Title: Granulomatosis with polyangiitis mimicking infective endocarditis in an adolescent male

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Abstract

Granulomatosis with polyangiitis (GPA) is a rare but serious small vessel vasculitis with heterogeneous clinical presentation ranging from mainly localised disease with a chronic course, to a florid, acute small vessel vasculitic form characterised by severe pulmonary haemorrhage and/or rapidly progressive vasculitis or other severe systemic vasculitic manifestations. Cardiac involvement is, however, uncommon. We report a case of a 16 year-old male who presented with peripheral gangrene and tricuspid valve vegetation, initially considered to have bacterial endocarditis but ultimately diagnosed with GPA. We provide an overview of the literature relating to cardiac involvement in GPA, and the diagnostic challenge relating to infective endocarditis in this context.

Keywords: Granulomatosis with polyangiitis, ANCA associated vasculitis, bacterial endocarditis, child.

Granulomatosis with polyangiitis (formerly Wegener's granulomatosis) is characterized by granulomatous inflammation involving the respiratory tract, with necrotizing vasculitis affecting small to medium-sized vessels (e.g. capillaries, venules, arterioles, and arteries). The disease may present in two non-mutually exclusive forms: a predominantly granulomatous disease with mainly localised disease affecting the respiratory tract or orbits; and a florid, acute small vessel vasculitic form characterised by severe pulmonary haemorrhage and/or rapidly progressive glomerulonephritis or other severe systemic vasculitic manifestations. Cardiac involvement is uncommon [1,2,3], but when it does occur the features can mimic infective endocarditis, leading to diagnostic delay. Furthermore, anti-neutrophil cytoplasmic antibodies (ANCA) have been reported to be present in some cases of true infective endocarditis, adding to the diagnostic confusion [ref]. We report a case of a 16 year-old male with GPA who first presented with tricuspid valve vegetation, peripheral gangrene, and renal impairment initially considered to be due to infective endocarditis. We provide an overview of the literature relating to cardiac involvement in GPA.

A previously fit and well Caucasian 16 year-old male presented with a four week history of pyrexia, dyspnoea, anorexia and weight loss, without any obvious focus of infection. Examination revealed an extremely unwell adolescent male with fever of 39.0^{o}C, respiratory distress and dry gangrene of his toes and right forefoot (Figure 1A), with absence of peripheral pulses in the right foot. The pulps of his toes on the left were also ischaemic, but not gangrenous. Investigations revealed neutrophil leucocytosis: white cell count 32.27 x10^{9}/L (reference range [RR] 4-11), neutrophils 27.21 x10^{9}/L (RR 2-7), thrombocytosis 648 x10^{9}/L (RR 150-450), haemoglobin 9.3 g/dl (RR 13.0-16.0). Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were elevated at 105 mm/h (RR <10 mm/h); and >270 mg/L (RR <20mg/L) respectively. Creatinine was 290 umol/l (RR 55-96 umol/l) and the urine albumin/creatinine ratio was 509 mg/mmol (RR <11.3). Urine, sputum and repeated blood cultures, including fungal cultures, were sterile. The

chest radiograph showed a right pleural effusion with underlying ground-glass attenuation in the right lung. The patient also developed acute testicular pain requiring surgical exploration, which revealed a haematoma and infarction of the epididymis in the upper pole of the right testis. Echocardiography revealed a vegetation adjacent to the tricuspid valve, suggestive of infective endocarditis (Figure 1B), with possible secondary embolus causing ischaemia of the peripheries. In that context, the patient did not have any history of drug or substance abuse.

He was treated initially with broad spectrum antibiotics (cefotaxime, vancomycin, gentamicin, doxycicline) and antifungals (ambisome and fluconazole); he was also started on intravenous heparin and alteplase (recombinant tissue plasminogen activator), with poor response indicated by further deterioration of the gangrene, and ongoing severe systemic inflammation.

Subsequent investigations revealed strongly positive anti neutrophil cytoplasmic antibodies against proteinase 3 (PR3-ANCA: 194 EU/ml; RR <1.99). Computer tomography (CT) of his chest revealed segmental consolidations with widespread ground glass change/nodules (Figure 1C). Renal biopsy showed acute segmental necrotizing glomerulonephritis with expansive crescents (Figure 1D). The combination of renal and pulmonary findings, with strongly positive PR3-ANCA confirmed a diagnosis of GPA, complicated by triscupid valve involvement. Retrospectively, the patient gave a history of recurrent epistaxis for months prior to his acute presentation.

He received treatment with intravenous methylprednisolone (1g daily for 3 consecutive days) followed by high dose oral Prednisolone; ten days of therapeutic plasma exchange; rituximab (1g twice, two weeks apart) and intravenous cyclophosphamide (500 mg/m^2 every 3 weeks for 4 doses; cumulative dose 3.32 g) with prompt recovery of symptoms, resolution of the acute-phase response, and normalization of renal function. He later went on to have an amputation of the

gangrenous toes on the right foot, which healed uneventfully (Figure 1E). At transition to adult care at the age of eighteen years old he was in remission on treatment with Prednisolone 3mg once a day, Azathioprine 125 mg once a day and Amlodipine 5 mg once a day; creatinine was within normal range at 71 umol/l, although he still had mild-to-moderate albuminuria (35.9 mg/mmol).

Discussion

GPA is a rare but serious systemic autoimmune small vessel vasculitis. Although cardiac involvement is rare (6%-17%), it can be a serious complication associated with mortality, and may delay the diagnosis and treatment of GPA by mimicking infective endocarditis. Hence recognizing that GPA can involve the heart (including cardiac valves) is important in order to secure a prompt diagnosis and initiate appropriate therapy as early as possible[4,5]. Cardiac involvement in GPA is usually secondary to necrotizing vasculitis, with or without granulomatous infiltrates [ref]. Pericarditis and coronary vasculitis are the most frequent findings, but myocarditis, endocarditis, and conduction system granulomata are also described [ref]. The clinical presentation is very heterogeneous, ranging from subclinical manifestations, of which arrhythmia is the most common, to end-stage heart failure due to either myocardial infarct, valvular rupture or complete heart block. Valvular involvement is extremely rare, with aortic regurgitation, mitral regurgitation and aortic stenosis the most common findings described, usually associated with sterile valvular vegetations [6], as in the case described herein. Table 1 describes all reported cardiac manifestations in GPA.

To add to the diagnostic uncertainty, there have been reports of true infective endocarditis with transient ANCA positivity. We suggest that patients with cardiac valve vegetations who have other compelling clinical features of GPA (for example pauci-immune segmental necrotising glomerular nephritis, as in our case), with strongly positive ANCA, are most likely to have

ANCA associated vasculitis and should be treated as such. Clinicians may consider initiating immunosuppressive treatment combined with broad-spectrum antibiotics cover if there is ongoing concern regarding true infective endocarditis, however. Lastly, we emphasise that patients with established AAV who are immunosuppressed may be prone to opportunistic infection including infective endocarditis [ref], and the clinician must remain ever vigilant for this possibility.

In conclusion, we emphasise that cardiac valve vegetations in a febrile patient should not invariably be considered to be indicative of infective endocarditis, since GPA may also cause valve inflammation and sterile endocarditis. Whilst previous reports have suggested that patients with endocarditis may have transient ANCA positivity, this is rare and in the presence of other features of systemic vasculitis detection of ANCA usually indicates the presence of a true ANCA associated vasculitis.

Key messages:

1. Early recognition of possible cardiac involvement in GPA is crucial in order to promptly initiate and treatment and reduced the morbidity and mortality associated with this disease.
2. GPA should be considered in the differential diagnosis of young risk factor free patients presenting with presumed infective endocarditis.

The authors declare that they have no competing interests.

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