**BRIEF REPORT**

# ANCA-associated vasculitis and IgG4-related disease overlap syndrome: a case report and literature review

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**Abstract**

Anti-neutrophil cytoplasmic antibodies (ANCA)–associated vasculitides are infrequent autoimmune diseases characterized by inflammation of the walls of small vessels leading to tissue and endothelial damage. On the other hand, IgG4-related disease is a fibroinflammatory disease characterized histologically by lymphoplasmacytic infiltrates with IgG4+ plasma cells, storiform fibrosis, and obliterative phlebitis that may affect nearly every organ of the body. There are similarities in clinical, serological, radiological, and histopathological features between both diseases, and hence, they usually mimic each other complicating the differential diagnosis. Furthermore, reports of patients with the coexistence of both conditions (overlap syndrome) have been reported. We herein report a patient with an unequivocal diagnosis of ANCA-associated vasculitis, specifically granulomatosis with polyangiitis (posterior uveitis, polyneuropathy, pauci-immune glomerulonephritis with crescent formation and granulomas, and MPO-ANCA positivity) and IgG4-related disease (thoracic aortitis, tubulointerstitial nephritis with prominent IgG4+ plasma cell infiltration, fibrosis, and obliterative arteritis, high levels of serum IgG4, and eosinophilia) overlap syndrome.

**Keywords** Immunoglobulin G4–related disease · ANCA-associated vasculitis · Granulomatosis with polyangiitis · Overlap syndrome · Aortitis

## Introduction

IgG4-related disease (IgG4-RD) is a fibroinflammatory condition characterized by organ enlargement or pseudo-tumors, high IgG4 serum levels, and lymphoplasmacytic infiltration with IgG4+ plasma cells in affected organs. [1]. On the other hand, the anti-neutrophil cytoplasmic antibody (ANCA)–associated vasculitides (AAV) are a group of systemic autoimmune diseases characterized by predominantly small-vessel wall inflammation that can be divided into

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three clinicopathologic phenotypes: granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA) [2].

IgG4-RD and AAV share clinical, serological, radiological, and histopathological features, making one disease the differential diagnosis of the other. Moreover, cases where criteria for both diseases are met (overlap syndrome), although rare, are increasingly being reported in the medical literature [3, 4].

In this report, we describe the case of a patient with overlapped AAV and IgG4-RD, along with the similarities and disparities of these conditions and a relevant literature review. The patient gave his full consent for the publication of this case.

## Case presentation

A 54-year-old male Mexican farmer with no relevant medical history was admitted in November 2020 to our center in Mexico City during the Covid-19 pandemic. Nine months before his admission, he started with malaise, weight loss, and dry cough. Five months later, he noticed impaired vision predominantly on the left eye, pain, and muscular weakness in the lower extremities, as well as jaw claudication that prevented proper feeding. Antibiotics were prescribed with no improvement. Before his admission at the Institute, he was hospitalized for 3 weeks at a general hospital, where normocytic anemia, leukocytosis, thrombocytosis, and acute kidney injury with serum creatinine (sCr) of 4 mg/dL were reported. During that period, the impaired vision of the left eye progressed to sudden vision loss. The ophthalmological examination reported choroiditis with papilledema, and treatment with three doses of intravenous methylprednisolone of 1g each was prescribed. He was then referred to our tertiary care center to continue his diagnostic approach.

The patient interview revealed malaise, unintended 15-kg weight loss, impaired central vision of the left eye, jaw weakness that limited feeding, weakness of the upper limbs, which was more noticeable while working, and pain and paresthesia in the lower limbs, especially in distal regions of the legs and feet. He denied glandular enlargement, sicca symptoms, chest oppression, headache, dyspnea, fever, nasal discharge, or skin lesions.

Physical examination was remarkable for a heart rate of 69 bpm, respiratory rate of 19 bpm, 96.8°F temperature, and 96% oxygen saturation at room air. A neurological exam revealed stocking hypoesthesia in the left foot. Ophthalmological examination showed normal ocular movements, left eye with a hyporeactive pupil, and a pale optic nerve. Visual acuity in the right eye was 20/70, whereas the left eye perceived only hand movements. Choroiditis was not

observed. There were no other abnormalities in the physical examination.

Laboratory tests disclosed anemia with features of anemia of chronic disease, mild eosinophilia, thrombocytosis, serum albumin 2.5 mg/dL, serum globulins 5.4 g/dL, sCr 7.9 mg/dL, urinalysis without proteins or hematuria, and 24-h proteinuria of 815 mg with no albuminuria. Serum protein electrophoresis showed increased polyclonal globulins, serum free light chains showed increased kappa (337 mg/L, reference 6.7–22.4), and lambda (414 mg/L, reference 8.3–27) chains, with kappa/lambda ratio within the reference range (0.81, reference 0.31–1.56). Serum immunoglobulin G was elevated at 2739 mg/dL, with increased serum IgG4 at 965 mg/dL. Serum complement C3 (125 mg/dL) and C4 (36 mg/dL) were within the reference range. Positive ANCA with cytoplasmic pattern (C-ANCA) at 1:320 dilution were detected, with positive anti-myeloperoxidase (MPO)-ANCA of 42.3 U/mL (reference below 2 U/mL). SARS-CoV-2 PCR was negative, tuberculosis screening was negative (Quantiferon-TB, PPD, sputum smear microscopy, and PCR), and syphilis screening was negative (VDRL, FTA-Abs test). Table 1 summarizes all the laboratory tests.

A high-resolution thoracic computed tomography (CT) scan was performed and revealed a concentric thickening of the ascending aorta and the aortic arch, with extension to the left subclavian artery, findings compatible with aortitis (Fig. 1). A full-body $^{18}$fludeoxyglucose ($^{18}$FDG) PET-CT scan confirmed the mural thickening of the aortic arch with extension to the left subclavian artery with abnormal, albeit low, $^{18}$FDG (SUVmax: 1.8), suggestive of an inflammatory process (Fig. 1). It also disclosed bilateral hypermetabolism of the renal cortex and a diffuse increment in the bone marrow metabolism. A nerve conduction velocity test of the lower extremities revealed a length-dependent motor and sensitive axonal polyneuropathy. Table 2 shows the results of the complementary tests.

Due to the unexplained renal failure, a diagnostic percutaneous kidney biopsy was performed. The histopathological analysis showed chronic tubulointerstitial nephritis (Fig. 2a), with abundant plasma cell infiltration (Fig. 2b), associated with chronic non-caseating granulomatous inflammation with dirty central necrosis (Fig. 2c). Eosinophil infiltration was not seen. Out of a total of 23 glomeruli, 3 of them showed intracapillary hypercellularity and fibrocellular crescent formation (Fig. 2d). Interstitial fibrosis was estimated in 30% and tubular atrophy in approximately 90% (Fig. 2a). No storiform fibrosis was observed. Medium size arteries showed obliterative endarteritis with transmural lymphocyte, hemosiderin-laden macrophages, and plasma cell infiltration (Fig. 2e), abundant subendothelial collagen deposition with severe luminal obstruction was best observed with the trichrome stain of Masson (Fig. 2f). Duplication of the internal elastic lamina was identified (Fig. 2e). Direct

**Table 1** Laboratory test results

| Laboratory test | Results* |
| --- | --- |
| Hemoglobin, g/dL | 7.8 (13–16.6) |
| Leukocytes/μL | 10,200 (4000–10,000) |
| Eosinophils/μL | 936 (<500) |
| Platelet count/μL | 745,000 (150,000–400,000) |
| Serum creatinine, mg/dL | 7.9 (0.6–1.2) |
| Complement C3, mg/dL | 125 (87–200) |
| Complement C4, mg/dL | 36 (19–52) |
| ESR, mm/H | 27 (2–30) |
| CRP, mg/dL | 14.85 (0–1) |
| Urinalysis | Proteins 30 (+) |
| Urine sediment | No dysmorphic red blood cells |
| 24-h proteinuria, mg/24 h | 815 (<150) |
| 24-h albuminuria, mg/24h | 6.6 (0–30) |
| Cerebrospinal fluid | Normal, pH 7, glucose 55 mg/dL (40–70), proteins 25.4 mg/dL (15–45), 0 cells, no microorganisms |
| VDRL and FTA-ABS | Negative |
| Quantiferon-TB | Negative |
| HBV, HCV, and HIV serologies | Negative |
| Histoplasma PCR | Negative |
| Antinuclear antibodies (IIF) | Homogeneous 1:160 (≤1:80) |
| Anti-double stranded DNA | 802 (≤9.6) |
| ANCA (IIF) | C-ANCA 1:320 (≤1:20) |
| MPO-ANCA (ELISA), U/mL | 42.3 (≤2) |
| PR3-ANCA (ELISA), U/mL | 2.1 (≤5.2) |
| Serum IgG, mg/dL | 2739 (635–1741) |
| Serum IgG4, mg/dL | 965 (3–201) |
| Angiotensin-converting enzyme (U/L) | 34.8 (13.3–63.9) |
| SARS-CoV-2 PCR | Negative |
| Serum electrophoresis and immunofixation | Peak in the gamma fraction without a monoclonal spike. |

*Numbers in brackets represent normal reference values

*ANCA*, Anti-neutrophil cytoplasmic antibody; *CRP*, C-reactive protein; *ESR*, erythrosedimentation rate; *FTA-ABS*, fluorescent treponemal antibody absorption test; *HBV*, hepatitis B virus; *HCV*, hepatitis C virus; *HIV*, human immunodeficiency virus; *PCR*, polymerase chain reaction; *IIF*, indirect immunofluorescence; *MPO-ANCA*, myeloperoxidase-ANCA; *PR3-ANCA*, proteinase 3-ANCA; *TB*, Tuberculosis; *VDRL*, venereal disease research laboratory

immunofluorescence reactions were negative for IgG, IgA, IgM, C1q, C3c, fibrinogen, albumin, kappa, and lambda. Warthin-Starry stain and anti-Treponema antibody immunohistochemistry were negative. Immunostaining for IgG4 and IgG disclosed 40 IgG4+ and 44 IgG+ plasma cells per HPF with an IgG4+/IgG ratio of 90% (Fig. 3).

All infectious and other systemic conditions, such as multiple myeloma and sarcoidosis, were ruled out. It was then considered that the patient's symptoms were best explained by a concomitant diagnosis of AAV, specifically GPA (posterior uveitis, polyneuropathy, pauci-immune glomerulonephritis with crescent formation and granulomas, and MPO-ANCA positivity), and IgG4-RD (thoracic aortitis, tubulointerstitial nephritis with prominent IgG4+ plasma cell infiltration, fibrosis and obliterative arteritis, high levels

of serum IgG4, and eosinophilia). Due to the severity of the clinical manifestation, we started treatment with prednisone 1 mg/kg/day for 1 month with subsequent tapering and intravenous monthly cyclophosphamide (500 mg/m² body surface area). He was discharged from hospitalization with renal support with biweekly hemodialysis.

He completed six cyclophosphamide infusions with gradual improvement of symptoms and laboratory parameters. Hemodialysis was stopped at the third month of follow-up with kidney function stabilizing at stage 4 chronic kidney disease. After 6 months of follow-up, he remains asymptomatic and dialysis-free. The last ophthalmological exam and ocular computed tomography reported only choroiditis sequelae. His last laboratory examination showed resolution of proteinuria, negative MPO-ANCA, and IgG and IgG4

**Fig. 1** Chest CT in sagittal/oblique candy-cane (**a**), coronal (**b**), and axial (**c**) views showing concentric thickening of the ascending aorta and the aortic arch. $^{18}$FDG PET-CT scan (**d**) showing thickening of the aortic arch with high $^{18}$FDG uptake
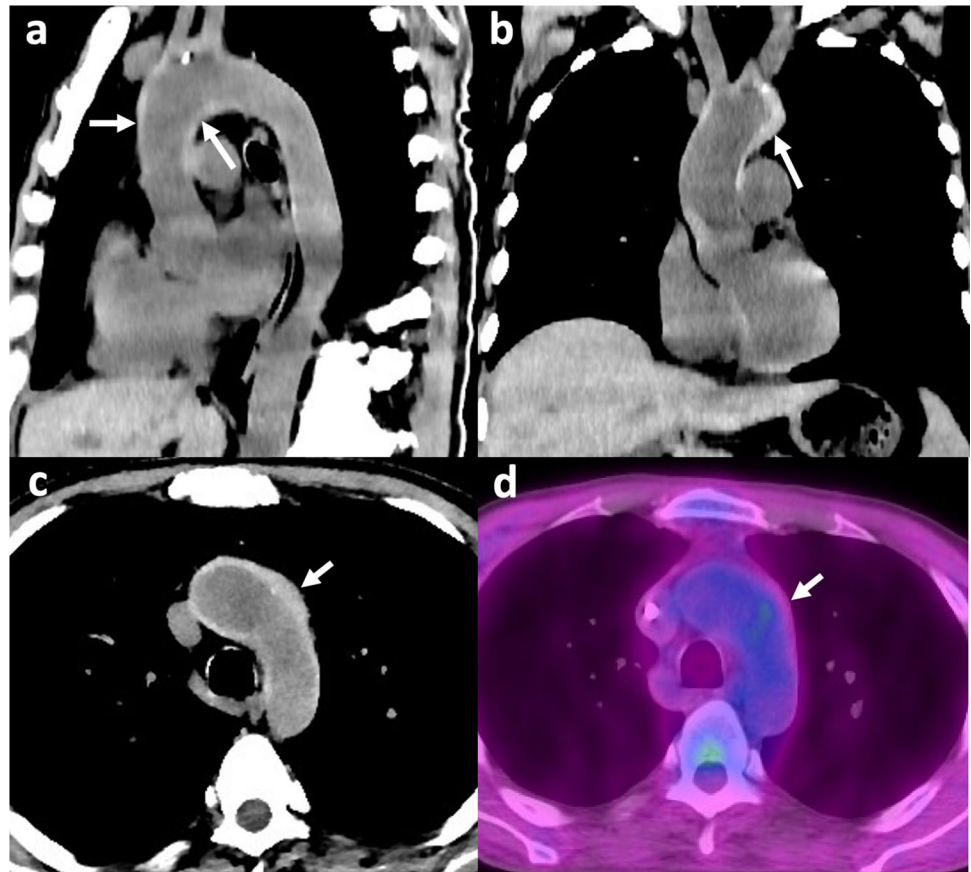


**Table 2** Complementary studies

| Test | Result |
| --- | --- |
| Brain magnetic resonance imaging | Normal |
| Temporal and carotid artery ultrasound | Normal |
| Paranasal sinuses computed tomography | Normal |
| Nerve-conduction velocity test of the lower extremities | Motor and sensitive axonal polyneuropathy |
| Bone marrow biopsy | Hypercellular bone marrow with adequate maturation of all three hematopoietic cell lines. 20% CD138+ mature plasma cells, without light chain restriction (κ/λ ratio: 1:1) and absent myelofibrosis; 34 IgG4+ plasma cell per HPF with an IgG4+/IgG+ ratio of 100%. |

levels within the reference range (1157 mg/dL and 105 mg/dL, respectively). The aortic thickening was stable in the last thoracic CT scan.

## Discussion

As systemic autoimmune diseases, AAV and IgG4-RD share some clinical manifestations and are considered in the differential diagnosis of each other (Table 3). Previous evidence has been heterogeneous and controversial [4]. However, some cases have reported an unequivocal diagnosis of both diseases in the same patient [3, 5–7].

Table 4 summarizes the evidence concerning the relationship between AAV and IgG4-RD.

Danlos et al., in a multicenter European retrospective study, reported 18 patients with overlapped AAV and IgG4-RD [3]. A simultaneous presentation was found in 13/18, AAV preceded IgG4-RD diagnosis in 3/18, whereas IgG4-RD preceded AAV in 2/18. Analogous to our case, IgG4-RD manifestations consisted of tubulointerstitial nephritis in 22%, although none of them had aortitis. Interestingly, only two patients from their cohort exhibited histopathological patterns of both diseases in the same tissue sample, one from an orbital mass biopsy and another from a paranasal sinuses sample. Our patient presented
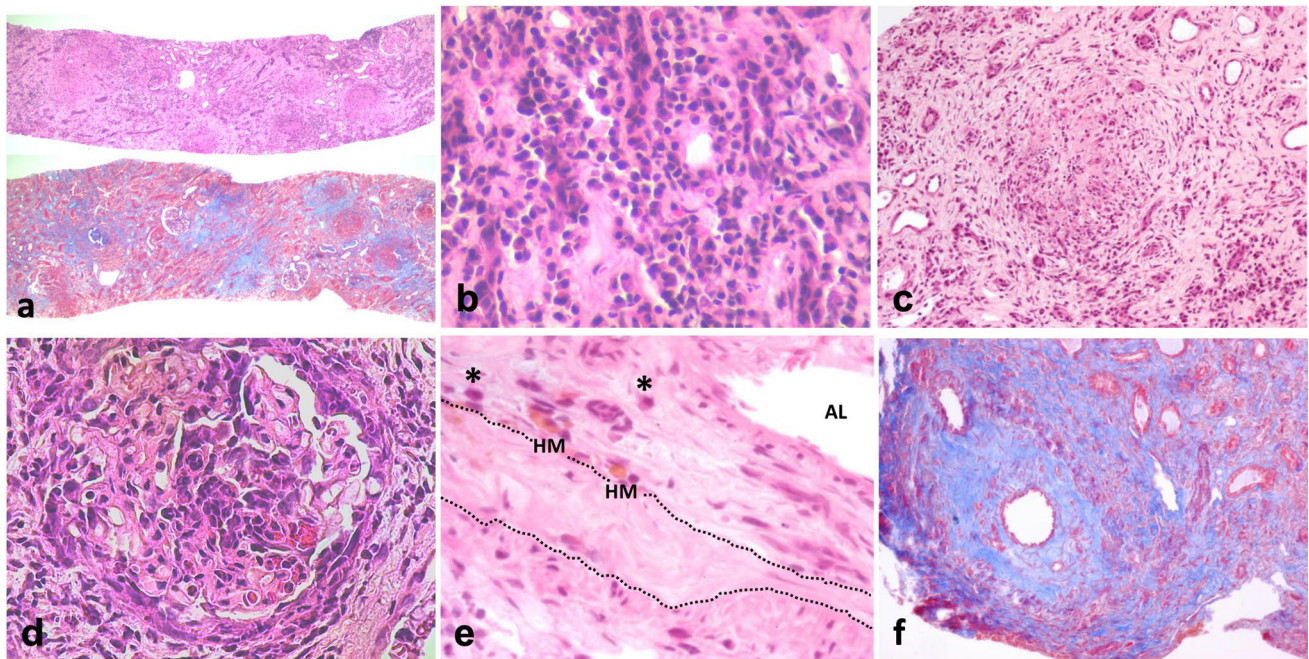
**Fig. 2 a** Kidney biopsy shows prominent inflammatory infiltrate and moderate interstitial fibrosis (H&E [up], trichrome stain [down], 4×). **b** Interstitial inflammation was mainly composed by plasma cells (H&E, 40×). **c** A non-caseating granuloma in renal cortex (H&E, 10×). **d** Glomerulus with a fibrocellular crescent and endocapillary hypercellularity (PAS, 40×). **e** Obliterative endarteritis with plasma cells (*) and hemosiderin laden macrophages (HM) contribute to arterial luminal (AL) reduction; there is also duplication of the internal elastic lamina (dotted lines) (H&E, 40×). **f** Trichrome stain demonstrates severe arterial luminal obstruction (10×)



**Fig. 3** Immunostaining shows abundant **a** IgG+ (IgG × 60) and **b** IgG4+ (IgG4 × 60), there were more than 40 IgG4+ plasma cells per high-power field, with an IgG4+/IgG+ ratio of about 90%
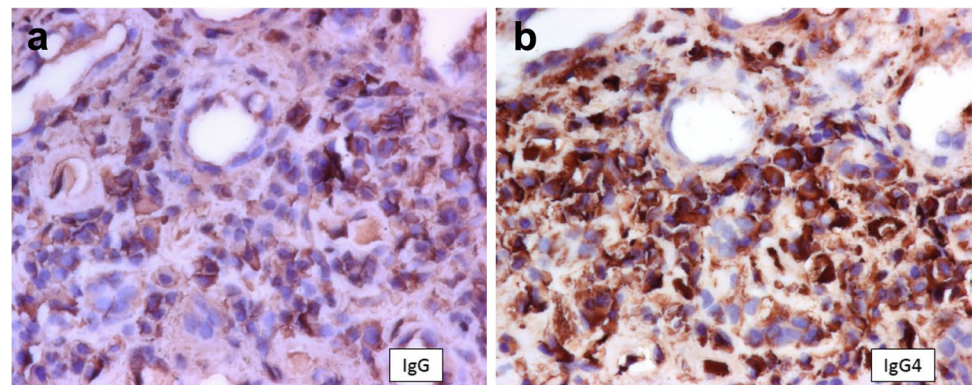
histological characteristics of both disorders in the kidney biopsy [3].

The exact prevalence of this overlap syndrome in cohorts of AAV or IgG4-RD is not well established. Our group previously reported only one patient with IgG4-RD diagnosis within a cohort of 247 AAV patients (prevalence of 0.4%), of which 11.3% had a concomitant systemic autoimmune disease [6]. Conversely, in a French cohort of 109 ANCA-associated glomerulonephritis (ANCA-GN) patients, 15.1% had a concurrent diagnosis of systemic autoimmune diseases, but none had IgG4-RD [29]. Likewise, the prevalence of concomitant AAV in cohorts of IgG4-RD patients seems to

be very low. Inoue et al. reported only one patient with AAV in a cohort of 235 IgG4-RD patients (prevalence: 0.5%) [30].

Furthermore, Ma et al. reported 10 cases of concomitant ANCA-GN and IgG4-RD with renal biopsy [31]. These patients had elevated serum IgG4 levels and positive MPO-ANCA, eosinophilia, higher levels of serum globulin, IgG, IgE, and C-reactive protein than patients in the AAV alone group. Most of the patients in the concurrent group presented renal histological findings of both AAV and IgG4-RD, including crescents, segmental necrosis, storiform fibrosis, and lymphoplasmacytic infiltration in renal interstitium with IgG4+ plasma cells. In a similar study,

**Table 3** Clinical, serological, and pathological features in Granulomatosis with Polyangiitis and IgG4-related disease

| Feature | GPA | IgG4-RD | References |
|---|---|---|---|
| Posterior uveitis | 0.9–3.6% | Limited to case reports | [8–11] |
| Jaw claudication | Possible | Absent | [12] |
| Weight loss | 44% | Uncommon | [13] |
| Aortitis | Limited to case reports | 10% | [14,15] |
| Peripheral neuropathy | 19% | Limited to case reports | [13, 16] |
| Eosinophilia | 25.4% | 30% | [1, 16] |
| Elevated IgG4 | 89% | 82% | [15, 17] |
| ANCA by IIF | 91.5% | 0–56% | [13, 18, 19] |
| PR3-ANCA | 65–78.7% | 3.3–4.5% | [4, 13, 18, 20] |
| MPO-ANCA | 11.6–30% | 6.7–26.6% | [4, 13, 18, 20] |
| Plasma cell-rich interstitial nephritis | 15% of ANCA-GN | Always present in IgG4-TIN | [21, 22] |
| Granulomas | Present | Very infrequent | [23–26] |
| Obliterative arteritis | Absent | May be present in lung, pancreas and kidney | [25–27] |
| Crescent formation | Present | Absent | [21, 28] |

*ANCA, Anti-neutrophil cytoplasmic antibody; ANCA-GN, ANCA-associated glomerulonephritis; GPA, Granulomatosis with polyangiitis; IgG4-RD, IgG4-related disease; IgG4-TIN, IgG4-related tubulointerstitial nephritis; IIF, indirect immunofluorescence; MPO-ANCA, myeloperoxidase-ANCA; PR3-ANCA, proteinase 3-ANCA*

Li et al. described 19 patients with concomitant ANCA-GN and IgG4-related kidney disease (IgG4-RKD) [32]. In both cohorts, IgG4-RD was limited to the kidney (only one patient in the Li et al. cohort had a characteristic IgG4-RD feature, namely, autoimmune pancreatitis), and inclusion in Li et al. cohort was based on diagnostic criteria requiring only >10 IgG4+ plasma cells per HPF without requiring an IgG4+/IgG+ ratio > 40%, raising the question whether those cases were only ANCA-GN with IgG4+ plasma cell infiltration [31, 32]. And although some patients exhibited storiform fibrosis, a characteristic feature of IgG4-RD, it could be present in other conditions that commonly mimic IgG4-RD, including AAV [23, 39–42].

Of note, the presence of IgG4+ plasma cell infiltrates in AAV tissue biopsies is well known. Chang et al. reanalyzed 43 biopsies from GPA patients and performed IgG4 immunostaining. In 8/43 cases, increased IgG4+ plasma cells, defined as >30 per HPF and >40% in IgG4+/IgG+ ratio, were found in biopsies from the head and neck region [33]. Interestingly, two out of the four kidney biopsies included had >10 IgG4+ plasma cells per HPF and an IgG4+/IgG+ ratio >40%, the cutoff values most widely used in consensus and proposed criteria for supporting IgG4-RKD [21, 24]. Another study by Raissian et al. found that 40% of patients with pauci-immune glomerulonephritis had >10 IgG4+ plasma cells per HPF [34]. Furthermore, Houghton et al. found that 5 out of 16 patients with necrotizing and crescentic glomerulonephritis with interstitial nephritis had >10 IgG4+ plasma cells per HPF, all of them positive for either PR3- or MPO-ANCA [35]. Finally, a report by Masuzawa

et al. focusing on the meaning of plasma cell infiltrate in ANCA-GN described 3 cases of plasma cell-rich ANCA-GN with >10 IgG4+ plasma cells per HPF and an IgG4+/IgG+ ratio >40%; they coined the entity as "plasma cell-rich ANCA-GN" stressing its potential to mimic IgG4-RKD [22]. The studies mentioned above indicate that the presence of an IgG4+ plasma cell-rich infiltrate is not specific for IgG4-RKD and, if found in an ANCA-GN biopsy, we should not rush to diagnose concomitant IgG4-RKD in the absence of other organ involvement characteristic of IgG4-RD.

Another consideration is the presence of ANCA positivity in patients with IgG4-RD, and vice versa, the presence of high IgG4 serum levels in AAV. Studies have reported a prevalence of ANCA positivity of 0–56% in different IgG4-RD cohorts [4, 18–20]. Our group previously reported that 14 out of 25 (56%) patients with IgG4-RD were ANCA positive by IIF and 5 out of 22 by ELISA; none of them were diagnosed with overlapping AAV [18]. The presence of ANCA positivity and other autoantibodies in IgG4-RD is believed to represent an epiphenomenon due to the accumulation of non-pathogenic autoantibodies due to chronic inflammation [18, 43, 44]. This hypothesis might explain the positivity of other autoantibodies (i.e., ANA and anti-dsDNA) in the present case.

On the other hand, high serum IgG4 levels have been reported in AAV even before the recognition of IgG4-RD as a distinct entity [36]. In 1991, Brouwer et al., in the seminal work that described that ANCA are predominantly of the IgG1 and IgG4 isotypes, found that IgG4 levels were elevated in 64% of MPO-ANCA AAV [36]. Other studies

**Table 4** Evidence regarding the relationship between AAV and IgG4-RD

| | |
|---|---|
| Danlos et al. [3] | Multicenter European study reporting 18 patients with AAV/IgG4 overlap syndrome. |
| Martín-Nares et al. [6] | The prevalence of IgG4-RD in a cohort of 247 Mexican AAV patients was 0.4% (one patient). |
| Guibert et al. [29] | French study exploring concomitant systemic autoimmune diseases in a cohort of 109 ANCA-GN; none have overlapping IgG4-RD. |
| Inoue et al. [30] | The prevalence of AAV in a cohort of 235 Japanese IgG4-RD was 0.5% (one patient). |
| Ma al [31] | Chinese cohort of 10 patients with concomitant ANCA-GN and IgG4-RD. Patients had elevated serum IgG4 levels and positive MPO-ANCA, eosinophilia, higher levels of serum globulin, IgG, IgE, and C-reactive protein than patients in the AAV alone group. |
| Li et al. [32] | Chinese cohort of 10 patients with concomitant ANCA-GN and IgG4-RKD. |
| Chang et al. [33] | The study analyzed the presence of IgG4+ plasma cells in GPA biopsies. Eight out of 43 biopsies from head and neck region had >30 IgG4+ plasma cells per HPF and IgG4/IgG >40%. Two out of 4 kidney biopsies had >10 IgG4+ plasma cells per HPF and IgG4/IgG >40%. |
| Raissan et al. [34] | Six out of 15 (40%) patients with pauci-immune glomerulonephritis had >10 IgG4+ plasma cells per HPF. |
| Houghton et al. [35] | Five out of 16 patients with necrotizing and crescentic glomerulonephritis with interstitial nephritis had >10 IgG4+ plasma cells per HPF, all of them positive for either PR3- or MPO-ANCA. |
| Masuzawa et al. [22] | Study that coined the entity "plasma cell-rich ANCA-GN". They described 3 cases of plasma cell-rich ANCA-GN with >10 IgG4+ plasma cells per HPF and an IgG4+/IgG+ ratio >40%. |
| Erden et al. [4] | Three out of 29 (10.3%) patients were positive for ANCA in a Turkish IgG4-RD cohort, 2 for MPO-ANCA and 1 for PR3-ANCA. None fulfilled criteria for AAV. |
| Martín-Nares et al. [18] | Positive ANCA by IIF in 14 (56%) of 25 patients and by ELISA in 5 (22.7%) of 22 patients in a Mexican IgG4-RD cohort. None fulfilled criteria for AAV. ANCA-positive IgG4-RD patients by IIF had more frequent lymph node and kidney involvement, high IgG1 levels and ESR, and positive ANA. ANCA were more frequent in the Mikulicz/systemic phenotype. |
| Detlefsen et al. [19] | 17 Danish patients with type 1 autoimmune pancreatitis tested negative for C-ANCA. |
| Sekiguchi et al. [20] | 9 out of 30 (30%) mostly Caucasian IgG4-RD patients tested positive for ANCA, 8 for MPO-ANCA, and one for PR3-ANCA. None fulfilled criteria for AAV. |
| Brouwer et al. [36] | 64% of MPO-ANCA AAV had high IgG4 serum levels. |
| Yoo et al. [17] | 75% of MPA and 88.9% of GPA Korean patients had elevated IgG4 serum levels. |
| Yamamoto et al. [37] | 20% of MPA and 80% of EGPA Japanese patients had elevated IgG4 serum levels. |
| Vaglio et al. [38] | 75% of active EGPA Italian patients had elevated IgG4 serum levels. Serum IgG4 levels correlated with the number of disease manifestations and BVAS. |

*AAV,* ANCA-associated vasculitis; *ANA,* antinuclear antibodies; *ANCA,* anti-neutrophil cytoplasmic antibodies; *ANCA-GN,* ANCA-associated glomerulonephritis; *BVAS,* Birmingham vasculitis activity score; *EGPA,* eosinophilic granulomatosis with polyangiitis; *ESR,* erythrocyte sedimentation rate; *GPA,* granulomatosis with polyangiitis; *HPF,* high power field; *IgG4-RD,* IgG4-related disease; *IgG4-RKD,* IgG4-related kidney disease; *IIF,* indirect immunofluorescence; *MPA,* microscopic polyangiitis

have replicated this finding with the prevalence of high IgG4 serum levels depending on the AAV clinicopathological phenotype. As such, prevalence is 89% for GPA, 20–75% for MPA, and 75–80% for EGPA [17, 37, 38]. None of the patients were diagnosed as IgG4-RD, proposing that the elevation of serum IgG4 may reflect disease activity and chronic inflammation in AAV [17, 38].

Our case could be regarded as GPA with high IgG4 levels and IgG4+ plasma cell-rich ANCA-GN. However, certain features made us conclude we were facing an overlapped condition. First, aortic involvement in AAV is unusual, with only about 13 cases reported in the literature [14, 45–48]. Conversely, aortitis is a classic manifestation of IgG4-RD [15]. IgG4-RD accounts for a significant proportion of all non-infectious aortitis and for approximately 75% of lymphoplasmacytic thoracic aortitis [49, 50]. Thus, in the present case, thoracic aortitis was most likely a manifestation of IgG4-RD. Second, the vascular

lesion found in kidney biopsy was not consistent with vasculitis (i.e., no signs of fibrinoid necrosis, vessel wall destruction, rupture of the elastic membrane) but with the obliterative vascular lesion seen in IgG4-RD, namely, partial or complete obliteration of vessel channels by the lymphoplasmacytic infiltrate [24, 39]. Although obliterative phlebitis is the most characteristic vascular lesion, arteritis has been reported in pancreas, lung, and kidney biopsies of IgG4-RD [25–27]. There are also reports of choroiditis in the context of IgG4-RD; however, we consider that choroiditis in this patient was most likely a manifestation of AAV. Posterior uveitis, including choroiditis, has been reported in 0.9–3.6% of GPA patients [9–11].

EGPA was also considered in the differential diagnosis due to the presence of mild eosinophilia at presentation and positivity for MPO-ANCA. However, mild eosinophilia is frequent in both IgG4-RD and GPA (up to 30% of patients) [1, 16] and, while MPO-ANCA is the predominant ANCA

specificity found in EGPA, 11.6–30% of patients with GPA are MPO-ANCA positive [2, 13]. Furthermore, necrotizing pauci-immune glomerulonephritis in EGPA presents with prominent eosinophil-rich interstitial infiltrates and rarely with renal granulomatosis [51]. Finally, ocular involvement such as uveitis is infrequent in EGPA patients.

Our case was also atypical because the most frequent ANCA specificity in the presence of positive C-ANCA is PR3-ANCA; however, it has been described that some patients with MPO-ANCA have a C-ANCA pattern by IIF [52, 53].

Regarding treatment, it has been suggested that patients with AAV/IgG4-RD overlap syndrome would benefit from anti-CD20 therapy, given the evidence of the efficacy of rituximab in both conditions [3, 7]. Due to economic constraints, rituximab treatment could not be given. We, therefore, opted for cyclophosphamide treatment, which besides being recommended in severe AAV, has proven to be effective in IgG4-RD [54].

## Conclusion

AAV and IgG4-RD may overlap. Given the multiple manifestations of our patient, the best way to explain all of them is to consider an overlap between MPO-ANCA+ GPA and IgG4-RD. Careful correlation of clinical, serological, radiological, and pathological data is of paramount importance when assessing patients with these characteristics. A treatment strategy tailored to target both conditions needs to be pursued.

**Data availability** All data shown.

**Code availability** Not applicable.

## Declarations

**Ethical approval** This case complies with the ethical standards of our Institution.

**Consent to participate** Written permission was obtained from the patient to publish this case report.

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

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