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CASE BASED REVIEW

Aortitis caused by antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitis: a case-based review

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Abstract

Antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitis (AAV) is a systemic necrotizing small vessel vasculitis primarily affecting elderly patients. Neutrophil apoptosis and release of pro-inflammatory mediators promote small vessel inflammation and hence multi-organ disease. It rarely affects larger vessels with extremely rare aortic involvement. Diagnosis is made based on clinical presentation, tissue biopsy of affected organ, as well as immunofluorescence and ELISA assays for ANCA. Management includes immunosuppression (e.g., glucocorticoids, cyclophosphamide and rituximab) and supportive therapy. We present a rare case of a younger patient with AAV involving the aorta. The patient's diagnosis was supported by clinical presentation, systemic organ involvement, strongly positive c-ANCA, and skin as well as aortic tissue biopsy results. After failing multiple immunosuppressants, he responded well to rituximab with improved symptoms, inflammatory markers, and imaging findings. Based on our literature review, we were only able to find ten cases of ANCA-related vasculitis involving the aorta. This is the first reported case of successful treatment of AAV-related aortitis using rituximab. Our case report and literature review provide insight into treatment of severe cases of AAV with aortic involvement.

Keywords Antineutrophil cytoplasmic antibodies (ANCA) · Vasculitis · Aortitis · Rituximab

Introduction

Antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitis (AAV) is a necrotizing small vessel vasculitis that is mostly associated with positive antibodies against myeloperoxidase (MPO-ANCA) or proteinase 3 (PR3-ANCA) [1, 2]. ANCA-negative AAV has been rarely reported in the literature [3]. The major subtypes of AAV include granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), renal-limited vasculitis (RLV), and eosinophilic granulomatosis with polyangiitis (EGPA) [1, 2].

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AAV equally affects both genders and is commonly diagnosed in older Caucasian adults at their 65–74 years of age [4–6]. An overall incidence rate of 13–20 million AAV cases has been reported in Europe [6].

Patients with AAV usually present with constitutional symptoms including fatigue, weight loss, decreased appetite and fever [4, 7, 8]. Patients with MPA and GPA can also present with orbital, ear, nose, throat, airway, pulmonary, and cutaneous manifestation. Furthermore, pauci-immune glomerulonephritis has been reported [4, 5, 8]. Patients with EGPA typically present with asthma, rhinosinusitis and peripheral eosinophilia [9]. They can also develop mononeuritis multiplex, carditis and various dermatologic manifestations [9].

Although small vessel vasculitis is a known manifestation of AAV, large vessel involvement is very uncommon. Furthermore, AAV-related aortitis is even much less reported, with literature limited only to case reports [10]. Based on our literature review, we were only able to find ten cases reported worldwide of AAV involving the aorta (Table 1). While there were positive titers for either p-ANCA or c-ANCA, six out of these ten patients were older than

Table 1 Literature review of AAV with aortic involvement

Paper	Location	Age	Gender	ANCA classification	Type of aortic involvement	Other affected vessels reported	Primary immuno-suppressive treatment
Sasaki et al. 2016 [26]	Japan	66	Male	c-ANCA	Saccular aneurysms in the thoracic and abdominal aorta	Renal artery	Cyclophosphamide
Carels et al. 2015 [27]	Belgium	63	Male	p-ANCA	Inflammatory aneurysm of abdominal aorta, periaortitis	Artery bifurcating from temporal artery	Cyclophosphamide
Takenaka et al. 2015 [28]	Japan	47	Female	p-ANCA	Wall thickening in thoracic arch	Alveolar capillaries	Tocilizumab
Amos et al. 2012 [29]	Australia	64	Male	c-ANCA	Periaortic edema of the abdominal aorta, edema of both the thoracic arch and region inferior to the origin of renal arteries	Glomerulus	Cyclophosphamide, methotrexate
Chirinos et al. 2004 [10]	United States	50	Female	p-ANCA	Dissection from the first intercostal artery to the iliac bifurcation, soft tissue density anterior to the thoracic aorta	Glomerulus, small and medium sized vessels, pulmonary vessels	Cyclophosphamide
Schildhaus et al. 2002 [30]	Germany	63	Male	c-ANCA	Inflammatory infiltration into descending thoracic aorta	Renal, interlobular, coronary, and small pulmonary arteries Small arteries in the periadrenal soft tissue/skeletal muscle/spleen Small vessels and capillaries in nasal wings, earlobes, lower legs, fingers, and toes	None
Nakabayashi et al. 2000 [31]	Japan	73	Female	p-ANCA	Thickened thoracic aorta, main branch artery stenosis	Right subclavian artery, glomerulus, coronary artery, pulmonary capillaries, small vessels of fingers	None
Nakabayashi et al. 2000 [31]	Japan	68	Female	p-ANCA	Calcified abdominal aorta wall, thickened thoracic aorta wall, irregularities of abdominal aortic wall	Left axillary artery, left subclavian artery	N/A
Blockmans et al. 2000 [32]	Belgium	42	Male	c-ANCA	Retroperitoneal inflammation surrounding the abdominal aorta, dilatation and dissection of abdominal aorta	Nasal, pulmonary, nervous and renal vascular involvement, inferior mesenteric artery	Cyclophosphamide
Morshuis et al. 1997 [33]	Netherlands	53	Male	c-ANCA	Aortic regurgitation, aortic valve inflammation, thickening of aortic wall	Coronary ostium, left main coronary artery, glomerulus	Cyclophosphamide

60 years of age. The majority of these cases were treated with a regimen that included cyclophosphamide.

We present a rare case of AAV-related aortitis that manifested in a younger patient with both thoracic and abdominal aortic involvement. He failed an initial management trial with high-dose steroids and then tocilizumab; he finally responded well to rituximab which, to our knowledge, was the first time it has been used to treat AAV-related aortitis.

Case report

A 50-year-old man with a medical history of obesity presented with a 14-day-history of substernal chest discomfort with dyspnea, fever (39.4 °C at home), muscle ache, night sweats, and chills. Vital signs noted a left upper extremity blood pressure of 119/65 mmHg, heart rate of 133 beats/min, and body mass index (BMI) of 37.24 kg/m^2. Physical examination demonstrated an obese man with fast, irregular and distant heart sounds, harsh breathing sounds, mild ankle edema and bilateral shin petechial rash. Pertinent abnormal laboratory (lab) results demonstrated a white blood count (WBC) of 16.6 thou/mm^3, platelet count of 496 thou/mm^3, hemoglobin of 11.1 g/dL, significantly elevated erythrocyte sedimentation rate (ESR) of 96 mm/h and C-reactive protein (CRP) of 26 mg/dL. Echocardiogram revealed severe pericardial effusion with 13 mm separation of pericardial layers. To discern the presence of vascular abnormalities, a CT angiography of the neck, chest, abdomen, and pelvis was performed and demonstrated ascending aortic enlargement (61 × 57 mm) with significant wall thickening (up to 10 mm) involving the ascending aorta, aortic arch and abdominal aorta (Fig. 1a–c). CT also demonstrated the presence of mediastinal lymphadenopathy and lung nodules. Skin biopsies of the left leg rash revealed superficial perivascular infiltrate composed of predominately neutrophils and lymphocytes. Mild endothelial cell swelling was also seen (Fig. 2a, b). Further autoimmune workup revealed strongly positive proteinase 3-antineutrophil cytoplasmic antibodies (c-ANCA) (> 1:160), and mildly elevated antinuclear antibody (Speckled 1:80) and rheumatoid factor (33.3 IU/mL), but normal IgG4 levels.

An initial diagnosis of inflammatory aortitis was made with possible underlying etiologies including giant cell arteritis, rheumatoid arthritis or ANCA-related vasculitis. The patient was initially started on a high dose of prednisone (60 mg/day) with resolution of pericardial effusion and skin rash. However, over the course of several months, patient continued to require high doses of prednisone (60–80 mg a day) without complete improvement of symptoms, labs (ESR and CRP) or imaging (aortic wall thickening). Thus, a weekly injection of subcutaneous tocilizumab 162 mg was tried for 12 weeks without significant response. Although

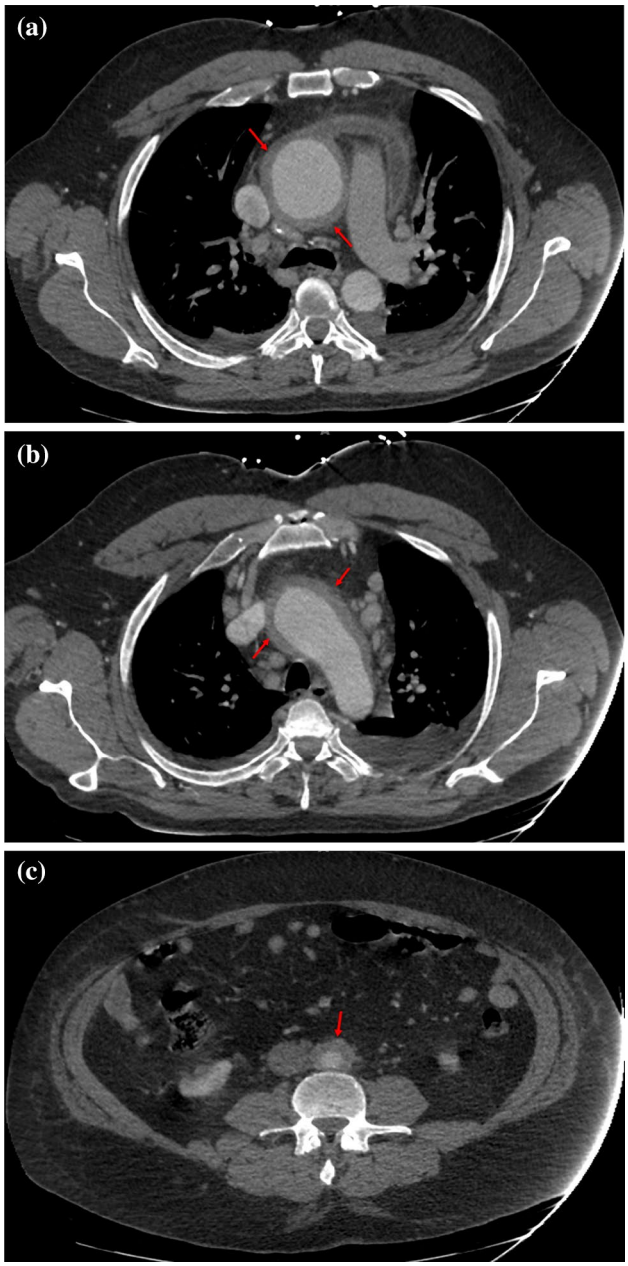

Fig. 1 Transverse images of a CT angiogram of chest and abdomen revealing wall thickening of the **a** ascending aorta (8 mm), **b** aorta arch wall (8.8 mm), **c** abdominal aorta (10 mm)

rarely reported, ANCA-related aortitis was finally diagnosed based on systemic involvement (including lung, skin, and heart), strongly positive ANCA (PR3), and skin rash biopsy results. The patient responded very well to three courses of intravenous rituximab (375 mg/m^2 weekly for 4 weeks) administered 6 months apart as he demonstrated significant improvement of symptoms (fatigue, night sweats, chest pain), inflammatory markers (ESR = 22 mm/h and CRP = 3.94 mg/dL), and imaging findings (reduced wall thickening, Fig. 3a, b). The prednisone dose was tapered

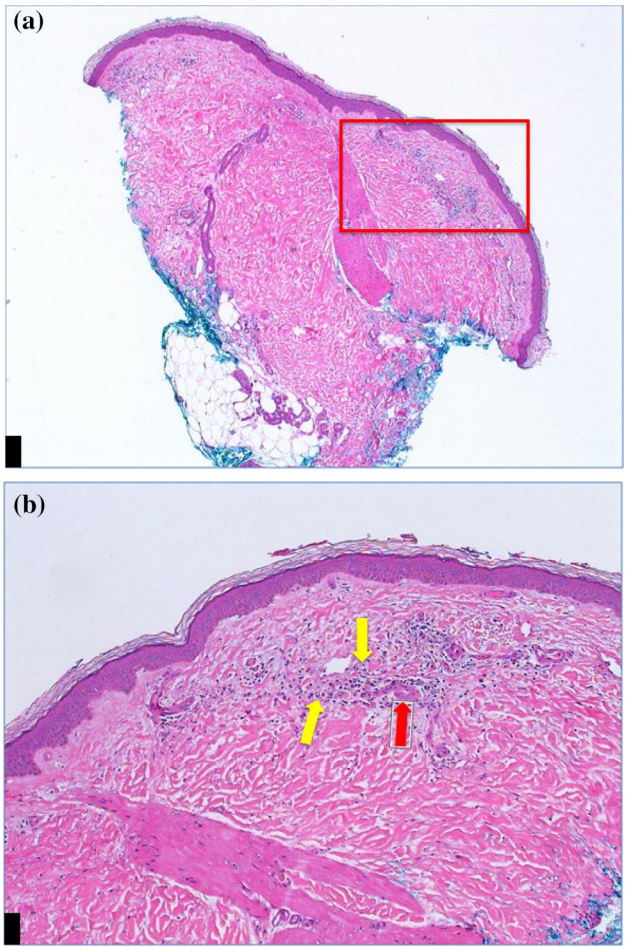

Fig. 2 **a** Low power view of skin biopsy, hematoxylin and eosin stain. Within the upper dermis, there is a superficial perivascular mixed inflammatory cell infiltrate, as indicated by the red box. **b** ×20 view, hematoxylin and eosin stain. A superficial perivascular infiltrate composed of predominately neutrophils and lymphocytes is indicated by the yellow arrows. Mild endothelial cell swelling is seen as indicated by red arrow

down to 15 mg daily. Soon after the initial response to the first rituximab dose, he had undergone successful open aortic aneurysm repair with biopsy showing patchy aortic infiltrates with lymphocytes, plasma cells, neutrophils and rare eosinophils (Fig. 4a, b).

Search strategy

We systematically reviewed the literature to identify all relevant reports of AAV with aortic involvement by searching PubMed databases for all full-text articles published in English between January 1st, 1970 and July 6th, 2018. Key search terms included "antineutrophil cytoplasmic antibodies", "ANCA", "ANCA-associated vasculitis", "AAV", "aorta", "aortic involvement", and "aortitis". Case reports

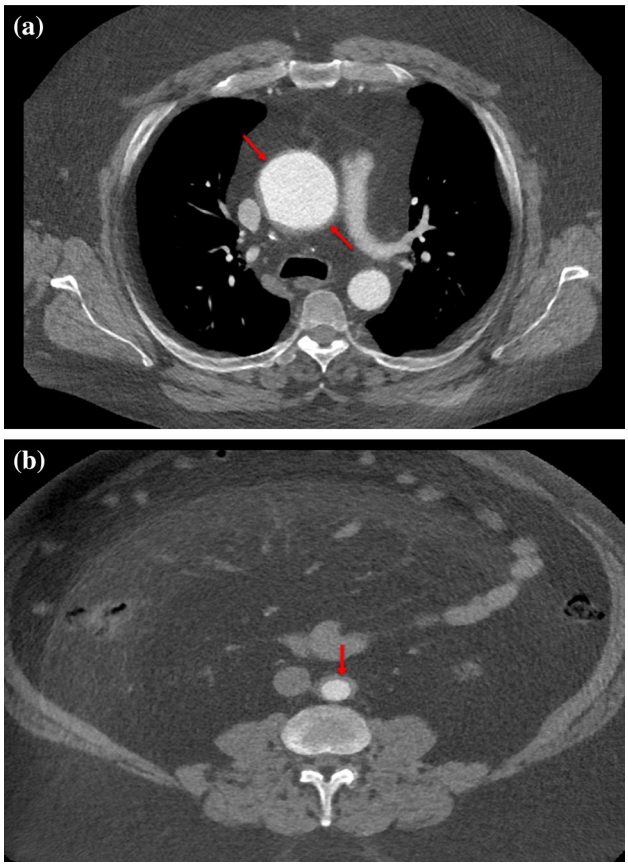

Fig. 3 Transverse images of a CT angiogram of chest and abdomen revealing improved wall thickening of the **a** ascending aorta (2 mm) and **b** abdominal aorta (3 mm)

and case series of patients with diagnosed AAV and documented aortitis were eligible for inclusion. Publications were excluded if they: did not fulfill the above criteria, were published outside of our search range, or were not available in English.

Discussion

There have been several attempts to standardize the diagnostic and classification criteria for AAV; however, some of these criteria have limitations [11]. Histopathologic examination of affected tissue may be necessary to confirm the diagnosis. While a consensus on a validated diagnostic criteria has not been reached, it has been proposed that AAV was diagnosed based on a combination of ANCA titer, multiorgan involvement, and biopsy results [12]. Our patient fits such criteria based on cardiopulmonary and integumentary organ involvement, strongly positive ANCA (PR3) and suggestive results of the skin and aortic tissue biopsies. Since vascular biopsy can be risky, CTA and MRA are well-established non-invasive imaging tools to help diagnose and

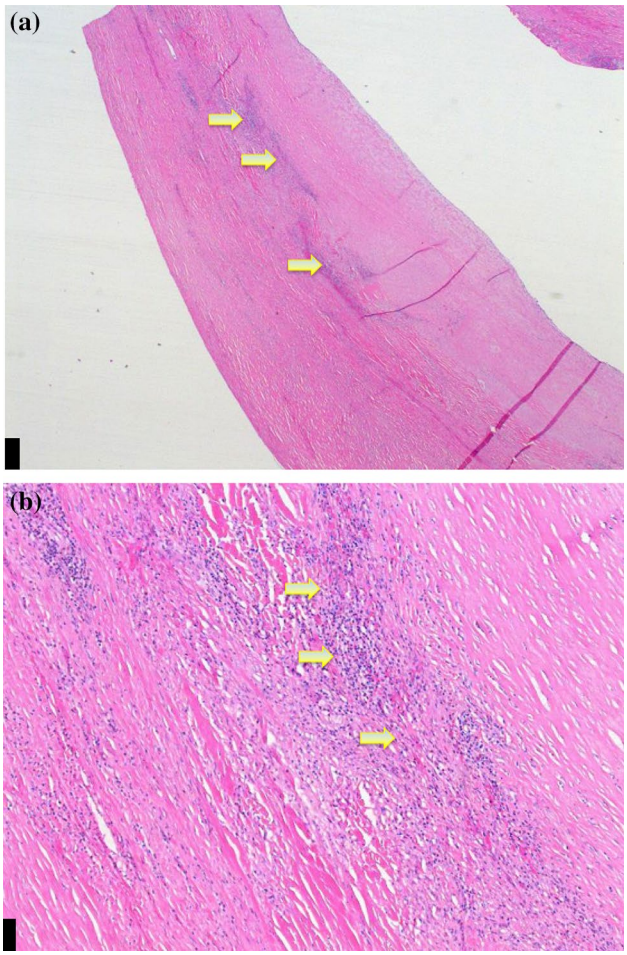

Fig. 4 **a** Biopsy of ascending aorta. Low power view of vessel wall, hematoxylin and eosin stain. Mixed inflammatory infiltrate indicative of aortitis is noted by the yellow arrows. **b** ×10 view, hematoxylin and eosin stain. Patchy aortitis with lymphocytes, plasma cells, neutrophils and rare eosinophils as indicated by yellow arrows. No giant cells are identified

grade inflammatory vascular stenosis related to this type of vasculitis [13, 14]. We use CT and MR angiogram images in patients with large vessel vasculitis to evaluate arterial wall thickening and edema, and to determine the degree of stenosis.

The treatment of AAV consists of induction of remission followed by maintenance therapy achieved by immunomodulatory therapy. For induction therapy, cyclophosphamide or rituximab in addition to pulse glucocorticoid therapy and, in certain situations, plasma exchange has been used [15–17]. For maintenance therapy, azathioprine [18, 19], methotrexate [19], mycophenolate mofetil [20] and rituximab have been recommended [21, 22].

AAV primarily affects small vessels, including arterioles, venules, and capillaries. Medium and large vessel involvement with ANCA-related vasculitis has been rarely reported—it is noted in less than 10% of cases [10, 23, 24]. Based on our literature review, we were only able to find 10 reported cases with AV-related aortitis (Table 1). All five c-ANCA patients were male, and four out of the remaining five p-ANCA patients were female. Additionally, all patients fell between the age of 42 and 73, with an average age of 58.9 (± 10.2) years. In addition to the aorta, all patients had small vessel involvement mostly affecting the glomerular and pulmonary vessels. Management primarily included immunosuppressive agents; six patients were treated with cyclophosphamide, one with tocilizumab, one with methotrexate, and two were managed conservatively. One case of AAV with aortic involvement lacked treatment information.

Our patient presented with a rare combination of abdominal and thoracic aortitis, which was only reported in four other cases. This case confirms male predominance in c-ANCA related aortitis [24, 25]. While other reported cases of AAV-related aortitis were predominantly treated with cyclophosphamide and glucocorticoids, our case showed good response only to rituximab.

Our case report and literature review shed light on a very rare presentation of AAV with aortitis. While more common types of vasculitides should be initially considered when evaluating a patient with aortitis, AAV should also be among the differentials. Given the atypical presentation and disease manifestation of our patient, it was more than a year when the final diagnosis of AAV was made. Furthermore, our patient was younger than most reported cases of AAV-related aortitis with rare involvement of both thoracic and abdominal aorta. This is also the first reported case of AAV-related aortitis that was successfully treated with rituximab which should probably be considered as a first-line therapy for such rare presentation.

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Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest (COI disclosure with author-identifying information on separate title page).

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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

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