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REVIEW ARTICLE

Clinicopathological findings of immunoglobulin G4-related kidney disease

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Abstract Immunoglobulin (Ig) G4-related kidney disease characterizing tubulointerstitial nephritis (TIN) is an organ complication recognized in IgG4-related systemic diseases that has some unique aspects compared to other types of TIN. TIN lesions in the kidney can be tumor-like, focal or diffuse. Abnormal urinalysis is usually mild or absent even in the cases with deteriorated renal dysfunction. Some cases are accidentally diagnosed from radiological findings without renal dysfunction and/or abnormal urinalysis. The typical pathological findings of TIN are unique fibrosis and infiltration of massive lymphocytes and IgG4-positive plasma cells. Glomerular lesions are rare but the complication of mesangial proliferative glomerulonephritis and membranous nephropathy is occasionally reported. Pathogenic mechanisms are unclear until now; however, autoimmune and allergic mechanisms have been suspected from laboratory data. The initial response to steroid agents is generally favorable; however, recurrence is possible after the discontinuation of steroid treatment. Long-term follow-up is necessary with continuous systemic checks for organ disorders due to IgG4-related systemic diseases.

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Introduction

Many articles regarding immunoglobulin (Ig) G4-related systemic diseases have been published in Japan. IgG4-related kidney diseases, in particular, have been reported by many Japanese nephrologists and rheumatologists. Tubulointerstitial nephritis (TIN) is a specific pathological feature of IgG4-related kidney disease in IgG4-related systemic diseases.

IgG4-related systemic diseases have common pathological features characterized by advanced scleral fibrosis with infiltration of dominant lymphocytes and plasma cells in each susceptible organ. Auto-immune pancreatitis (AIP) was first described as a unique subtype of chronic pancreatitis with hypergammaglobulinemia by Sarles et al. [1] in 1961. Consequently, in 2001, Hamano et al. [2] documented that elevated serum IgG4 levels were closely related to the pathogenesis of AIP. Most cases diagnosed as AIP in Japan show histological findings characteristic of IgG4-related sclerosing pancreatitis; however, it has been noted that Japanese cases differ from Western cases [3]. Despite similarities in various organ damage observed in Sjögren's syndrome and IgG4-related Mikulicz's disease, it has recently been considered that there are marked clinical differences between them in Japan. Anti-SS-A/Ro and anti-SS-B/La have been detected in the former, while the latter has no such abnormalities [4]. Japanese rheumatologists believe AIP and other organ involvement associated with IgG4-related systemic disease are mostly recognized in cases of Mikulicz's disease and not in Sjögren's syndrome. TIN has also been reported in patients with Sjögren's

syndrome [5, 6] and similar pathological findings are certainly observed. An international controversial discussion concerning diagnosis of Sjögren's syndrome and Mikulicz's disease might produce a different interpretation of TIN associated with both types of diseases.

IgG4-related kidney diseases were first reported as organ complications associated with AIP by Japanese authors [7, 8] in 2004. Their pathological findings were comparable to TIN and had unique mixed features showing abundant infiltration of lymphocytes and IgG4-positive plasma cells into cortex lesions and advanced cortical fibrosis. Diagnostic criteria for IgG4-related systemic disease were proposed by Masaki et al. [4] in 2009; elevated serum IgG4 (>135 mg/dl) and histopathological features, including lymphocytes and IgG4-positive plasma cells infiltration (IgG4+ plasma cells/IgG+ plasma cells >50% on a highly magnified slide checked at 5 points) in target organs. Masaki et al. called IgG4-related systemic disease 'IgG4-positive multi-organ lymphoproliferative syndrome (IgG4+ MOLPS)'. These criteria are generally used in the diagnosis of IgG4-related kidney disease.

In this paper we will integrate clinicopathological findings and pathogenic mechanisms implicated in IgG4-related kidney disease.

IgG4-related kidney disease in IgG4-related systemic diseases

Various organ injuries in IgG4 systemic diseases are already known; these include AIP [7, 8], Mikulicz's disease [4, 9], sclerosing cholangitis [10], retroperitoneal fibrosis [11, 12], etc. Table 1 summarizes susceptible organs and associated disease findings [4, 7–32]. Although single organ cases were certainly noted, multi-organ cases were more common in IgG4-related systemic disease. The kidney is also a susceptible organ in systemic multi-organ cases. Zen et al. [27] performed a cross-sectional study evaluating 114 cases with IgG4-related systemic diseases and described 10 cases (8.8%) with renal lesions and other organ involvement. In most previous cases, renal lesions were found in pleural organ involvement, with only a few cases of renal lesions alone [28, 29]. In our summary (Table 2), 2 (5.4%) of 37 cases were reported as IgG4-related kidney disease without other organ involvement.

From the viewpoint of IgG4-related kidney disease, AIP is the most frequent organ complication; the rate of complication was 19 (51.4%) of 37 cases (Table 2). The salivary and lacrimal glands were the second major targets. A cross-sectional study by Zen et al. [27] documented salivary and lacrimal lesions in 53 (46.5%) of 114 cases. In IgG4-related kidney disease, we should be aware of the complication of AIP and head and neck lesions.

Table 1 Susceptible organs and associated disease findings in IgG4-related systemic diseases

Head and neck lesions	
Hypopituitarism, diabetes insipidus	[13]
Hearing loss	[14]
Lacrimal gland inflammation	[9]
Sialadenitis (Mikulicz's disease)	[15]
Riedel's thyroiditis, Hashimoto's thyroiditis	[16, 17]
Cardiac lesions	
Constrictive pericarditis	[18]
Pulmonary lesions	
Mediastinitis, hilar lymphadenopathy	[19]
Interstitial pneumonitis, pseudoinflammatory tumor	[20, 21]
Bronchitis, bronchial wall thickening	
Gastrointestinal lesions	
Gastric ulcer	[22]
Swelling of papilla of Vater	[23]
Hepatic lesions	
Sclerosing cholangitis	[10, 24]
Pancreatic lesions	
Autoimmune pancreatitis	[7, 8]
Renal lesions	
Tubulointerstitial nephritis	[27–30]
Renal pelvis wall thickening	[31, 32]
Prostatic lesions	
Prostatitis	[33]
Retroperitoneal lesions	
Aortitis, periaortitis, abdominal aortic aneurysm	[25, 26]
Retroperitoneal fibrosis	[11, 12]

Urological lesions of IgG4-related systemic disease

In the field of urology, with the exception of TIN, the following diseases have been reported as IgG4-related systemic diseases. Kuroda et al. [30] reported that chronic sclerosing pyelitis was a urological form of IgG4-related systemic disease. His case showed swelling of major and minor salivary glands and the lacrimal glands and biopsy specimens of the minor salivary gland were compatible with scleral fibrosis suggesting IgG4-systemic disease. A kidney showed hydronephrosis due to tumor-like swelling of the pelvis and the same pathological findings were confirmed in operative specimens obtained from the pelvis. Originally retroperitoneal fibrosis was thought to be an idiopathic fibrotic disease; however, recently some cases appear to have been developed from IgG4-related systemic disease. Hamano et al. [31] pathologically proved that abundant infiltration of IgG4-positive plasma cells caused retroperitoneal fibrosis and AIP from the histological examination of ureteral and pancreatic lesions. Yoshimura et al. [32] reported a case with prostatitis and AIP. This

Table 2 Laboratory data of IgG4-related kidney disease

Case no.	References	Publication year	Male/female	Age (years)	S-Cr (mg/dl)	UP (g/day)	Hematuria (/hpf)	IgG (mg/dl)	IgG4 (mg/dl)
1	Takeda et al. [7]	2004	Male	66	2.3	0.3	(−)	2690	550
2	Uchiyama-Tanaka et al. [8]	2004	Male	64	3.9	1.5	5/hpf	5410	665
3	Nakamura et al. [33]	2006	Male	52	0.8	(−)	(−)	3180	1430
4	Rudmik et al. [34]	2006	Male	52	66 μmol/l	NA	NA	Elevated	Elevated
5	Watson et al. [35]	2006	Male	67	304 μmol/l	2.4	4+	Elevated	2125
6	Shiomoyama et al. [36]	2006	Female	40	0.74	(−)	(−)	3450	221
7	Yoneda et al. [37]	2007	Male	68	1.7	0.1	1+	5520	2350
8	Yoneda et al. [37]	2007	Male	69	2.5	0.1	1+	1930	221
9	Cornell et al. [38]	2007	Male	71	0.9–1.1	NA	NA	1990	1030
10	Cornell et al. [38]		Male	57	Normal	NA	NA	NA	NA
11	Cornell et al. [38]		Female	68	0.9–1.6	NA	NA	3650	NA
12	Cornell et al. [38]		Male	78	3.0	NA	NA	Elevated	NA
13	Cornell et al. [38]		Male	45	7.0	1	(+)	NA	NA
14	Morimoto et al. [39]		Male	80	1.4	0.4	(−)	4657	660
15	Aoki et al. [40]	2009	Female	48	2.52	1.2	5–9/hpf	3729	1410
16	Yamamoto et al. [41]	2009	Male	56	0.9	(+)	(−)	1920	248
17	Tsubata et al. [29]	2010	Male	76	5.6	0.3	(−)	2963	1800
18	Saeki et al. [42]	2010	Female	58	0.67	0.23	(±)	7319	4630
19	Saeki [42]		Female	76	0.69	(−)	(−)	2721	769
20	Saeki et al. [42, 43]		Male	76	0.71	(−)	(−)	3486	1030
21	Saeki et al. [42]		Male	70	0.9	(±)	(−)	3496	623
22	Saeki et al. [42–44]		Male	61	1.09	(−)	(−)	6569	730
23	Saeki et al. [42]		Male	74	1.1	(−)	(−)	4837	13220
24	Saeki et al. [42]		Male	58	1.15	(−)	(−)	2850	1470
25	Saeki et al. [42]		Male	62	1.3	(−)	(±)	8194	NA
26	Saeki et al. [42]		Male	75	1.34	(+)	(−)	5380	587
27	Saeki et al. [42, 44]		Male	68	1.37	(−)	(−)	2995	670
28	Saeki et al. [42]		Male	83	1.48	2.3	3+	3144	924
29	Saeki et al. [42]		Male	60	1.7	(−)	(−)	8841	1028
30	Saeki et al. [42, 43]		Male	60	1.75	(−)	(±)	5188	305
31	Saeki et al. [42]		Male	61	2	NA	NA	8005	2390
32	Saeki et al. [42]		Male	55	2.1	(+)	(−20)	5040	1780
33	Saeki et al. [42]		Male	69	2.36	0.25	(±)	4001	1340
34	Saeki et al. [42]		Male	64	2.9	NA	NA	5100	1360
35	Saeki et al. [42]		Male	76	5.4	0.3	(+)	2963	1800

Table 2 continued

Case no.	References	Publication year	Male/female	Age (years)	S-Cr (mg/dl)	UP (g/day)	Hematuria (/hpf)	IgG (mg/dl)	IgG4 (mg/dl)
36	Saeki et al. [42]		Male	78	6.17	1.4	2+	3731	1860
37	Saeki et al. [42]		Male	68	6.87	2+	2+	4661	1120

Case no.	References	Publication year	Male/female	Age (years)	Hypocomplementemia	ANF	RF	Other organ injury	Glm	HD treatment
1	Takeda et al. [7]	2004	Male	66	(+)	(+)	(+)	AIP	mesPGN	
2	Uchiyama-Tanaka et al. [8]	2004	Male	64	(+)	(+)	(+)	AIP	MN	Transient HD
3	Nakamura et al. [33]	2006	Male	52	(−)	(−)	(+)	AIP, Sa, Lu		
4	Rudmik et al. [34]	2006	Male	52	NA	NA	NA	AIP		
5	Watson et al. [35]	2006	Male	67	(−)	(−)	(−)	AIP	MN	
6	Shiomoyama et al. [36]	2006	Female	40	(+)	(−)	(+)	Da, Sa, Lu		
7	Yoneda et al. [37]	2007	Male	68	(+)	(−)	NA	AIP, SC		
8	Yoneda et al. [37]	2007	Male	69	(−)	(−)	NA	AIP, Sa		
9	Cornell et al. [38]	2007	Male	71	NA	(−)	NA	SC S/O		
10	Cornell et al. [38]		Male	57	NA	NA	NA	AIP		
11	Cornell et al. [38]		Female	68	(+)	(+)	NA	SC, Da,	mesPGN	
12	Cornell et al. [38]		Male	78	(+)	(+)	NA	AIP		
13	Cornell et al. [38]		Male	45	NA	(−)	NA	SC	mesPGN	
14	Morimoto et al. [39]		Male	80	(+)	(+)	NA	AIP	MPGN	
15	Aoki et al. [40]	2009	Female	48	(−)	(+)	(−)	Da, Sa		
16	Yamamoto et al. [41]	2009	Male	56	(+)	(+)	(−)	Da, Sa, Ly	mesPGN	
17	Tsubata et al. [29]	2010	Male	76	(+)	(−)	(−)			
18	Saeki et al. [42]	2010	Female	58	(−)	(−)	(+)	AIP, Da, Sa, Ly		
19	Saeki et al. [42]		Female	76	(−)	(+)	(−)	Da, Sa, Ly, Lu		
20	Saeki et al. [42, 43]		Male	76	(+)	(−)	(−)	AIP, Sa		
21	Saeki et al. [42]		Male	70	(+)	(+)	(−)	AIP		
22	Saeki et al. [42–44]		Male	61	(+)	(+)	NA	AIP, Sa, Ly		
23	Saeki et al. [42]		Male	74	(+)	(+)	(+)	Sa		
24	Saeki et al. [42]		Male	58	(−)	(+)	NA	SC		
25	Saeki et al. [42]		Male	62	(+)	(+)	(+)	AIP, Da, Sa, Ly		
26	Saeki et al. [42]		Male	75	(+)	(+)	(+)	Sa, Da, Lu		
27	Saeki et al. [42, 44]		Male	68	(+)	(+)	(−)	Sa		
28	Saeki et al. [42]		Male	83	(+)	(+)	NA	MN		
29	Saeki et al. [42]		Male	60	(+)	(+)	(−)	Sa, Lu, Ly		
30	Saeki et al. [42, 43]		Male	60	(+)	(+)	(+)	Sa, Ly		
31	Saeki et al. [42]		Male	61	(+)	(+)	(−)	Sa, Ly		

Table 2 continued

Case no.	References	Publication year	Male/female	Age (years)	Hypocomplementemia	ANF	RF	Other organ injury	Glm	HD treatment
32	Saeki et al. [42]		Male	55	(−)	(+)	(+)	AIP, Sa		
33	Saeki et al. [42]		Male	69	(+)	(−)	NA	AIP		
34	Saeki et al. [42]		Male	64	(+)	(+)	(−)	Da, Sa		
35	Saeki et al. [42]		Male	76	(+)	(−)	(−)	Sa		
36	Saeki et al. [42]		Male	78	(+)	(−)	(−)	AIP, Sa	MN	Permanent HD
37	Saeki et al. [42]		Male	68	(+)	(+)	(−)	Da, Sa, Lu, Pr, Ly	ECPGN	

NA, not available, (+) positive, (−) negative, *ANF* anti-nuclear antibody, *RF* rheumatoid factor, *S-Cr* serum creatinine, *UP* urine protein, *Glm* glomerular lesion, *HD* hemodialysis, *AIP* autoimmune pancreatitis, *Sa* sialadenitis, *Lu* lung lesion, *SC* sclerocholangitis, *Da* dacroadenitis, *Ly* lymph node, *Pr* prostatitis, *mesPGN* mesangial proliferative glomerulonephritis, *MN* membranous nephropathy, *ECPGN* endocapillary proliferative glomerulonephritis

case showed common histological findings in prostate, salivary glands and pancreas, namely, infiltration of lymphocytes and plasma cells accompanying dense fibrosis.

In the evaluation of 114 cases with IgG4-related systemic diseases by Zen et al. [27], 13 (11.4%) cases were diagnosed as retroperitoneal fibrosis, 10 (8.8%) cases as aortitis, 1 case (0.9%) as prostatitis and 10 (8.8%) cases as TIN; these cases accounted for 34 cases (29.8%). IgG4-related urology diseases or retroperitoneal diseases are found in approximately 25% of IgG4-related systemic diseases.

TIN as IgG4-related kidney disease

Disorders in laboratory data

To date, 37 cases have been reported as IgG4-related kidney disease exhibiting TIN in English case reports (Table 2). Male patients were dominant and their ages at renal biopsy ranged from 40 to 83 years. Their serum creatinine levels ranged from 0.63 to 7.0 mg/dl. Deteriorated renal function was confirmed in approximately two-thirds of patients, while the remainder showed no renal dysfunction in spite of the progression of TIN. In urinalysis, proteinuria was generally mild or absent but cases with glomerulonephritis had moderate proteinuria. Microscopic hematuria was not confirmed apart from the cases with glomerulonephritis. Ten (27.0%) of 37 cases had complicated glomerulonephritis including mesangial proliferative glomerulonephritis (mesPGN), membranous nephropathy (MN), membranoproliferative glomerulonephritis (MPGN) and endocapillary proliferative glomerulonephritis (ECPGN). Some cases without renal dysfunction and abnormal urinalysis were found from radiological abnormalities by computed tomography (CT) scanning.

Renal tubular markers such as *N*-acetyl-beta-D-glucosaminidase (NAG) and alpha1-microglobulin may be elevated in cases with AIP. Nishi et al. [45] conducted a retrospective cohort analysis of 47 patients with AIP. Before treatment for AIP, renal dysfunction comparable to an estimated glomerular filtration rate of 30 and 15 ml/min/1.73 m^2 were recognized in 5 (10.6%) and 1 (2.1%) cases, respectively. Nevertheless, NAG and alpha1-microglobulin levels increased in 11 (78.6%) of 14 and 4 (30.8%) of 13 examined cases, respectively. NAG and alpha1-microglobulin may become sentinel markers suggesting tubular damage in IgG4-related kidney disease.

The elevation of serum IgG4 is essential for the diagnosis of IgG4-related systemic disease. According to the criteria of IgG4+ MOLP by Masaki et al. [4], the critical level of serum IgG4 is >135 mg/dl. Total IgG also increases in most cases but IgA and IgM usually stay

within normal ranges. This point is important for the differential diagnosis between IgG4-related kidney disease and TIN associated with collagen diseases or systemic vasculitis with polyclonal gammopathy. Other serological disorders such as hypocomplementemia, positive antinuclear antibody and rheumatoid factor are often detected. In Table 2 over half of the cases with IgG4-related kidney disease showed hypocomplementemia and positive antinuclear antibody. The elevation of IgE and eosinophilia are also abnormal findings seen in some cases [42]. In spite of the disorders suggesting auto-immune or allergic diseases, apparent collagen and allergic diseases, such as systemic lupus erythematosus, rheumatoid arthritis and bronchial asthma, are not usually complicated with IgG4-related kidney disease.

Radiological examination

IgG4-related kidney disease was often noticed from radiological abnormalities in CT scanning [42, 46, 47]. TIN lesions develop in restricted areas of renal cortex and therefore produce unilateral or bilateral tumor-like shadows or localized lesions on CT scanning. These lesions always show no enhancement effect by contrast medium exhibiting clear margins between TIN lesions and normal areas. A diffuse low-density lesion is another type of abnormal shadow on CT scanning; densities of cortex are usually irregular due to the degree of infiltrative cells. Additionally renal pelvis is a susceptible lesion in IgG4-related kidney disease. Thickening of smooth pelvis wall is a specific abnormal shadow and a differential diagnosis is required from carcinomatous changes of pelvis [30, 46, 47].

Triantopoulou et al. [46] documented renal lesions on CT scanning in 18 cases with AIP. Seven patients had renal involvement (38.8%). None of the lesions was visible on non-contrast-enhanced CT scanning. Parenchymal lesions appeared as multiple nodules with decreased enhancement in 4 (57.1%) of 7 cases. One of them represented a large mass-like lesion and two cases had diffuse thickening of the renal pelvis wall at the same time. Takahashi et al. [47] also reported radiological changes of 40 cases with AIP by CT scanning and magnetic resonance imaging (MRI); fourteen (35.0%) cases had renal involvement, 12 with intra-parenchymal involvement and five with peripheral cortex involvement. The low-density areas were divided into multiple nodules, wedge-shaped lesion and irregular diffuse patchy lesions; multiple nodular lesions were a dominant pattern in all of them. Thickening of renal pelvic wall was detected in 3 (21.4%) of 14 cases. MRI was also effective in diagnosing suspecting inflammatory reaction due to TIN. Seven (87.5%) of 8 IgG4-related kidney disease cases showed parenchymal low areas on MRI, particular in the corticomedullary phase.

The availability of fluorodeoxyglucose positron emission tomography (FDG-PET) was useful in the diagnosis of IgG4-related systemic diseases. FDG may accumulate into the pseudo-inflammatory lesions of IgG4-related systemic disease. Lee et al. [48] reported FDG uptake was seen in kidney and salivary glands as well as pancreas suffering AIP.

Pathological findings

Saeki et al. [42] performed a clinicopathological study in 23 Japanese cases with IgG4-related kidney disease. They summarized the pathological findings of interstitium into 4 specific lesions by light microscopy: (1) the infiltrate was predominantly composed of lymphocytes and plasma cells, and also eosinophils in some cases (Fig. 1a), (2) the distribution of lymphoplasmacytic infiltration was not only diffuse but also patchy and usually with clear margin (Fig. 1b), (3) tubular atrophy or diminishment developed according to the severity of cell infiltration and fibrosis in the fibrotic interstitium, collagen fibers exhibited a swirling pattern or an arabesque outline in periodic acid-methenamine silver (PAM) stain, and inflammatory cells infiltrated into the collagen fibers, producing a unique pattern (Fig. 1c). Among them the most characteristic feature was collagen fibers showing an arabesque outline or a striform pattern in PAM stain. In AIP, a similar characteristic feature was called a striform pattern [49]. Zen et al. [27] reported 7 types of common pathological features in IgG4-related systemic diseases: (1) plasma cell infiltration (>50 per high-power field, hpf; 10× eyepiece and 40× lens), (2) neutrophilic infiltration (>10 per hpf), (3) eosinophilic infiltration (>5 per hpf), (4) lymph follicles with a germinal center (>10 per low-power field, lpf; 10× eyepiece and 40× lens), (5) obliterative phlebitis, (6) obliterative arteritis, and (7) the presence of granuloma. It is doubtful if all seven features are recognized in IgG4-related kidney disease. Lymph follicles, obliterative phlebitis, obliterative arteritis, and the presence of granuloma have seldom been previously reported in IgG4-related kidney disease.

Pathological stages are considered to progress from the early stage showing cell infiltration to the late stage characterized by unique fibrosis. Through this progression, massive cell infiltration with IgG4-positive plasma cells may destroy tubular structure and produce advanced fibrosis surrounding a single or a few cells in interstitium. This characteristic fibrotic lesion called an arabesque or striform is sometimes referred to as 'bird's eye'. The pathological aspect with pronounced and specific fibrosis is considered to be helpful for the differential diagnosis between TIN associated with IgG4-systemic disease and TIN of other origins.

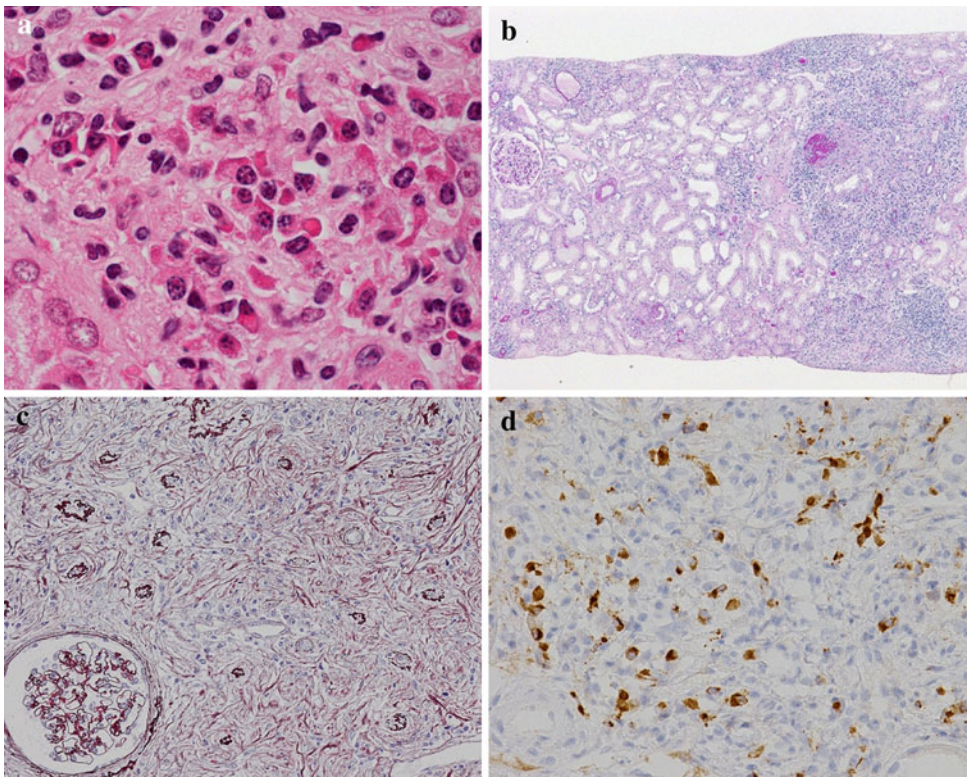

Fig. 1 **a** Predominant infiltration of lymphocytes, plasma cells and eosinophils into interstitium. H&E stain, ×400 lens. **b** Patchy lymphoplasmacytic infiltration with clear margin. Periodic acid-methenamine silver (*PAM*) stain, ×200 lens. **c** Collagen fibers exhibiting a swirling pattern or an arabesque outline in PAM stain, ×200 lens. **d** Immunohistochemistry with anti-IgG4 antibody. Numerous positive plasma cells in interstitium, ×200 lens

Glomerular changes were reported in 10 (27.0%) of 37 cases (Table 2). Among them mild mesPGN (4 cases, 10.6%) and MN (4 cases, 10.6%) were dominant, and MPGN and ECPGN were also noted in each case, respectively. Watson [35] and Saeki [42] confirmed that IgG4 was also positive on capillary wall with MN in IgG4-related kidney disease by immunofluorescency. The reason for the complication between MN and positive glomerular IgG4 deposition is unknown but this is a curious point when we consider the pathogenesis of IgG4-related kidney disease.

In immunofluorescency of routine examination, significant depositions of immunoglobulins and complements were not observed apart from our 2 review cases with MN. Immunostaining in paraffin sections with anti-IgG4 antibody easily proved the infiltration of numerous IgG4-positive plasma cells into the interstitium (Fig. 1d). Since the infiltration of IgG4-positive plasma cells in other types of TIN has not yet been fully evaluated, the infiltrative finding of IgG4-positive plasma cells into interstitium is not sufficient evidence compared with histological diagnosis. The consideration of clinical and histological features suggesting IgG4-related systemic diseases is important for a precise diagnosis.

Information regarding electron microscopic findings is restricted in IgG4-related kidney disease at the present time. Some cases showed electron dense deposits (EDDs) on tubular basement membrane (TBM) and glomerular basement membrane (GBM) [7, 35, 38]. Ultrastructural abnormalities concerning interstitium and glomeruli were scarcely evaluated in previous cases. A further evaluation is necessary for the resolution of this disease etiology.

Differential diagnosis

Fundamentally the diseases which induce TIN become the targets to differentiate from IgG4-related kidney disease. Auto-immune, inflammatory and malignant diseases also reveal higher levels of IgG4 in serum samples. The elevation of IgG4 is not an absolute reliable marker in the diagnosis of IgG4-related kidney disease. Most cases of IgG4-related kidney disease indicate no elevation of IgM and IgA [42]. However, IgM and IgA levels usually rise in TIN associated with auto-immune and inflammatory diseases. This is an important differential point. All diseases described in Table 3 potentially exhibit TIN as a renal lesion, thus they must be carefully excluded from IgG4-related kidney disease in the differential diagnosis.

Pathogenic mechanism

The hypotheses including auto-immune disorder and allergic reaction have been argued as etiologies in IgG4-related kidney disease and systemic diseases [50], while true pathogenic mechanisms have not yet been clarified. The elevated titers of antinuclear antibody, rheumatoid

Table 3 Diseases that exhibit TIN as renal lesions

Sarcoidosis
Uveitis–tubulointerstitial nephritis
ANCA-associated nephropathy
Systemic vasculitis
Drug-induced TIN
Malignant lymphoma
Plasmacytoma
TIN-associated collagen diseases
Castleman's disease
Post-transplant plasma cell dyscrasia

factor hypocomplementemia, support auto-immune disorders behind this disease [42]. Omokawa et al. [51] reported a case whose renal biopsy showed lupus nephritis (Class II) with severe TIN. Immunophenotyping of infiltrating cells disclosed a predominance of T cells in interstitium. Among them CD8-positive cytotoxic T cells mainly infiltrated into peritubular interstitial lesions and some of them infiltrated the tubules. B cell-rich lymphoid follicles were also observed. IgG subclass analyses showed significant glomerular deposition of IgG1, IgG2 and IgG4. Additionally positive staining of IgG4 was observed in the peritubular interstitium and along the TBM with abundant IgG1-, IgG3- and IgG4-positive plasma cells in the interstitium. IgG4 might play a role in the development of interstitial injuries of lupus nephritis. However, there is a marked difference in that IgG4-related kidney disease has no significant immunoglobulin deposition including IgG4 in glomerular lesions. The meaning of IgG4 deposition may be distinguished in lupus nephritis and IgG4-related kidney disease.

Yamamoto et al. [52] attempted to survey auto-antigens from immune complexes by surface-enhanced laser desorption/ionization−time of flight−mass spectrometry (SELDI–TOF–MS) in patients with Mikulicz's disease or AIP. They detected a 13.1-kDa common protein from all samples of the patients but not from control healthy volunteers and patients with Sjögren's syndrome. They suspected that 13.1-kDa protein was a candidate of the auto-antigens of IgG4-related systemic diseases.

The subclass molecules of IgG have distinct characteristics in immunological reaction. It is known that IgG4 molecule had no ability to activate complement cascade [53]. Using an experimental model with phospholipase-A antigen, Van der Zee et al. [54, 55] demonstrated that IgG4-containing immune complexes did not activate complement effectively and IgG4 antibodies inhibited immune precipitation and complement activation induced by IgG1 antibodies. They thought IgG4 antibodies played a role in protecting against the biological effects of the complement activation in IgG subclasses. These data are negative for an auto-immune hypothesis.

An allergic theory is another expected etiology. Eosinophilia is often detected in a patient with IgG4-related kidney disease. Aalberse et al. [56] proved that long-time exposure to antigens produced an elevation of IgG4 antibody in humans. For instant, bee keepers showed a shift in the IgG1/IgG4 ratio in response against phospholipase-A, a major chemical substance of bee venom. An IgG4-dominated response was recognized after approximately 2 years of bee-keeping experience. Nakashima et al. [57] evaluated cytokine production patterns among different types of TINs including IgG4-related kidney disease. Their data concluded no expression of interleukin (IL)-2, interferon (IFN)-gamma, IL-17 and IL-6, whereas the production of IL-4, IL-10 and tumor growth factor (TGF)-beta were remarkably elevated in IgG4-related kidney disease. Based on these cytokine analyses, they insisted Th2 and T regulatory cells played a central role in IgG4-related kidney disease; however, unfortunately no common allergic antigens have been found in cases with IgG4-related kidney disease.

Treatments and prognosis

IgG4-related kidney disease generally shows a favorable response to steroid treatment as well as IgG4-related systemic diseases including AIP. Even in cases with deteriorated renal function, functional recovery is expected by active steroid treatment. Initial oral doses of prednisolone varied from 20 to 60 mg/day in previous case reports [44]. In a review concerning IgG4-related systemic diseases, standard initial doses of prednisolone were recommended from 30 to 40 mg/day [58]. In our 37 review cases, only one case required maintenance hemodialysis after steroid treatment. Unresolved problems are the duration of continuous steroid treatment and maintenance steroid doses. It is known that discontinuation of steroid administration induces relapse of AIP in some cases [58]. A case report described a patient who progressed to end-stage renal disease after discontinuation of steroid treatment for AIP [44]. Systemic and long-term follow-up is absolutely essential in the treatment of IgG4-related kidney disease.

Conclusion

IgG4-related systemic diseases are focused in multi-medical fields and case reports and clinical researches are increasing now. The disease entity appears to be almost established and is gradually recognized not only in Japan but also worldwide. IgG4-related kidney disease may have unique clinical and histological features in IgG4-systemic

diseases. Further studies for the resolution of etiological mechanisms and the establishment of clinical criteria are necessary for IgG4-related kidney disease (Japanese Society of Nephrology IgG4-related kidney disease working group will publish clinical criteria in the near future).

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