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Do ANCA-associated vasculitides and IgG4-related disease really overlap or not?

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Abstract

Background: Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) and immunoglobulin G4-related disease (IgG4-RD) have some common features. The co-occurrence/concurrence of AAV and IgG4-RD was recently published by the collaborative European Vasculitis Study Group. First, we aimed to investigate ANCA positivity of our IgG4-RD cohort. Second, a literature review of co-occurrence/concurrence of AAV and IgG4-RD was done.

Methods: Data of 62 patients with IgG4-RD in Hacettepe Vasculitis Center Database were used. Patient dataset was designed to include demographic data, clinical characteristics, imaging and IgG4-RD, AAV and ANCA test results. At the next step, we performed a systematic literature review in PUBMED database covering the time period from 1976 until April 2018. Relevant publications were searched using these MeSH terms ''IgG4-related disease and Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis'', "IgG4-related disease and Eosinophilic Granulomatosis with Polyangiitis", "IgG4-related disease and Microscopic Polyangiitis" and "IgG4-related disease and Granulomatosis with Polyangiitis".

Results: Three (10.3%) of 29 patients had low titer ANCA positivity. These three patients didn't have any findings of vasculitis and no granuloma was seen in biopsy. In the literature review, we found 17 cases had features of both IgG4-RD and AAV. These cases were re-evaluated according to the Comprehensive Diagnostic Criteria for IgG4-RD. ANCA were positive in 15 of 17 patients (88%).

Conclusion: None of our IgG4-RD patients overlapped with AAV. Only two patients in the literature review seemed to be fully compatible with both diseases. Even though AAV and IgG4-RD share similar clinical features, we think this might be a co-occurrence instead of a histopathological link.

KEYWORDS

ANCA-associated vasculitis, Churg-Strauss syndrome, eosinophilic granulomatosis with polyangiitis (EGPA), granulomatosis with polyangiitis (GPA), IgG4-related disease

1 | INTRODUCTION

Immunoglobulin G4-related disease (IgG4-RD) is an emerging fibroinflammatory condition characterized with both single and multiple organ involvements.[1] Pancreatitis, retroperitoneal fibrosis and salivary gland involvement are the most frequent features of IgG4-RD.

Antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitides (AAV) include granulomatosis with polyangiitis (GPA), eosinophilic granulomatosis with polyangiitis (EGPA) and microscopic polyangiitis (MPA). They are mainly characterized by manifestations related to necrotizing small-vessel vasculitis and some of them may be related to granulomatous inflammation, particularly in GPA and EGPA.[2,3]

Pseudotumor orbita, pachymeningitis, periaortitis may be seen in both AAV and IgG4-RD. Due to these similar clinical features sometimes it may be difficult to differentiate these two diseases. The co-occurrence/ concurrence of AAV and IgG4-RD was recently published by the collaborative European Vasculitis Study Group.[4]

In this study, we evaluated the patients with an IgG4-RD diagnosis. Therefore, we aimed to report ANCA positivity rate in our IgG4-RD cohort. In addition, we made a comprehensive literature review about the possible relationship between these two clinical entities.

2 | METHODS

2.1 | Patient selection

The institutional ethics committee of Hacettepe University approved the study. There were 62 IgG4-RD patients registered at Hacettepe Vasculitis Center. In 2017 we published the data of 52 patients followed up in our center.[1] A standardized dataset including demographic data, clinical characteristics, imaging and laboratory findings of IgG4-RD was filled for each patient. ANCA tests were performed by immunofluorescence assay (IFA). Enzyme-linked immunosorbent assay (ELISA) method was also used for determination of target antigens of ANCAs as proteinase-3 (PR3) or myeloperoxidase (MPO). Concentrations of the IFA assay were used to indicate antibody titer.

Patients were diagnosed with IgG4-RD according to 'Comprehensive diagnostic criteria for IgG4-related disease'. In 2011, Umehara et al published the article about the criteria with 3 features: (1) clinical/radiological examination showing characteristic diffuse or localized swelling or masses in single or multiple organs; (2) serum IgG4 concentration >135 mg/dL; (3) histopathological examination showing (i) marked lymphocyte and plasmocyte infiltration and fibrosis, and (ii) infiltration of IgG4+ plasma cells with ratio of IgG4+/IgG+ plasma cells greater than 40% and a total of ≥10 IgG4+ plasma cells per high-power field.[5] All 3 criteria (1 + 2 + 3) are needed for definite diagnosis of IgG4-RD.

Second, in 2012, Deshpande et al published the article 'Consensus statement on the pathology of IgG4-related disease'. In the article, three major histopathological features were underlined as associated with IgG4-RD: (1) dense lymphoplasmacytic infiltrate; (2) fibrosis, arranged at least focally in a storyform pattern; (3) obliterative phlebitis.[6]

Recently, Danlos et al hypothesized that there may be an overlap between AAV and IgG4-RD.[4] We performed a systematic literature review in PUBMED database covering the time period from 1976 until April 2018 (Table 1). Relevant publications were searched using these MeSH terms: ''IgG4-related disease and Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis'', "IgG4-related disease and Eosinophilic Granulomatosis with Polyangiitis", "IgG4-related disease and Microscopic Polyangiitis" and "IgG4-related disease and Granulomatosis with Polyangiitis". Results were restricted to studies in humans and articles written in English language. The articles were excluded if the information was given in a form of general information and the cases which were not reviewed in detail. We found 17 cases that had both features of IgG4-RD and AAV.

2.2 | Statistical analysis

Statistical analysis was performed with SPSS 22.0 (IBM, Armonk, NY, USA). Descriptive statistics included mean (standard deviation, SD) and proportion.

3 | RESULTS

Twenty-nine patients (46.7%) in our cohort had positive ANCA results. Twenty of 29 (68.9%) patients were female. Mean age of the patients was (SD) 49.2 (14.6). Fifteen (51.7%), 10 (34.5%) and 4 (13.8%) patients were considered as being probable, possible and definite IgG4-RD patients, respectively. Three of 29 patients (10.3%) had ANCA positivity. Types and titers of ANCA tests were; MPO-ANCA 1/100, MPO-ANCA 1/32 and PR3 ANCA 1/100, respectively. None of these patients had granuloma formation in their biopsies and clinical features related with AAV. The 3 patients were considered as definite, probable and possible regarding the Ig G4- RD criteria. Two of three patients were male (66.6%). None of the patients with negative ANCA test had a clinical feature suggesting AAV.

Cases reviewed from literature were re-evaluated according to the 'Comprehensive Diagnostic Criteria for IgG4-RD (Table 1). Diagnosis of IgG4-RD were definite in 10 cases, probable in two cases and possible in five cases. ANCA were positive in 15 of 17 patients (88%). ANCA were directed against PR3-ANCA in six patients and MPO-ANCA in five patients. Another four cases had both MPO-ANCA and PR3-ANCA positivity. All PR3-ANCA positive cases have high titers of antibodies, whereas only 1 MPO-ANCA positive case had high titers of ANCA antibodies.

Seven cases (41.1%) were compatible with IgG4-RD, especially with regard to biopsy (or with clearly definitive clinical findings). The cases had either negative ANCA or positive ANCA with low-titers and they showed no findings supportive for vasculitis (Case numbers: 1, 2, 7, 11, 12, 13 and 17).

TABLE 1 Cases that have both features of IgG4-related disease and AAV in the literature

No	Author	Age and sex	Clinical findings	IgG4-RD based on CDC[5]	Ig levels	Biopsy	ANCA status	Findings about AAV	Treatment regimen
1	Popkirow et al[14]	52, M	Blurred vision, hearing loss, tinnitus, vertigo, pachymeningeal thickening with contrast enhancement	Probable (Clinical + Biopsy)	Not tested	*Meningeal biopsy*: Plasma cell-rich inflammatory cell infiltration.	MPO-ANCA (+)	No signs of cerebral vasculitis and no signs of granulomatous changes.	IV MPZ PO MPZ IV CYC PO AZA IV RTX
2	Sakairi et al[15]	62, M	Fever, fatigue, episcleritis, acute kidney injury, mild proteinuria, swollen nontender right parotid gland	Definite (Clinical + Biopsy + IgG4 level)	IgG: 1964 mg/dL IgG4: 262 mg/dL	*Kidney biopsy (after steroid therapy)*: Tubulointerstitial nephritis, lymphocyte and plasma cell infiltration, IgG4+/ IgG+ plasma cell rate = 70%, fibrinoid necrosis in an interlobular artery *Parotis biopsy*: Wartin tumor and IgG4+/ IgG+ plasma cells = 20%	MPO-ANCA (−) PR3-ANCA (−)	No FDG uptake compatible with AAV. However, episcleritis and fibrinoid necrosis in interlobular artery and high serum CRP levels support vasculitis.	PO PZ
3	Iguchi et al[16]	64, F	Blurred vision and facial paresthesia, also contrast enhancement of the cranial base with thickening of the dura mater extending to the bilateral orbital areas, bilateral orbital lesions (involving the bilateral lacrimal glands and external ocular muscles, and orbital fissures infiltrating to the cavernous sinuses)	Possible (Clinical + IgG4 level)	IgG: 1881 mg/dL IgG4: 187 mg/dL IgE: 354 IU/mL	*Orbital tumor biopsy*: Neutrophil and lymphocyte infiltration, IgG4+/ IgG+ plasma cells < 5%. No phlebitis was evident. "Although there was no evidence of granuloma formation, rupture of the elastic layer of the arterial walls with neovascularization and a small number of giant cells were observed"	MPO-ANCA = (+) 40 IU/mL (<20 IU/mL) PR3-ANCA = (+) 7.8 IU/mL (<3.5 IU/mL)	No finding in support of systemic vasculitis and granuloma formation	IV PZ (100 mg) PO PZ IV MPZ (1000 mg) PO CYC
4	Touge et al[17]	61, M	Cough, 10-cm diameter mass in the lower lobe of right lung, mediastinal lymphadenopathies	Definite (Clinical + Biopsy +IgG4 level)	IgG: 2.211 mg/dL IgG4: 258 mg/dL	*Transbronchial lung biopsy*: Inflammatory granuloma formation, lymphocyte and plasma cell infiltration, >20 HPF IgG4-positive plasma cell	PR3-ANCA = (+) 246 U/mL (<3.5 U/mL)	No evidence for AAV except granuloma	PO PZ
5	Della-Torre et al[18]	51, F	Swelling of the left lacrimal gland, left orbital pain	Definite (Clinical + Biopsy + IgG4 level)	IgE: 1798 IU/mL IgG4: 253mg/dL	*Lacrimal gland:* Storiform fibrosis, lymphoplasmacytic infiltrate, IgG4+/ IgG + plasma cell rate > 40% Vasculitis or granuloma formation not observed. *Lung:* Chronic granulomatous inflammation, leukocytoclastic vasculitis and geographical necrotic areas, it is supportive for GPA. In addition, there are numerous IgG4-positive plasma cells throughout GPA lesions	c-ANCA (+) (Both IgG4 and IgG1 subclass) PR3-ANCA = (+) 423 AU (<20 AU)	Pulmonary nodules and a cavitary mass (lesion) in right lung, Biopsy findings is supportive for AAV	PO PZ IV RTX
6	Hanioka et al[19]	72, M	Edema, purpura, sensory abnormalities in the lower extremities, painless swelling of lacrimal glands, Dry eyes (Schirmer's test right/left = 4/5 mm), bilaterally swollen lachrymal and submandibular glands without tenderness.	Definite (Clinical + Biopsy +IgG4 level)	IgE: 454 IU/mL IgG: 2.093 mg/dL IgG4: 343 mg/dL	*Skin biopsy*: Leukocytoclastic vasculitis with eosinophilic infiltration *Nasal mucosa biopsy*: IgG4 positive plasmocytes and eosinophils, storiform fibrosis, IgG4+/IgG + plasma cells >40%	MPO-ANCA: (+) 758.0 U/mL (<6.5 U/mL)	Eosinophilia (32.3%, 2,150/μL) and high level of serum IgE, thickening of the nasal mucosa, Multiple mononeuropathies (as confirmed by EMG examination)	PO PZ IV MPZ IVIG

(Continues)

TABLE 1 (Continued)

No	Author	Age and sex	Clinical findings	IgG4-RD based on CDC[5]	Ig levels	Biopsy	ANCA status	Findings about AAV	Treatment regimen
7	Ayuzawa et al[20]	68, F	Productive cough, exertional dyspnea, rash at dorsum of the feet, polyarthralgia, polymyalgia, swollen salivary glands with tenderness, paralysis of right upper extremity. Previous history: history of biopsy-proven membranous glomerulonephritis (12 y ago), asthma (6 mo since diagnosis) CT findings: ground glass opacity, halo sign, bronchial wall thickening and interlobular septal thickening.	Possible (Clinical + IgG4 level) (Biopsy criteria is not obtainable)	IgE: 5.398 U/mL IgG: 1.997 mg/dL IgG4: 275 mg/dL	*Kidney biopsy:* Membranous glomerulonephritis, tubulointerstitial nephritis, patchy infiltration of inflammatory cells, including lymphocytes, plasma cells, and eosinophils, IgG4+/IgG + plasma cell rate = 10% *Skin biopsy:* Eosinophils were predominant in infiltrate. Focal infiltration of neutrophils, eosinophils, lymphocytes, and histiocytes with nuclear fragmentation. No granulomatous angiitis, IgG4+/IgG + plasma cells = 10%	MPO-ANCA (–) PR3-ANCA (–)	WBC: 2.0 × 10^4/mL Eosinophilia: 1.35 × 10^4/mL EMG: neuropathy of right median nerve However, there was no evidence of crescentic and/or necrotizing glomerulonephritis.	PO PZ IV MPZ
8	Su et al[21]	42, M	Recurrent epigastric pain, acute kidney injury and acute pancreatitis history (with normal serum IgG4 and Ig levels)	Definite (Clinical + Biopsy +IgG4 level)	*6 months ago* IgG: 18.7 g/L IgG4: 1.02 g/L IgG4/IgG: 5.4% *At admission* IgG: 25.2 g/L IgG4: 1.83 g/L IgG4/IgG: 7.2%	*Kidney biopsy:* C3 accumulation, necrotizing crescentric glomerulonephritis, periglomerular granuloma formation; massive diffuse lymphocyte and plasma cell infiltration in the tubulointerstitial area. IgG4+/IgG + plasma cells > 40% A storiform interstitial fibrosis was observed in the second renal biopsy specimens.	p-ANCA (+) MPO-ANCA: (+) >200 IU/mL ANCA antibody subtypes: IgG4 (77.3%), IgG1 (22.7%), IgG2 and IgG3 (not detectable)	Glomerulonephritis, periglomerular granuloma formation, chronic paranasal sinusitis, MPO-ANCA positivity, and eosinophilia.	IV MPZ IV CYC PO PZ IV RTX
9	Alexandraki et al[22]	38, F	Amenorrhea, bilateral galactorrhea, polydipsia, polyuria, temporal headache. Bilateral orbital pseudotumor, absence of pituitary posterior bright spot on MRI of hypophysis.	Definite (Clinical + Biopsy +IgG4 level)	IgG4 levels: 3.770 g/L (0.03-2), Serum IgG4/IgG ratio > 50	*Skin biopsy:* Leukocytoclastic vasculitis *Retrobulbar biopsy:* Compatible histopathological findings with IgG4-RD. IgG4+/IgG + plasma cells > 50%.	ANA: 1/1250 p-ANCA (+) MPO-ANCA: (+) 24.4U/mL (<10)	Lung nodules and ground glass opacities support AAV. Leukocytoclastic vasculitis which have either developed after RTX or in the course of vasculitis. CRP is also supportive for vasculitis.	PO PZ PO AZA IV RTX
10	Bravais et al[12]	31, F	Fever (38°C), weight loss, dysphonia, bronchial respiratory sounds (left upper lob), consolidation of both upper lobes and multiple mediastinal lymphadenopathy on CT, bilateral dacryoadenitis, ulcerations of the nasal septum.	Definite (Clinical + Biopsy +IgG4 level)	2.27 g/L (<1.35 g/L)	*Vocal cord granuloma:* Non-diagnostic *Lung:* Storiform fibrosis, plasma cell infiltration IgG4 + plasma cells > 20% (HPF)	MPO-ANCA: 3.4 UA (<2 UA)	Ulcerations on nasal septum.	Pulse MPZ PO PZ
11	Maher et al[23]	79, F	Delirium, slurred speech, back pain, fever, constitutional symptoms, elevated CRP level, IgA MGUS, thickened and enhanced spinal dural lesion with no evidence for cranial dural involvement.	Definite (Clinical + Biopsy +IgG4 level)	High level serum IgG4 (Level is not obtainable)	*Dural biopsy:* Storiform fibrosis, mixed lymphoplasmacytic and histiocytic infiltration, transmural inflammation, damaged vascular walls with organized thrombus. No signs of granuloma or multinuclear giant cell. IgG antibody test?? highlighted many plasma cells (up to 110 positive cells per HPF; n = 3), and an IgG4 antibody test?? revealed a large subset of plasma cells (up to 27 positive cells per HPF; n = 3)	MPO-ANCA positive (Level is not obtainable)	No systemic vasculitis or granuloma formation.	PO PZ IV MPZ IV RTX

(Continues)

TABLE 1 (Continued)

No	Author	Age and sex	Clinical findings	IgG4-RD based on CDC[5]	Ig levels	Biopsy	ANCA status	Findings about AAV	Treatment regimen
12	Masey et al[24]	70, M	Occipital headache, transient vision loss, cough and valsalva maneuver-related syncope, pachymeningeal thickening of intracranial dura on MRI, intracranial hypertension, ureteral obstruction due to suspected enlargement of retroperitoneal lymph nodes in medical history.	Definite (Clinical + Biopsy +IgG4 level)	IgG4: 2.33 g/L (0.08-0.89 g/L)	*Dura biopsy:* Storiform fibrosis, hypertrophic fibrotic tissue IgG4 stained plasma cells >50 HPF There was no granuloma formation.	p-ANCA (+) (1:80) MPO-ANCA: (+) 30 U/mL (<5 U/mL)	No systemic vasculitis or granuloma formation.	IV MPZ PO PZ
13	Ohno et al[25]	73, E	Nasal obstruction, hearing loss, bilateral otitis media, proteinuria CT findings: nasal septum perforation and bilateral pansinusitis	Definite (Clinical + Biopsy +IgG4 level)	IgG: 3085 mg/dL IgG4: 249 mg/dL	*Inferior concha biopsy/nasal mucosa:* Lymphoplasmacytic infiltration, storiform fibrosis (IgG4: 30/HPF; IgG4/IgG ratio, 42%) There is no finding compatible with AAV *Kidney biopsy:* Mesangial proliferative glomerulonephritis and glomerulosclerosis (without necrotizing vasculitis and crescentic glomerulonephritis) There was no IgG4 stained plasma cell.	MPO-ANCA slightly positive 8.3 IU/mL PR3-ANCA (-)	No finding other than pansinusitis and nasal septum perforation for systemic vasculitis	PO PZ PO AZA
14	Drobysheva et al[26]	12, E	Swollen left eye lid and ptosis Contrast-enhanced mass exhibited both preseptal and postseptal components.	Probable (Clinical + Biopsy)	(Not available)	*Eye lid:* Multinuclear giant cells, mixed inflammatory infiltration, granulomatous and necrotizing vasculitis, fibrinoid necrosis, IgG4/IgG ratio: 50%	c-ANCA (1:20) (after treatment)	Biopsy findings (granuloma formation and necrotizing vasculitis) are supportive for both AAV and IgG4-RD	IV MPZ PO PZ PO MTX
15	Kotani et al[27]	55, E	Abdominal discomfort, dry eye and mouth, hydroureteronephrosis. PET-CT: increased FDG uptake at salivary glands and soft tissue density around the abdominal aorta. No FDG uptake in nasal area and pancreas. In history: chronic pancreatitis (9 y ago), chronic sinusitis (3-4 mo ago).	Possible (Clinical + IgG4 level)	IgG: 2.928 mg/dL, IgG1: 1.570 mg/dL (49%) IgG2: 1.190 mg/dL (37%) IgG3: 82 mg/dL (3%) IgG4 351 mg/dL (11%)	*Nasal polyp (before final diagnosis):* Chronic inflammation, lymphocyte and plasma cell infiltration (without granuloma formation or vasculitis), IgG4+/IgG + ratio is unknown.	PR3-ANCA: 43.9 EU (<10)	There is no supportive finding for vasculitis except prior history of sinusitis.	PO PZ PO AZA
16	Tošovský et al[28]	47, M	Fever of unknown origin, weight loss, high level of ESR and CRP. PET-CT: increased FDG uptake in the mass in posterior mediastinum, under the bifurcation of abdominal aorta and aortic arch. In patient history: HLA-B27 positivity, bilateral sacroiliitis and inflammatory back pain for 14 y	Definite (Clinical + Biopsy +IgG4 level)	IgG4: 4.7 g/L	*Mediastinal mass biopsy*: Storiform fibrosis, 50% IgG4 + plasma cells, there was no vasculitis *Kidney biopsy*: Acute focal segmental necrotizing pauci-immune glomerulonephritis and cellular crescents	PR3-ANCA: 136.8 U/mL	Kidney biopsy and ANCA positivity are supportive for AAV	IV MPZ (1000 mg) IV CYC PO MPZ
17	Paulus et al[29]	66, M	Ectropion, erythema and irritation in right eye. Ocular biomicroscopy: Scleritis, fine keratic precipitants, anterior chamber inflammation, synechia. Thickening in infratemporal region of sclera. High level of serum CRP.	Definite (Clinical + Biopsy +IgG4 level)	IgG4: 143 mg/dL (<86) IgG1: 1300 mg/dL (<929)	*Orbital biopsy:* No histopathological evidence for MALT lymphoma or monoclonal plasma cell proliferation. Dense lymphoplasmacytic infiltrates and fibrosis, IgG4+/IgG + plasma cells: 50.3%	PR3-ANCA: 1/80 (<1/20)	No finding in support of systemic vasculitis and granuloma formation	Triamcinolone depot intraocular PO PZ

Note: References are given at the end of the article.

Abbreviations: ANCA, antineutrophil cytoplasmic antibodies; AAV, ANCA-associated vasculitis; AS, ankylosing spondylitis; AZA, azathioprine; CRP, C-reactive protein; CT, computed tomography; CYC, cyclophosphamide; EMG, electromyography; ESR, erythrocyte sedimentation rate; F, female; FDG, fluorodeoxyglucose; GPA, granulomatous with polyangiitis; HLA, human leucocyte antigen; HPF, high-power field; IgG, immunoglobulin G; IgG4, immunoglobulin G4; IV, intravascular; M, male; MPO, myeloperoxidase; MGUS, monoclonal gammopathy of undetermined significance; MPZ, methylprednisolone; MRI, magnetic resonance imaging; PET-CT, positron emission tomography/computed tomography; PO, per oral; PR3, proteinase 3; PZ, prednisolone; RTX, rituximab].

Only one case (5,8%) among cases that had negative ANCA or positive ANCA with low-titers demonstrated findings compatible with IgG4-RD together with vasculitis-supportive clinical and histopathological findings (Case numbers: 9).

There were compatible biopsy findings with both AAV (granuloma) and IgG4-RD in 5 patients (29.4%) who had high titers of ANCA. These cases had no clinical findings for vasculitis (Case numbers: 4, 5, 8, 10 and 14).

Two cases (11.7%) showed high titers of ANCA and they also exhibited biopsy findings compatible with both AAV (granuloma) and IgG4-RD. Further, these cases manifested clinically supportive findings for vasculitis (Case numbers: 6 and 16).

4 | DISCUSSION

In our evaluation of the literature, only 2 (11.7%) cases which were reported to be IgG4-RD and AAV overlap, met the criteria for both diseases.

When our IgG4-RD database was reviewed, none of the patients had features of AAV, and ANCA positivity was detected only in three patients (10.3%; ANCA test was performed in 29 patients).

The presence of arteritis does not exclude the diagnosis of IgG4-RD and systemic vasculitis might also be regarded as a secondary vasculitis associated with IgG4-RD.[6,7] It was seen that only 3 (17.6%) of 17 cases had findings for vasculitis in our literature review.

On histological examination, AAV, especially GPA, can mimic IgG4-RD. AAV histological examination can reveal findings suggestive of vasculitis and/or granulomatous inflammation, and also some fibrosis and/or lymphoplasmacytic infiltration.[8] In our evaluation of the literature, 5 (5/17) cases were diagnosed as IgG4-RD, despite the presence of granulomatous infiltrates. However, the 'consensus statement on the pathology of IgG4-RD' formed the opinion that presence of granulomas excludes the diagnosis of IgG4-RD.[6] From this point of view, although they fulfilled the criteria for IgG4-RD, we believe that these cases had concomitant AAV. While granuloma formation seen in biopsy means the exclusion of IgG4-RD, the presence of other features for IgG4-RD (especially lymphoplasmacytic infiltration) could be a source of confusion for AAV diagnosis. After all, the authors who declare the overlap of these two disease stated that: "… histologic patterns did not overlap in the same tissue samples".[4] It should be kept in mind that the criterion used for AAV diagnosis is a classification criterion. It should also be noted that the International Chapel Hill Consensus Conference (CHCC) is a nomenclature system (nosology) for AAVs. As they have stated, these criteria should not be used as diagnostic criteria.

Biopsy is important for the diagnosis of these diseases. However, in some cases biopsy does not include eligible diagnostic information or biopsy cannot be performed due to patients' preferences or localization of an involved tissue (such as aortitis). Therefore, clinical features and supportive imaging or laboratory findings can lead to diagnosis in some cases for AAV or IgG4-RD. However, these diagnoses often are called as possible or probable, especially in IgG4-RD. It is appropriate to assess patients with a definite diagnosis when we are talking about overlap as a new entity. The patients with definite diagnosis should be evaluated to define the limits of this new concept, because possible or probable diagnoses can be confusing. Further, ANCA positivity or high levels of IgG4 may be caused by a lot of conditions, not only AAV and IgG4-RD.

Compared with the other IgG subclasses, IgG4 has a negligible ability to activate the classic complement pathway, and its binding capacity to Fcγ receptors is lower than IgG1.[9] IgG4 antibodies are thought to be blocking antibodies neutralizing antigens.[9] ANCA antibodies, generally IgG1 subclass, are able to activate neutrophils and play a main role in pathophysiological mechanisms of AAV. Furthermore, the IgG4 subclass of ANCA can play a role in AAV.[10] On the other hand, high serum level of IgG4 in some patients can be explained by the predominance of IgG4 subclasses of ANCA in patients with granulomatosis with GPA.[11] Moreover, reproducibility for antibody serology varies between laboratories. These technical properties may be a reason for an incorrect diagnosis. Particularly, it should be considered in patients who have insufficient clinical features.

Bravais et al supposed that the IgG4 production found in IgG4-RD might promote the development of AAV in some specific patients.[12] Activation of T-regulator (T-Reg) and T-helper 2 (TH2) responses are responsible for elevated IgG4 levels in IgG4-RD. Vaglio et al hypothesized that predominant TH2 responses in patients diagnosed as eosinophilic granulomatosis with polyangiitis may enhance the production of IgG4 antibodies,[9] and their study demonstrated this. In their study, they found highly elevated serum IgG4 levels in EGPA patients with active disease. However, in situ analysis of IgG4 immune responses in tissue biopsies taken from active EGPA patients showed that there was marked IgG4+ plasma cell infiltration in a few cases. These finding suggest that IgG4 responses occur as a systemic perturbation rather than localized reaction, in EGPA.[9]

Chang et al wrote two articles including 26 patients with GPA and 43 cases with IgG4-RD, respectively. In their initial study based on 26 GPA cases, they reported increased IgG4+ cells (increase in IgG4+ cells was defined as greater than 30 per high-power field [HPF]) in biopsy of eight cases and all of them were taken from head and/or neck including sinonasal and orbital regions.[10,13] In their last study, biopsy of 8/43 (18.6%) patients with GPA showed increased IgG4+ plasma cells.[13] These patients were the same as the previous study; all of the biopsies were obtained from head and/or neck area met the criteria for increased IgG4+ cells (>30 per HPF and >40% in IgG4+/IgG+ cells). All eight cases with increased IgG4+ cells had ANCA positivity. They concluded that the morphologic and clinical manifestations of GPA and IgG4-RD may overlap; it could be a significant diagnostic pitfall in the differential diagnosis of these entities.[13] Other histologic features such as granulomas and necrotizing vasculitis should be considered before making a diagnosis of IgG4-RD, especially in the presence of ANCA positivity.[13]

According to the literature and our data, we realized it is not easy to imply with the existing findings that these two diseases overlap. As we clarified above, we always observed that evidence is mostly incomplete in terms of diagnosis for both diseases in the available literature. Based upon our explanation on physiopathology, we believe there is a synergy in the laboratory rather than an overlap.

CONFLICT OF INTEREST

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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