-induced cytidine deaminase (AID), IgG4 germline transcripts (GLTs), productive

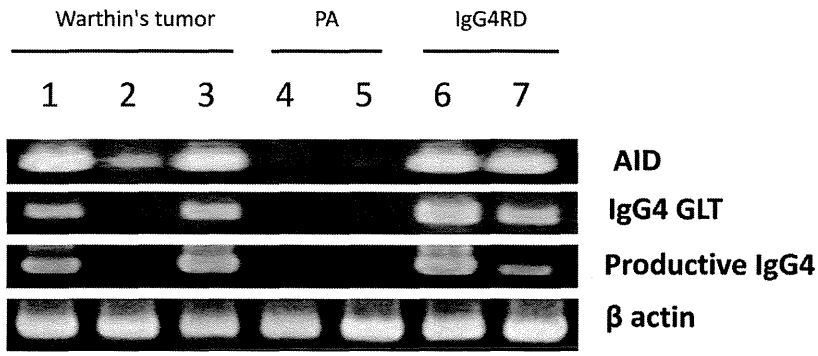

Fig. 1 Class-switch recombination in Warthin tumors, pleomorphic adenomas, and IgG4-RDs was assessed by RT-PCR. mRNA levels of IgG4 GLTs, productive IgG4, and AID were examined in the glands of patients with Warthin tumor, IgG4-RD, and pleomorphic adenoma (PA). Lanes 1-3, Warthin tumor; lanes 4 and 5, PA; and lanes 6 and 7, IgG4-RD.

IgG4, and β-actin. The oligonucleotide sequences, numbers of cycles, and annealing temperatures of these primers were as follows: AID, forward 5′-CGCAATAAGAACGGCTGC-CACG-3′, reverse 5′-AGGTGAACCAGGTGACGCGG-3′, 35 cycles, 54°C; IgG4 GLT, forward 5′-ACGAGGAACAT-GACGGGATGC-3′, reverse 5′-GGGACCATATTTG-GACTC-3′, 33 cycles, 60°C; productive IgG4, forward 5′-GACACGGCTGTGTATTACTGTGCG-3′, reverse 5′-ATGGGCATGGGGGACCATTTGGA-3′, 33 cycles, 60°C; and β-actin, forward 5′-GACCTGACTGACTACCTCAT-GAAGA-3′, reverse 5′-GGGGCCGGACTCGTCA-TACTCCTGC-3′, 28 cycles, 54°C [13-16].

After PCR, 10-μL aliquots of the products were subjected to 2.0% agarose gel electrophoresis and then stained with ethidium bromide.

2.5. Statistics

The means of 2 groups were compared using the Mann-Whitney U test. P values less than .05 were regarded as statically significant.

3. Results

3.1. Main clinical data

Main clinical data of patients with Warthin tumor and pleomorphic adenoma are shown in Tables 1 and 2. Of the 18 patients with Warthin tumor, 9 had some complications,

Table 1 The clinical and serologic data of 18 patients with Warthin tumor

Case	Age (y)	Sex	Laterarity	Serum IgG (mg/dL; 870–1700)	Serum IgG4 (mg/dL; <135)	IgG4/IgG (%)	Serum IgE (IU/mL; <250)	Complications
1	71	M	Bilateral	1957	629	32	954	AIP, IAAA
2	60	M	Bilateral	1629	26.7	2	318	None
3	57	M	Right	1178	5	0	5.4	None
4	53	M	Bilateral	1380	95.5	7	139	None
5	67	M	Left	1531	69.5	5	197	None
6	59	M	Left	918	11.1	1	15.6	None
7	76	M	Right	1510	54.1	4	198	None
8	56	M	Right	1193	114	10	626	None
9	47	M	Right	997	14	1	130	Hypothyroidism
10	54	M	Left	1780	22.7	1	5.6	Rheumatoid arthritis
11	56	M	Left	1313	131	10	274	Amyloidosis
12	72	M	Right	1213	147	12	537	None
13	59	M	Bilateral	1271	135	11	315	Panhypopituitarism
14	42	M	Left	1030	156	15	156	None
15	70	M	Left	1249	21.4	2	5	MGUS
16	68	M	Right	905	104	11	143	IPMN
17	65	M	Bilateral	1137	37.7	3	11.9	Interstitial pneumonia
18	68	M	Bilateral	2127	1040	49	227	RPF

Abbreviations: F, female; AIP, autoimmune pancreatitis; IAAA, inflammatory abdominal aortic aneurysm; IPMN, intraductal papillary mucinous neoplasm; M, male; MGUS, monoclonal gammopathy of undetermined significance; RPF, retroperitoneal fibrosis.

Table 2 The clinical and serologic data of 19 patients with pleomorphic adenoma

Case	Age (y)	Sex	Serum IgG (mg/dL; 870-1700)	Serum IgG4 (mg/dL; <135)	IgG4/IgG (%)	Serum IgE (IU/mL; <250)
19	57	M	1270	70	6	124
20	58	F	1225	21.8	2	129
21	74	M	1330	21	2	202
22	63	F	1077	25.3	2	548
23	68	M	1521	58.5	4	151
24	75	M	1097	30.8	3	117
25	73	F	662	14.7	2	77.5
26	78	F	1021	26.3	3	51.3
27	83	F	1230	25.3	2	72.6
28	34	M	710	16.1	2	138
29	36	M	1153	10.5	1	111
30	35	F	1352	21.5	2	438
31	36	M	1241	43.5	4	46
32	55	M	740	49.2	7	628
33	47	M	818	42.4	5	58.1
34	52	M	1283	91.3	7	522
35	61	F	1144	13.9	1	141
36	57	M	971	22.3	2	8.1
37	58	F	1088	11	1	7.3

Abbreviations: F, female; M, male.

including autoimmune pancreatitis (AIP) and inflammatory abdominal aortic aneurysm (patient 1), hypothyroidism (patient 9), rheumatoid arthritis (patient 10), amyloidosis (patient 11), panhypopituitarism (patient 13), monoclonal gammopathy of undetermined significance (patient 15), intraductal papillary mucinous neoplasm (patient 16), interstitial pneumonia (patient 17), and retroperitoneal fibrosis (patient 18). None of the 19 patients with pleomorphic adenoma had a history of significant concomitant diseases such as autoimmune diseases. The bilateral parotid glands were affected in 6 patients with Warthin tumor. All patients with Warthin tumor (18) and approximately half of the patients with pleomorphic adenoma (8/19) had a history of smoking. However, there was no correlation between serum IgG4 levels and the Brinkman index in the Warthin tumors and in all the patients (data not shown).

The serum IgG4 level (reference range, <135 mg/dL) was increased in 5 of 18 patients with Warthin tumors (patient 1, 629 mg/dL; patient 12, 147 mg/dL; patient 13, 135 mg/dL; patient 14, 156 mg/dL; and patient 18, 1040 mg/dL) but not in any of the 19 patients with pleomorphic adenomas. All serum IgG4/IgG proportions in these cases (patients 1, 12, 13, 14, and 18) were greater than 8%.

3.2. Serum IgG, IgG4, and IgE levels

Serum IgG and IgG4 levels in patients with Warthin tumors (IgG: 905-2127 mg/dL [mean, 1351 mg/dL; median, 1260 mg/dL]; IgG4: 5-1040 mg/dL [mean, 156 mg/dL; median, 82.5 mg/dL]) were higher than those in patients with pleomorphic adenomas (IgG: 662-1521 mg/dL [mean, 1102 mg/dL; median, 1144 mg/dL]; IgG4: 10.5-91.3 mg/dL [mean, 32 mg/dL; median, 25.3 mg/dL]) (Fig. 2). In contrast, serum IgE levels in patients with Warthin tumors (IgE: 5-954 IU/mL [mean, 237 IU/mL; median, 176.5 IU/mL]) were not significantly higher than those in patients with pleomorphic adenomas (IgE: 7.3-628 IU/mL [mean, 188 IU/mL; median, 124.0 IU/mL]).

3.3. Immunohistochemical detection of IgG and IgG4

The results of immunostaining of IgG and IgG4 are shown in Figs. 3, 4, and 5. IgG-positive plasma cells and IgG4-positive plasma cells were diffusely distributed in the lymphoid component of the affected parotid glands of patients with Warthin tumor in patients 1, 8, 14, and 18 (Fig. 3). The numbers of IgG- and IgG4-positive plasma cells per HPF in these patients ranged from 63 to 120/HPF and from 40 to 72/HPF, respectively (Fig. 4). The proportion of IgG4/IgG-positive plasma cells ranged from 50.6% to 68% (Fig. 5). The number of IgG- and IgG4-positive plasma cells and the proportion of IgG4/IgG-positive plasma cells were significantly increased in Warthin tumor. Approximately half of the patients with Warthin tumor and pleomorphic adenoma underwent fine-needle aspiration biopsies. However, there were no changes related to this procedure in the specimens analyzed.

3.4. Class-switch recombination to IgG4 in salivary glands

RT-PCR for IgG4 mRNA transcripts, AID and GLT, which are the components of class-switch recombination, was performed to determine whether class switch had occurred in affected salivary glands. Class switch is

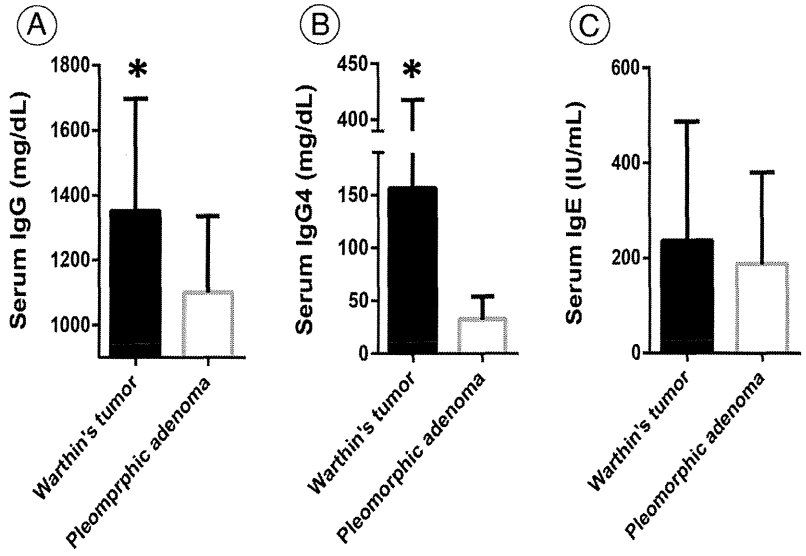

Fig. 2 Serum IgG (A), IgG4 (B), and IgE (C) levels in 18 patients with Warthin tumors (black bars) or 19 with pleomorphic adenomas (white bars). Serum IgG, IgG4, and IgE levels in patients with Warthin tumors were compared with those in patients with pleomorphic adenomas. Data are presented as mean ± SD; $*P < .05$.

accompanied by looping-out deletions of DNA segments, and AID and GLT are involved in this step [17].

IgG4 mRNA transcripts were detected in 2 of 3 glands of patients with Warthin tumor and in all glands of patients with IgG4-RD, whereas no gland of patients with pleomorphic adenoma showed IgG4 expression (Fig. 1). Moreover, mRNA of AID and GLT was detected in the glands of all patients with Warthin tumor and IgG4-RD. Expression of

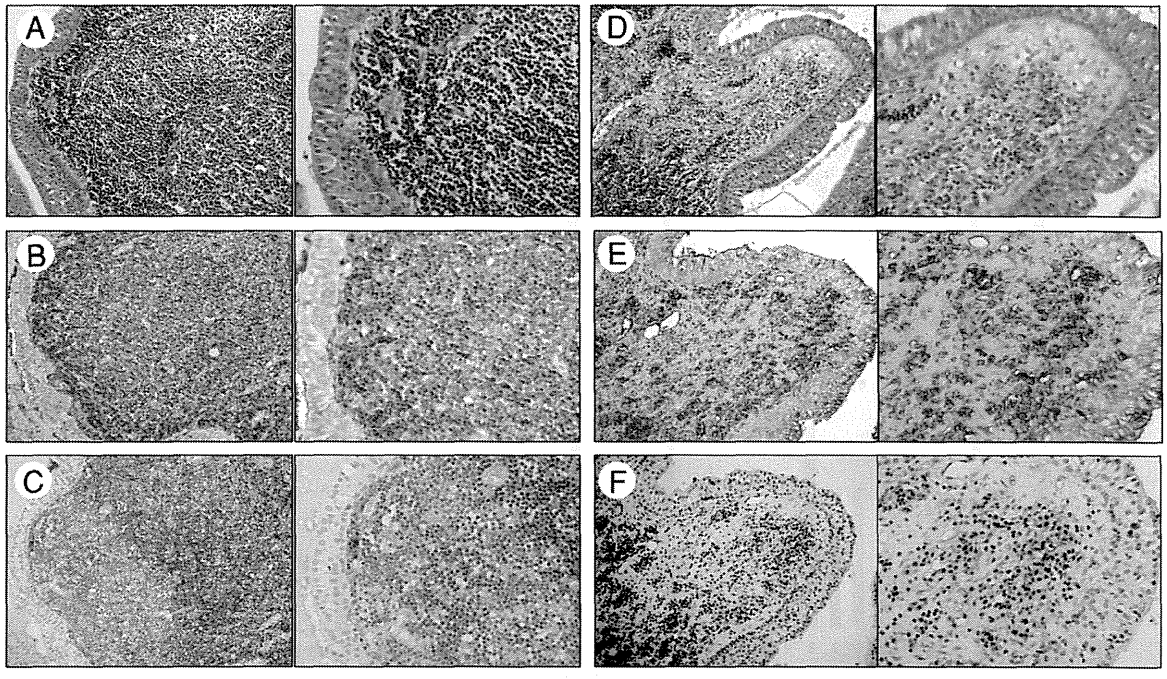

Fig. 3 Pathological findings in the parotid gland of patients with Warthin tumor (A-C: patient 1; D-F: patient 8). Warthin tumors are composed of glandular and cystic structures, lined by oncocytic epithelial cells and lymphoid stroma, with abundant lymphocyte infiltration. Immunohistochemistry of IgG (B and E) and IgG4 (C and F) in the parotid gland of patients with Warthin tumors. Many IgG-positive plasma cells were diffusely distributed in the lymphoid component of Warthin tumors, and most of these plasma cells were positive for IgG4. A-F, hematoxylin and eosin, original magnification ×200 (left) and ×400 (right).

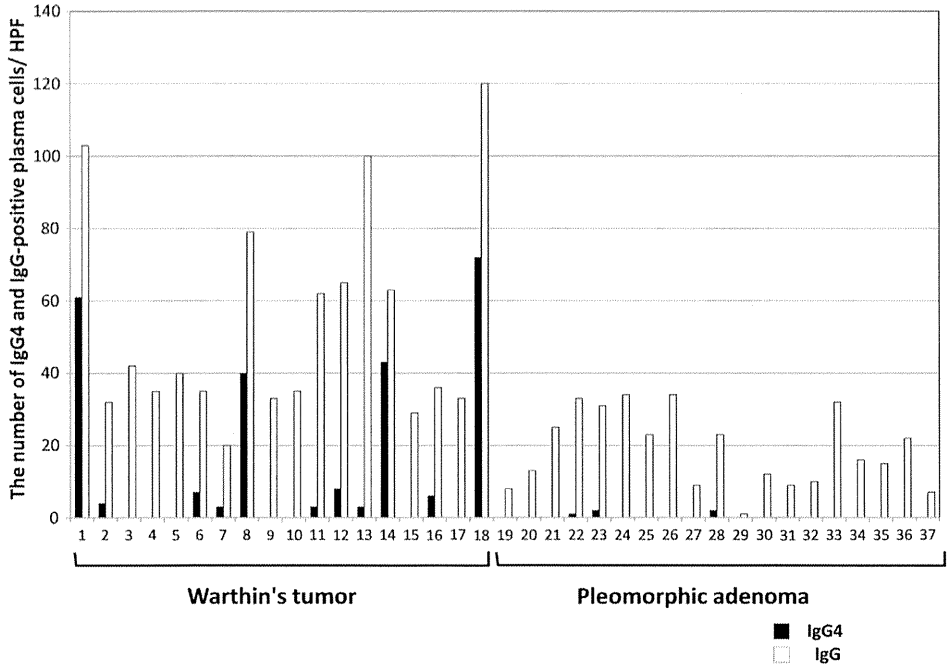

Fig. 4 Distribution of the number of IgG4- and IgG-positive plasma cells (black bars and white bars, respectively) in the salivary gland tissue of individual cases of Warthin tumor (18 cases) and pleomorphic adenoma (19 cases). The difference in the number of IgG- and IgG4-positive plasma cells between Warthin tumor and pleomorphic adenoma was significant ($P < .05$).

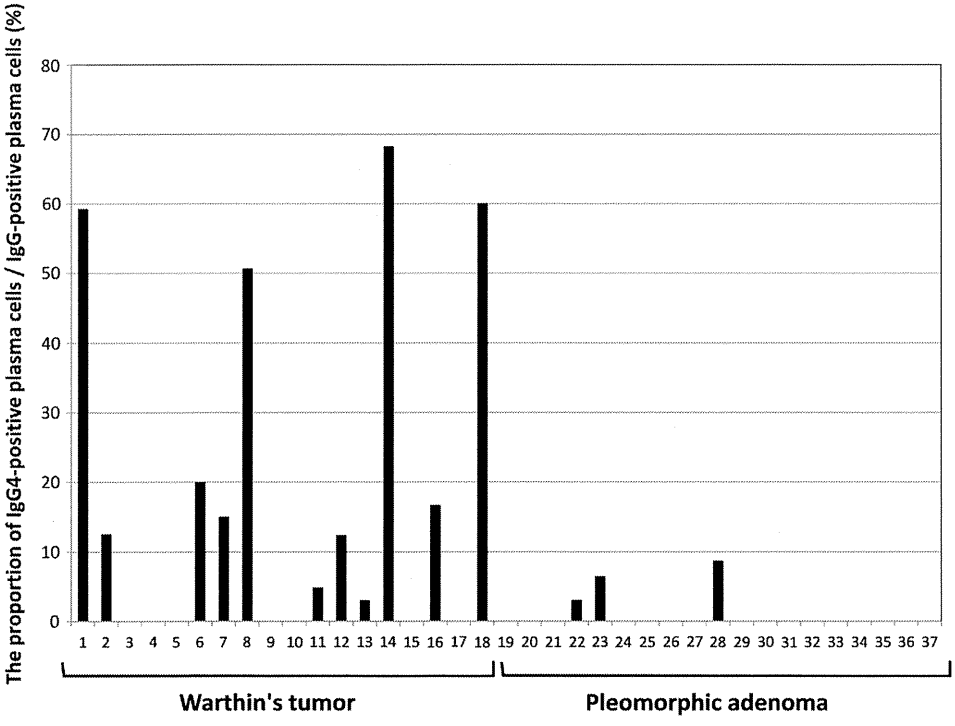

Fig. 5 Distribution of the proportion of IgG4-positive plasma cells/IgG-positive plasma cells in the salivary gland tissue of individual cases of Warthin tumor (18 cases) and pleomorphic adenoma (19 cases). The difference in the proportion of IgG4/IgG-positive plasma cells between Warthin tumor and pleomorphic adenoma was significant ($P < .05$).

productive IgG4, AID, and GLT are appropriate markers for class switch. Therefore, these results suggested that the glands of patients with Warthin tumor and IgG4-RD are characterized by the local induction of class-switched IgG4.

4. Discussion

The detailed mechanism underlying increased serum IgG4 levels in Warthin tumor and IgG4-RD remains unknown. IgG4 is the least abundant IgG subtype and accounts for only 3% to 6% of the total immunoglobulin in healthy individuals. Increased serum IgG4 levels have been reported in allergic conditions with chronic antigen exposure, such as Churg-Strauss syndrome [18], and autoimmune diseases, including pemphigus vulgaris and pemphigus foliaceus [19]. It has been thought that Th2 cytokines such as IL-4, IL-5, and IL-10 are important in allergy. It is known that they act on the proliferation and induction of eosinophils and class switching to IgE [20,21]. IL-5 is the representative cytokine, which activates eosinophils [22], and the signals of IL-4/IL-13 and activation of the CD40 signal pathway induce IgE class switching [9,10]. Zen et al [7] reported that these cytokines (mainly IL-10) promote the production of IgG4 in AIP. IL-10 decreases IL-4–induced IgE switching. Therefore, IgE versus IgG4 production can be differentially regulated by IL-10 [23].

In the presence of antigen, mature B cells diversify their antibody repertoire through class-switch recombination. These processes take place in the germinal centers of secondary lymphoid follicles. Class switch is accompanied by looping-out deletion of DNA segments and requires nucleotide mutations, which are dependent on AID. Furthermore, the selection of a target switch region occurs by germline transcription from an intron promoter located 5′ to each switch region. Therefore, AID and GLT are appropriate markers for class-switch recombination [17].

This study revealed that AID is expressed within Warthin tumors. AID is a DNA deaminase that initiates class-switch recombination and somatic hypermutation of immunoglobulin loci, resulting in diversification of the antibody repertoire and production of high-affinity antibodies [24]. Some researchers have elucidated that AID mRNA transcripts exist not only in secondary lymphoid organs but also in local inflammatory tissues. AID is expressed within affected glands in IgG4-RD [25,26] as well as a systemic autoimmune disease, Sjögren syndrome [27]. We also detected the expression of GLTs and class-switched mature transcripts of IgG4 in Warthin tumors. These results suggest that IgG4-producing background promotes the development of not all but a certain proportion of Warthin tumor. AID is essential for nonspecific immunoglobulin class-switch recombination (from IgM to IgG1, IgG2, IgG3, IgG4, IgA, and IgE) [24]; thus, up-regulation of AID could also contribute to an up-regulation of IgG4-specific class-switch recombination in Warthin tumor. It is tempting to speculate that the induction of AID and initiation of class-switch recombination in Warthin tumors causes B cells to differentiate into IgG4-positive plasma cells. Further study is required to clarify this working hypothesis.

Moreover, we revealed that serum IgG4 levels were increased and IgG4-positive plasma cells infiltrated the affected parotid gland in some patients with Warthin tumors. These data raise the question of whether Warthin tumor is an "IgG4-RD."

IgG4-RD is a recently recognized multiorgan system condition with pathological features that are largely consistent across a wide range of organ systems. It shows hyper–IgG4–γ-globulinemia and IgG4-positive plasma cell expansion in affected organs. This first came to light in 2001 when Hamano et al [11] showed increased serum IgG4 levels in AIP, and a subsequent case report [28] demonstrated retroperitoneal fibrosis, mediastinal fibrosis, and increased IgG4 levels without AIP, highlighting the spectrum of IgG4-RD.

However, some studies have suggested other clinical entities that mimic IgG4-RDs. Serum IgG4 levels were increased in some patients with Churg-Strauss syndrome [18], pemphigus vulgaris, pemphigus foliaceus [19], rheumatoid arthritis, systemic sclerosis, chronic hepatitis, and liver cirrhosis [29]. In some cases, IgG4-positive plasma cells were also observed in Rosai-Dorfman disease [30], salivary duct carcinoma [31], and mucoepidermoid carcinoma [32].

Recently, the pathological consensus statement of the First International Symposium on IgG4-RD in Boston [33] suggested that the diagnosis should be primarily based on morphologic characteristics such as lymphoplasmacytic infiltrate, a storiform pattern of fibrosis, and obliterative phlebitis on biopsy. Although Warthin tumor is composed of epithelial and lymphoid components, in most cases, it has no fibrosis or obliterative phlebitis, which is characteristic of IgG4-RD. For this reason, it could be thought that Warthin tumor is not included in IgG4-RD.

In some cases, Warthin tumor mimicked IgG4-RD because of the peculiar characteristics of its pathophysiology. Although the most commonly accepted theory is that the tumors develop from salivary ducts imprisoned in intraparotid lymph nodes, during embryogenesis or from heterotopic salivary glands [34,35], other theories credit tumor origin to the presence of lymphocytic infiltration in a preexisting adenoma [36]. Nikai and Schroeder [3] analyzed the composition of lymphoid stroma in Warthin tumors and suggested that it represents an immune reaction. These data suggest the involvement of unknown inflammatory background with an immune reaction in the pathogenesis of Warthin tumor. Moreover, Eveson and Cawson [37] reviewed a total of 323 Warthin tumors and found 20 cases (6.2%) with extensive necrosis, fibrosis, and inflammation. Patey and Thackray [38] also reported that Warthin tumors may be infected by 3 possible routes through the ducts, blood stream, or lymphatics.

Meanwhile, IgG4 antibodies are structurally and functionally monovalent. Therefore, they have low potential for inducing immune responses themselves. However, they may interfere with inflammation and immune reactions caused by other antibodies. In addition, Th2 cells activated by chronic inflammation induce polyclonal B-cell activation, and IgG4 is induced by a modified Th2 response [39,40]. Thus, increased IgG4 levels in Warthin tumor may represent a secondary response to a primary immune-mediated process caused by an unknown stimulus.

This study also suggested that serum IgG levels in patients with Warthin tumor are significantly increased compared with those in patients with pleomorphic adenoma. There is a body of evidence suggesting that in some solid tumors, serum IgG levels are increased [41]. It is possible that elevation of serum IgG levels would be a characteristic of this unique tumor.

5. Concluding remarks

In conclusion, this study revealed increased serum IgG4 levels in some patients with Warthin tumor as well as in patients with IgG4-RDs. Inflammation with IgG4-positive plasma cells was also detected in the parotid specimen of Warthin tumor. Moreover, we showed the local initiation of class-switch recombination to IgG4 in Warthin tumor. Although Warthin tumor is not included as an entity of IgG4-RD because of its pathological characteristics, further exploration of a potential pathogenetic relationship between Warthin tumor and IgG4-RDs is essential for understanding these diseases.

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