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Unusual association of diseases/symptoms

Complements do not lie

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Summary

A 74-year-old patient presented with constitutional symptoms and was found to have acute kidney injury. He was known to have a prosthetic aortic valve. He was febrile with splenomegaly and vasculitic lesions on both hands. Nephritic screen revealed strongly positive cytoplasmic-antineutrophil cytoplasmic antibodies (c-ANCA). Differential diagnosis thus included a small vessel vasculitis or infective endocarditis. Transoesophageal echocardiography demonstrated no vegetations and serial blood cultures were negative. Immunosuppression for presumed granulomatosis with polyangiitis (Wegeners granulomatosis) was therefore instituted. The patient deteriorated, requiring multi-organ support. Renal biopsy showed a proliferative glomerulopathy and complements were low. Atypical screen for culture negative endocarditis revealed a strongly positive IgG-antibody titre against *Bartonella henselae*. Immunosuppression was discontinued and treatment for chronic Bartonellosis commenced. The patient made a remarkable recovery. His renal function quickly returned to normal, and ANCA titres and complements normalised. He was discharged home after completing a 6 week course of antibiotic therapy.

BACKGROUND

This case highlights the difficulties in differentiating between infective endocarditis, particularly culture negative, and antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitis in light of their similar spectrum of presentation and overlapping symptomatology. The importance of taking a clear history and performing thorough and tailored investigations is reinforced. Interpretation of results, in this case particularly the low complements, is key and without identification of a culture negative organism, the correct diagnosis may never have been made and the outcome may have differed dramatically.

CASE PRESENTATION

A 74-year-old man presented with 10 weeks of general malaise, lethargy, anorexia and a ten kilogram weight loss (13% body weight). He denied any other symptoms. History from his wife revealed two brief episodes of confusion.

His medical history comprised a minimally-invasive bovine aortic valve replacement in 2005 for severe aortic regurgitation, paroxysmal atrial tachyarrhythmias, hypertension, hypercholesterolaemia and two transurethral prostate operations for benign prostatic hyperplasia. His premorbid condition was good and he regularly swam and cycled. He was taking aspirin 75 mg and simvastatin 40 mg only. Travel history included a trip to Cape Verde in 2008 and to Texas in 2006. He had two cats at home.

Prior to hospital presentation, he had attended his general practitioner with general malaise when it was noted that his serum creatinine was 264 micromol/l, having been 84 micromol/l the previous year. An urgent nephrology outpatient appointment was made.

In the meantime, he presented as an emergency with worsening lethargy and dyspnoea and it was found that his renal function had further deteriorated (creatinine of 486 µmol/l, with active urinary sediment and protein: creatinine ratio (PCR) of 300 mg/mmol). Clinically he had splenomegaly and a soft pansystolic murmur at the apex. He was febrile with a temperature of 38.5°Celsius. Blood tests revealed pancytopenia (white cell count 2.7×10^9/l, haemoglobin 9.5 g/dl, platelets $<42\times10^9$/l). Three sets of blood cultures were negative. A full nephritic screen showed a strongly positive c-ANCA (PR 3 ELISA >100 AU/ml, antimyeloperoxidase antibodies <5 AU/ml), low complement C3 and C4 levels, negative ANA, negative rheumatoid factor and cryoglobulins and negative anti-glomerular basement membrane antibodies. Serum electrophoresis revealed a diffuse increase in α-globulins.

In view of his prosthetic valve, he was investigated for infective endocarditis by both transthoracic (TTE) and transoesophageal (TOE) echocardiography, neither of which revealed any valvular lesion. He also had a bone marrow aspirate to investigate the pancytopenia which showed a reactive picture. Abdominal ultrasound demonstrated normal sized kidneys and confirmed 15 centimetre splenomegaly. He was then referred to our hospital for further assessment.

The summary to date was that of a patient with acute kidney injury, a bovine aortic valve, a strongly positive c-ANCA (PR3> 100 AU/ml), consumed complements, splenomegaly and thrombocytopenia. Because of thrombocytopenia he was deemed high risk for a renal biopsy and was initially treated with both three pulses of methylprednisolone for vasculitis, and covered for infective endocarditis with vancomycin and flucloxacillin, upon microbiology advice. Within 3 days, his platelet count improved sufficiently to perform a renal biopsy. This showed acute tubular injury and a mildly proliferative glomerulonephritis with neutrophils (figure 1). The glomerular changes suggested an infection- related process rather than small vessel

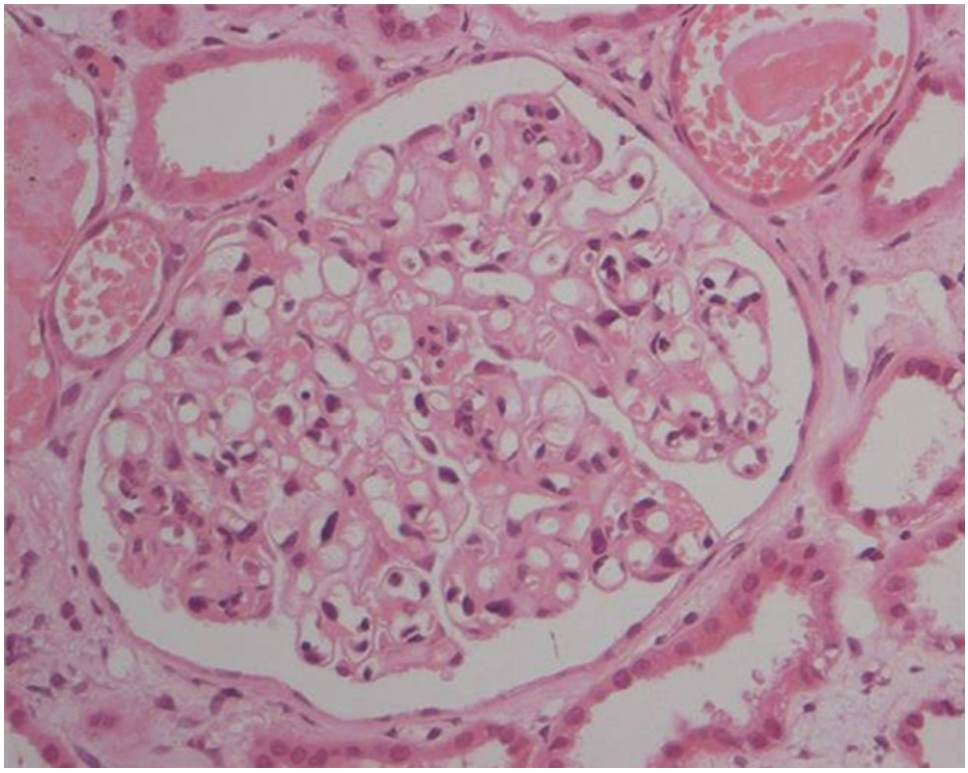

Figure 1 Renal biopsy H&E.

vasculitis, although no immune complexes were seen on immunohistochemistry.

In view of this histology and the lack of evidence of a focal and segmental necrotising crescentic glomerulonephritis, which would be expected with a vasculitis, no further immunosuppression was administered. Antibiotic therapy was continued. Several sets of blood cultures remained negative. A further TTE and TOE (done 7 and 10 days later respectively) again showed no vegetations, although the aortic valve leaflets were thickened and there was now moderate aortic regurgitation.

The clinical suspicion of endocarditis remained, and in the face of negative cultures and fairly recent foreign travel, atypical serology for culture negative organisms was requested. The patient, however, then deteriorated rapidly and was admitted to the intensive care unit (ICU), requiring mechanical ventilation and renal replacement therapy. Purpuric vasculitic skin lesions on his face and arms were noted, and repeat abdominal ultrasound scan of the abdomen showed multiple splenic lesions suggestive of granulomata. High-resolution CT of his chest revealed no evidence of pulmonary granulomata or haemorrhage. CT of chest, abdomen and pelvis revealed no evidence of malignancy. A repeat TOE showed that his left ventricular cavity was now dilated with globally severely impaired systolic function. MRI of the brain was also reported as showing vasculitic changes.

Now 1 month post admission, the diagnosis remained unclear. There had been no response to antibiotic therapy for endocarditis (by now including vancomycin, piperacillin, imipenem and flucloxacillin upon microbiology advice), and he had a persistently raised PR3 of >100 AU/ml. It was felt that there was little option but to treat as an ANCA-associated small vessel vasculitis. He was given three pulses of 0.5 grams of methylprednisolone and initially improved with a sharp decrease in his inotropic and ventilatory requirements. He was also commenced on cyclophosphamide 100 mg once daily and prednisolone 60 mg once daily and discharged from the ICU. Within a few days, however, he again deteriorated and required readmission to ICU.

At this point, the results of the atypical organism screen were obtained, showing a strongly positive titre for *Bartonella Henselae* IgG (1: 512) and a weakly positive titre for *Coxiella* spp (1:80). Hepatitis A, B and C, *Treponema pallidum*, Leishmaniasis, Schistosomiasis, cytomegalovirus, Chlamydia serology, Ebstein–Barr virus and the human immunodeficiency virus were negative.

On the basis of this serology and the lack of response to immunosuppression and conventional antibiotics, cyclophosphamide was discontinued and the steroid dose reduced. Treatment with clarithromycin 500 mg twice daily with gentamicin 80 mg once daily was commenced for presumed Bartonellosis.

INVESTIGATIONS

Figure 1 – Renal biopsy H&E

DIFFERENTIAL DIAGNOSIS

In general, a positive ANCA is associated with the small vessel vasculitides (SVV). Other causes of ANCA positivity are reported and include both infectious and non-infectious diseases, including Bartonella endocarditis.[1–3] The categories of associations are listed in figure 2. In this case particularly infective endocarditis, SVV and malignancy

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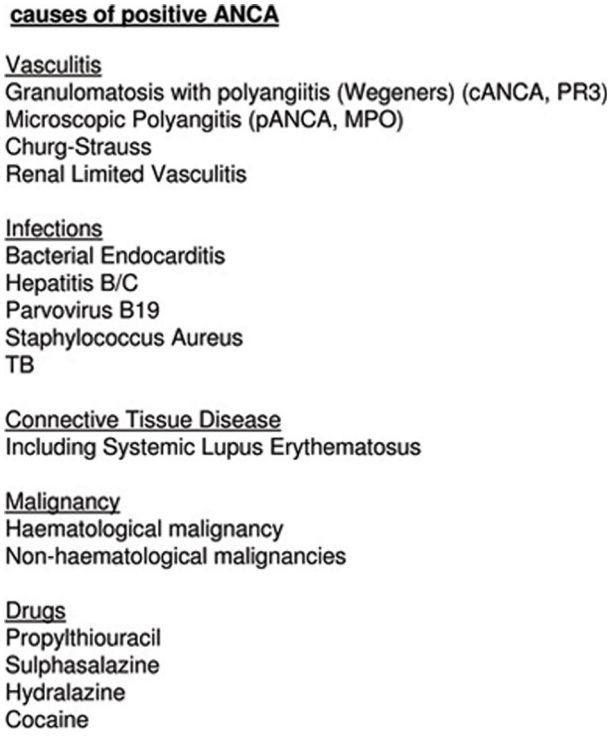

Figure 2 Causes of a positive antineutrophil cytoplasmic antibodies.

were considered. The differences between infective endocarditis presenting with a positive ANCA, and a SVV presenting with endocardial involvement have been previously documented.[4] These are noted in table 1 for comparison and many of these were pertinent to our case. Hypocomplementaemia is only associated with certain renal lesions, the most common of which are postinfectious glomerulonephritis, infective endocarditis and lupus nephritis, and would not routinely be expected in a case of vasculitis. The low C3 and C4 in this case thus favour the diagnosis of endocarditis. Causes of a positive ANCA are illustrated in figure 2.

OUTCOME AND FOLLOW-UP

Within 3 days, the patient's clinical condition dramatically improved. He became alert and orientated, was weaned off ventilatory support and renal replacement and underwent rehabilitation. A repeat TOE demonstrated improvement in his left ventricular systolic function. After 3 weeks, his PR3 titres had sharply fallen to 15 AU/ml and his complement levels had normalised. The patient was discharged home after completing the recommended 6 weeks of antibiotics. He was mentally alert and was able to walk with a stick.

DISCUSSION

There are several cases reported in the literature of infective endocarditis presenting as and masquerading as an ANCA-associated vasculitis.[5 6] Here we report a rare case of culture negative endocarditis presenting as a cytoplasmic ANCA-associated vasculitis (c-ANCA) with acute kidney injury, and highlight the diagnostic and therapeutic challenges such a case poses.

Table 1 Differentiation between vasculitis and endocarditis

Features common to both vasculitis and infective endocarditis	Features seen predominantly in infective endocarditis
Presentation with constitutional symptoms	Thrombocytopenia
Fever	Hypocomplementaemia
Active urinary sediment	Immune complexes
Skin involvement	Other positive autoantibodies
Renal impairment	Low titre antineutrophil cytoplasmic antibodies/ELISA negative
Raised inflammatory markers	Splenomegaly

ANCA and endocarditis

Increasing evidence exists that ANCA is pathogenic in the development of small vessel vasculitis rather than being simply an epiphenomenon.[7 8] It has been shown that there can be transient induction of, particularly PR3, antibodies during infection.[1 9] Studies indicating the close link between granulomatosis with polyangiitis (Wegeners granulomatosis) and chronic nasal *Staphylococcus aureus* carriage were key in linking the development of ANCA with infection.[10–12] Further work done on molecular mimicry,[13] the role complementary PR3[14 15] and a new subset of ANCA, lysosomal-associated membrane protein 2,[8 16 17] further serve to reinforce this link.

Both infectious and non-infectious diseases have been reported as causing ANCA positivity by immunofluorescence, but these are often at low titre or ELISA negative.[2] Bacterial endocarditis presenting with both c-, and less commonly p-ANCA positivity, have been documented.[5 6]

Non-infectious endocardial involvement is also known as a feature of ANCA-associated vasculitides (in particular c-ANCA).[8 18 19] Clinically, infective endocarditis and SVV have a very similar spectrum of presentation and clearly the differentiation between the two is of paramount importance in terms of initiating treatment. Comparison has been made between infective endocarditis occurring in association with ANCA versus endocardial involvement with idiopathic ANCA.[4] This concluded subtle differences in clinical presentation, presence of splenomegaly (rare in SVV), presence of other autoimmune markers (also rare in SVV), levels of complement (should be normal in SVV) and echocardiographic findings and clinical and valvular course, which are pertinent to our case.

Diagnostic challenge

The diagnosis was confounded by several factors. Initially, the patient's presentation with renal failure on the background of a bovine aortic valve replacement and systemic symptoms favoured a diagnosis of infective endocarditis, which could have explained the splenomegaly and consumed complements. The persistently negative blood cultures and cardiac investigations, however, coupled with a lack of clinical response to antibiotic therapy refuted this. It is known that ANCA is 99% specific for vasculitis in the correct clinical context[20] and the consistently high PR3 titres, pauci-immune appearance of the biopsy and possibility of both coronary and cerebral vasculitis steered the diagnosis in favour of a small vessel vasculitis. We therefore decided to initiate immunosuppressive therapy, which was administered for 2 weeks but did not

lead to any sustained clinical improvement. This treatment was discontinued upon receiving a positive result for *B henselae*, prompting treatment with clarithromycin and gentamicin. The testing for and identification of Bartonella was key in the progression of the management of the case.

Bartonella infection

Bartonella species (spp), first isolated in 1988,[21] are intracellular, fastidious gram-negative proteobacteria and are associated with diseases such as cat scratch disease (*B henselae*, as in our patient), trench fever (*Bartonella quintana*, more common in the homeless and alcohol dependent population) and oroya fever or verruga peruvana (*Bartonella bacilliformis*, most prevalent in South America). Across various studies, the seroprevalence of antibodies to *B henselae* in healthy persons ranges from 3.6% to 6% and in many patients, the disease is self-limiting. Initially, a primary inoculation skin lesion can be observed at the site of the scratch, and regional lymphadenopathy is a common finding. Bacteraemia can lead to systemic infection and multiorgan involvement. Systemic disease is more commonly found in immunosuppressed patients, but can also occur in healthy people.

Symptoms include general malaise, myalgia, arthralgia, anorexia, weight loss and intermittent fever. It is recognised that kidney injury, splenomegaly, granuloma formation and encephalopathy may develop,[22] all of which our patient displayed.

Confirmation of the diagnosis can be challenging. *Bartonella* spp can be cultured on selective media but sensitivity of this method is at best 20 per cent. Direct smear with Warthin-Starry Silver stain of the tissues, including heart valves, could help in establishing the diagnosis. Our patient underwent biopsy of the skin lesions but histopathological examination with this staining did not reveal any positive findings. A high titre of IgG antibody against *Bartonella* spp is usually suggestive of chronic infection as was in our patient with a titre of >1:512 against *B henselae*. An IgG titre of greater than 1:256 is considered diagnostic of current or past Bartonella infection. PCR can also be performed on various samples, for example EDTA blood sample and skin lesions. The PCR results of EDTA blood sample and skin biopsies of our patient were both negative. It is described that any other samples apart from heart valves may not yield high sensitivity.[23]

Bartonella spp have been associated with culture negative endocarditis and account for up to 3% of infective endocarditis cases.[24] A retrospective study performed among 348 patients in France suggested that *Bartonella* spp was responsible for 28% cases of culture negative endocarditis.[25] *B quintana* was three times more prevalent than *B henselae* as the cause of culture negative endocarditis.[25] It has been described that more than half of the patients with *Bartonella* spp infective endocarditis have had known valvular disease. Fever may not be a common feature.[26] Infection with *Bartonella* spp mimicking small vessel vasculitis has also been described.[3 27 28] Myocarditis is a known but rare feature of Bartonella infection.[29 30]

Learning points

- Differentiating between infective endocarditis and SVV is challenging and it is important to be aware of their similar presentation and overlapping symptomatology.
- The importance of clear history taking and performing tailored investigations is reinforced.
- Although c-ANCA is highly specific for vasculitis, it is vital to be aware of causes of false-positivity as the treatment options vary significantly – beware of culture negative endocarditis.
- Here, without the correct diagnosis, the outcome may have differed dramatically and the patient might not have survived his illness.

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Competing interests None.

Patient consent Obtained.

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