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ORIGINAL ARTICLE

Consideration concerning similarities and differences between ANCA-associated vasculitis and IgG-4-related diseases: case series and review of literature

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Abstract

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) and immunoglobulin G4-related diseases (IgG4-RD) are regarded as entirely different disease types with different etiological mechanisms. However, we experienced two cases that had clinical features of both AAV and IgG4-RD. The first case is an 81-year-old woman who showed periaortitis and retroperitoneal fibrosis and periarteritis with elevation of myeloperoxidase-anti-neutrophil cytoplasmic antibody and IgG4 levels. The second case is a 63-year-old woman who had dura mater, ear, nose, lung, and kidney involvement with serum negative for ANCA and elevated IgG4. Renal biopsy revealed tubulointerstitial nephritis involving $IgG4^+$ plasma cells ($IgG4^+/IgG^+$ cell ratio of ≥ 40%). On the other hand, lung biopsy showed features of granulomatosis with polyangiitis (GPA). These two cases suggested that AAV and IgG4-RD might overlap. To investigate the similarities and differences between AAV and IgG4-RD, we retrospectively analyzed 13 cases of typical GPA, a subtype of AAV, and 13 cases of typical IgG4-RD at our hospital for comparison of clinical features and found some differences that can be useful in the differential diagnosis between the two diseases. Although AAV and IgG4-RD are distinguishable based on characteristic findings in many cases, the diagnosis can be unclear in rare cases, in which clinicians should consider possible coexistence of AAV and IgG4-RD when performing further workup. Here, we discuss the similarities and differences between AAV and IgG4-RD on the basis of our results and past literature.

Keywords ANCA-associated vasculitis · IgG4-related disease · Similarity and difference · Retroperitoneal fibrosis · Granulomatosis with polyangiitis

Introduction

Immunoglobulin G4-related disease (IgG4-RD) is characterized by tumor-like swelling in multiple sites caused by lymphoplasmacytic infiltration and sclerosis. It is associated with elevated serum IgG4 levels and infiltration of IgG4-positive cells in the organs, such as lacrimal gland swelling (32.2%), lymphadenopathy (65.3%), sialadenitis (64.4%), dacryoadenitis (50.8%), autoimmune pancreatitis (38.1%), pulmonary involvement (27.1%), periaortitis/retroperitoneal fibrosis (RPF) (26.3%), prostatitis (35.4% of male patients), renal involvement (24.6%), sclerosing cholangitis (17.8%), and sinusitis (12.7%) [1, 2].

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is characterized by pauci-immune necrotizing vasculitis involving small vessels, and classified into three subtypes: microscopic polyangiitis, granulomatosis with polyangiitis (GPA), and eosinophilic GPA. AAV involves many organs, such as the orbital region, sinuses, lungs, kidneys, and meninges [3], which often overlap with organs impaired by IgG4-RD.

Although serum IgG4 elevation has been considered a useful marker of IgG4-RD, increased serum concentration of

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IgG4 has been observed in other diseases unrelated to IgG4-RD, such as malignant tumor and autoimmune disease [4–6]. It has been reported that infiltration of IgG4-positive cells in tissues has been observed in some patients with GPA [7]. Regarding the relationship between ANCA and IgG4-RD, ANCA positivity in IgG4-RD has also been reported [8].

As stated above, some published case reports and case series suggest a relationship between AAV and IgG4-RD, while current knowledge does not enable determination as to whether patients with such symptoms have AAV or IgG4-RD, or both. We experienced two cases that exhibited characteristics of both AAV and IgG4-RD. Furthermore, to examine the association between AAV and IgG4-RD, we retrospectively compared clinical features with GPA (13 cases) and IgG4-RD (13 cases) in our hospital. Here, we discuss the similarities and differences between ANCA-related vasculitis and IgG4-RDs on the basis of our case series and past literature.

Case presentation

Case 1

An 81-year-old Japanese woman was admitted to our hospital because of a 20-day history of low-grade fever and malaise. Her past medical history included lung cancer, for which she underwent video-assisted thoracic surgery, hypertension, overactive bladder, and acute pyelonephritis. Her body temperature was 37.0 °C, blood pressure 126/68 mmHg, and pulse 104 beats per minute. The otolaryngology area was normal and lacrimal glands and salivary glands were not enlarged. The remaining outcomes of the examination were normal.

Laboratory examination revealed elevated white blood cell (WBC) count at 10400 cells/μL, with 84.8% neutrophils, 8.7% lymphocytes, 5.9% monocytes, and 0.4% eosinophils. Hemoglobin level was 9.7 g/dL, erythrocyte sedimentation rate (ESR) was 108 mm/h, and C-reactive protein (CRP) level was 121 mg/L. Liver functions were within normal limits; serum creatinine level was 0.66 mg/dL. Levels of total IgG, IgA, IgM, and IgG4 were 1968, 400, 54, and 187.0 mg/dL, respectively. Serum levels of CH50, C3, and C4 were 54.6 U/mL, 158 mg/dL, and 37 mg/dL. Myeloperoxidase-anti-neutrophil cytoplasmic antibody (MPO-ANCA) was 274 U/mL (reference range < 3.5 U/mL). Antinuclear antibody testing (ANA) and proteinase 3 (PR3)-ANCA were negative. Other autoimmune antibodies were unremarkable. Urinalysis revealed a microscopic hematuria of 30–49/HPF, WBC count at 5–9/HPF, (+/−) proteinuria, and 1 to 4 hyaline casts/LPF. Cultures of urine and blood were negative. A chest radiograph was normal. Enhanced computed tomography (CT) scan showed bilateral hydronephrosis and soft tissue lesions surrounding the abdominal aorta, findings consistent with periaortitis and RPF (Fig. 1a). These findings and the elevated serum IgG4 were consistent with IgG4-RD. However, given the highly elevated MPO-ANCA and CRP, AAV was a possible differential diagnosis.

The patient received a diagnosis of AAV or IgG4-RD, and 30 mg/day of oral prednisolone (PSL) was started on the 16th hospital day. One month after the treatment, a CT scan showed that the soft tissue lesions had mostly disappeared (Fig. 1b) and the CRP level had decreased to 0.3 mg/L. She was discharged home on the 45th hospital day. Three months after the treatment, IgG4 level had decreased to 85 mg/dL. At 1-year follow-up examination, MPO-ANCA level had decreased to 68.1 U/mL and the dosage of oral PSL was tapered to 10 mg/day.

Case 2

A 63-year-old Japanese woman received repeated treatment of PSL because of organizing pneumonia since 17 months before admission. Four months before admission, she presented to our hospital because of fever, headache, otalgia, and hearing loss and was admitted to our hospital to evaluate these symptoms. She had no special history except for organizing pneumonia and was taking 10 mg/day of oral PSL because of organizing pneumonia.

On physical examination, her body temperature was 38.1 °C, blood pressure 138/76 mmHg, pulse 76 beats per minute, respiratory rate 18 breaths per minute, and oxygen saturation 99% while the patient was breathing ambient air. Lacrimal glands and salivary glands were not enlarged. Heart sounds and breath sounds were normal. There was no skin rash. Neurologic examination revealed loss of sensation in V2 region of trigeminal nerve, facial weakness, and sensorineural hearing loss on the left side. Other cranial nerve functions and the remaining outcomes of the examination were normal.

Laboratory examination revealed elevated WBC count at 18200 cells/μL, with 85% neutrophils, 7.5% lymphocytes, 7.5% monocytes, and 0.0% eosinophils. Hemoglobin level was 9.9 g/dL. ESR was 100 mm/h and CRP level was 64 mg/L. Liver function was within the normal limits. Serum creatinine level was 0.86 mg/dL. Serum levels of total IgG, IgA, IgM, and IgE were 1726, 335, 61 mg/dL, and 405 U/mL, respectively. Serum IgG4 was 407.0 mg/dL. Serum levels of CH50, C3, and C4 were 65.9 U/mL, 134 mg/dL, and 48 mg/dL. ANA, PR3-ANCA, and MPO-ANCA were all negative. Other autoimmune antibodies were unremarkable. Urinalysis revealed mild microscopic hematuria of 5–9/HPF and WBC count at 5–9/HPF, no proteinuria, and 0 to 1 hyaline casts/LPF. Urinary β2microglobulin and NAG were 9040 μg/L and 43.4 IU/L. Cultures of sputum, urine, blood, and cerebrospinal fluid were all negative. A chest radiograph showed consolidation in the bilateral upper lung. Head CT showed right maxillary sinusitis. Chest CT showed bilateral infiltration in the upper and middle lung lobes (Fig.

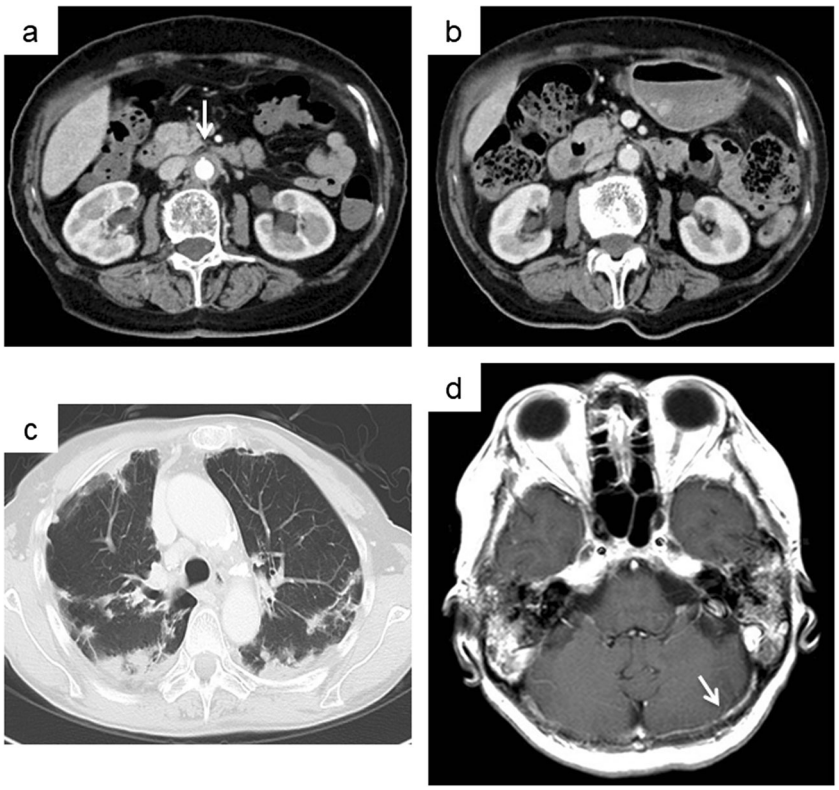

Fig. 1 Enhanced abdominal CT before treatment (**a**) and after tretment (**b**) in case 1. **a** The presence of bilateral hydronephrosis and periaortic fibrotic tissue, findings consistent with periaortitis and RPF (arrow). **b** After the treatment, periaortic fibrotic tissue mostly disappeared. CT of the chest (**c**) and enhanced MRI of head before treatment (**d**) in case 2. **c** Bilateral infiltration in the upper and middle lung lobes. **d** Possible mild thickening of dura mater (arrow), a finding that suggested hypertrophic pachymeningitis

1c). Gadolinium-enhanced MRI revealed possible mild thickening of dura mater, a finding that suggested hypertrophic pachymeningitis (Fig. 1d). The serum creatinine level increased from 0.86 to 1.34 mg/dL during the first 2 weeks after admission.

Summarizing this case, she had dura mater, ear, nose, lung, and kidney involvement with normal ANCA titer and elevated IgG4 level, which indicated the possibility of ANCA-negative GPA or IgG4-RD. To develop a differential diagnosis, histological examination of nasal cavity (on

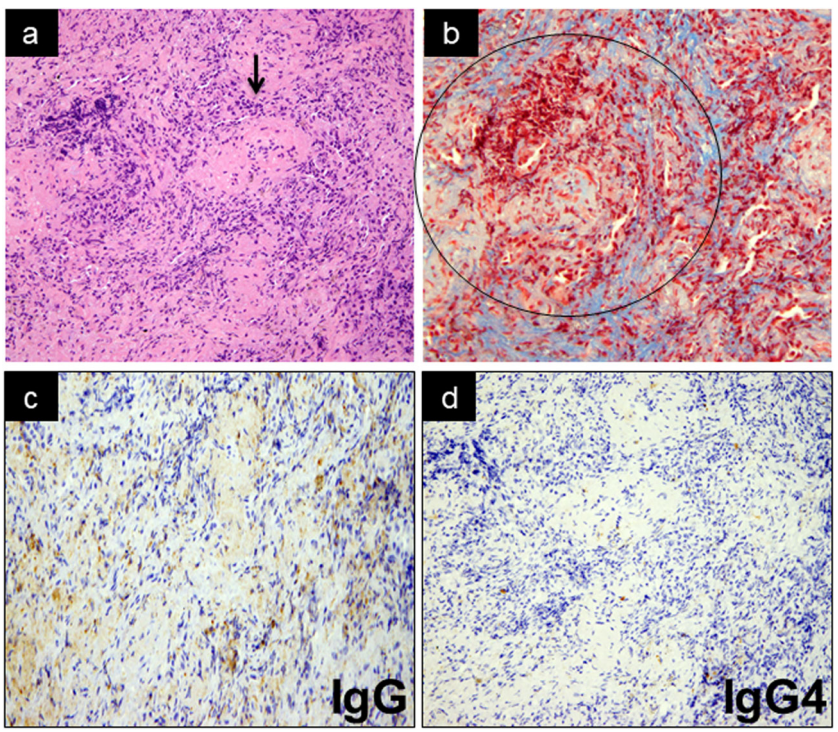

Fig. 2 Histology of a lung biopsy specimen by bronchoscopy: **a** HE stain 200×, **b** Masson-Noguchi stain 200×, **c**, **d** immunohistochemistry 200×. A lung biopsy specimen revealed granuloma (**a**, arrows) and necrotizing vasculitis (**b**, oval area), suggestive of GPA. Immunohistochemistry revealed infiltration of IgG^+ plasma cells (**c**) but no $IgG4^+$ plasma cells (**d**)

the 11th hospital day), histological examination by bronchoscopy (on the 18th hospital day), and renal biopsy (on the 22th hospital day) were performed. Nasal specimens revealed nonspecific chronic inflammation without granuloma or vasculitis. Infiltration of IgG4-positive plasma cells was not found. The lung tissue specimen revealed granuloma (Fig. 2a) and necrotizing vasculitis (Fig. 2b), suggestive of GPA. Immunohistochemistry revealed infiltration of IgG^+ plasma cells but no $IgG4^+$ plasma cells (Fig. 2c, d). A percutaneous ultrasound-guided renal biopsy specimen revealed tubulointerstitial nephritis (Fig. 3a) and necrotizing vasculitis (Fig. 3b) with infiltration of lymphocytes, including plasma cells. Seven glomeruli were present in the biopsy and glomeruli were intact. Immunohistochemistry revealed sporadic infiltration of $IgG4^+$ plasma cells. The $IgG4^+/IgG^+$ cell ratio was about 50% and ≥ 10/HPF (Fig. 3c). Lung histology indicated GPA, and renal histology showed angionecrosis damage and interstitial population increase of $IgG4^+$ plasma cells, indicated IgG4-RD, and therefore she received the diagnosis of ANCA-negative GPA in IgG4-RD.

Because the result of renal biopsy showed severe interstitial nephritis, treatment with 3 days of intravenous mPSL pulse followed by oral PSL (1 mg/kg/day) and intravenous cyclophosphamide pulse therapy (IV-CY) (500 mg per month) was started on the 25th hospital day. After the treatment, all of her symptoms improved and the lung infiltration had promptly disappeared. She was discharged home on the 67th hospital day, and the dosage of oral PSL was gradually tapered. After that, serum creatinine level had not worsened, and by 4 months later, urinary β2 microglobulin and NAG decreased to 206 μg/L and 2.2, respectively. By 3 months after the treatment, IgG4 level had decreased to 89.4 mg/dL.

Results

Retrospective analysis of clinical features in patients with GPA and patients with IgG4-RD in our hospital

To evaluate similarities and differences between AAV and IgG4-RD, we retrospectively reviewed electronic medical records of patients with GPA (13 cases), a subtype of AAV, and IgG4-RD (13 cases) in our hospital between March 2012 and October 2017. A diagnosis of GPA was made based on the 2012 Revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides [3].

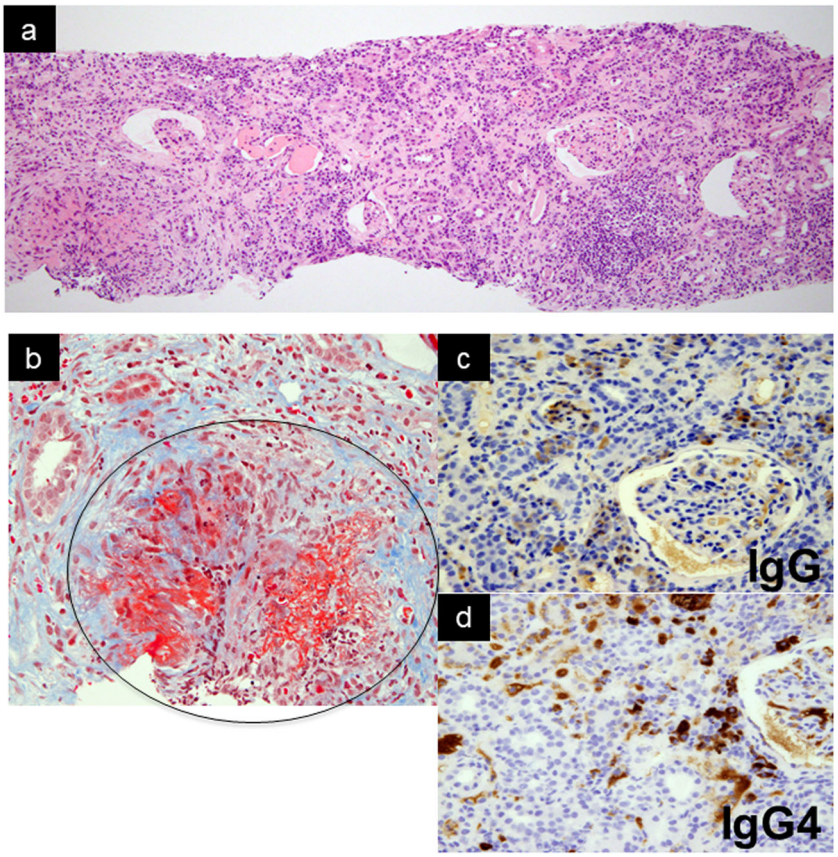

Fig. 3 Histology of a left renal biopsy specimen: **a** HE stain 20×, **b** Masson-Noguchi stain 200×. **c**, **d** Immunohistochemistry 400×. A percutaneous ultrasound-guided renal biopsy specimen revealed tubulointerstitial nephritis (**a**) and necrotizing vasculitis (**b**, oval area) with infiltration of lymphocytes, including plasma cells. Glomeruli were intact. Immunohistochemistry revealed infiltration of $IgG4^+$ plasma cells. The $IgG4^+/IgG^+$ cell ratio was about 50% and ≥ 10/HPF (**d**)

Table 1 Clinical characteristics of GPA and IgG4-RD

Characteristic	GPA ($n = 13$)	IgG4-RD ($n = 13$)	P
Age (years, mean ± SD)	62.6 ± 15.9	65.3 ± 12.3	0.63
Female, *n* (%)	7 (53.8%)	4 (30.8%)	0.23
Organ involvement			
Fever	8 (61.5%)	1 (7.7%)	< 0.005
Central nerve, *n* (%)	4 (30.8%)	1 (7.7%)	0.13
Dura mater, *n* (%)	1 (7.7%)	0 (0%)	0.31
Lacrimal gland swelling, *n* (%)	0 (0%)	3 (23.1%)	0.065
Scleritis, *n* (%)	3 (23.1%)	0 (0%)	0.065
Ears or nose, *n* (%)	8 (61.5%)	3 (23.1%)	0.047
Salivary glands, *n* (%)	0 (0%)	6 (46.2%)	0.0052
Lung, *n* (%)	11 (84.6%)	1 (7.7%)	< 0.005
Pancreatitis, *n* (%)	0 (0%)	6 (46.2%)	0.0052
Retroperitoneal fibrosis, *n* (%)	0 (0%)	4 (30.8%)	0.030
Nephritis, *n* (%)	8 (61.5%)	1 (7.7%)	< 0.005
Skin, *n* (%)	2 (15.4%)	1 (7.7%)	0.54
Histological findings[a]	6/10	3/9	
Eosinophil (%)	1.0 ± 1.9	4.1 ± 4.1	0.028
CRP (mg/L, mean ± SD)	86.0 ± 72.0	4.7 ± 5.6	< 0.005
ESR 60 (mm, mean ± SD)	74.0 ± 30.0	69 ± 40.1	0.81
MPO-ANCA	59.8 ± 98.6	–	–
PR3-ANCA	21.8 ± 49.6	–	–
IgG (mg/dL, mean ± SD)	1191 ± 407.8	2333 ± 766	< 0.005
IgG4 (mg/dL, mean ± SD)	–	664 ± 390.6	–
Medications, *n* (%)			
PSL, *n* (%)	12 (92.3%)	12 (92.3%)	1.0
PSL (mg/day)[b]	37.9 ± 16.7	25.2 ± 14.1	0.050
IV-CY, *n* (%)	6 (46.1%)	0 (0%)	0.0052
Rituximab, *n* (%)	2 (15.4%)	0 (0%)	0.14

IgG4-RD IgG4-related disease, *GPA* granulomatosis with polyangiitis, *CRP* C-reactive protein, *ESR* erythrocyte sedimentation rate, *MPO-ANCA* myeloperoxidase-anti-neutrophil cytoplasmic antibody, *PR3-ANCA* proteinase 3-anti-neutrophil cytoplasmic antibody, *PSL* prednisolone, *IV-CY* intravenous cyclophosphamide pulse therapy, *mPSL* methylprednisolone pulse

[a] (Number of patients with positive histology)/(Total number of patients who underwent histologic evaluation)

[b] In the GPA group, the mean value excluded one patient given steroid pulse therapy (mPSL 1 g/day)

Statistical analysis was performed using JMP software version 9.0 (SAS Institute Japan, Tokyo, Japan). Normally distributed continuous data were analyzed using parametric tests (Student's *t* test). Non-normally distributed data were analyzed using nonparametric tests (Mann-Whitney *U* test or Spearman's rank correlation coefficient). Categorical data were analyzed using Chi-square test or Fisher's exact test

IgG4-RD patients met the over the possible of 2011 comprehensive diagnostic criteria [9].

Clinical characteristics of the two groups are shown in Table 1. There were no significant differences in age or sex between the two groups. Fever ≥ 38 °C (61.5% vs. 7.7%, $P < 0.005$), ears or nose involvement (61.5% vs. 23.1%, $P = 0.047$), lung involvement (84.6% vs. 7.7%, $P < 0.005$), and nephritis (61.5% vs. 7.7%, $P < 0.005$) were more frequent in the GPA patients than in the IgG4-RD patients. On the other hand, salivary gland swelling (0.0% vs. 46.2%, $P = 0.0052$), pancreatitis (0.0% vs. 46.2%, $P = 0.0052$), and retroperitoneal fibrosis (0.0% vs. 30.8%, $P = 0.030$) were more frequent in the IgG4-RD patients. There were no significant differences in other involved organs between the two groups.

Eosinophil count was significantly elevated in the IgG4-RD patients (4.1 ± 4.1%) compared to the GPA patients (1.0 ± 1.9%, $P = 0.028$). CRP was significantly elevated in the GPA patients (86.0 ± 72.0 mg/L) compared to IgG4-RD patients (4.7 ± 5.6 mg/L, $P < 0.005$). In GPA patients, the average of MPO-ANCA was 59.8 ± 98 U/mL and the average of PR3-

Table 2 Reports of ANCA-positive RPF/periaortitis

First author (year) [reference]	Age/ sex	Fever/organ involvement	CRP (mg/L)	ANCA	IgG4 (mg/dL)
ter Maaten (1993) [10]	49/M	Fever (N/A)/conjunctivitis, rhinitis kidney, lung,	N/A	PR3-ANCA 1:64	N/A
Kaipiainen-Seppanen (1996) [11]	52/M	Fever (+)/none	57	c-ANCA 100 IU	N/A
Sakemi (1998) [12]	63/F	Fever (high)/none	98.3	p-ANCA 413 EU	N/A
Vaglio (2002) [13]	74/F	Fever (high)/none	24	c-ANCA 1:160	N/A
	57/M	Fever (−)/kidney	61	MPO-ANCA 354 EU/mL	N/A
Van Bommel (2002) [14]	65/F	Fever (high)/temporal arteritis	N/A	MPO-ANCA 160 U/mL	N/A
Roux-Serratrice (2002) [15]	47/M	Fever (high)/none	88	PR3-ANCA 62 IU/mL	N/A
Aslangul (2003) [16]	82/F	Fever (N/A)/none	N/A	PR3-ANCA 1518 U/mL	N/A
Carels (2005) [17]	63/M	Fever (high)/temporal arteritis	200	MPO-ANCA 28 U/mL	N/A
Mavragani (2007) [18]	52/M	Fever (−)/none	N/A	c-ANCA	N/A
Martinez-Odriozola (2008) [19]	46/M	Fever (low)/kidney	37.1	PR3-ANCA 179 U/mL	N/A
Kasagi (2011) [20]	61/F	Fever (low)/scleritis, otitis, medina, dura, lung	92.8	MPO-ANCA 66 U/mL	N/A
Kotani (2012) [21]	55/M	Fever (N/A)/sinusitis	7.9	PR3-ANCA 43.9 U/mL	351
Present case 1	81/F	Fever (low)/none	121	MPO-ANCA 274 U/mL	187

RPF retroperitoneal fibrosis, *MPO-ANCA* myeloperoxidase-anti-neutrophil cytoplasmic antibody, *PR3-ANCA* proteinase 3-anti-neutrophil cytoplasmic antibody, *pANCA* perinuclear-ANCA, *cANCA* cytoplasmic-ANCA

ANCA was 21.8 ± 49.6 U/mL. In IgG4-RD patients, ANCA was evaluated in 5 cases among 13 cases, and all were negative. In IgG4-RD patients, the average IgG4 level was 664 ± 390.6 mg/dL. In GPA patients, IgG4 was evaluated in 1 case (15.9 mg/dL) among 13 cases.

Histopathological findings were available for 10 of the 13 GPA patients and 9 of the 13 IgG4-RD patients. Among the GPA patients, specific findings were necrotizing glomerulonephritis in 3 of 3 cases evaluated by renal biopsy; necrotizing vasculitis or necrotizing granulomatous inflammation in 3 of 6 cases evaluated by nasal cavity biopsy; and nonspecific inflammation in 1 case evaluated by auricular biopsy. Among the IgG4-RD patients, specific findings were lymphocytic infiltration and fibrosis in 3 of 3 cases evaluated by bile duct biopsy, including 1 case with an $IgG4^+/IgG^+$ cell ratio of ≥ 40%; an $IgG4^+/IgG^+$ cell ratio of ≥ 40% in 2 of 3 cases evaluated by submaxillary gland biopsy; lymphocytic infiltration without detectable $IgG4^+$ cells in 1 case evaluated by retroperitoneal biopsy; an $IgG4^+/IgG^+$ cell ratio of 30% in 1 case evaluated by renal biopsy; and leukocytoclastic vasculitis in 1 case evaluated by skin biopsy.

In medication, there was no significant difference in PSL use (92.3% vs. 92.3%, $P = 1.00$) between the two groups. IV-CY (46.1% vs. 0.0%, $P = 0.0052$) and rituximab (15.4% vs. 0.0%, $P = 0.14$) were used more often in GPA patients than in IgG4-RD patients.

Discussion

We identified three important clinical issues. First, a relationship between ANCA and RPF is suggested. Second, even without RPF, clinical features of AAV and IgG4-RD can coexist in rare cases. Third, the retrospective comparative analysis of GPA cases and IgG4-RD cases at our hospital revealed some differences that can be useful in the differential diagnosis between the two diseases. These are detailed in turn below.

Regarding the first issue, we encountered a patient with periaortitis and RPF accompanied by elevated serum IgG4 and MPO-ANCA, as presented in case 1. Our literature search identified 13 other published cases of ANCA-positive RPF/periaortitis [10–21], which together with our case 1 are summarized in Table 2. Of these 14 cases, 6 were positive for MPO- or perinuclear-ANCA, and 8 were positive for PR3- or cytoplasmic-ANCA. Serum IgG4 concentrations were not mentioned in any cases except the case reported by Kotani

Table 3 Case reported in the literature of patients with AAV and IgG4-RD

Case no. [reference]	Age/ sex	Organ involvement, histology	CRP (mg/ L)	ANCA (U/mL)	IgG4 (mg/ dL)	Therapy
1. [22]	38/F	Fever, pituitary gland, **orbit**, lung, *skin*	167	MPO 24.4	377	GC, AZA, RTX
2. [23]	47/M	Fever, **mediastinum**, *kidney*	110	PR3 136.8	470	mPSL, GC, CY
3. [24]	73/M	Ear, **nose**, sinuses, *kidney*	26	MPO 8.3	249	GC, AZA
4. [25]	72/M	Lacrimal gland, submandibular gland, **nasal mucosa**, lung, *skin*, nerve	23	MPO 758	343	mPSL, GC, IVIG
5. [26]	66/M	**Eye** (**sclera**, uvea)	26	MPO 1:80	143	GC, MTX, TMC
6. [8]	52/F	**Lacrimal gland**, *lung*	21	PR3 423	253	GC, RTX
Present case 1	81/F	Fever, RPF	121	MPO 274	187	GC
Present case 2	63/F	Fever, dura mater, ear, nose, *lung*, **kidney**	64	MPO < 1.0	407	mPSL, GC, CY

Adapted from Table 1, Della-Torre E, et al. [8]

RPF retroperitoneal fibrosis, *MPO* myeloperoxidase-anti-neutrophil cytoplasmic antibody, *PR3* proteinase 3-anti-neutrophil cytoplasmic antibody, *GC* glucocorticoids, *AZA* azathioprine, *RTX* rituximab, *MTX* methotrexate, *mPSL* methylprednisolone pulse, *CY* cyclophosphamide, *IVIG* intravenous immunoglobulins, *TMC* triamcinolone (ocular)

Italics indicates positive histology for AAV, and bold text indicates positive histology for IgG-RD

et al., thereby making our case 1 as the second reported case of IgG4-related RPF with increased ANCA. Characteristic manifestations of ANCA-positive RPF, compared with typical RPF, include increased fever and inflammatory markers, occasionally with concurrent vasculitis such as glomerulonephritis. For treatment, steroids were used in all 14 cases, concomitantly with non-steroidal immunosuppressive agents in 11 cases, except for 3 cases of case 1 and the literature cases 8 and 10 (data not shown). ANCA levels improved with treatment in all 14 cases.

Regarding the second issue, i.e., coexistence of AAV and IgG4-RD clinical features in rare cases even without RPF, a report by Della-Tolle E et al. [8] summarized published cases of IgG4-RD with suspected AAV [8, 22–26] (Table 3). Characteristics of these cases with histologic evidence of both IgG4-RD and AAV, compared with typical IgG4-RD cases, included a tendency toward slightly higher CRP and other inflammatory markers as well as common concomitant use of immunosuppressive medication.

Regarding the third issue, the comparative analysis of GPA cases and IgG4-RD cases at our hospital revealed two differences that can be useful in the differential diagnosis between the two diseases. The first difference is that the typical organ involvement in GPA was the ear/nose region, lungs, and kidneys, while that in IgG4-RD was lacrimal and salivary gland swelling, RPF, and pancreatitis. The second difference is that fever and CRP were significantly higher with GPA than with IgG4-RD. Thus, the distribution of affected organs and the level of inflammatory response appear to be useful in the differential diagnosis between the two diseases. As for histologic evaluation, on the other hand, interpretation of findings requires caution, because many cases lack specific findings, and IgG4-positive plasma cells may exist even in GPA, as described in a published report [7]. Taken together, the condition in our case 2 appeared to be closer to ANCA-negative GPA rather than IgG4-RD, given that the patient had upper respiratory tract symptoms with organ involvement of the lungs and kidneys, hyperthermia, and high inflammatory response, but possible coexistence of both diseases could not be excluded given that renal histology showed interstitial nephritis primarily with IgG4-positive cells without glomerular disease.

Limitations of this report include the unfortunate lack of histologic evaluation of the retroperitoneal lesion and kidneys in case 1.

In conclusion, we experienced two cases that had clinical features of both AAV and IgG4-RD. Serum IgG4 elevation and IgG4-positive cell infiltration in the tissue can be seen in AAV. Some reports suggested a possible pathogenic effect of ANCA-IgG4 [27–29]. But our two cases have clinical features of both AAV and IgG4-RD, so this study suggests that AAV and IgG4-RD may overlap. Distinguishing between these diseases is essential for treatment planning, because IgG4-RD responds well to steroid therapy alone, while AAV often requires concomitant immunosuppressant use. Although AAV and IgG4-RD are distinguishable based on characteristic findings in many cases, the diagnosis can be unclear in some cases, in which

clinicians should consider possible coexistence of AAV and IgG4-RD when performing further workup.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the ethical committee of Narita Red Cross Hospital and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Data obtained in this study did not interfere with course of treatment for patients included.

Human and animal rights This article does not contain any studies with animals performed by any of the authors.

Informed consent Informed consent was obtained from all individual participants included in the study.

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