studies [21, 22] demonstrated clinicopathological features of IgG4-related tubulointerstitial nephritis (TIN) that included high levels of serum IgG4, IgG, and IgE; hypocomplementemia; and TIN with copious IgG4-positive plasma cell infiltration with fibrosis. However, the clinical course and histological changes occurring after corticosteroid therapy have not yet been well characterized. In addition, although IgG4-RD is thought to be steroid responsive, not all cases achieve recovery of normal renal function [23], with, for example, one case report describing a patient who required maintenance hemodialysis despite corticosteroid therapy [24]. Therefore, in order to establish the optimal treatment plan to prevent progressive kidney damage, renal re-biopsy seems to be necessary. We undertook this study to evaluate the influence of corticosteroid therapy on the clinical and histopathological findings in IgG4-related TIN.

Materials and methods

Patients and materials

Between 1 September 2005 and 31 August 2010, we identified 11 IgG4-RD patients with kidney involvement, including renal parenchymal and pelvic lesions. We diagnosed IgG4-RD according to the provisional diagnostic criteria for IgG4-RD of Masaki et al. [25]. Renal biopsies were performed in six patients in whom IgG4-related TIN was highly suspected because of renal dysfunction, elevation of renal tubular markers, or abnormal imaging finding, and we diagnosed them with IgG4-related TIN based on diagnostic criteria proposed by Kawano et al. [26] and Raissian et al. [22]. Two patients (patients 1 and 5 in Table 1) had been included in our earlier studies [27, 28], two (patient 1 and 6) in a report by Saeki et al. [21], and one (patient 1) in a report by Yamaguchi et al. [29].

All six patients underwent re-biopsy while receiving corticosteroid therapy, as re-evaluation of the extent of cell infiltration and fibrosis was necessary to assess the future dosage regimen of corticosteroid. One patient (patient 1 in Table 1) underwent re-biopsy 14 months after the start of therapy, one (patient 2) 7 months later, three (patients 3, 4, and 5) 4 months later, and one (patient 6) only 1 month later. These biopsy specimens were obtained randomly, not specifically from the mass lesions. We examined these 12 specimens histologically and immunohistochemically. With regard to the extent of the renal interstitial lesion, diffuse TIN was defined as being present when $\geq$80% of the renal interstitium in renal biopsy specimens was affected and focal TIN when <80% was affected. We also retrospectively evaluated the clinical and radiographic findings of these six patients. Serial laboratory data during the clinical course were analyzed, and the computed tomography (CT) findings of renal lesions were investigated before and after corticosteroid therapy in all patients. This study received institutional ethics board approval, and informed consent for all data and samples was obtained from each patient. The research was in compliance with the Declaration of Helsinki.

Single immunostaining

Bouin's fluid- or formalin-fixed and paraffin-embedded renal specimens of six patients with IgG4-related TIN were used for the immunostaining of IgG4, CD138, CD4, CD8, and Foxp3. The immunostaining was performed using a monoclonal antibody against human IgG4 (Zymed Laboratory, San Francisco, CA, USA), CD138 (AbD Serotec, Oxford, UK), CD4 (Nichirei, Tokyo, Japan), CD8 (Nichirei), and Foxp3 (AbD Serotec). The deparaffinized sections were microwaved in citrate buffer (pH 6.0) for 15 min. Cells positive for IgG4, CD138, CD4, CD8, or Foxp3 were counted in five different high-power fields (HPF: 10× eyepiece and 40× lens) with intense cell infiltration.

Dual fluorescent immunostaining of CD4 and CD25

All Bouin's fluid-fixed and paraffin-embedded renal specimens were used for dual fluorescent immunostaining of CD4 and CD25. The deparaffinized sections were microwaved in citrate buffer (pH 6.0) for 20 min and incubated with normal donkey serum for protein blocking for 30 min. The specimens were incubated with a mouse monoclonal antibody to CD25 (Leica Microsystems, Wetzlar, Germany) and a rabbit monoclonal antibody to CD4 (Spring Bioscience, CA, USA) overnight at 4°C. Then, the specimens were incubated for 1 h at room temperature with Alexa Fluor 488-labeled donkey anti-mouse IgG antibodies and Alexa Fluor 594-labeled donkey anti-rabbit IgG antibodies (Molecular Probes, Carlsbad, CA, USA) and observed under a laser microscope and digitally merged. No positive staining was observed when the primary antibodies were replaced with normal donkey serum in the negative control of the staining procedures.

Statistical analysis

Statistical analysis was performed using the Wilcoxon signed rank test for continuous non-normally distributed data. Significant differences were defined as $P < 0.05$.

Results

Patient profiles

We analyzed six patients [four men and two women; average age 71.0 (range 59–79) years] with IgG4-related

Table 1 Clinicopathological characteristics of six patients with immunoglobulin (Ig)G4-related tubulointerstitial nephritis

No.	Age/sex	Cr at pre-Tx (*N* 0.6–1)	IgG (*N* 870–1,600)	IgG4 (*N* < 105)	IgE (*N* < 250)	CH50 (*N* 32–47)	C3 (*N* 65–135)	C4 (*N* 13–35)	ANA	RF	U-β2MG (*N* < 250)
1	59/M	1.15	2,850	1,470	456	34	81	16	(−)	(−)	335
2	79/M	0.54	4,756	409	457	8	41	3	(+)	(−)	496
3	77/W	0.59	2,256	984	292	60	110	27	(+)	(−)	78
4	68/M	1.90	3,830	736	242	3	33	1	(+)	(+)	7,375
5	75/W	2.55	3,695	486	1,226	2	18	2	(+)	(−)	35,490
6	68/M	7.26	4,661	1,120	335	5	10	7	(+)	(+)	3,240

No.	Age/sex	U-NAG (*N* < 10)	Eosinophilia	Allergy	U-Pr	CT findings	Initial renal biopsy findings	Initial Tx of post-biopsy	Cr at re-biopsy (*N* 0.6–1)	Period between initial biopsy and re-biopsy (months)
1	59/M	1.6	(+)	(−)	(−)	LDLs	fTIN	PSL 30	1.06	14
2	79/M	19	(−)	(−)	(−)	(−)	fTIN + EndPGN	PSL 20	0.51	7
3	77/W	0.4	(−)	Rhinitis	(−)	LDLs + P	fTIN	PSL 20	0.63	4
4	68/M	8.8	(−)	BA	(−)	LDLs	fTIN + IgAGN	PSL 30	1.20	4
5	75/W	5.9	(−)	(−)	(+)	S	dTIN + HSPN	PSL 30	1.05	4
6	68/M	16.9	(−)	(−)	(+)	S	dTIN + EndPGN	PSL 30	1.45	1

Conversion factor for Cr: mg/dl to μmol/l, ×88.4

ANA antinuclear antibody, *BA* bronchial asthma, *CH50* serum CH50 at initial renal biopsy (U/ml), *Cr* serum creatinine (mg/dl), *CT* computed tomography, *C3* serum C3 at initial renal biopsy (mg/dl), *C4* serum C4 at initial renal biopsy (mg/dl), *dTIN* diffuse tubulointerstitial nephritis, *EndPGN* endocapillary proliferative glomerulonephritis *fTIN* focal tubulointerstitial nephritis, *HSPN* Henoch–Schönlein purpura nephritis, *IgAGN* IgA nephropathy, *IgG* serum immunoglobulin G at initial renal biopsy (mg/dl), *IgG4* serum immunoglobulin G4 at initial renal biopsy (mg/dl), *IgE* serum immunoglobulin E at initial renal biopsy (IU/ml), *LDLs* multiple low-density lesions of the renal parenchyma, *P* diffuse thickening of the renal pelvic wall, *post-biopsy* post-renal biopsy, *PSL* prednisolone mg/day, *re-biopsy* renal re-biopsy, *RF* rheumatoid factor, *S* diffuse bilateral renal swelling, *Tx* treatment, *U-β2MG* urine β2-microglobulin at initial renal biopsy (μg/l), *U-NAG* urine *N*-acetyl-β-D-glucosaminidase at initial renal biopsy (U/l), *U-Pr* proteinuria

TIN. None had been treated with corticosteroid or any other immunosuppressants before the diagnosis. All patients had other organ involvement associated with IgG4-RD: four (66.7%) dacryoadenitis and/or sialoadenitis, six (100%) multiple lymphadenopathy, and three (50.0%) lung lesions. Pancreatic lesion was detected in only one patient (16.7%). Prostate, liver, and joint lesion was detected in one patient each. All patients were treated with prednisolone at an initial dose of 20–30 mg/day after the initial renal biopsy (Table 1).

Laboratory findings and changes associated with corticosteroid therapy

At presentation, all patients showed elevated levels of serum IgG4 (average 867.5 mg/dl, range 409–1,470 mg/dl, normal range <105 mg/dl) and IgG (average 3,675 mg/dl, range 2,256–4,756 mg/dl, normal range 870–1,700 mg/dl). Five patients (83.3%) showed elevated serum IgE levels (average 501.3 IU/ml, range 242–1,226 IU/ml, normal range <250 IU/ml), and only one patient had eosinophilia (eosinophils >5%). Four patients (66.7%) had hypocomplementemia. Antinuclear antibodies were positive in five patients (83.3%) and rheumatoid factor in two (33.3%). Serum creatinine concentration was elevated in four patients (66.7%). Urine β2-microglobulin (β2-MG) excretion was elevated in five patients (83.3%) and urine *N*-acetyl-β-D-glucosaminidase (NAG) level in two (33.3%), whereas two patients (33.3%) had proteinuria (Table 1). In three patients who showed severe renal dysfunction (serum creatinine >1.5 mg/dl) before corticosteroid therapy (patients 4, 5, and 6 in Table 1), serum creatinine rapidly declined within 1 month after the start of therapy. However, some degree of renal dysfunction persisted in two of them (Fig. 1a). Four patients had hypocomplementemia before corticosteroid therapy (patients 2, 4, 5, and 6 in Table 1), and corticosteroid therapy promptly improved serum complement levels within 2 months in three of them; recovery of serum complement level was very slow in one other (Fig. 1b). On the other hand, urine β2-MG and NAG concentrations fluctuated despite the corticosteroid therapy (data not shown).

Computed tomography findings and changes associated with corticosteroid therapy

Computed tomography revealed some radiologic findings of the renal parenchymal lesions in five patients. Among them, multiple low-density lesions on enhanced CT (Fig. 2a, c, e) were the most frequent findings and were observed in three patients (patients 1, 3, and 4 in Table 1), one of whom also had diffuse thickening of the renal pelvic wall (Fig. 2c). On the other hand, the renal parenchymal

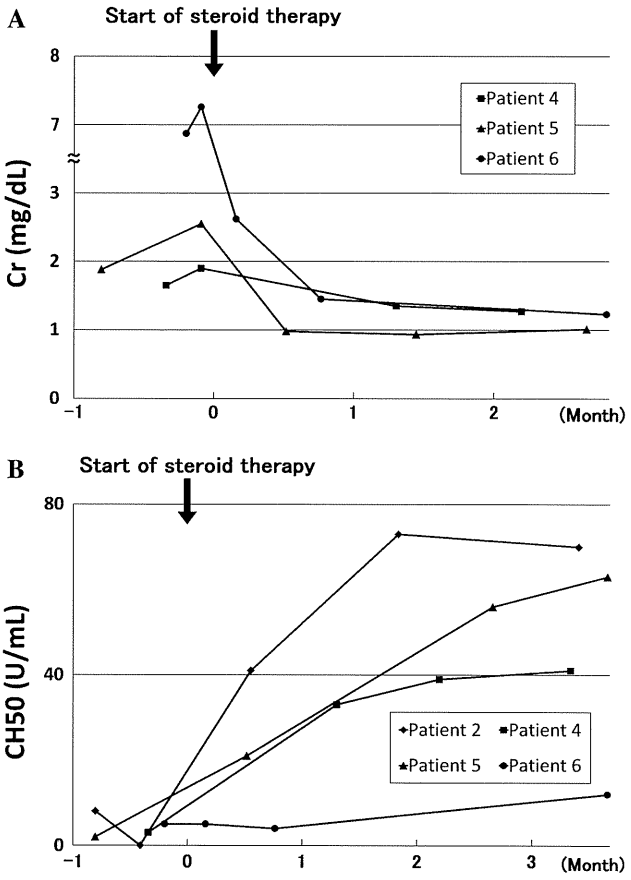

Fig. 1 Patient's clinical course. Serum creatinine concentrations rapidly declined within 1 month after corticosteroid therapy in patients 4, 5, and 6, who showed severe renal dysfunction before therapy (**a**). Hypocomplementemia was improved by corticosteroid therapy within 2 months in patients 2, 4, and 5, but response to therapy was insufficient in patient 6 (**b**)

lesion observed in two patients (patients 5 and 6 in Table 1) who underwent only plain CT because of severe renal dysfunction before corticosteroid therapy was diffuse bilateral renal swelling (Fig. 2g, i). No radiological abnormal findings were apparent in only one patient (patient 2 in Table 1).

On the whole, corticosteroid therapy quickly ameliorated renal lesions. Three patients with multiple low-density lesions on enhanced CT showed recovery of contrast enhancement of the renal cortex after therapy. However, scar-like focal cortical atrophy persisted in two of them (Fig. 2b, f). Two patients with diffuse bilateral renal swelling showed apparent improvement of the renal swelling after therapy (Fig. 2h, j). A few small scar-like focal cortical atrophy persisted in one of them (Fig. 2h), whereas relatively uniform contrast enhancement was observed in the other (Fig. 2j). Diffuse thickening of the renal pelvic wall became thinner after therapy in patient 3 (Fig. 2d).

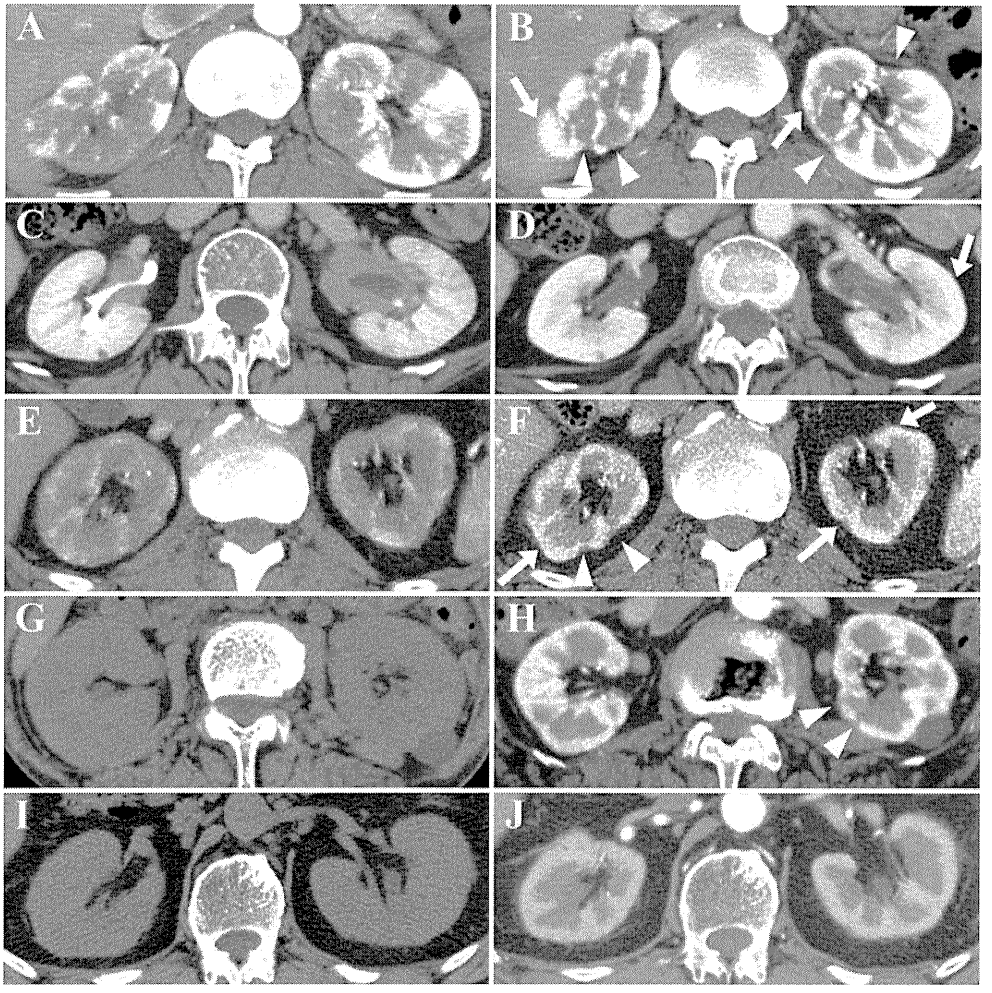

Fig. 2 Contrast-enhanced (**a**–**f**, **h**, **j**) or plain (**g**, **i**) computed tomography (CT) findings of immunoglobulin (Ig)G4-related renal lesions and changes induced by corticosteroid therapy. Multiple low-density lesions on enhanced CT (**a** patient 1, **c** patient 3, **e** patient 4), diffuse bilateral renal swelling on plain CT (**g** patient 5, **i** patient 6), and diffuse thickening of the renal pelvic wall (**c**) were observed before therapy. Contrast enhancement of the renal cortex recovered after therapy in all patients with multiple low-density lesions (**b**, **d**, **f** *arrows* show recovering lesions), though some atrophic areas of decreased enhancement remained (**b**, **f** *arrowheads* show atrophic lesions). Diffuse bilateral renal swelling was improved with small areas of decreased enhancement 4 months after therapy in patient 5 (**h** *arrowheads* show lesions with decreased enhancement) and with relatively uniform contrast enhancement 1 month after therapy in patient 6 (**j**). Diffuse thickening of the renal pelvic wall became less marked 4 months after therapy in patient 3 (**d**)

Histological and immunohistochemical findings and changes associated with corticosteroid therapy

Histological findings of six renal specimens before corticosteroid therapy were as follows: Dense lymphoplasmacytic infiltration and sparse distribution of atrophic renal tubules in the renal interstitium were present (Fig. 3a–c). The findings of renal tubulitis were mild (Fig. 3a, e, f). The interstitial lesions were often localized, and the border of the lesion was fairly clear (Fig. 3b). On the other hand, the interstitial lesion was diffuse in two patients (patients 5 and 6 in Table 1) with severe renal dysfunction whose plain CT images before therapy showed diffuse bilateral renal swelling (Fig. 3c). In one case (patient 6), inflammation extended beyond the renal capsule (Fig. 3d). Fibrosis with occasional infiltrating cells was observed (Fig. 3e, f). Lymph follicles were not evident in any patient. Glomerular lesions were observed in four: one showed Henoch–Schönlein purpura nephritis [28], another IgA nephropathy, and the other two focal endocapillary proliferation. Immunohistochemically, in addition to IgG4-positive plasma cells (Fig. 5a), Foxp3+ cells (Fig. 5b) and CD4+CD25+ T cells (Fig. 5c) were detected in the interstitial lesions of IgG4-related TIN. CD4+ T cells (Fig. 6a) and CD8+ T cells (Fig. 6b) were also found there.

The re-biopsy specimen obtained 1 month after corticosteroid therapy from patient 6 showed that areas with intense cell infiltration remained (Fig. 4a), but infiltration of IgG4-positive plasma cells (Fig. 5d), Foxp3+ cells (Fig. 5e), and CD4+CD25+ T cells (Fig. 5f) considerably decreased, and there was little obvious fibrosis of the renal

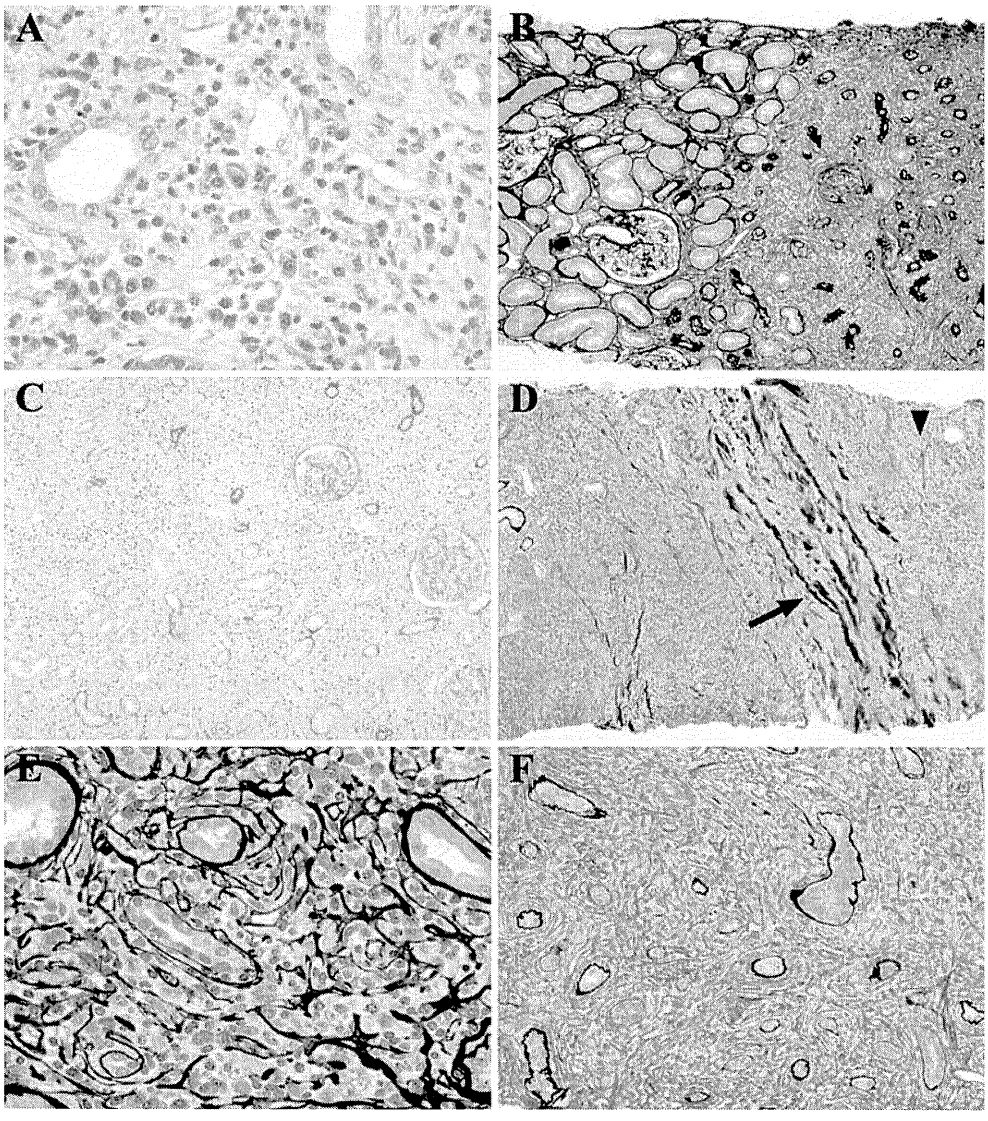

Fig. 3 Light microscopy findings of the renal interstitium before corticosteroid therapy. Severe lymphoplasmacytic infiltration with tubular atrophy was observed (**a** patient 6, **b** patient 4, **c** patient 6). Interstitial lesions were often focal, and the borderline between lesion and nonlesion was fairly clear (**b**). In two patients with severe renal dysfunction, interstitial lesion was diffuse (**c**). Inflammatory lesion beyond the renal capsule was detected (**d** patient 6, *arrow* shows the renal capsule, and *arrowhead* shows inflammation beyond the renal capsule). A characteristic fibrosis that appeared to surround infiltrating cells was observed (**e** patient 4, **f** patient 5) [**a** Hematoxylin and eosin (H&E) staining ×400; **b**, **d** periodic acid-methenamine-silver (PAM)-H&E staining ×100; **c** periodic acid-Schiff (PAS) staining ×100; **e**, **f** PAM-H&E staining ×400]

interstitium (Fig. 4a). The re-biopsy specimen 14 months after therapy from patient 1 demonstrated an obvious decrease of cell infiltration except for small localized infiltrations, whereas patchy marked fibrosis remained (Fig. 4b). In the re-biopsy specimens 4 months after therapy from patient 5 who showed severe renal dysfunction before therapy, we observed mixed lesions where cell infiltration was dense or fibrosis was predominant or neither of these features was noted (Fig. 4c, d, e, respectively). In the re-biopsy specimens 4 months after therapy from patient 3 who showed normal renal function before therapy, we observed the same three components as in patient 5, but fibrosis was not marked. In one patient with diffuse renal interstitial cell infiltration and sparse distribution of atrophic tubules (patient 6), tubular atrophy and sparseness of tubular distribution seemed to partially improve after therapy (Figs. 3c, 4f). In the immunostaining specimens, cell count of various infiltrating cells in the lesions with intense cell infiltration before and after corticosteroid therapy revealed that the characteristic infiltrating cells, such as IgG4-positive plasma cells and Foxp3+ cells, showed significant decreases after corticosteroid therapy (Figs. 5d, e, 7a–c). Other CD4+ T cells and CD8+ T cells were relatively persistent, even in the later stage of therapy

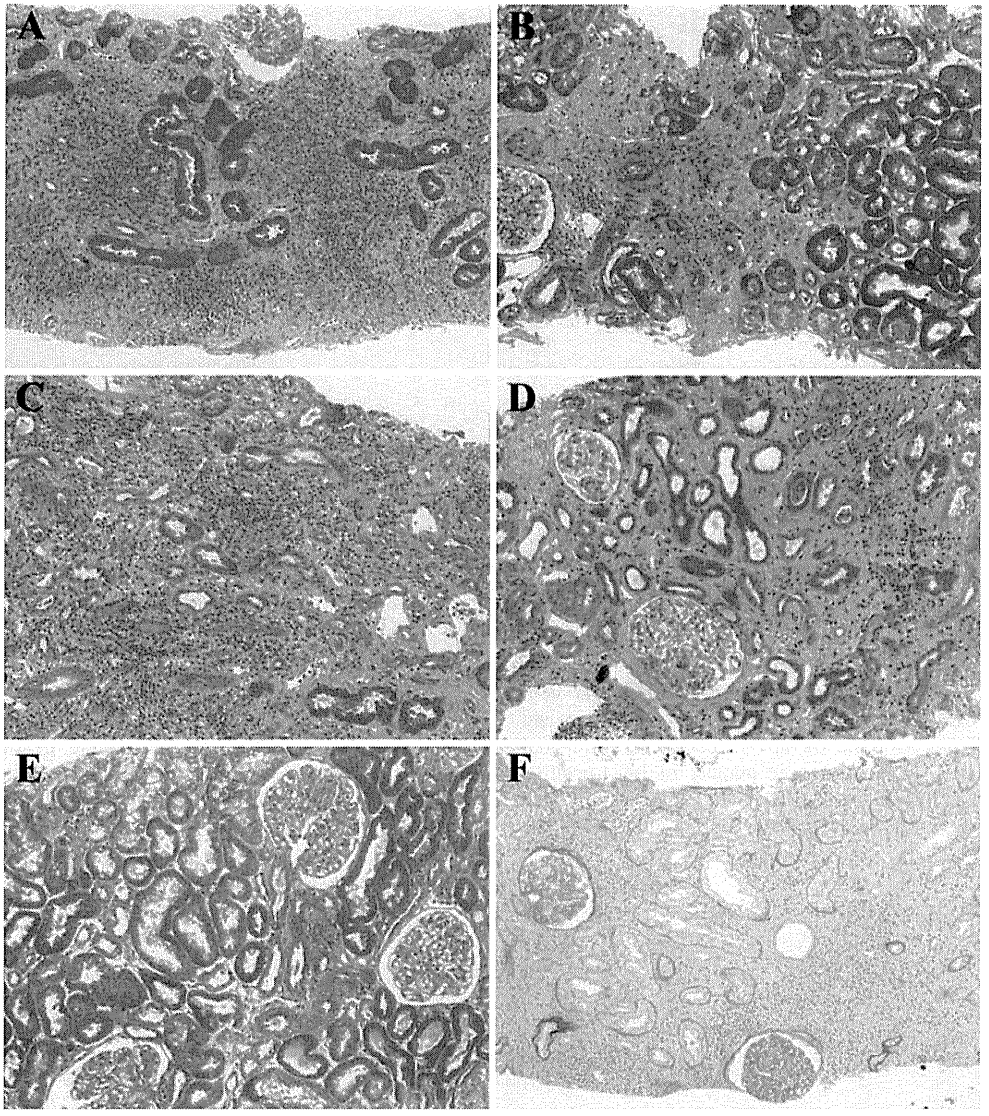

Fig. 4 Changes in light microscopy findings of the renal interstitium after corticosteroid therapy. Azan staining showed that interstitial fibrosis was not evident 1 month after corticosteroid therapy in patient 6 (**a**), whereas localized severe fibrosis was observed 14 months after therapy in patient 1 (**b**). There were mixed lesions where cell infiltration was dense (**c**) or fibrosis was predominant (**d**) or neither of them was noted (**e**) 4 months after therapy in patient 5. Interstitium in the posttreatment specimen of patient 6 seemed to show recovery of some renal tubules 1 month after corticosteroid therapy (**f**) [**a–e** Azan staining ×100, **f** periodic acid-Schiff (PAS) staining ×100]

(Figs. 6c, d, 7d, e). The average number of IgG4-positive plasma cells in five different HPF decreased from 156.4/HPF (range 102–210) to 2.0/HPF (range 0–3) in patient 1; 41.8/HPF (range 36–60) to 7.2/HPF (range 1–15) in patient 2; 50.2/HPF (range 25–77) to 12.2/HPF (range 5–36) in patient 3; 27.6/HPF (range 9–46) to 5.0/HPF (range 3–11) in patient 4; 62.2/HPF (range 45–80) to 4.8/HPF (range 3–7) in patient 5; and 73.2/HPF (range 50–108) to 20.8/HPF (range 19–22) in patient 6 (Fig. 7a). In the same way, the average number of Foxp3+ cells decreased from 35.4/HPF (range 26–52) to 8.4/HPF (range 1–16) in patient 1; 25.4/HPF (range 18–45) to 3.8/HPF (range 2–6) in patient 2; 18.0/HPF (range 10–23) to 1.2/HPF (range 0–3) in patient 3; 41.8/HPF (range 36–46) to 4.8/HPF (range 4–6) in patient 4; 33.2/HPF (range 30–35) to 3.0/HPF (range 0–5) in patient 5; and 23.0/HPF (range 19–30) to 3.2/HPF (range 1–5) in patient 6 (Fig. 7c).

Discussion

This study examined the clinicopathological features in patients with IgG4-related TIN before and after corticosteroid therapy. The characteristic laboratory findings before therapy were elevated serum IgE levels or eosinophilia, high incidence of hypocomplementemia, and hyper-β2

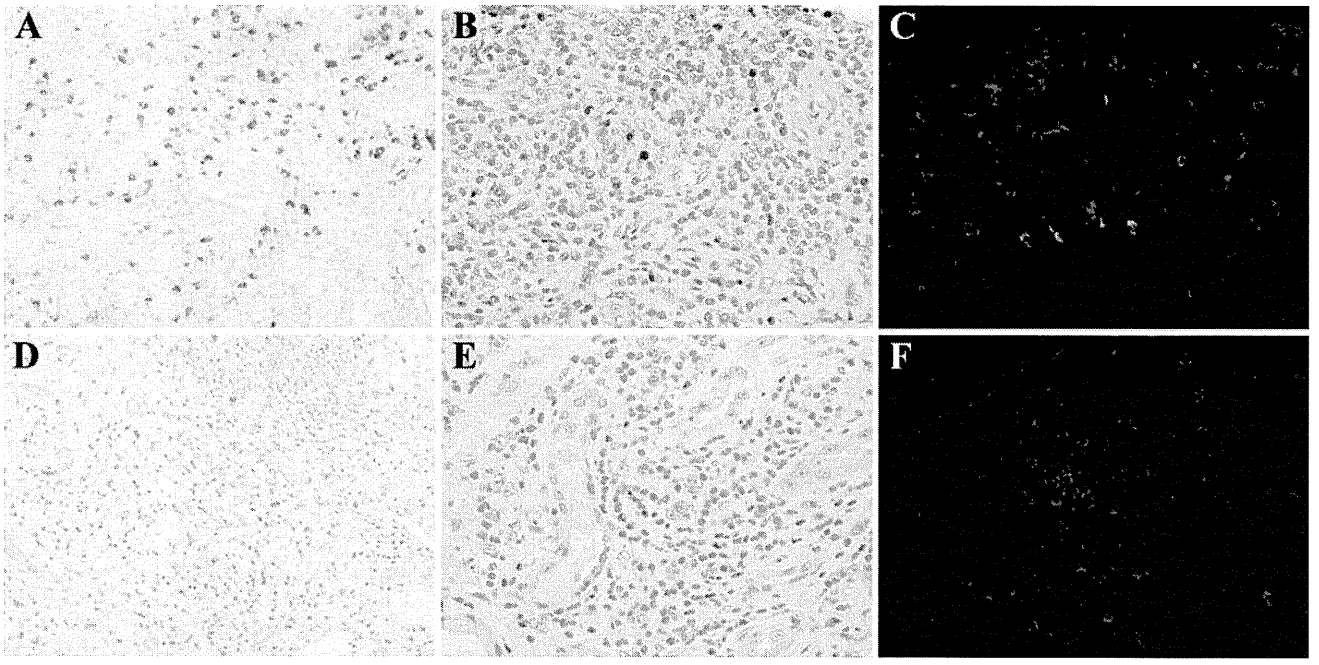

Fig. 5 Changes in immunoglobulin (Ig)G4-positive plasma cell, Foxp3+ cell, and CD4+CD25+ cell infiltration before (**a–c**) and 1 month after (**d–f**) corticosteroid therapy in patient 6. Compared with the pretreatment specimens (**a**), the number of IgG4-positive plasma cells in the lesions was markedly diminished in the posttreatment specimens (**d**). In the same way, compared with the pretreatment specimens (**b**), the number of Foxp3+ cells obviously decreased in the posttreatment specimens (**e**). Some CD4+CD25+ cells in the lesions were observed before treatment (**c**), whereas almost none were detected after therapy (**f**) [**a**, **d** IgG4 ×200, **b**, **e** Foxp3 ×400, **c**, **f** CD4 (*red*) and CD25 (*green*) ×400]

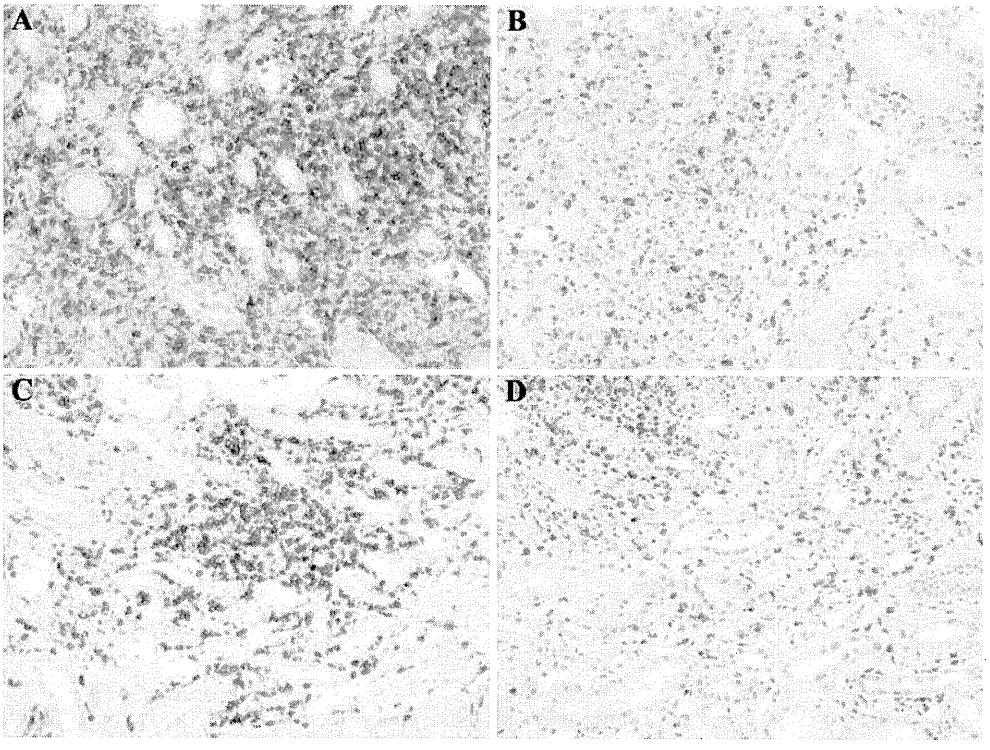

Fig. 6 Changes in CD4+ and CD8+ T cell infiltration before (**a**, **b**) and 4 months after (**c**, **d**) corticosteroid therapy in patient 5. The extent of CD4+ T cell (**a**, **c**) and CD8+ T cell (**b**, **d**) infiltration in the lesions remained largely constant, even after therapy (**a**, **c** CD4 ×100, **b**, **d** CD8 ×100)

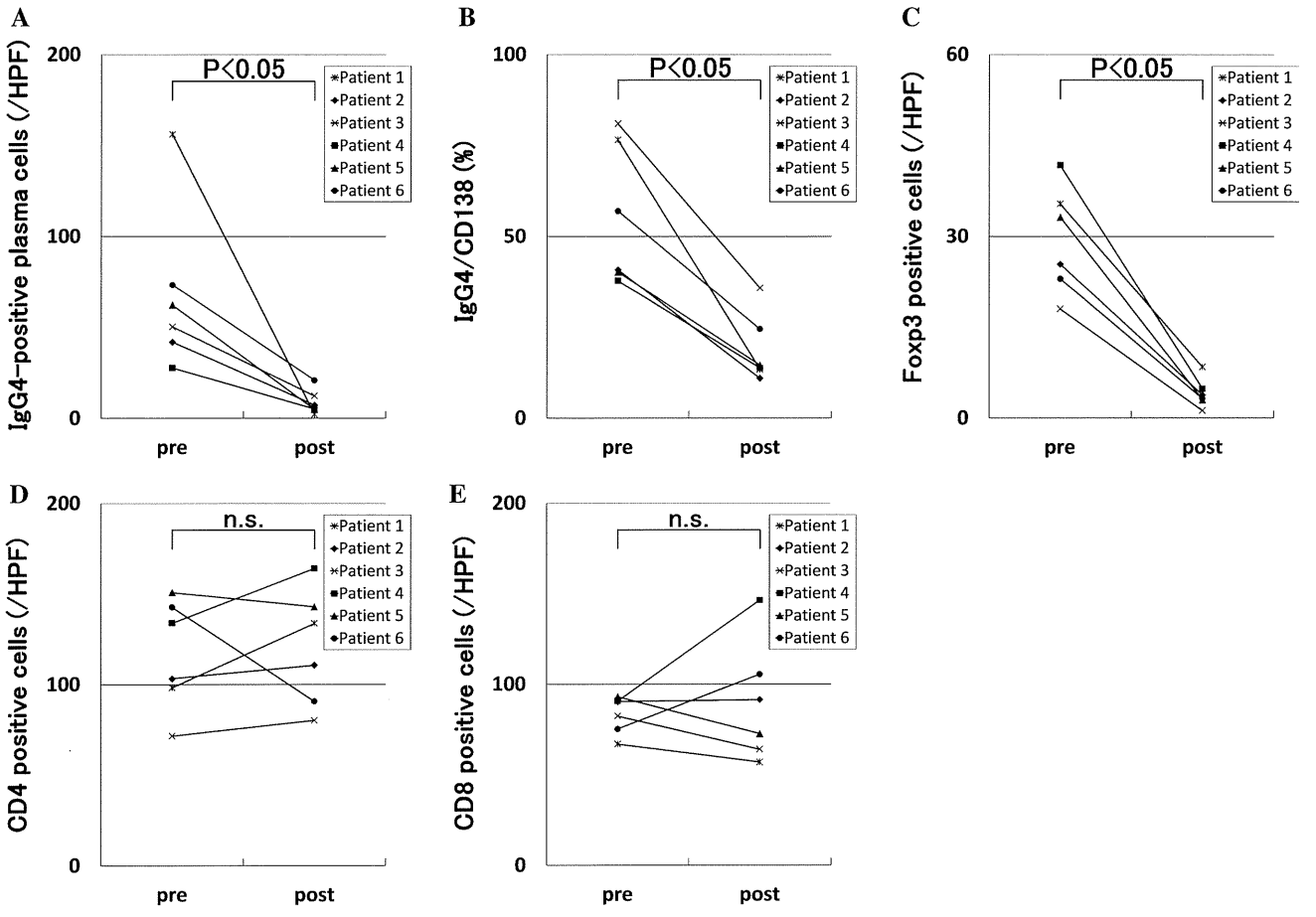

Fig. 7 Changes in numbers of infiltrating cells before and after corticosteroid therapy. In six IgG4-related TIN cases, the average of IgG4-positive plasma cell numbers and the ratio of IgG4-positive cells to CD138-positive cells in the lesions significantly decreased after compared with before corticosteroid therapy (**a**, **b**, respectively). Similarly, average of Foxp3+ cell numbers significantly decreased (**c**). However, average of CD4+ and CD8+ T cell numbers did not change (**d**, **e**, respectively)

microglobulinuria. Renal insufficiency was also frequent, and almost all patients with IgG4-related TIN had some radiographic abnormalities. Therapy with 20–30 mg/day of prednisolone rapidly improved renal function in three patients with severe renal dysfunction, whereas some renal insufficiency persisted in two. Radiographic abnormalities persisted in half of the patients. Histologically, infiltration of CD4+CD25+ T cells and Foxp3+ cells in addition to IgG4-positive plasma cells was characteristic in IgG4-related TIN. Notably, IgG4-positive plasma cells, Foxp3+ cells, and CD4+CD25+ cells had already decreased 1 month after corticosteroid therapy in one case (patient 6), whereas small to moderate numbers of CD4+ T cells and CD8+ T cells infiltrated where inflammation persisted in all patients. In the later stage after treatment, patchy or regional fibrosis remained to some extent.

In this study, radiographic findings of renal lesions were almost the same as those noted in past reports [21, 30]. Multiple low-density lesions on enhanced CT, diffuse bilateral renal swelling, and thickening of the renal pelvic wall were the major features. Past reports mentioned that corticosteroid therapy was effective in improving the appearance of renal lesions on imaging study, although cortical scar or renal capsular dimpling persisted in a small number of cases [30–33]. In our study, although some renal parenchymal lesions showed recovery of contract enhancement, others progressed to scar-like atrophy in three of six cases. In contrast to past studies [30–33], both imaging study and histological analysis were performed before and after corticosteroid therapy in all patients in this study. Our data might suggest that these atrophic lesions in imaging study correspond to the histological fibrotic lesions. In addition, recovery of contrast enhancement might relate to the partially normalized renal interstitium observed in the posttreatment specimens of patients 5 and 6, who showed diffuse TIN and renal tubular atrophy before therapy. In this way, IgG4-related TIN could leave macroscopic atrophy and microscopic fibrosis, which might explain why renal function did not totally recover after corticosteroid therapy in our patients with severe renal insufficiency. The possibility of these sequelae must be considered when determining the corticosteroid dose and optimal timing of the initiation of treatment.

The main histological findings before corticosteroid therapy were consistent with previously published histological features of IgG4-related TIN [21, 22, 34]. In addition, extension of inflammation beyond the renal capsule reported by Yamaguchi et al. [29] was also observed and seemed to correspond to the extension of lesions beyond the pancreatic capsule in autoimmune pancreatitis (AIP). Zen et al. [35] reported infiltration of CD4+CD25+ T cells and Foxp3+ cells in the lesions of IgG4-related pancreatitis and cholangitis and that those lesions had significantly increased levels of Th2 and regulatory T-cell cytokines. Nakashima et al. [36] also reported increased Th2 and regulatory cytokines in the lesions of IgG4-related TIN. In this study, we similarly confirmed the presence of CD4+CD25+ T and Foxp3+ cells in the renal interstitium where lymphocytes and IgG4-positive plasma cells infiltrated. Accordingly, the presence of CD4+CD25+ T or Foxp3+ cell infiltration might be another distinctive finding of IgG4-related TIN. As Houghton and Troxell [37] reported that an abundant infiltration of IgG4-positive plasma cell is not so specific for IgG4-related TIN, it will be necessary to survey the presence or absence of these regulatory cells in TIN diseases other than IgG4-related TIN.

We focused on histological and immunohistochemical changes of IgG4-related TIN during the clinical course of corticosteroid therapy. The area with infiltrating cells in the renal interstitium decreased with the passage of time after therapy was initiated. Conversely, more obvious regional fibrosis was observed in the re-biopsy specimens, although there was the possibility of sampling bias due to randomly performed biopsies. Reflecting these histological findings, the radiological lesions to some degree showed recovery following therapy, whereas in some parts, there was progression to scar formation. These findings suggest the need to search for ways to prevent fibrosis in addition to control of inflammation. Whether early initiation of corticosteroid therapy can prevent fibrosis remains to be verified, as there was no untreated control group in this study and so this point could not be concluded definitively. However, comparing posttreatment findings of patients 3 and 5, both of whom underwent re-evaluation 4 months after the start of therapy, macroscopic atrophy and microscopic fibrosis were more marked in patient 5 with severe renal dysfunction before therapy than in patient 3 with normal renal function then. This difference implies that early initiation of corticosteroid therapy prevents fibrosis to some extent. The possibility should also be considered that corticosteroid therapy alone is insufficient to prevent residual fibrosis despite early initiation. Other treatment options should be examined, as rituximab therapy, for example, has been reported to be effective in achieving clinical improvement in IgG4-RD [38, 39]. The characteristic cells, including CD4+CD25+ T cells, Foxp3+ cells, and IgG4-positive plasma cells, seemed to disappear quickly after corticosteroid initiation and did not reappear as long as corticosteroid was administered, whereas other CD4+ T and CD8+ T cells persisted for a long time in lesions where cell infiltration was still observed. This finding suggests that we cannot precisely evaluate IgG4-positive plasma cell infiltration in diagnosing IgG4-related TIN if corticosteroid therapy has already been initiated. The pathogenic significance of this finding remains unclear. More accumulation of clinical and histological data of IgG4-related TIN, including recurrences during corticosteroid tapering or after cessation of corticosteroid therapy and basic research based on those data, are essential to elucidate the roles of these cells in the pathogenesis of IgG4-related TIN.

Biomarkers that could be used as a goal for treating IgG4-related TIN have not yet been established. It was reported that in AIP, serum IgG4, IgG, and circulating immune complex decreased after corticosteroid therapy and increased at relapse, whereas serum C3 and C4 levels showed reciprocal changes [40]. Tabata et al. [41] suggested that the measurement of serial serum IgG4 levels was useful to determine disease activity of IgG4-RD. Nevertheless, whether normalization of serum IgG4 levels could be a treatment goal is unclear, as it is not always observed despite apparent clinical remission [41]. Cutoff values of these markers as a goal should be further examined. Nishi et al. [42] reported that elevated urine NAG and/or α1-microglobulin concentrations were useful markers for detecting renal abnormalities in their AIP patients with or without clinically detected renal involvement. However, neither urine β2-MG nor NAG entirely responded to corticosteroid therapy and fluctuated despite the continuation of treatment in our study. Thus, reliable markers showing a goal for treatment remain to be identified. Further studies are required to seek such markers, including novel candidates.

The small number of cases is a limitation of our study that relates to the rarity of this disease, and the inconsistent follow-up times of radiological and histological data in each patient is another limitation. However, with increasing worldwide awareness of IgG4-related TIN as a distinct disease entity [21, 22], we can expect larger studies that include many more cases and anticipate that, with more patients enrolled in each stage of corticosteroid therapy, especially in the very early and later stages, the dynamics of various infiltrating cells during the clinical course will be better clarified.

In conclusion, our investigations suggest that, clinically, persistent renal insufficiency associated with macroscopic atrophy and microscopic fibrosis is not so rare in IgG4-related TIN. Pathologically, the behavior of regulatory T cells during the clinical course of corticosteroid therapy is

quite similar to that of IgG4-positive plasma cells, and the distinctive behavior pattern of those cells may provide a clue to the mechanisms underlying this disease. Further studies are required to elucidate the total picture of this disease, including its clinical and pathogenic aspects.

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Conflict of interest None.

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Henoch-Schönlein purpura nephritis in a patient with IgG4-related disease: A possible association

Kiyoaki Ito[1], Kazunori Yamada[1], Ichiro Mizushima[1], Motohiko Aizu[1], Hiroshi Fujii[1], Kazuaki Mizutomi[2], Masami Matsumura[3], Kenshi Hayashi[4], Masakazu Yamagishi[4], Hisanori Umehara[5], Yutaka Yamaguchi[6], Michio Nagata[7] and Mitsuhiro Kawano[1]

[1]Division of Rheumatology, Department of Internal Medicine, Graduate School of Medical Science, Kanazawa University, Kanazawa, [2]Department of Internal Medicine, Kaga City Hospital, Kaga, [3]Research Center for Medical Education, [4]Division of Cardiology, Department of Internal Medicine, Graduate School of Medicine, Kanazawa University, Kanazawa, [5]Hematology and Immunology, Kanazawa Medical University, Ishikawa, [6]Yamaguchi's Pathology Laboratory, Matsudo, Chiba, and [7]Department of Kidney and Vascular Pathology, Graduate School of Comprehensive Human Sciences, University of Tsukuba, Tsukuba, Japan

Key words
Henoch-Schönlein purpura nephritis – tubulointerstitial nephritis – IgG4-related disease

Abstract. We report a case of Henoch-Schönlein purpura nephritis (HSPN) associated with tubulointerstitial nephritis (TIN) and chronic sclerosing sialoadenitis. The patient is a 75-year-old Japanese woman who had bilateral submandibular gland swelling, palpable purpura on the lower legs, and decreased renal function with hematoproteinuria and marked hypocomplementemia, but no skin lesion suggestive of systemic lupus erythematosus (SLE), and did not fulfill the classification criteria for SLE. Her serum IgG4 level was high and immunostaining of renal biopsies revealed marked infiltration by IgG4-positive plasma cells in the interstitium, confirming the diagnosis of IgG4-related disease. On the other hand, glomeruli showed endocapillary proliferative glomerulonephritis with mesangial IgA and C3 deposition demonstrated by immunofluorescence staining, which were typical glomerular lesions for HSPN. The glomerular and tubulointerstitial lesions responded to steroid therapy dramatically, and her renal function recovered to within the normal range within a month. This case suggests a possible new association between HSPN and IgG4-related disease.

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Correspondence to
Mitsuhiro Kawano, MD
Division of Rheumatology, Department of Internal Medicine, Graduate School of Medical Science, Kanazawa University, Takara-machi 13-1, Kanazawa, Ishikawa 920-8641, Japan
sk33166@gmail.com

Introduction

The kidney is a representative target organ of IgG4-related disease, and tubulointerstitial nephritis (TIN) with fibrosis with abundant IgG4-positive plasma cell infiltration is a diagnostically important histopathological feature of this disease [1]. IgG4-related disease is a systemic inflammatory disease mainly affecting the pancreas, retroperitoneum, lacrimal and salivary glands, and common clinical features are elderly-onset, male predominance, and allergic predisposition [2, 3]. Henoch-Schönlein purpura (HSP) or allergic purpura also shows a close relation to allergic reaction [4]. However, only a few reports are available about the coexistence of allergic purpura and IgG4-related disease [5, 6]. Here we present a patient with Henoch-Schönlein purpura nephritis (HSPN) associated with IgG4-related TIN, and discuss the possible relationship between these two diseases.

Case report

A 75-year-old Japanese woman was admitted to our hospital for close examination of decreased renal function. One year before admission, she had noticed bilateral submandibular gland swelling. She consulted an otolaryngologist and underwent a biopsy of the submandibular gland, but no malignant lesion was identified. Eight months before, she had noted small palpable purpura on her legs (Figure 1). A skin biopsy revealed leukocytoclastic vasculitis. One month earlier, her serum creatinine had been 1.52 mg/dl (vs. 0.56 mg/dl 5 months earlier), and urinalysis disclosed proteinuria and microscopic hematuria. Hypergammaglobulinemia (IgG

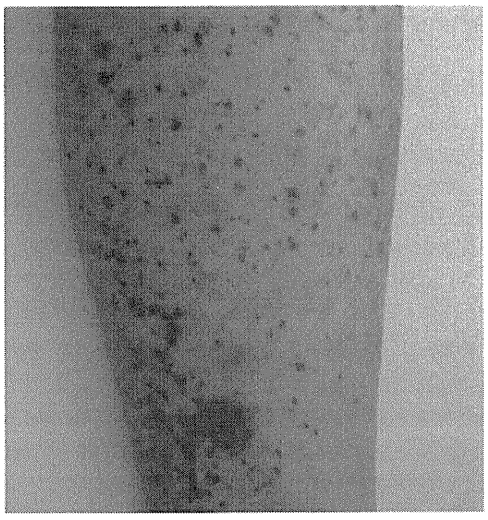

Figure 1. The lower leg shows a diffuse purpuric rash.

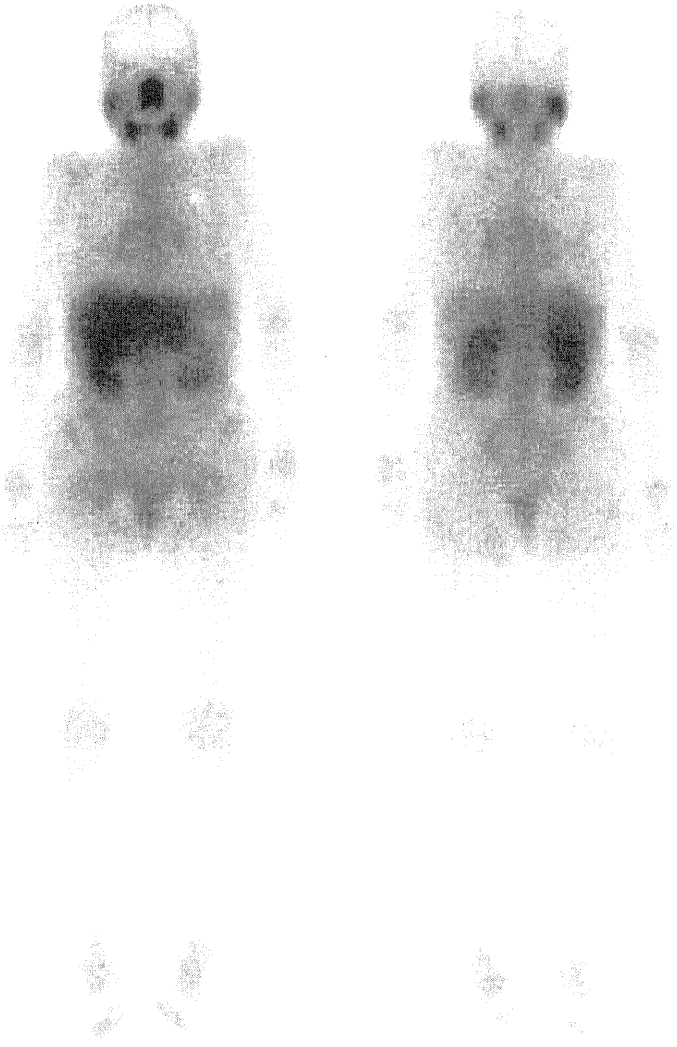

Figure 2. Gallium scintigraphy shows intense uptake in bilateral parotid and submandibular glands and bilateral kidneys.

3,695 mg/dl) and hypocomplementemia were detected at the same time. Her serum IgG4 level was high at 486 mg/dl (normal, 30 – 135 mg/dl). She was referred to our hospital for close examination and treatment. Her past medical history was complete atrioventricular block and she had undergone implantation of a permanent pacemaker. She had no familial history of tuberculosis.

On admission, physical examination showed bilateral neck and axillary lymph node swelling. Respiratory sounds were normal. No hepatosplenomegaly was noted. Palpable purpura on legs was noted. Urinalysis revealed 2+ proteinuria and 2+ occult blood. The amount of proteinuria per 24 hours was 3.0 g. Other laboratory findings included hemoglobin 8.7 g/dl (normal: 11.2 – 14.5 g/dl), hematocrit 27.5% (normal: 33.3 – 43.6%), white blood cells 5,680/μl (normal: 3,300 – 8,800/μl), platelets 170×10^3/μl (normal: 130 $\times$ 10^3 – 350 $\times$ 10^3/μl), blood urea nitrogen 31 mg/dl (normal: 8 – 22 mg/dl), serum creatinine 1.88 mg/dl (normal: 0.50 – 0.80 mg/dl), sodium 138 mEq/l (normal: 135 – 149 mEq/l), potassium 4.4 mEq/l (normal: 3.5 – 4.9 mEq/l), chloride 108 mEq/l (normal: 96 – 108 mEq/l), total protein 8.5 g/dl (normal: 6.7 – 8.3 g/dl), albumin 3.5 g/dl (normal: 4.0 – 5.0 g/dl), lactate dehydrogenase (LDH) 187 IU/l (normal: 119 – 229 IU/l), aspartate aminotransferase (AST) 23 IU/l (normal: 13 – 33 IU/l), alanine aminotransferase (ALT) 8 IU/l (normal: 6 – 27 IU/l), amylase 74 IU/l (normal: 40 – 113 IU/l), IgG 3,695 mg/dl (normal: 870 – 1,700 mg/dl), IgA 155 mg/dl (normal: 110 – 410 mg/dl), IgM 134 mg/dl (normal: 46 – 260 mg/dl), IgE 1,226 IU/ml (normal: less than 250 IU/ml), C3 18 mg/dl (normal: 44 – 102 mg/dl), C4 2.0 mg/dl (normal: 14 – 49 mg/dl), and total hemolytic complement (CH50) 2.0 U/ml (normal: 32 – 47 U/ml). Serum rheumatoid factor, antibody to the Ro and La, myeloperoxidase (MPO) anti-neutrophilcytoplasmic antibodies (ANCA), proteinase-3 (PR3) ANCA, anti-glomerular basement membrane (anti-GBM) antibody, and cryoglobulin were all negative. Only anti-double-stranded DNA antibodies were positive with a low titer (28 IU/ml, normal: less than 12 IU/ml). Antinuclear antibodies were positive in a titer of 1 : 1,280 with a homogeneous pattern (Table 1). Gallium scintigraphy showed intense

Table 1. Laboratory data.

Urinalysis		Blood chemistry			
Protein	(2+)	TP	8.5 g/dl	IgG	3,695 mg/dl
	3 g/d	Alb	3.5 g/dl	IgA	155 mg/dl
Occult blood	(2+)	AST	23 IU/l	IgM	134 mg/dl
Sediment		ALT	8 IU/l	IgG4	486 mg/dl
RBC	5 – 9 /HPF	LDH	187 IU/l	IgE	1,226 IU/ml
Granular cast	(2+)	ALP	193 IU/l	sIL-2R	4,020 U/ml
		γGTP	11 IU/l	ACE	23.9 IU/ml
Blood Count		Amy	74 IU/l	ANA	× 1,280 (H)
RBC	308 × 10⁴/mm³	CK	39 IU/l	RF	< 10 IU/ml
Hb	8.7 g/dl	BUN	31 mg/dl	Anti-dsDNA	28 IU/ml
Ht	27.5%	Cr	1.88 mg/dl	Anti-SSA	< 10 EU
WBC	5,680/mm³	Na	138 mEq/l	Anti-SSB	< 15 EU
Neu	59.0%	K	4.4 mEq/l	Anti-Sm	< 7 EU
Eo	5.0%	Cl	108 mEq/l	Anti-RNP	< 15 EU
Lymph	27.0%	FPG	120 mg/dl	MPO-ANCA	< 20 EU
Plts.	17.0 × 10⁴/mm³	C3	18 mg/dl	C-ANCA	< 10 EU
Inflammation		C4	2.0 mg/dl	Anti-GBM	< 10 EU
ESR	112 mm/h	CH50	2.0 U/ml	cryoglobulin	(–)
CRP	1.2 mg/dl				

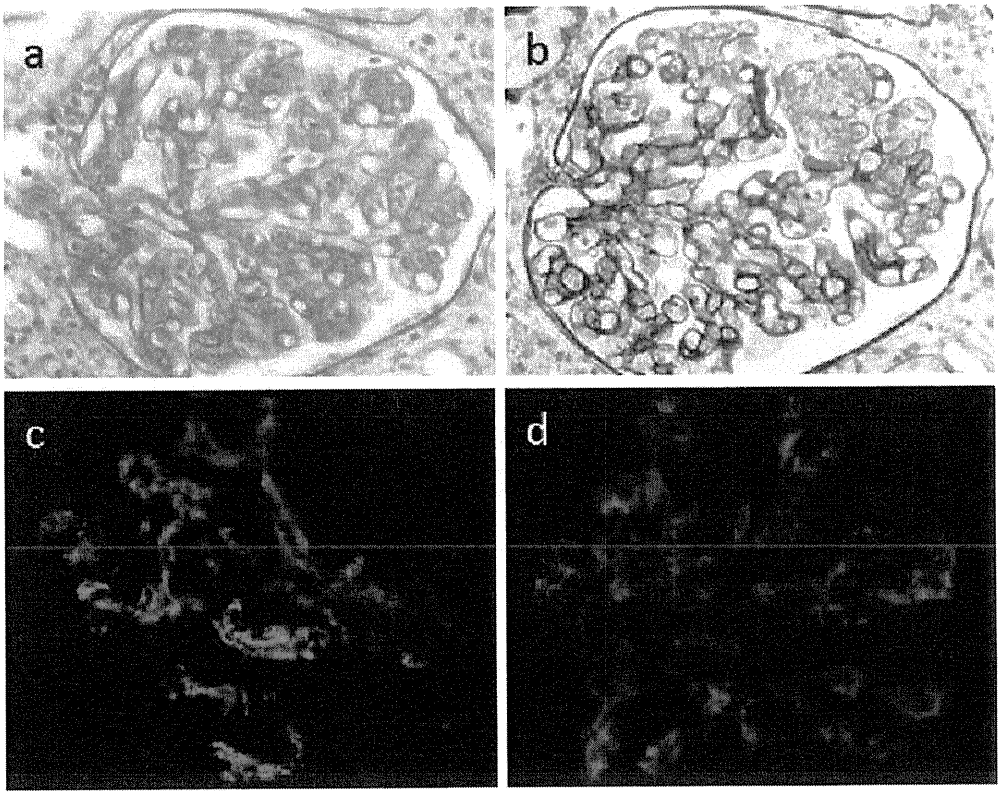

Figure 3. Light microscopy and immunofluorescent findings of the renal glomeruli. Endocapillary proliferative glomerulonephritis was observed (a, b). Immunofluorescence study revealed mesangial C3 and IgA deposition (c, d). (a: Periodic acid Schiff (PAS) staining × 400, b: Periodic acid-methenamine-silver (PAM)-Hematoxylin and Eosin (HE) staining × 400, c: C3 × 400, d: IgA × 400).

trace uptake in bilateral parotid and submandibular glands and bilateral kidneys (Figure 2). Computed tomography (CT) revealed multiple micronodular opacities in the lungs with bilateral hilar lymphoadenopathy and swelling of the bilateral kidneys. Bilateral submandibular gland swelling was also noted. However, pancreatic swelling, a typical radiographic finding of autoimmune pancreatitis (AIP), was not observed.

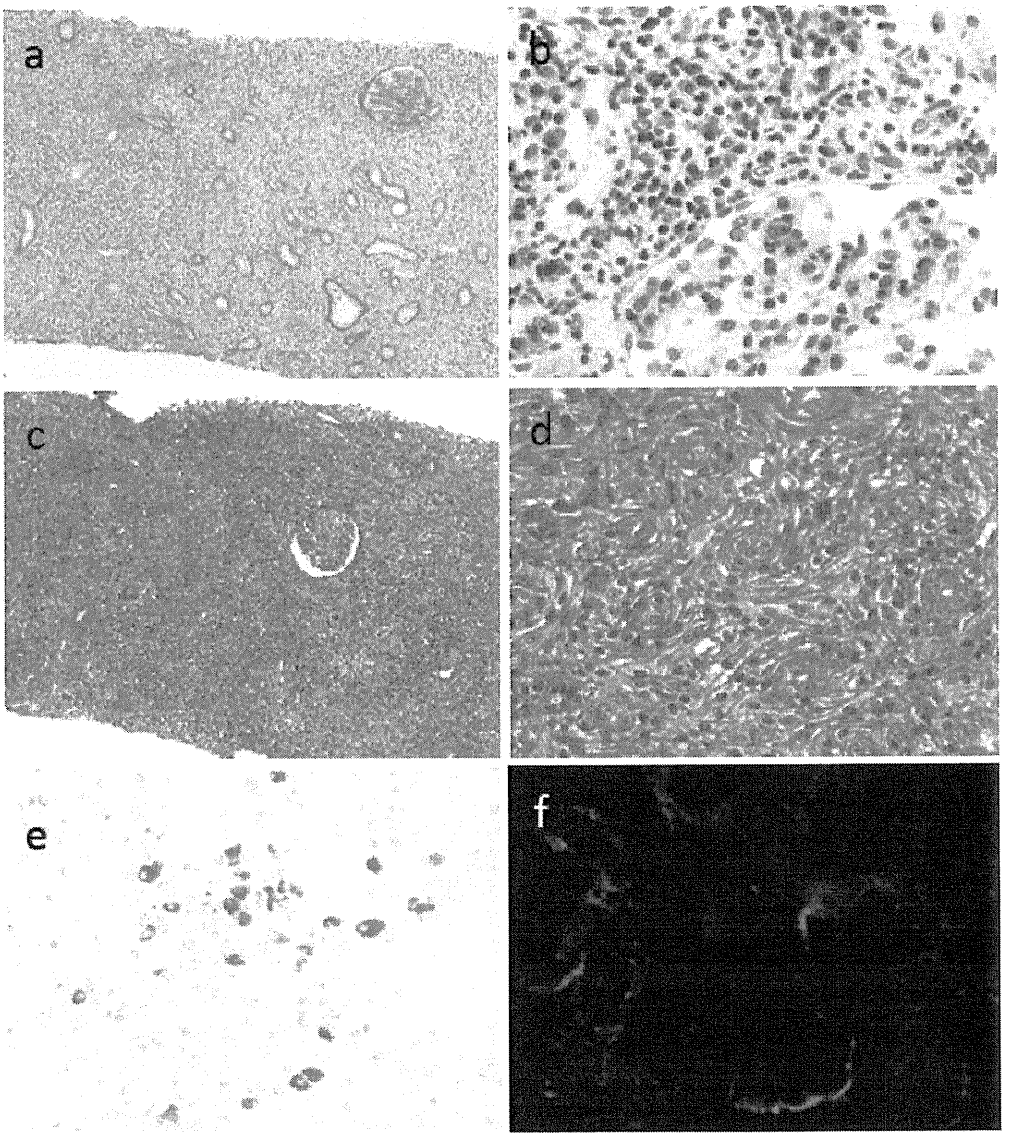

Figure 4. Light microscopy and immunofluorescent findings of the renal interstitium. Interstitium showed marked mononuclear cell infiltration with tubular atrophy (a). Many plasma cells were infiltrating (b) and severe interstitial fibrosis was noted by Azan staining (c, d). Immunostaining revealed most of the infiltrating plasma cells to be IgG4 positive (e). Immunofluorescence study showed granular deposition of C3 along with tubular basement membrane (f). (a: PAS × 100, b: HE × 400, c: Azan × 100, d: Azan × 400, e: IgG4 × 400, f: C3 × 200).

A skin biopsy from the leg showed leukocytoclastic vasculitis without IgG4-positive plasma cell infiltration. Minor salivary gland biopsy showed chronic sialadenitis with plasma cell infiltration, while only small numbers of plasma cells were IgG4 positive. Bronchoscopy was conducted to investigate the lung lesion. Transbronchial lung biopsy (TBLB) showed interstitial pneumonia with IgG4-positive plasma cell infiltration (> 20/hpf) compatible with IgG4-related lung disease. There was no evidence of sarcoidosis. The renal biopsy specimen for light microscopy contained 19 glomeruli, one of which was globally sclerotic. Most glomeruli showed endocapillary and mesangial cell proliferation (Figure 3a, b). Three glomeruli had cellular crescents. Double contour was also observed. Immunofluorescence study revealed IgA (Figure 3c), C3 (Figure 3d), and C1q deposits in the mesangium lesion. C3 and C1q deposition was observed along the capillary walls. Interstitium showed marked lymphocyte and plasma cell infiltration with fibrosis, while 10% of the interstitium had no inflammation (Figure 4a, b, c, d). In immunostaining, abundant IgG4-positive plasma cells were detected in the interstitium (Fig-

Table 2. Organ involvement of IgG4-related disease. The affected organs of this patient are indicated by boldface.

Organ involvement of IgG4-related disease
Hypophysitis
Sclerosing dacryoadenitis
Sclerosing sialoadenitis
Riedel thyroiditis
Sclerosing cholangitis
Sclerosing cholecystitis
Autoimmune pancreatitis
Inflammatory pseudotumor of the liver
Interstitial pneumonia (inflammatory pseudotumor of the lung)
Lymphadenopathy
Retroperitoneal fibrosis
Tubulointerstitial nephritis
Inflammatory abdominal aortic aneurysm
Gastrointestinal lesions
Prostatitis

ure 4e). Immunofluorescence study showed granular deposition of C3 and C1q along with tubular basement membrane (Figure 4f). There was no apparent deposition of IgG, IgM, or fibrinogen in the glomeruli or interstitium (data not shown).

The patient had a low titer of anti-double-stranded DNA antibodies, but did not fulfill the classification criteria of systemic lupus erythematosus (SLE). Although she did not have AIP, which is the prototype of IgG4-related disease, parotid and submandibular gland involvement and tubulointerstitial nephritis with IgG4 positive plasma cell infiltration, which are representative extrapancreatic lesions of IgG4-related disease, were present. Therefore, we diagnosed IgG4-related disease associated with Henoch-Schönlein purpura nephritis, and 30 mg per day of prednisolone was administered. After 4 weeks of prednisolone at this dose her serum creatinine level decreased to 0.87 mg/dl and the amount of proteinuria was decreased to 0.3 g per day, and the dosage of prednisolone was gradually tapered. To decide the tapering regimen and the maintenance dose of corticosteroid, re-biopsy was conducted 4 months after the beginning of the therapy. The glomeruli showed marked improvement of endocapillary proliferation, and only 3 of 35 glomeruli had adhesions between glomerular capillary loops and Bowman's capsule. No crescents were seen in the glomeruli. In the interstitium, the number of IgG4 positive plasma cells was decreased with mild fibrosis. Fifteen months after the initiation of steroid therapy, her renal function was normalized without hematuria or proteinuria at a maintenance dose of 7 mg per day of prednisolone.

Discussion

We report a patient with IgG4-related disease accompanied by HSPN. Bilateral submandibular gland swelling preceded purpura by four months, and her renal function gradually deteriorated within one year after the first symptoms. A renal biopsy disclosed that her deteriorated renal function was due to glomerular and tubulointerstitial lesions. Endocapillary proliferative glomerulonephritis with crescent formation and C3 and IgA deposition in mesangium by immunofluorescence, being a typical histopathological feature of HSPN, were the prominent glomerular lesions. In addition, leukocytoclastic vasculitis in a skin biopsy from purpura confirmed the diagnosis of HSPN. On the other hand, massive IgG4-positive plasma cell infiltration with fibrosis in the renal interstitium with C3 and C1q deposition in tubular basement membranes was a typical feature of IgG4-related TIN [1]. Both lesions dramatically responded to corticosteroid therapy. Although no IgG4 positive plasma cell infiltration was detected in her skin lesions, some features of her clinical course suggest some kind of relationship between these diseases.

The most important differential diagnosis in this case is hypocomplimentemic urticarial vasculitis syndrome (HUVS). Although our case and HUVS shared severely decreased C3 and C4 levels and glomerulonephritis as common clinical features, HUVS differs from our case in the distribution and characteristics of the eruption [7]. In our case, the distribution of the eruption was limited to the bilateral legs, and it was composed of 5 mm-sized purpura with occasional fusing without urticarial eruption. Similarly, SLE is less likely because of the absence of glomerular deposition of IgG and and because the patient did not fulfill the classification criteria of SLE.

IgG4-related disease is a systemic disease with multiple organ involvement represented by autoimmune pancreatitis (AIP) (Table 2) [2, 3]. IgG4-related disease had been classified as autoimmune disease since the new disease entity of AIP was proposed [8]. However, IgG4-related disease has gradually been considered to be rather more allergic than autoimmune in nature because of its close relationship with bronchial asthma and other allergic diseases [1]. Masaki et al. [3] showed that 40.6% of patients with IgG4-related disease had allergic rhinitis, a frequency significantly higher than that of typical Sjögren syndrome (SS). They also showed that the frequency of bronchial asthma was 14.1% in comparison to that of 3.2% in SS. Moreover, serum IgE levels were significantly increased in IgG4-related disease (307.4 IU/ml vs. 15.3 IU/ml) in their study. These findings support the allergic nature of IgG4-related disease.

The representative disease of IgG4-related disease is AIP. Although many reported cases of IgG4-related kidney disease were associated with AIP, several reports of IgG4-related kidney disease without AIP are available, and these cases are especially associated with lacrymal or salivary gland lesions like our case [9, 10]. Hypocomplementemia is an outstanding feature of IgG4-related disease, and is more frequently found in IgG4-related kidney disease than in other IgG4-related disease [1].

HSP is a systemic vasculitis characterized by deposition of IgA containing immune complexes [11]. Although its etiology is still unclear, allergic predisposition, such as drug allergy [12] or vaccine hypersensitivity [13] is a well-known important trigger of HSPN. Davin et al. [4] compared plasma IgE levels between HSPN and IgA nephropathy and found that the incidence of increased plasma IgE levels was significantly higher in HSPN patients. Kawasaki et al. [14] reported that serum IL-5 concentrations were higher in the acute phase of HSPN than those in the recovery phase. These findings suggest that HSPN is a Th2 dominant disease. Zen et al. [15] demonstrated that Th2 dominant cytokine production was increased in affected organs in IgG4-related disease. Thus, both HSP and IgG4-related disease seem to belong to Th2 dominant disease.

Two cases of purpura associated with IgG4-related disease and renal lesions were reported recently. Naitoh and colleagues [5] described a case with autoimmune pancreatitis with allergic purpura and endocapillary proliferative glomerulonephritis. Although this case is very similar to our case, the lack of any description of IgA or C3 deposits in glomeruli makes the diagnosis of Henoch-Schönlein purpura nephritis difficult and the relationship between the skin and renal lesions is unclear. Another notable case is a case report of a purpuric rash and renal vasculitis in a patient with AIP [6]. Histological examination of the skin lesion revealed leukocytoclastic vasculitis, and renal biopsy showed moderately severe TIN with focal fibrinoid necrosis of arterioles without glomerular lesions. Although neither case had typical glomerular lesions of HSPN, these cases might support some relationship between HSP or HSPN and IgG4-related disease.

A representative renal manifestation of IgG4 related disease is TIN with abundant IgG4 positive plasma cell infiltration, while several case reports of glomerular involvement are also available. In these, membranous nephropathy [16, 17, 18] has been the most frequently reported glomerular lesion accompanied by IgG4-related disease. In addition, other glomerular lesions have been reported. Katano et al. [19] reported endocapillary proliferative glomerulonephritis with TIN and marked IgG4 positive plasma cells. Morimoto et al. [20] reported membranoproliferative glomerulonephritis-like glomerular lesions with IgG4-related TIN. Our case adds a possible new glomerular lesion complicated with IgG4-related TIN.

In summary, our case suggests some relationship between HSP or HSPN and IgG4-related disease. To clarify the etiologic role of allergy in IgG4-related disease, attention should be paid to IgG4-related disease associated with HSP.

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NOTE

Putative IgG4-related pituitary disease with hypopituitarism and/or diabetes insipidus accompanied with elevated serum levels of IgG4

Ai Haraguchi[1)], Ai Era[1)], Junichi Yasui[1)], Takao Ando[1)], Ikuko Ueki[1)], Ichiro Horie[1)], Misa Imaizumi[1)], Toshiro Usa[1)], Kuniko Abe[2)], Tomoki Origuchi[1)] and Katsumi Eguchi[1)]

[1)]*First Department of Medicine, Nagasaki University School of Medicine, Nagasaki 852-8501, Japan*
[2)]*Department of Pathology, Nagasaki University School of Medicine, Nagasaki 852-8501, Japan*

Abstract. IgG4-positive plasma cell infiltration into multiple organs or tissues, such as the pancreas and salivary glands, associated with increased serum levels of IgG4 is a characteristic finding seen in IgG4-related disease. Affected organs may appear tumorous as a result of chronic inflammatory processes accompanied with progressive fibrosis. Recent cases of this disorder in which the pituitary gland was affected include cases of diffuse enlargement of the pituitary and/or its stalk associated with central diabetes insipidus and/or impaired anterior hormone production. Here we report two such cases, as well as two additional previously undiagnosed cases found in our database. In order to make a correct diagnosis of pituitary lesion involvement with IgG4-related disease, the clinical background and concomitant disorders should be carefully taken into consideration and the measurement of serum levels of IgG4 seems to be useful.

Key words: IgG4, Pituitary, Hypopituitarism, Diabetes insipidus

IGG4-RELATED disease, also called IgG4-positive multi-organ lymphoproliferative syndrome [1-3], is characterized by dense infiltration of IgG4-positive plasma cells (>50% of infiltrated IgG-positive cells) into multiple organs or tissues in association with increased serum levels of IgG4 (>135 mg/dL [1-3]). This disorder is frequently seen in older males who frequently have allergic disorders, and multiple organs or tissues can be affected, including the salivary glands (Mikulicz disease), pancreas (autoimmune pancreatitis), lungs (interstitial pneumonitis), retroperitoneal space (retroperitoneal fibrosis), kidneys (interstitial nephritis), and arachnoids (pachymeningitis); in addition, the disease can result in inflammatory pseudotumors at sites such as the orbits and lungs [2, 3]. Because of the chronic inflammatory process associated with progressive fibrosis in the lesions involved, the affected organs may appear tumorous.

Autoimmune pancreatitis (AIP) and Mikulicz disease (MD) are the major components of IgG4-related disease. AIP is one of the forms of chronic pancreatitis causing painless obstructive jaundice due to associated sclerosing pancreatitis. AIP is frequently seen in olderly males (mean age: 68.3 years old; ratio of males to females: 4 to 1), and impaired exocrine and/or endocrine pancreatic function is also frequently seen [3]. MD is a clinical condition characterized by bilateral, painless, and symmetrical swelling of the lachrymal, parotid, and submandibular glands with mild dry eye and mouth. This disorder has long been confused as a subtype of Sjögren syndrome. Negative anti-SS-A and SS-B antibodies, high serum levels of IgG4, and an infiltration of IgG4-positive cells within the salivary gland now distinguish MD from Sjögren syndrome [3].

The pituitary gland can also be affected in IgG4-related disease (IgG4-related pituitary disease). There have been 8 published cases of pituitary lesions associated with this disease [4-11]. Central diabetes insipidus and/or disturbed anterior hormone production

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Correspondence to: Takao Ando, M.D., Ph.D., First Department of Medicine, Nagasaki University School of Medicine, 1-7-1 Sakamoto, Nagasaki, Nagasaki 852-8501, Japan.
Email: takaoando@gmail.com
The first three authors (A.H., A.E., and J.Y.) contributed equally to the study.

with tumor or tumor-like lesion formation in or near the pituitary, are commonly seen in these cases. A recent review of such cases described 22 clinical patients, most of them in Japan [12]. There was a clear preponderance of olderly males (~95% being male and the median age being 64 years old). Either anterior (~80%) or posterior pituitary function (~50%) was impaired with MRI findings of pituitary and/or stalk swelling. Most of the cases had either AIP and/or MD concomitantly. Serum levels of IgG4, when measured, were mostly elevated [12]. Here we report two such cases who developed panhypopituitarism associated with diabetes insipidus, and two additional cases found in our database.

Case 1

A 74-year-old female was referred to our department due to an acute development of pituitary failure. She had no allergic diathesis, but had been diabetic for 30 years and became anorectic after frequent episodes of hypoglycemia caused by insulin therapy. She was diagnosed with adrenal insufficiency based on her low serum levels of ACTH (13.4 pg/mL) and cortisol (4.6 μg/dL), and treated with 10 mg/day of hydrocortisone. Her clinical conditions improved, including her loss of appetite, but she noticed polydipsia and polyuria upon treatment. An anterior pituitary function test performed after admission showed a partial impairment of ACTH, LH, FSH (Fig. 1A) and GH (peak GH after stimulation with 100 μg of GHRP-2; 4.429 ng/mL). Masked diabetes insipidus was also diagnosed clinically and biochemically, and desmopressin spray was initiated.

Pituitary MRI showed a diffuse swelling of the entire pituitary; the pituitary stalk was markedly enhanced with gadolinium (Fig. 1B and C). In blood testing, the levels of angiotensin-converting enzyme, AFP, CEA, and anti-neutrophil cytoplasmic antibodies were not remarkable, and anti-thyroid autoantibodies were negative. Systemic CT scan and tuberculin skin test did not suggest active tuberculosis. Gallium scintigraphy showed hot spots in the cervical and hilar lymph nodes, but accumulation in the pituitary gland was not apparent (results not shown). We biopsied the cervical lymph node, which showed an infiltration of plasma cells, including IgG4-positive cells (~10% of IgG-positive cells) (Fig. 1F to I). Serum levels of IgG4 were also elevated (Fig. 1J), suggesting IgG4-related disease involving the pituitary gland. There was a dramatic reduction of the swelling of the pituitary and its stalk after 2 weeks of treatment with 30 mg/day of prednisolone (Fig. 1D and E). A reduction of the serum levels of IgG4 and a slight increase of LH, FSH, and IGF-1 (Fig. 1J) were also observed during the tapering of prednisolone (prednisolone was reduced 5 mg/day every two weeks) down to a maintenance dose of 10 mg/day without apparent relapse for longer than four months.

Case 2

A 68-year-old male without any previous allergic disorders was admitted to our university hospital for treatment of diabetes insipidus. The pituitary MRI revealed a loss of the high signal in the pituitary posterior lobe in association with a pituitary mass-like lesion extending to the stalk (Fig. 2A and B). His anterior pituitary function was spared (Fig. 2G). Blood tests for angiotensin-converting enzyme, AFP, and CEA were negative, and a systemic CT scan and tuberculin skin test did not suggest active tuberculosis. This mass lesion was suspected to be lymphocytic infundibuloneurohypophysitis. The patient declined tumor biopsy or therapeutic diagnosis using glucocorticoids and he was discharged with replacement treatment of desmopressin. Three years after admission, he developed right-sided leg edema caused by retroperitoneal fibrosis, a diagnosis supported by the pathological findings of lymphocytic infiltration and fibrosis seen in the retroperitoneal mass around the right iliac artery. Hydrocortisone and thyroxine therapy were initiated 5 years after the first presentation as a result of the gradual loss of anterior pituitary function.

Seven years after the first admission, the patient was admitted again with a complaint of persistent headache that seemed to be caused by the enlarged pituitary lesion (Fig. 2C and D). Repeated blood testing including an assay for anti-thyroid autoantibodies did not suggest any causative disorders that might be causative of pituitary failure (Fig. 2G) except high serum levels of IgG4 (Fig. 2H). We were also able to measure the serum level of IgG4 one year prior to the last admission by using the stock sera; the serum IgG4 was 151 mg/dL at this time point. There was gallium accumulation in the cervical, supraclavicular, and bilateral hilar lymph nodes, and a retroperitoneal mass around the right iliac artery, but accumulation in the