

## Case report

# Successful use of rituximab in granulomatosis with polyangiitis with aortic inflammation

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Received on September 1, 2017; accepted  
in revised form on January 9, 2018.

*Clin Exp Rheumatol* 2019; 37 (Suppl. 117):  
S144-S147.

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EXPERIMENTAL RHEUMATOLOGY 2019.

**Key words:** ANCA-vasculitis,  
aortitis, rituximab

### ABSTRACT

*Large-vessel inflammation, although rare, has been increasingly recognised as a complication of granulomatosis with polyangiitis (GPA) in recent years. The presentation is highly variable, ranging from an incidental finding to aortic dissection and rupture. Treatment has predominately consisted of a combination of cyclophosphamide and high dose corticosteroids with surgical intervention when indicated. We present the case of a 34-year-old male diagnosed with GPA after presenting with sinus and eye inflammation and the ensuing investigation revealed large-vessel involvement that remarkably improved after 6 months of treatment with the combination of rituximab infusions, methotrexate and corticosteroids.*

### Introduction

Inflammation of the aorta and other large vessels is generally thought to be a feature exclusive of vasculitides like giant cell arteritis and Takayasu's arteritis. It is important to recognise that involvement of large vessels may also occur in patients with granulomatosis with polyangiitis (GPA) resulting in the potential life-threatening complications including aortic dissection and rupture (1). Of the reported cases in the literature, treatment has mostly consisted of corticosteroids, cyclophosphamide, and surgical intervention when warranted. We report a case of GPA involving the thoracic aorta and its branches and review the literature to describe available evidence for using rituximab and other treatment agents for large-vessel involvement in GPA.

### Case presentation

A 34-year-old male with a medical history of asthma presented to the emergency department with a 1 month histo-

ry of facial swelling, nasal congestion, epistaxis, subjective fevers and weight loss. He had no other past medical or surgical history. He was a non-smoker and had no relevant family history. On exam the patient was in no distress and vital signs were remarkable for a pulse of 122 beats/minute and blood pressure of 130/93 mmHg. Relevant exam findings included periorbital and nasal bridge swelling. A facial bones CT scan and brain MRI noted diffuse opacification of the paranasal sinuses and prominent lacrimal glands with mild nodularity. The patient was discharged with oral antibiotics and referred to the Ear, Nose, Throat (ENT) clinic.

At the ENT clinic 3 months later, he reported atraumatic nasal pain and deformity and eye redness of 2 month duration that failed to improve with a topical corticosteroid/antibiotic preparation. His exam was remarkable for conjunctival injection and a saddle-nose deformity and resolution of facial swelling. Flexible fiberoptic nasal endoscopy showed the presence of synechiae in the right nasal cavity and large amount of crust-material filling the left nasal cavity. These findings were suspicious for GPA and he was referred to the Rheumatology and Ophthalmology clinics.

At the Ophthalmology clinic the patient presented with persistent eye redness and progressive vision loss. Exam showed severe bilateral eye inflammation, absence of light perception in the right eye and ability to count fingers at two inches in the left eye. He was diagnosed with necrotising scleritis and panuveitis possibly secondary to GPA and was admitted to the hospital for further management. Upon admission he denied a history of joint swelling, haemoptysis, dyspnea, haematuria, chest pain, numbness, tingling, weak-

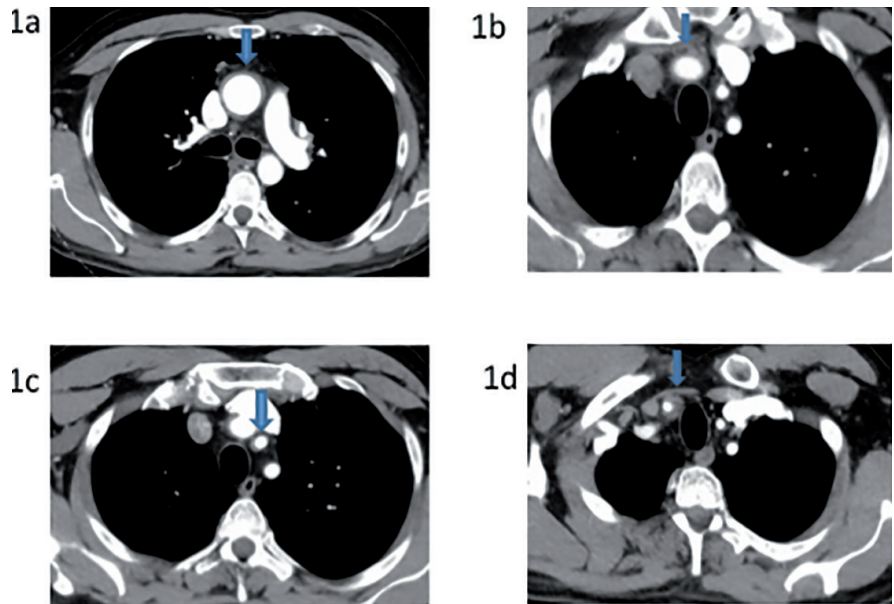
Competing interests: none declared.

ness or rash. He was afebrile, with a normal pulse rate and blood pressure of 140/86 mmHg. Exam was remarkable for a saddle nose deformity and bilateral scleral injection with markedly diminished vision. There was no evidence of synovitis, rash, murmur, focal neurologic deficits or basilar rales.

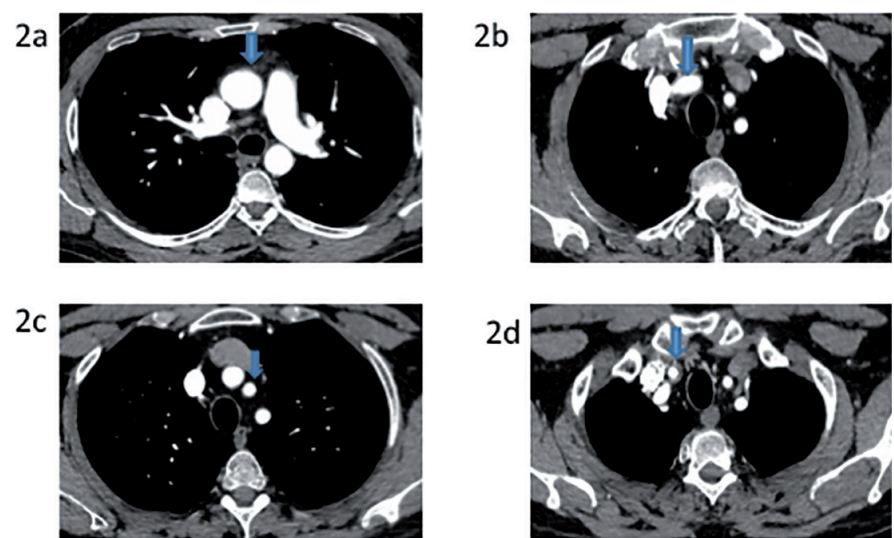
Laboratory tests were remarkable for creatinine 0.7 mg/dl and GFR >60 ml/min/1.73 m<sup>2</sup>, normal electrolytes and liver function tests, normal urinalysis, white cell count of 11.5 x 10<sup>9</sup>/L, haemoglobin 11.8 gr/dl, platelets 501 x10<sup>9</sup>/L, sedimentation rate of 50 mm/hr, and negative tests for hepatitis B and C, human immunodeficiency virus, and tuberculosis. Anti-neutrophil cytoplasmic antibody (ANCA) testing revealed a negative *p*-ANCA, positive *c*-ANCA >1:4096, and PR3 >8.

Nasal endoscopy repeated by ENT showed similar findings as before and biopsy showed non-specific findings, namely, the presence of marked chronic and focal acute inflammation of sinonasal mucosa, with vascular inflammation involving scattered capillary/small vessels and purulent exudates. There was no evidence of granulomas. A chest CT scan to assess for lung involvement showed multiple pulmonary nodules, some with ground glass halo suggestive of perilesional haemorrhage and multifocal areas of bronchial wall thickening with peribronchovascular opacities in the upper lobes. Additionally, the report noted circumferential wall thickening of the ascending aorta, brachiocephalic artery and bilateral common carotid arteries without luminal dilation or narrowing consistent with inflammation (Fig. 1).

The patient was treated with methylprednisolone 1 gram for five days followed by oral prednisone 1 mg/kg, and two infusions of rituximab 1000 mg two weeks apart. His hospital course was notable for improvement in eye inflammation, and he was subsequently discharged. Tapering of prednisone was started at week 2 after discharge. At 1-month follow-up the patient reported notable improvement in vision from the left eye, but no change from the right. Given the severity of eye involvement he was given a second



**Fig. 1.** Contrast enhanced axial CT images (mediastinal window) before treatment show concentric wall thickening of the ascending aorta (1a), innominate artery (1b), left common carotid artery (1c), and right common carotid artery (1d) (arrows).



**Fig. 2.** Contrast enhanced axial CT images (mediastinal window) showing complete resolution and decrease in the wall thickening following treatment with rituximab of the ascending aorta (2a), innominate artery (2b), left common carotid artery (2c) and right common carotid artery (2d) (arrows).

round of rituximab at 4 months. He was initiated on maintenance methotrexate 15 mg/week and folic acid. At the 6-month follow-up visit he was taking prednisone 25 mg per day due to persistent ocular inflammation. A chest CT with contrast was repeated at 6 months showing significant interval decrease in the wall thickening around the ascending aorta and common carotid and brachiocephalic arteries suggestive of substantial improvement of vascular inflammation (Fig. 2).

## Discussion

Granulomatosis with polyangiitis is an ANCA-associated vasculitis that commonly involves medium and small size vessels causing necrotising inflammation and granuloma formation more commonly seen in upper and lower respiratory tracts and kidneys (2). Involvement of the large and medium-sized vessels is a rare event in GPA and a poor prognostic factor. When found in patients with GPA it can potentially lead to dissection, rupture and death.

Furthermore, this presentation is not exclusive to GPA. Several reports have been made in patients with microscopic polyangiitis (MPA) (1). Most of the data on this phenomenon comes from published case reports and their respective review of the literature. Not surprisingly, given the rarity of aortic involvement, there were no clinical trials found in our search of the literature (1). To the best of our knowledge, there are 26 cases reported in the literature describing aortic involvement in GPA and MPA, with considerable variability of patient age, clinical presentation, anatomic vascular distribution, ANCA antibody profile, nature of vascular lesions (stenosis, aneurysmal dilation, dissection, or rupture), and outcomes. Chirinos *et al.* reviewed 13 cases where large-vessel involvement in ANCA vasculitis occurred in 6 females and 7 males and with ages at presentation ranging from 27-71 years old (1). Additionally, Minnee *et al.* reviewed 13 cases with a male to female ratio of 12:1 and a similar age range (3). Incidental diagnosis of vascular involvement on contrast-enhanced CT scan imaging after patients present with non-specific symptoms seems to be rule. Soussan *et al.* advocated for a potential role of positron emission tomography with computed tomography in diagnosis and therapy monitoring as it can potentially discriminate between active inflammation and inactive sequelae (4). Symptoms including lower back, abdominal and chest pain are retrospectively attributed to the inflammatory vascular process. More often the diagnosis of GPA or MPA was made in the months to years before patients were noted to have medium- or large-vessel inflammation or less often contemporaneously. Only in three patients was the diagnosis of GPA confirmed after abnormal vascular imaging was found (2, 5-7). Vessel involvement is highly variable, including large and medium-sized vessels. The aorta is the most commonly affected vessel, followed by renal artery and hepatic artery. Lesions in intracranial vessels, pancreatico-duodenal artery, and left gastric artery have also been reported (2, 3, 5-7). Our case of a young male

with limited symptoms that could be attributed to vascular pathology and diagnosed with aortic involvement during his workup for GPA fits this profile. Medical management for large-vessel inflammation does not differ from typical regimens used for ANCA-associated vasculitis with small-vessel involvement and largely consists of a combination of cyclophosphamide (daily oral or monthly intravenous pulses) and high dose corticosteroids (1, 5, 8). Optimal doses or length of treatment with corticosteroids remain to be determined and have yet to be examined in a prospective trial (9). Additional agents include mycophenolate which was successfully used in two cases, one of which was concomitantly treated with intravenous immunoglobulin and plasma exchange (2, 5, 6). We found one recently reported case of a patient with ANCA-associated vasculitis and large-vessel involvement successfully treated with rituximab after failing to respond to cyclophosphamide (10). The need for surgical intervention was not infrequent, occurring in at least six patients, and invasive percutaneous interventions like stent placements and aneurysm coiling or embolisation were additionally described in four more cases (2, 5). In their review of the literature, Ohta *et al.* reported on eight cases of large-vessel aneurysm as result of GPA, five of which required surgical intervention, and all resulted in a good outcome (2). Out of the 14 cases reviewed by Chirinos *et al.*, three had evidence of aortic dissection, of which two died due to rupture (1). Our patient was incidentally found to have inflammation of the thoracic aorta and its branches concurrent with his diagnosis of GPA and did not require any invasive intervention. He was treated with high dose corticosteroids, induction with rituximab infusions at time 0 and another at 4 months and maintenance methotrexate with remarkable improvement in vascular inflammation after a 6-month follow-up. Which of these agents was primarily responsible for this outcome is difficult to determine. Rituximab may have played a major role in decreasing vessel wall inflammation. The MAINRITSAN trial

by Pugno *et al.* showed improvement in physical abilities in patients placed on rituximab maintenance compared to azathioprine (11). Current evidence suggests ANCA-associated vasculitis pathogenesis includes B-cell activation, production of ANCA by activated B-cells, and autoreactive B-cells found in granulomatous lesions of patients with vasculitis (12). The role of inflammation in the vasa vasorum in large vessels has been proposed but remains unproven (13). We might expect that these mechanisms take place irrespective of vessel size or anatomic location. Rituximab may be effective in reducing vascular inflammation by removing certain pathologic B-cells from the circulation. Furthermore, there are several reports of the successful use of rituximab in other large-vessel vasculitides, mainly Takayasu's arteritis (8, 12, 14, 15).

In conclusion, we present a case of a young male with GPA who had successful resolution of aortic involvement by using combination rituximab infusions with methotrexate maintenance on a background of corticosteroids.

## References

1. CHIRINOS JA, TAMARIZ LJ, LOPES G *et al.*: Large vessel involvement in ANCA-associated vasculitides: report of a case and review of the literature. *Clin Rheumatol* 2004; 23: 152-9.
2. OHTA N, WAKI T, FUKASE S *et al.*: Aortic aneurysm rupture as a rare complication of granulomatosis with polyangiitis: a case report. *J Med Case Rep* 2013; 7: 202.
3. MINNEE RC, VAN DEN BERK GE, GROENEVELD JO *et al.*: Aortic aneurysm and orchitis due to Wegener's granulomatosis. *Ann Vasc Surg* 2009; 23: 786.
4. SOUSSAN M, ABAD S, MEKINIAN A, DHOTE R, EDER V: Detection of asymptomatic aortic involvement in ANCA-associated vasculitis using FDG PET/CT. *Clin Exp Rheumatol* 2013; 31 (Suppl. 75): S56-58.
5. ARLET JB, LE THI HUONG D, MARINHO A, CLUZEL P, WECHSLER B, PIETTE JC: Arterial aneurysms in Wegener's granulomatosis: case report and literature review. *Semin Arthritis Rheum* 2008; 37: 265-8.
6. UNLU C, WILLEMS M, TEN BERGE JJ, LEGEMATE DA: Aortitis with aneurysm formation as a rare complication of Wegener's granulomatosis. *J Vasc Surg* 2011; 54: 1485-7.
7. AMOS LA, ROBERTS MA, BLAIR S, MCMAHON LP: cANCA-associated aortitis. *Clin Kidney J* 2012; 5: 47-9.
8. UNIZONY S, STONE JH, STONE JR: New treatment strategies in large-vessel vasculitis. *Curr Opin Rheumatol* 2013; 25: 3-9.

9. CHAIGNE B, GUILLEVIN L: Unsolved questions and concerns about treatment of anti-neutrophil cytoplasm antibody-associated vasculitides. *Clin Exp Rheumatol* 2016; 34 (Suppl. 97): S121-128.
10. OZAKI T, MAESHIMA K, KIYONAGA Y *et al.*: Large-vessel involvement in granulomatosis with polyangiitis successfully treated with rituximab: A case report and literature review. *Mod Rheumatol* 2017; 27: 699-704.
11. PUGNET G, PAGNOUX C, TERRIER B *et al.*: Rituximab versus azathioprine for ANCA-associated vasculitis maintenance therapy: impact on global disability and health-related quality of life. *Clin Exp Rheumatol* 2016; 34 (Suppl. 97): S54-59.
12. JONES RB: Rituximab in the treatment of anti-neutrophil cytoplasm antibody-associated vasculitis. *Nephron Clin Pract* 2014; 128: 243-249.
13. CHIRINOS JA, CORRALES VF, LICHTSTEIN DM: ANCA-associated large vessel compromise. *Clin Rheumatol* 2006; 25: 111-112.
14. ERNST D, GREER M, STOLL M, MEYER-OLSON D, SCHMIDT RE, WITTE T: Remission achieved in refractory advanced takayasu arteritis using rituximab. *Case Rep Rheumatol* 2012; 2012: 406963.
15. O'CONNOR MB, O'DONOVAN N, BOND U, PHELAN MJ: Successful treatment of Takayasu arteritis with rituximab as a first-line immunosuppressant. *BMJ Case Rep* 2017 Jan 10; 2017.