Bacterial endocarditis associated with proteinase 3 anti-neutrophil cytoplasm antibody

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Introduction

Anti-neutrophil cytoplasm antibodies (ANCA) are useful diagnostic markers in a range of small vessel vasculitides. While non-specific ANCA have been reported in association with a variety of autoimmune, haematological and infectious conditions, the combination of a cytoplasmic staining pattern on indirect immunofluorescence (IIF) of human neutrophils, with antibodies specific for proteinase 3 (PR3) by enzyme-linked immunosorbent assay (ELISA), is reported to be 99% specific for Wegener’s granulomatosis versus disease controls [1]. This serological finding in association with other diseases that manifest vasculitic phenomena can therefore result in diagnostic uncertainty and erroneous treatment decisions. We report three cases of bacterial endocarditis in association with PR3-ANCA and discuss the implications for diagnosis and management.

Case 1

A previously well 30-year-old male presented with a 1-month history of constitutional symptoms of fatigue, night sweats and arthralgia. He developed a painless rash on his extremities and had three episodes of epistaxis associated with crusting of the nasal airways. Initial blood tests revealed elevated inflammatory markers, with serum C-reactive protein (CRP) of 178 mg/L and accelerated erythrocyte sedimentation rate (ESR) of 67 mm/h. He was anaemic, haemoglobin (Hb) 8.3 g/dL, and had impaired renal function, serum creatinine 254 μmol/L. His platelet count and coagulation profile were normal. Urinalysis demonstrated proteinuria and haematuria, with dysmorphic red blood cells seen on microscopy. Renal tract ultrasonography and chest radiography were normal.

ANCA with a cytoplasmic staining pattern (c-ANCA) were demonstrated by IIF and a specific anti-PR3 antibody titre of 13 (negative < 6) was confirmed on ELISA. Antimyeloperoxidase (anti-MPO) antibodies were negative. A rheumatoid factor was present at a titre of 207 IU/mL (negative < 20). Tests that were notably negative or within the normal range included anti-nuclear antibodies (ANA), double-stranded DNA (dsDNA), complement C3 and C4, cryoglobulins and eosinophil count.

Blood cultures subsequently grew Gemella haemolysans in five of six bottles after 48 h incubation. Echocardiography demonstrated a 15-mm vegetation on the posterior cusp of a bicuspid aortic valve, with aortic regurgitation, and a diagnosis of bacterial endocarditis was made. He was initially treated with high-dose antibiotics but went on to require emergency mechanical aortic valve replacement for worsening volume overload of the left ventricle and embolic complications including a splenic infarct. Histological examination of the aortic valve confirmed endocarditis and the presence of gram-positive cocci. There was no evidence of granulomatous inflammation. Cultures of the valve tissue yielded no growth.

Following surgery, the patient’s symptoms rapidly improved. The rash resolved and he had no further episodes of epistaxis. His inflammatory markers normalized, the serum CRP falling to 7 mg/L. His urinary abnormalities and renal dysfunction resolved, the serum creatinine improving to 95 μmol/L. Immunofluorescence remained weakly positive for c-ANCA; however, his anti-PR3 titre became negative.

After 1 year follow-up, he has no evidence of any underlying primary vasculitis or ongoing infection.

Case 2

A 78-year-old man presented with a progressive history of lethargy, fevers and lumbar back pain. His medical history revealed coronary artery bypass surgery with tissue aortic valve repair 4 years previously. On examination, he was febrile with a non-blanching rash on the chest, abdomen and extremities. Auscultation demonstrated a systolic flow murmur, with no diastolic component.
Systemic examination was otherwise unremarkable. Initial blood tests revealed a marked inflammatory response (CRP 284 mg/L, ESR 113 mm/h) with anaemia (Hb 8.5 g/dL) and renal dysfunction (creatinine 164 μmol/L). Urgent magnetic resonance (MR) imaging of the spine showed evidence of L2/3 discitis and a transoesophageal echocardiogram showed a 15-mm vegetation on the tissue aortic valve with mild regurgitation.

**Enterococcus faecalis** was subsequently grown in multiple blood cultures. Antibiotic therapy was commenced with amoxicillin and gentamicin. The patient subsequently developed a superimposed urticarial rash. A skin biopsy showed perivascular inflammation with infiltrates of lymphocytes, neutrophils and eosinophils, in keeping with a drug-induced reaction. Amoxicillin was therefore substituted with linezolid.

However, his renal function deteriorated further, the serum creatinine rising to 417 μmol/L. Urinalysis showed microscopic haematuria, with red cells seen on microscopy, and proteinuria, quantified with a protein:creatinine ratio of 94 mg/mmol. Renal tract ultrasonography was normal. An autoantibody profile revealed c-ANCA on IIF and anti-PR3 antibodies at a titre of 143 U/mL (normal < 25 U/mL). Rhumatoid factor was present at a titre of 1:320, and protein electrophoresis showed polyclonal hypergammaglobulinaemia. Tests for anti-MPO antibodies, ANA, dsDNA and anti-glomerular basement membrane (anti-GBM) antibodies were negative; complement, platelets and eosinophil count were within the normal range.

Renal biopsy showed a mild focal segmental increase in mesangial matrix and cellularity, with mesangial staining for IgM, C3, IgA and C1q on immunofluorescence and subendothelial deposits on electron microscopy, consistent with an immune complex glomerulonephritis. There was also an acute tubulitis and eosinophilic interstitial infiltrate consistent with an active tubulointerstitial nephritis, presumed secondary to the penicillin drug reaction. Steroid therapy was withheld due to ongoing uncontrolled endocarditis, discitis and bacteraemia.

He was treated with an extended course of antibiotics and showed clinical resolution of his symptoms, inflammatory response and bacteraemia. His renal function showed improvement (serum creatinine falling to 219 μmol/L) and his anti-PR3 titre fell to 93 U/mL when last checked. He was discharged from hospital after 2 months, to continue long-term antibiotic therapy. One month later, he presented to hospital in cardiogenic shock and died suddenly. Post-mortem examination revealed atheromatous coronary artery disease as the underlying cause. The aortic valve showed granulation tissue with calcifications, consistent with a previous chronic endocarditis. Histological examination of the other organs did not reveal evidence of vasculitis.

**Case 3**

A 65-year-old man with a history of hypertension, diabetes and non-alcoholic steatohepatitis (NASH), presented with a 1-month history of lethargy, myalgia, fever and weight loss. Initial blood tests showed mild renal impairment (creatinine 115 μmol/L) and a marked inflammatory response (CRP 220 mg/L, ESR 112 mm/h, leucocytes 19.6 × 10^9/L). Blood cultures subsequently grew *Staphylococcus aureus* and treatment with high-dose flucloxacillin was initiated. An underlying cause for the bacteraemia was sought. An initial transthoracic echocardiogram did not show evidence of vegetations, and cross-sectional computed tomography and MR imaging did not reveal any abscess, soft tissue infection or osteomyelitis. Cirrhotic liver appearances and mild splenomegaly were in keeping with his diagnosis of NASH.

Despite antibiotic therapy, the patient’s condition deteriorated progressively, developing a purpuric rash and acute renal failure with haematoproteinuria on urine dipstick. IIF demonstrated the presence of c-ANCA and anti-PR3 antibodies were present at 475 U/mL (normal 0–25 U/mL). Tests which were negative or within the normal range included ANA, complement, dsDNA, anti-MPO antibodies, anti-GBM antibodies and rheumatoid factor, though there was a polyclonal increase in immunoglobulins. A diagnosis of primary ANCA-associated vasculitis (AAV) was considered, although immunosuppressive therapy was avoided because of the recent bacteraemia of unresolved cause.

Progressive renal failure complicated by pulmonary oedema necessitated admission to the intensive care unit for renal replacement and ventilation. A transoesophageal echocardiogram at this time demonstrated a large mitral valve vegetation in keeping with bacterial endocarditis. A skin biopsy of the rash demonstrated supplicative inflammation suggesting septic embolization. Despite appropriate antibiotic treatment for endocarditis, he continued to deteriorate and therefore received low-dose pulsed methylprednisolone and intravenous immunoglobulin for treatment of possible associated vasculitis. There was no clinical response and the patient died from complications of sepsis and multi-organ failure 4 weeks after admission. Post-mortem examination was not performed.

**Discussion**

We report three cases of bacterial endocarditis in patients found to have circulating PR3-ANCA. In each case, the patients presented with fever, constitutional symptoms, skin rash, renal impairment with haematoproteinuria and, in Case 1, upper airways disease. These features were strongly suggestive of a diagnosis of Wegener’s granulomatosis. However, each patient was subsequently proven to have bacterial endocarditis as defined by the Modified Duke’s Criteria [2]. In Cases 1 and 2, the patients responded to antibiotic therapy alone and did not show any evidence of underlying primary vasculitis on follow-up. In addition, Case 3 deteriorated following immunosuppressive therapy.

Bacterial endocarditis frequently manifests with features of small vessel vasculitis including purpura and glomerulonephritis. These vasculitic features are usually attributed to microembolism and/or the effects of circulating immune complexes on the vascular endothelium [3]. Differentiating endocarditis from other causes of small vessel vasculitis is a difficult though not infrequently encountered clinical problem, and one of obvious importance, given the contrasting therapeutic strategies which each requires. Since
their first description in the mid 1980s, ANCA have become useful diagnostic markers in vasculitis, and PR3-ANCA are accepted to be highly specific for Wegener’s granulomatosis.

PR3-ANCA is rare; however, it has been reported in bacterial endocarditis. A review of the literature identified seven such cases [4]. A further two cases associated with c-ANCA with dual positivity for PR3 and MPO antigens have since been reported [5]. In these nine cases, non-cardiac organ involvement was limited to the skin and kidneys. As such, Case 1 reported here, is unique in that it is the first reported case of bacterial endocarditis with involvement of the upper respiratory tract, a characteristic feature of Wegener’s granulomatosis. The pathogenesis of the upper respiratory tract manifestations in this patient is not clear. Nasal crusting and epistaxis are not features of immune complex-mediated vascular injury. G. haemoly-
sans, the causative organism of endocarditis in this case, is an upper respiratory tract commensal but colonization is not usually associated with clinical manifestations.

The possibility of an underlying diagnosis of Wegener’s granulomatosis was considered in each case, especially as endocardial involvement in Wegener’s is reported [6], and may conceivably render valves susceptible to secondary bacterial infection. However, the response to antibiotic therapy alone seen in Cases 1 and 2 (and the absence of clinical, histological or serological evidence of an underlying vasculitis on follow-up) make the diagnosis of Wegener’s very unlikely.

The induction of ANCA and other autoantibodies, such as rheumatoid factor, seen in bacterial endocarditis is not fully understood and may relate to the persistent antigenic stimulation of B cells seen in chronic infection, resulting in non-specific polyclonal immunoglobulin production. A process of molecular mimicry between microbial proteins and ANCA antigens has also been implicated in the induction of ANCA based on, for example, the observed homology between S. aureus peptides and complementary PR3 [7]. In addition, a recently described ANCA subtype, which recognize lysosomal membrane protein-2 (LAMP-2), cross-react with bacterial adhesin FinH, to which a LAMP-2 epitope has considerable homology [8]. Similar processes may account for the presence of ANCA in our patients.

The pathogenic potential of the ANCA seen in these cases is unclear. There is mounting experimental evidence that ANCA has a direct pathogenic role in vasculitis [9], and it is notable that, of the previously reported cases of endocar-ditis associated with PR3-ANCA, one was found to have a pauci-immune necrotizing glomerular lesion more consistent with ANCA-associated disease, with no evidence of the immune complex deposits typical of endocarditis [10]. In addition, infection has long been postulated as an aetiological factor in ‘idiopathic’ AAV and the association of S. aureus carriage and Wegener’s relapse is well recognized [11]. It is therefore conceivable that infection-induced ANCA may mediate some of the vasculitic manifestations seen in endocarditis, including the upper respiratory tract symptoms described in Case 1, although our experience would suggest that immunosuppresson may not be necessary and could be harmful in these cases.

Teaching points

(1) Clinicians should remember the rare but important association of bacterial endocarditis and circulating PR3-ANCA, since the finding of antibodies with this specificity in a patient with features of small vessel vasculitis may easily lead to an erroneous diagnosis and harmful treatment decisions.

(2) As these cases demonstrate, the diagnosis of bacterial endocarditis can be elusive and must always be considered, even in patients presenting with ‘classical’ clinical features of another small vessel vasculitis, including upper respiratory tract symptoms.

(3) It is possible that infection-induced ANCA may mediate some of the vasculitic phenomena seen in endocarditis, however, our experience suggests that immunosuppressive therapy may not be of benefit in these cases.

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References


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