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ORIGINAL ARTICLE

Prevalence of overlap of antineutrophil cytoplasmic antibody associated vasculitis with systemic autoimmune diseases: an unrecognized example of poliautoimmunity

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Abstract

We aimed to estimate the frequency of overlap of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) with systemic autoimmune diseases. Retrospective single-center study to identify patients with AAV diagnosis and concomitant autoimmune systemic diseases, simultaneously, before or after the diagnosis of AAV. Sociodemographic characteristics, such as comorbidities; follow-up time; type of AAV; disease duration; relapses; treatment and response; clinical, serological, and histological characteristics; disease activity and damage; prognosis; dialysis requirements, and death were assessed. Twenty-eight of two hundred and forty-seven patients (11.3%) with AAV had a concomitant diagnosis of autoimmune disease. The predominant AAV type was renal-limited vasculitis (39%), followed by granulomatosis with polyangiitis (29%), mycroscopic polyangiitis (25%), and eosinophilic granulomatosis with polyangiitis (7%). Mean age at AAV diagnosis was 50 ± 17 years and 24/28 were ANCA positive. The main clinical manifestations were renal (79%), otorhinolaryngologic (43%), and pulmonary and peripheral neuropathy (32%). Sixteen patients (57%) experienced partial or total remission at a median follow-up of 34 months, and four patients (14%) died. The most frequent autoimmune disease overlapped was rheumatoid arthritis (39%), followed by Sjögren's syndrome and systemic sclerosis (14%), mixed connective tissue disease (11%), systemic lupus erythematosus and juvenile idiopathic arthritis (7%), and ankylosing spondylitis and IgG4-related disease (4%). In nine patients (32%), both diagnoses were simultaneous; in the rest, median time elapsed between the autoimmune disease and AAV diagnosis was 173 months. The prevalence of overlap AAV with other autoimmune diseases was low. The most common AAV phenotype was renal-limited vasculitis, and the most frequent overlap disease was rheumatoid arthritis.

Keywords ANCA · Autoimmune diseases · Overlap syndromes · Vasculitis

Introduction

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) constitute a group of infrequent autoimmune multisystemic diseases characterized by necrotizing inflammation of small vessels and the presence of circulating pathogenic ANCA [1]. These diseases include granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), eosinophilic granulomatosis with polyangiitis (EGPA), and renal-limited vasculitis (RLV). AAV affect both genders equally, with an average age at diagnosis in the fifth decade and predominance for Caucasians and Hispanics. Estimated annual incidence of GPA and MPA vary from 2 to 12 cases per million population and prevalences from 23 to 160 cases per million population, while EGPA is less frequent, showing an incidence of 1 to 4 cases per million population and a prevalence of 10 to 20 cases per million population [1].

These conditions are rare, and this has impended large epidemiological and clinical studies, despite being an important cause of morbidity and mortality with end-organ dysfunction and failure [1]. The clinical manifestations of GPA and MPA

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are different, and the antibody profile (PR3-AAV vs. MPO-AAV) also determines variations with respect to treatment response, relapse, and outcome. With exception of the limited forms of the disease, most cases will involve more than one organ during the course of the disease, with a clinical picture that resembles other autoimmune conditions [1].

ANCA testing by indirect immunofluorescence (IIF) and enzyme-linked immunosorbent assay (ELISA) is a key feature in the diagnosis of AAV. Only 10–20% of patients with GPA or MPA and up to 60% of patients with EGPA are ANCA negative [1]. Moreover, certain vasculitic conditions (cryoglobulinemia, IgA vasculitis, giant cell arteritis); other autoimmune diseases (Goodpasture's disease, systemic lupus erythematosus (SLE), polymyositis, multiple sclerosis); infections (mycobacterium tuberculosis, hepatitis C, endocarditis); and miscellaneous conditions (sarcoidosis, cocaine abuse, cystic fibrosis) can be associated with positive ANCA tests, and should be considered in the differential diagnosis of AAV [2].

The condition when two or more systemic autoimmune diseases are identified in the same patient is called overlap syndrome [3]. These entities are well recognized in Rheumatology, being the coexistence of two or more connective tissue diseases the most frequent. However, coexistence of AAV with another systemic autoimmune disease is infrequent, and the literature is limited to case reports and multicentric case series. Therefore, we aimed to estimate the frequency of overlap of AAV with systemic autoimmune diseases in a single center over a period of observation of 15 years.

Materials and methods

We conducted a retrospective single-center study to identify by local database all patients > 18 years old with established AAV diagnosis (GPA, MPA, EGPA, or RLV), according to the American College of Rheumatology (ACR) 1990 classification criteria and/or definitions by the 2012 Chapel Hill Consensus, during the period comprised from March 2003 to March 2018. Our center, (Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán) is a tertiary care center in Mexico City, where mainly uninsured patients are referred from all over the country. Patients were included if they had a concomitant diagnosis of other autoimmune systemic disease, either simultaneously, before or after the diagnosis of AAV.

Autoimmune systemic diseases were defined according to established criteria: ACR/European League Against Rheumatism (EULAR) 2010 classification criteria for Rheumatoid Arthritis (RA); 1984 Modified New York criteria for ankylosing spondylitis (AS); ACR revised criteria for SLE; 2002 American-European Consensus Group criteria for primary Sjögren's syndrome (SS); ACR/EULAR 2013 classification criteria for systemic sclerosis (SSc); Alarcón-Segovia diagnostic criteria for mixed connective tissue disease (MCTD); International League of Associations for Rheumatology Classification Criteria for juvenile idiopathic arthritis (JIA); and 2012 Comprehensive diagnostic criteria for IgG4-related disease (IgG4-RD). Patients with insufficient data were excluded.

All data were abstracted from the medical records, including sociodemographic characteristics, comorbidities, and follow-up time. Information regarding AAV comprised the type of AAV; disease duration; relapses; treatment and response; clinical, serological, and histological characteristics; disease activity at diagnosis and damage at the last visit assessed using the Birmingham Vasculitis Activity Score for GPA (BVAS/GPA); and the Vasculitis Damage Index (VDI), respectively; prognosis was evaluated at diagnosis with the Five-Factor score (FFS); dialysis requirements (ever), and death.

Information regarding the overlap systemic autoimmune diseases included disease duration at the time of AAV diagnosis, clinical and serological manifestations, and treatment and response.

References for criteria, scores and indexes used in this study are shown in Online Resource 1.

Descriptive statistics were used, including *n,* percent, mean with standard deviation (SD) and median with minimum and maximum range. Research was conducted in compliance with the Helsinki Declaration. Informed consent was not obtained due to the retrospective nature of the study and no need for approval by the local ethical committee was needed.

This study did not receive any funding.

Results

Two hundred forty-seven patients with AAV diagnosis were identified in the database during the study period; of them, 28 (11.3%) had a concomitant diagnosis of systemic autoimmune disease. Mean age was 57 ± 14 years, 20 (71%) were female, with a median follow-up time after AAV diagnosis of 34 months (1–168). The most frequent comorbidities were arterial hypertension in 12 (43%), dyslipidemia in 6 (21%), diabetes mellitus and osteoporosis in 4 (14%) respectively, and hypothyroidism in 3 (11%).

ANCA-associated vasculitis

The predominant AAV type was RLV in 11 patients (39%), followed by GPA in 8 (29%), MPA in 7 (25%), and EGPA in 2 (7%). Mean age at AAV diagnosis was 50 ± 17 years and 24/28 were ANCA positive (either by IIF or ELISA). At diagnosis, mean BVAS/GPA was 6 ± 4, and median FFS of 2 (0–2), while VDI at the last visit was 3 (0–6). The main clinical

manifestations were renal (glomerulonephritis) in 22 (79%), otorhinolaryngologic in 12 (43%), and pulmonary and peripheral neuropathy in 9 (32%) respectively.

In 25/28 patients, histological confirmation of vasculitis was obtained in one or more organs or tissues, 21/28 had renal biopsy, while 7/28 had meningeal, skin, nasal, aortic valve, intestine, or peripheral nerve biopsies. Only one patient showed renal histological findings of both vasculitis and the overlap disease (SSc).

Treatment consisted mainly of prednisone (89%), azathioprine (64%), or cyclophosphamide (61%), to a lesser extent (< 10%) methotrexate, mycophenolate mofetil, or rituximab. Ten patients (36%) required dialysis (ever). Sixteen patients (57%) experienced partial or total remission at the end of follow-up, and four patients (14%) died.

Characteristics of patients with AAV and overlapped RA/JIA are summarized in Table 1, while Table 2 summarizes patients with AAV and other autoimmune systemic diseases. Figures 1, 2, 3, and 4 show representative cases.

Autoimmune diseases

Mean age at diagnosis of the autoimmune disease was 42 ± 14 years. The most frequent autoimmune disease overlapped was RA in 11 patients (39%), followed by SS and SSc in 4 (14%) respectively; MCTD in 3 (11%) and SLE and JIA in 2 (7%) respectively; AS and IgG4-RD in 1 (4%) respectively. In nine patients (32%), the diagnosis of AAV and systemic autoimmune disease was simultaneous; in the rest, the median time elapsed between the autoimmune disease and the diagnosis of AAV was 173 months (22–408). Only in one patient, the diagnosis of AAV preceded the autoimmune disease by 10 years. In 11 patients (39%), more than 1 autoimmune disease was present, being SS the most frequent (mainly in RA patients), followed by autoimmune liver disease (primary biliary cholangitis or autoimmune hepatitis), vitiligo, and autoimmune hyperthyroidism.

Fifteen patients (54%) had a stable disease at the time of AAV diagnosis. Treatment and serology varied according to the type of autoimmune disease. None of the patients received anti-TNFα therapy during the study period, and only two patients have received D-penicillamine (one with RA and one with SSc). Twenty patients (71%) achieved total remission at a median follow-up time of 61 months (1–418). This information is summarized in Tables 1 and 2.

Discussion

In our retrospective analysis of 247 patients with AAV, we identified 28 patients (11.3%) with concomitant diagnosis of other systemic autoimmune disease. The most common AAV phenotype was RLV, and the most frequent overlap disease was RA. Both diagnoses were simultaneous in 32%; the rest developed AAV in a median of 14 years after the diagnosis of the autoimmune disease.

To our knowledge, this is the first study exploring the prevalence of the entire spectrum of systemic autoimmune diseases in patients with AAV in a well-characterized single-center cohort.

ANCA antibodies can be present in patients with RA. Braun et al. determined the incidence of ANCA in 385 patients with RA and found that 16% were positive for pANCA. These patients exhibited more markers of inflammation and had more frequently rheumatoid vasculitis and lung involvement compared to pANCA negative patients with RA [4]. However, a true AAV picture in RA is rare, with less than 40 cases reported in the literature to date [5–8]. In most of these cases, the diagnosis of RA preceded AAV; renal involvement with typical pauci-immune necrotizing glomerulonephritis was common, and pANCA and MPO-ANCA antibodies were the most frequent, in agreement with our findings [5].

The association of AAV and JIA is exceptional, and only eight cases have been described to date. In every case, AAV followed JIA onset; the most frequent JIA subtype was systemic onset JIA, and the predominant clinical presentation was RLV. In agreement with the adult counterpart, AAV/JIA overlap syndrome tended to be pANCA or MPO-ANCA positive [9–12].

AS coexisting with several vasculitides has been documented in the literature, including Behçet's disease, polyarteritis nodosa, and Takayasu's arteritis [13] Moreover, ANCA positivity has been reported in 14 to 28% of patients with AS, mostly with a perinuclear pattern targeting several antigens like myeloperoxidase and lactoferrin [14].

Crescent formation in lupus nephritis is not rare. In a cohort of 327 Chinese patients with biopsy-proven lupus nephritis, crescentic glomerulonephritis accounted for 10% of the total cohort and 22% of lupus nephritis class IV-G, while the presence of crescents was associated with acute kidney injury and worse renal outcomes [15]. ANCA positivity in SLE patients ranges from 15 to 20%, with pANCA being the most common pattern identified by IIF and MPO-ANCA and lactoferrin-ANCA by ELISA [16]. Furthermore, the presence of ANCA antibodies in lupus nephritis has been reported to correlate with crescent formation [15]. Jarrot et al. described the characteristics of 8 patients with AAV/SLE overlap syndrome together with 31 additional cases from a review of the literature. Overall, patients were mostly female presenting with a clinical phenotype of MPA with rapidly progressive glomerulonephritis and presence of MPO-ANCA antibodies [17]. Both patients with AAV/SLE overlap syndrome from our cohort presented in a likely manner.

The overall prevalence of ANCA positivity in the context of primary SS is 9%; the majority with a pANCA pattern [18]. In a study of 82 patients with primary SS, ANCA antibodies

Table 1 Characteristics of patients with AAV and overlapped RA/JIA

	Sex	Age RA/JIA	Age AAV	Type of vasculitis	RA/JIA features	Time between RA/JIA and AAV (months)	AAV features	BVAS/GPA[a]	VDI[b]	FFS[c]	Treatment	Outcome
1	M	43	43	PR3-ANCA GPA	Symmetrical polyarthritis, RhF, anti-CCP, associated vitiligo	Simultaneous	HP, PN, ENT, pulmonary nodules	9	6	1	CS, CYC, AZA	CR
2	F	45	67	MPO-ANCA GPA	Symmetrical polyarthritis, RhF, anti-CCP	265	GN, ENT, pulmonary nodules, ILD, BS	10	5	2	CS, RTX, AZA	CR
3	F	49	49	MPO-ANCA GPA	Symmetrical polyarthritis, RhF, anti-CCP	Simultaneous	GN, ENT	6	3	2	CS, AZA, RRT	Dead
4	F	49	54	MPO-ANCA GPA	Symmetrical polyarthritis, RhF, anti-CCP, SSS	70	ENT	6	3	0	CS, CYC, AZA, MTX	PR
5	M	48	75	MPO-ANCA MPA	Symmetrical polyarthritis, RhF	306	GN, DAH	7	0	1	CS, CYC, AZA	CR
6	F	25	57	MPO-ANCA MPA	Symmetrical polyarthritis, RhF, SSS	379	GN, PN	10	2	2	CS, CYC	PR
7	F	55	60	MPO-ANCA EGPA	Symmetrical polyarthritis, RhF, anti-CCP, SSS	63	Asthma, PN, ENT, eosinophilia	4	6	0	CS, AZA	CR
8	M	40	55	MPO-ANCA RLV	Symmetrical polyarthritis, RhF, anti-CCP, SSS	178	GN	4	2	2	CS, CYC, AZA	PR
9	F	39	39	MPO-ANCA RLV	Symmetrical polyarthritis, anti-CCP	Simultaneous	GN	4	4	2	CS, CYC, AZA, RRT	NR
10	F	35	68	cANCA RLV	Symmetrical polyarthritis	408	GN	4	2	2	CS, CYC, AZA, RRT	NR
11	F	22	24	pANCA RLV	Symmetrical polyarthritis, RhF, anti-CCP	32	GN	6	3	1	CS, RRT	NR
12	F	14	36	MPO-ANCA GPA	Symmetrical polyarthritis, RhF	250	Subglotic stenosis	1	0	1	Local treatment	PR
13	F	10	36	pANCA RLV	Symmetrical polyarthritis, RhF, anti-CCP	325	GN	4	2	1	CS, RRT	NR

[a] At AAV diagnosis

[b] At last follow-up

[c] At AAV diagnosis

AAV ANCA-associated vasculitis, *anti-CCP* anti-cyclic citrullinated peptide, *AZA* azathioprine, *BS* bronchial stenosis, *BVAS* Birmingham Vasculitis Activity Score, *CR* complete remission, *CS* corticosteroids, *CYC* cyclophosphamide, *DAH* diffuse alveolar hemorrhage, *EGPA* eosinophilic granulomatosis with polyangiitis, *ENT* ear, nose, throat, *FFS* five-factor score, *GN* glomerulonephritis, *GPA* granulomatosis with polyangiitis, *HP* hypertrophic pachymeningitis, *ILD* interstitial lung disease, *JIA* juvenile idiopathic arthritis, *MPA* microscopic polyangiitis, *MTX* methotrexate, *NR* no response, *PN* peripheral neuropathy, *PR* partial remission, *RA* rheumatoid arthritis, *RhF* rheumatoid factor, *RLV* renal-limited vasculitis, *RTX* rituximab, *RRT* renal replacement therapy, *SSS* secondary Sjögren syndrome, *VDI* Vasculitis Damage Index

Table 2 Characteristics of patients with AAV and overlapped autoimmune diseases (AD)

	Sex	Age AD	Age AAV	Overlap syndrome	AD features	Time between AD and AAV (months)	AAV features	BVAS/GPA[a]	VDI[b]	FFS[c]	Treatment	Outcome
14	M	49	49	PR3-ANCA GPA/AS	IBP, sacroiliitis, HLA-B27+	Simultaneous	GN, DAH, ILD, BS, ENT, PN, skin, F	14	5	1	CS, CYC, AZA, MMF, PLEX, RRT	Dead
15	M	22	22	cANCA RLV/SLE	Arthritis, pleuritis, LAD, pericarditis, ascites, PRES, lymphopenia, ANA, anti-dsDNA, anti-nucleosomes, low C3/C4	Simultaneous	GN	4	3	2	CS, CYC, RRT	NR
16	F	41	41	MPO-ANCA MPA/SLE	Arthritis, hair loss, photosensivity, ANA, anti-dsDNA, anti-SSA/Ro, low C3/C4	Simultaneous	GN, DAH, ENT	12	3	2	CS, CYC, AZA	CR
17	F	47	50	MPO-ANCA MPA/SS	Sicca syndrome, parotidomegaly, arthralgias, SCLE, ANA, anti-SSA/Ro, anti-SSB/La, RhF, high IgG, associated PBC	35	GN, PN	4	2	2	CS, CYC, AZA	CR
18	F	48	48	MPO-ANCA RLV/SS	Xerophtalmia, leucopenia, + Schirmer test, + salivary gland biopsy, ANA, anti-SSA/Ro, low C3/C4	Simultaneous	GN	4	3	2	CS, RRT	NR
19	F	50	52	PR3-ANCA GPA/SS	Sicca syndrome, polyarthritis, RF, + Schirmer test, + salivary gland biopsy, ANA, ACA, associated vitiligo	22	GN, DAH, ENT, PN, CN	14	6	2	CS, CYC, PLEX, RTX, RRT	Dead
20[d]	F	38	30	MPO-ANCA GPA/SS	Sicca syndrome, parotidomegaly, LAD, splenomegaly, F, + Schirmer test, ANA, anti-SSA/Ro, RhF, high IgG, associated alopecia areata	120	ENT, scleritis, episcleritis, dacryoadenitis, orbital myositis, GN, erosive arthritis	4	1	2	CS, AZA, MTX	CR
21	M	40	69	MPO-ANCA MPA/SSc	SD, Telangiectasia, DU, PAH, ILD, GAVE	351	GN, PN, GI, F	13	2	2	CS, CYC, AZA	PR
22	F	52	58	MPO-ANCA EGPA/SSc	SD, RF, puffy fingers, polyarthritis, myositis, ILD, ANA, anti-Scl70, associated PBC	58	ENT, PN, skin, heart, eosinophilia	3	3	1	CS, CYC, AZA, MMF	CR
23	F	48	48	ANCA neg RLV/SSc	SD, telangiectasia, myositis, arthralgias, panniculitis, ANA, anti-Scl70, associated AIH/PBC overlap syndrome	Simultaneous	GN	3	1	1	CS, CYC, AZA	CR
24	M	65	79	cANCA RLV/SSc	SD, ED, ILD, PAH, PN, ANA, anti-RNA Pol III	168	GN	4	2	2	CS, PLEX, RTX	NR
25	F	36	52	MPO-ANCA RLV/MCTD	RF, SD, arthritis, myositis, puffy hands, ANA, anti-U1RNP, associated Graves' disease	244	GN	4	1	1	CS, CYC, AZA	PR
26	F	43	51	MPO-ANCA MPA/MCTD	SD, arthritis, myositis, puffy hands, calcinosis, ILD, ANA, anti-U1RNP, RhF	100	PN, ENT, panniculitis	8	2	0	CS, CYC, LFM	CR
27	M	54	59	ANCA neg RLV/MCTD	RF, SD, arthritis, myositis, puffy hands, PAH, ILD, ANA, anti-U1RNP, RhF	68	GN	4	2	1	CS, AZA	Dead
28	F	69	69	MPO-ANCA MPA/IgG4-RD	Dacryoadenitis, + biopsy	Simultaneous	GN, ILD, arthritis, ENT, F	7	4	2	CS, RRT	NR

[a] At AAV diagnosis

[b] At last follow-up

[c] At AAV diagnosis

[d] AD diagnosis after AAV

AAV ANCA-associated vasculitis, *ACA* anticentromere antibodies, *AIH* autoimmune hepatitis, *ANA* antinuclear antibodies, *AS* ankylosing spondylitis, *AZA* azathioprine, *BS* bronchial stenosis, *BVAS* Birmingham Vasculitis Activity Score, *CN* cranial neuropathy, *CR* complete remission, *CS* corticosteroids, *CYC* cyclophosphamide, *DAH* diffuse alveolar hemorrhage, *DU* digital ulcers, *ED* esophageal dismotility, *EGPA* eosinophilic granulomatosis with polyangiitis, *ENT* ear, nose, throat, *F* fever, *FFS* five-factor score, *GAVE* gastric antral vascular ectasia, *GI* gastrointestinal, *GN* glomerulonephritis, *GPA* granulomatosis with polyangiitis, *IBP* inflammatory back pain, *IgG4-RD* IgG4-related disease, *ILD* interstitial lung disease, *LAD* lymphadenopathy, *LFM* leflunomide, *MCTD* mixed connective tissue disease, *MMF* mycophenolate mofetil, *MPA* microscopic polyangiitis, *NR* no response, *PAH* pulmonary arterial hypertension, *PBC* primary biliary cholangitis, *PLEX* plasmapheresis, *PN* peripheral neuropathy, *PR* partial remission, *PRES* posterior reversible encephalopathy syndrome, *RhF* rheumatoid factor, *RF* Raynaud's phenomenon, *RLV* renal-limited vasculitis, *RTX* rituximab, *RRT* renal replacement therapy, *SCLE* subacute cutaneous lupus erythematosus, *SD* sclerodactily, *SLE* systemic lupus erythematosus, *SS* Sjögren syndrome, *SSc* systemic sclerosis, *VDI* Vasculitis Damage Index

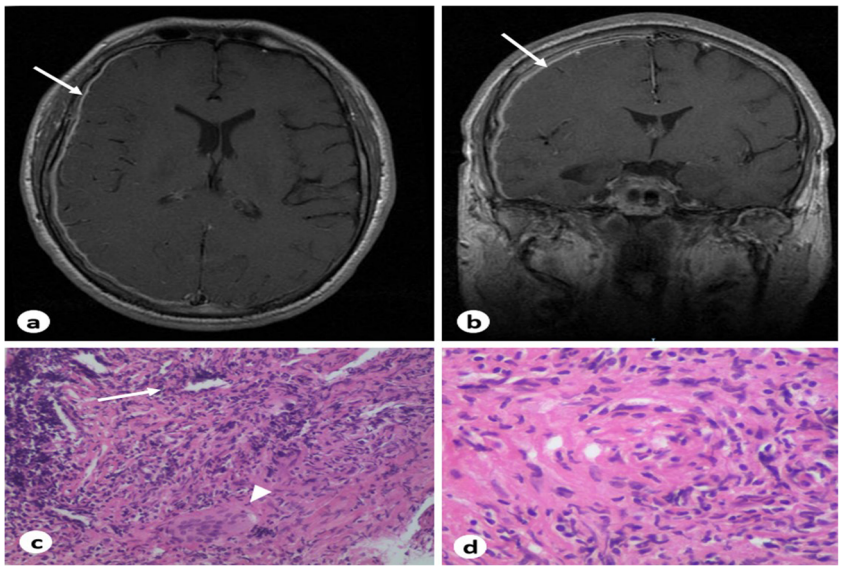

Fig. 1 Patient 1. Axial **a** and coronal **b** T1-weighted MRI with gadolinium showing dural thickening with enhancement over the right cerebral hemisphere consistent with hypertrophic pachymeningitis (arrows). Meningeal biopsy **c** showing inflammatory infiltrate at the vessel wall (arrow) and an adjacent multinucleated giant cell (arrowhead) (hematoxylin and eosin stain × 10). **d** Vessel with inflammatory infiltrate and occluded lumen (hematoxylin and eosin stain × 40)

were detected in 9 (11%). These patients exhibited higher frequency of extraglandular manifestations, such as cutaneous vasculitis, Raynaud's phenomenon, and peripheral neuropathy, compared to the ANCA negative patients with SS [19]. Only 24 cases of primary SS coexisting with AAV have been described in case reports and multicentric case series [18, 20, 21]. In most of the cases, AAV diagnosis was concomitant or followed SS diagnosis; the majority of patients had MPA or RLV with a predominant pANCA pattern and MPO-ANCA specificity [18]. Of note, most patients had experienced extraglandular manifestations of SS, in accordance with the finding that ANCA are associated with these manifestations [19].

Atypical ANCA have been detected in up to 35% of sera from patients with SSc without clinical features of AAV, being bacterial/permeability-increasing protein (BPI) and cathepsin G the main ANCA antigenic targets [22]. Akinomoto et al. reported 7 (9%) of patients in a cohort of 77 individuals with SSc positive for both pANCA and MPO-ANCA; only one of them showing a real AAV/SSc overlap syndrome [23]. Less than 60 cases of this overlap syndrome have been reported in the literature, mainly in single case reports. Revision of the existing reports in the literature found a majority of limited SSc cases, anti-Scl-70, pANCA, and MPO-ANCA positivity, and most common AAV phenotype being MPA and RLV [24, 25]. Interestingly, interstitial lung disease occurs in about 80% of patients with AAV/SSc overlap syndrome, more commonly than the prevalence of this manifestation in either disease alone [24]. This could be due to the higher frequency of MPO-ANCA antibodies in the overlap condition that have been found to contribute to pulmonary tissue injury and pulmonary fibrosis [26].

The association of AAV and MCTD is very rare, and only 11 cases have been reported in the literature to date [27–29]. Most patients developed AAV after MCTD diagnosis; the predominant phenotypes were RLV and MPA, with only two cases of GPA reported, and most patients were positive for MPO-ANCA. We found three patients with AAV/MCTD overlap syndrome in our cohort, and in accordance with the previous reports, two have RLV and 1 MPA, with two of them being MPO-ANCA positive. As the prevalence of renal involvement in MCTD is low, we believe that AAV should be ruled out in patients with MCTD presenting with glomerulonephritis.

IgG4-RD is a recently unified entity that shares many features with AAV, especially with GPA: both diseases can affect a similar array of anatomic sites and histopathological findings are consistent among different organs. Furthermore, AAV patients may exhibit elevated serum IgG4 levels, especially EGPA, and up to 18% of biopsies samples from GPA patients, especially those from head and neck sites, may show increased IgG4+ plasma cells [30, 31]. Raissan et al. reported IgG4+ plasma cell infiltration in 6 of 15 pauci-immune necrotizing glomerulonephritis biopsies [32]. Thus, it is not surprising that both conditions may mimic each other complicating the differential diagnosis. Recently, observations of ANCA positive IgG4-RD and true AAV/IgG4-RD overlap syndrome have been published as case reports [33]. Danlos et al. conducted an European multicenter observational study and found 18 cases of this overlap syndrome, mainly associated with GPA and PR3-ANCA, concluding that it is necessary to consider IgG4-RD if atypical manifestations are present in patients with AAV, such as chronic periaortitis, tubulointerstitial nephritis, and prevertebral fibrosis [31].

Whether there are differences in treatment response and outcomes in patients with AAV alone compared to AAV overlapped with systemic autoimmune diseases has not been formally compared due to the rarity of the latter condition. Frequency of treatment response depends on the specific overlapping autoimmune disease. It has been reported in 71, 76,

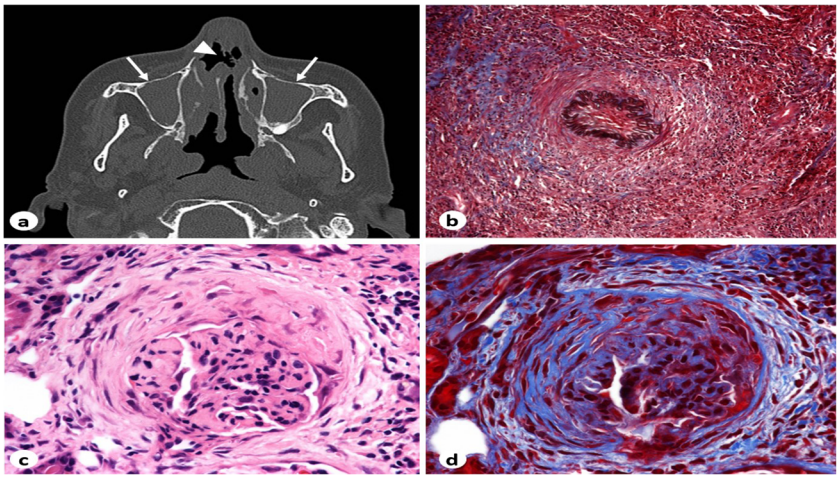

Fig. 2 Patient 19. **a** Axial head CT scan showing septum perforation (arrowhead) and complete occupation of maxillary sinuses (arrows). **b** Turbinate biopsy showing evidence of medium size vessel vasculitis with predominantly lymphocytic inflammatory infiltrate (Masson's trichrome stain × 40). Renal biopsy showed pauci-immune proliferative extracapillar and necrotizing glomerulonephritis; images c and d show a glomerulus with a fibrous crescent and extracapillar proliferation (hematoxylin and eosin stain and Masson's trichrome stain × 40)

77, and 82% of patients with AAV/RA, AAV/SLE, AAV/SS, and AAV/IgG4-RD overlap syndromes, respectively [5, 17, 18]. In the series of Quémeneur et al., six of seven patients with AAV/SSc overlap syndrome achieved remission, and none had end-stage renal failure or scleroderma renal crisis despite the use of high-dose corticosteroids for remission induction of AAV [25]. In accordance with this finding, none of our four patients with AAV/SSc overlap syndrome had scleroderma renal crisis, despite three of them had autoantibodies associated with risk for this complication, namely, anti-Scl70 and anti-RNA polymerase III. We found a lower frequency of treatment response in our cohort, with only 57% achieving AAV complete or partial remission at the end of follow-up. Although our study does not allow to draw conclusions regarding treatment of the overlap syndromes, the finding that 46% of our patients had active systemic autoimmune disease at the time of AAV diagnosis suggests that treatment approaches targeting both conditions are needed.

The occurrence of two autoimmune diseases in the same individual is explained by both environmental factors and the interplay with genetic susceptibility, a concept that has been coined as shared autoimmunity [3]. The predisposition to poliautoimmunity in our patients was demonstrated by the association with a third autoimmune disease in 39% of them.

Studies in AAV and in some other autoimmune diseases have shed light into common genetic susceptibilities. As an example, the 620W allele of the *PTPN22* gene has been reported as a risk for developing RA and AAV in Mexican patients [34, 35], and some polymorphisms in the uteroglobin and NF-kappaB2 genes have been implicated in susceptibility for RA and systemic vasculitides, including AAV [36]. Other possible explanations for the occurrence of these overlap

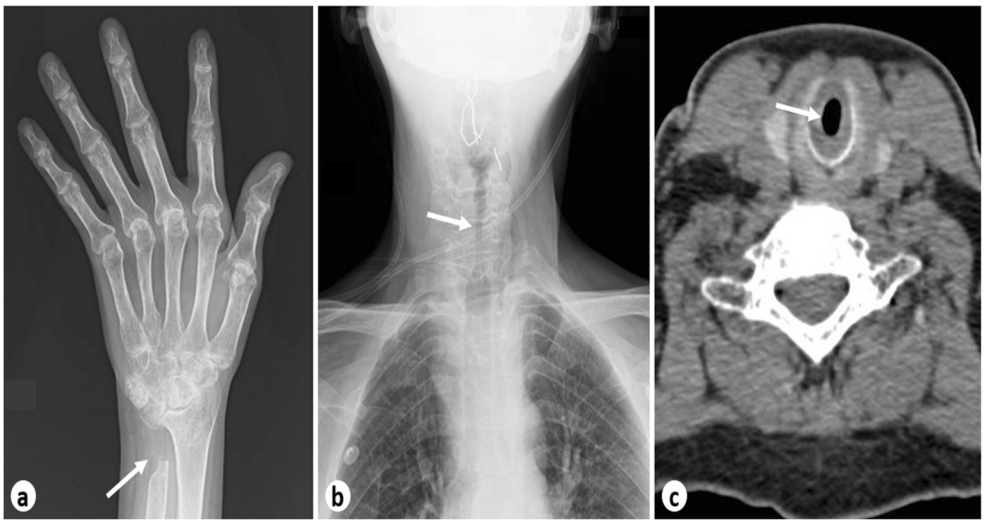

Fig. 3 Patient 12. **a** Hand x-ray showing changes of an inflammatory erosive arthropathy on carpal, metacarpophalangeal and proximal interphalangeal joints, along with severe resorption of the distal ulna (arrow). **b**, **c** Cervical x-ray and neck axial CT scan showing severe tracheal stenosis at the subglottic level (arrows)

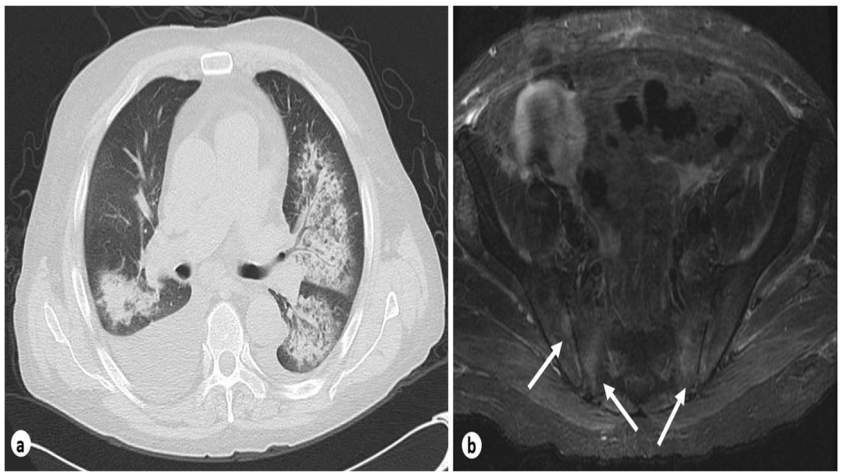

Fig. 4 Patient 14. **a** Axial chest CT scan (lung window) with bilateral patchy infiltrates with air broncogram and areas of ground grass opacities during an episode of diffuse alveolar hemorrhage. **b** Axial STIR sequence MRI at an axial plane of the sacroiliac joints shows high signal subchondral bone marrow edema (arrows) and small erosions in the iliac aspect of the right sacroiliac joint suggestive of bilateral sacroiliitis

syndromes could be shared associations with major histocompatibility complex alleles. Furthermore, MCTD and MPO-ANCA AAV have been associated with the HLA-DQ alleles, which may explain the tendency of this overlap syndrome to be MPO-ANCA positive [37, 38].

Another possible explanation for the appearance of AAV in the setting of established autoimmune disease is drug exposure. For instance, AAV may occur after anti-TNFα therapy [39]; however, none of the patients in our cohort have received anti-TNFα therapy. Moreover, D-penicillamine has also been associated with the induction of AAV in patients with RA and SSc [40]. In this regard, two patients in our cohort were exposed to this drug previous to AAV diagnosis; one of them (patient 21) developed AAV 29 years after D-penicillamine discontinuation, so a causal relationship is not likely, while the second patient (patient 6) was taking D-penicillamine at the time of AAV diagnosis, and therefore, a causal association of this drug cannot be excluded.

This study has some limitations. First, our Institution is a referral center for systemic autoimmune diseases; consequently, the prevalence of these overlap syndromes may be overestimated due to referral bias. Second, the sample size is relatively small; however, as AAV are rare diseases, our study contributes significantly to what has been published on this topic. Third, not all cases were biopsy-proven; nevertheless, we have no doubt about the certainty of AAV diagnosis using a clinical, serological, and radiological correlation.

Some strengths of our study include that we assessed the prevalence of systemic autoimmune diseases in a cohort of AAV patients, allowing us to contribute with our observations to the current published data, which is mostly derived from single case reports. Second, this was a single-center study that included patients diagnosed and treated in a similar manner.

In conclusion, systemic autoimmune diseases can rarely coexist in patients with AAV. The diagnosis of AAV ensue mostly after the appearance of the other systemic autoimmune disease or simultaneously. In our cohort, the most common AAV phenotype was RLV, followed by GPA and MPA, with the majority of cases being MPO-ANCA positive, while the most frequent overlapped disease was RA. These unique overlap syndromes represent another example of poliautoimmunity. Further studies are needed to investigate the possible shared mechanisms for developing overlap syndromes.

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Authors' contributions EMN and AHA designed the study; EMN and DZT participated in acquisition of data; AHA analyzed and interpreted data; EMN and AHA drafted the manuscript; EMN, DZT, and AHA revised the manuscript.

Compliance with ethical standards

Research was conducted in compliance with the Helsinki Declaration. Informed consent was not obtained due to the retrospective nature of the study and no need for approval by the local ethical committee was needed.

Disclosure None.

Ethical standards statement The manuscript does not contain clinical studies or patient data.

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