CASE REPORT

Rare manifestations of infective endocarditis: the long known, never to be forgotten diagnosis

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SUMMARY

Infective endocarditis (IE) is a life-threatening condition often manifesting as a multisystem disease; its heterogeneous features present a diagnostic challenge. We report two cases of IE masquerading as rare extracardiac complications: a splenectomised patient with a periarticular ankle abscess and acute encephalopathy; and a young man with a cutaneous vasculitis following a spontaneous intracerebral haemorrhage. In both cases, the diagnosis was suspected following detection of afebrile bacteraemia and confirmed with echocardiography. Risk factors included a pneumococcal bacteraemia in the asplenic patient and a previously undiagnosed bicuspid aortic valve in the second patient. Both patients recovered well with appropriate antibiotic therapy followed by valve surgery. IE is an important diagnosis to consider in patients with systemic symptoms or organ specific, otherwise unexplained relevant pathology especially in the presence of a cardiac murmur or risk factors for IE including structural heart disease, prosthetic valves or intravascular devices, and in immunosuppressed patients.

BACKGROUND

Infective endocarditis (IE) is a serious illness with significant morbidity and mortality, despite advances in its work up and treatment. Diagnosis is often delayed owing to the non-specific nature of its varying presentations. While it is known that septic arthritis, vertebral osteomyelitis and epidural or intramedullary spinal abscesses may occur, an extra-axial periarticular soft tissue abscess has not been, to our knowledge, previously reported in association with endocarditis. Symptomatic intracerebral haemorrhage (ICH) due to IE is rare, occurring in 3–7% of patients;^{1 2} and if it presents in isolation without a detectable aneurysm, IE may be overlooked. Highlighting rare presentations may contribute to raising the index of suspicion for this often elusive diagnosis.

CASE PRESENTATION**Case 1**

A 60-year-old Caucasian woman presented with new onset confusion and a painful swollen ankle. She had received an intra-articular steroid injection for a painful shoulder in the emergency department 2 weeks previously. She had a background of hypertension and post-traumatic splenectomy 18 years prior. She had received the pneumococcal polysaccharide vaccine 7 years before and was not taking prophylactic penicillin. She was a lifelong non-smoker, drank 7 units of alcohol weekly, played

tennis regularly and walked up to 7 miles/day. At presentation, she was afebrile and her vital signs were normal. Glasgow Coma Scale (GCS) score was 14 due to disorientation. Neurological examination was otherwise unremarkable. Right ankle and left shoulder joint areas were swollen, tender and warm. Range of movement was normal in the ankle but passive shoulder movements were restricted due to pain. Chest and cardiovascular examinations were documented to be normal. Three days later, following detection of bacteraemia, the patient was noted to have a pan-systolic murmur radiating to the axilla.

Case 2

A 36-year-old Caucasian sportsman presented with fatigue, dry cough, night sweats, anorexia, weight loss, blurred vision and minor epistaxis. He had felt unwell since he was diagnosed with an ICH 2 months before at another institution. Brain MRI at that time did not show any underlying structural abnormality. He had been diagnosed with pulmonary sarcoidosis and mild asthma 4 years previously. He was a non-smoker and drank alcohol only occasionally. He was afebrile on admission, with normal vital signs. His GCS score was 15 and neurological examination was normal. A purpuric rash was noted on both legs (figure 1). There were no splinter haemorrhages, Osler nodes or clubbing. His chest was clear and a systolic murmur was heard over the precordium. The splenic tip was palpable but there were no palpable lymph nodes.

INVESTIGATIONS**Case 1**

Investigations showed normocytic anaemia with haemoglobin (Hb) of 8.3 g/dL, raised total white

Figure 1 Vasculitic rash of the lower limb in a patient with infective endocarditis (case 2).

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cell count (WCC) of $33 \times 10^9/L$ with marked neutrophilia of $29 \times 10^9/L$ and normal platelet count. Creatinine was $51 \mu\text{mol/L}$. Liver function tests were deranged; alanine transaminase was 143 IU/L , γ -glutamyl transpeptidase 505 U/L , alkaline phosphatase 580 IU/L , bilirubin $36 \mu\text{mol/L}$, (direct bilirubin $31 \mu\text{mol/L}$) and albumin was 27 g/L with a normal International Normalised Ratio of 1.1. C reactive protein (CRP) was 189 mg/L . Chest X-ray was clear and ultrasound of abdomen and liver was normal. Urine dipstick showed 2+ blood and 2+ protein, and was negative for nitrates and leucocytes. There was a dry aspirate from the affected ankle and shoulder joints. X-rays of both joints were normal. As the inflammation of the right ankle joint persisted, open drainage was attempted in theatre, again yielding a dry tap. Frank pus was, however, drained from a periarticular soft tissue collection over the lateral malleolus, and this was culture negative. Serology for HIV I & II, hepatitis B virus and hepatitis C virus was negative. Blood cultures taken on admission grew *Streptococcus pneumoniae* on day 3 of hospitalisation with sterile cultures thereafter. Transthoracic echocardiography (TTE) demonstrated a perforated posterior mitral valve leaflet (PML) with mobile small echo-densities on the PML and moderately severe mitral regurgitation (videos 1 and 2). The findings were confirmed on transoesophageal echocardiography (TOE).

Case 2

Laboratory blood results included: Hb 10.9 g/dL , platelet count of $224 \times 10^9/L$, WCC $6.7 \times 10^9/L$, creatinine $86 \mu\text{mol/L}$, CRP 59 mg/L , lactate dehydrogenase 266 U/L , albumin 33 g/L and calcium of 2.2 mmol/L . Rheumatoid factor (RF) was positive. Microscopic haematuria was detected on dipstick urinalysis. Urine microscopy showed <50 white blood cells with 30 red blood cells per μL , and urine culture was sterile. Urine protein to creatinine ratio was 19 mg/mmol (0–15). CT of the thorax showed normal pulmonary parenchyma with no pathological mediastinal or hilar lymphadenopathy, with marked aortic valve calcification and no pleural or pericardial effusions. CT of the abdomen showed splenomegaly of 17.4 cm , two splenic abscesses and bilateral subtle renal infarcts at the lower poles of both kidneys. CT of the brain was normal. Histopathological findings from a skin biopsy of the rash were consistent with a leucocytoclastic vasculitis. Blood cultures taken on admission grew *Streptococcus sanguinis* in four bottles. Three subsequent blood culture sets were positive for the same organism before

Video 1 Transthoracic echocardiogram (TTE) showing mitral valve vegetation (case 1).

Video 2 TTE showing moderately severe mitral regurgitation (case 1).

clearance of bacteraemia. On TTE, an abnormal aortic valve (AV) with a vegetation and at least moderate aortic regurgitation was seen (video 3). TOE confirmed a bicuspid AV and moderately severe aortic incompetence (video 4).

DIFFERENTIAL DIAGNOSIS

Case 1

The clinical diagnostic threshold for possible infective endocarditis was reached using the Modified Duke criteria with one major and one minor criterion: a positive echocardiogram and a single positive blood culture. Additionally, in this patient, the presentation with a soft tissue periarticular abscess and encephalopathy were further features that could be attributed to IE. As endocarditis was not suspected on admission, repeat blood cultures were only taken 3 days later and were negative, most likely due to the patient being on empiric antibiotic therapy. This may represent a pitfall in terms of reliability of blood culture results when applying Duke's diagnostic criteria. Therefore, the patient was treated based on definite echocardiographic findings consistent with IE. Pathological specimens obtained at surgery confirmed the diagnosis. Initial work up included examination of peripheral blood film ruling out haematological malignancy as the cause of anaemia with marked neutrophilia, oligoarthritis and encephalopathy. CT of the brain and cerebrospinal fluid analysis were normal, excluding structural brain pathology or meningoenitis. Vascular encephalopathy associated with IE was the likely cause of the patient's acute confusion at presentation.

Case 2

This patient's presentation clearly fulfilled the Modified Duke criteria, two major criteria (positive blood cultures and positive echocardiographic findings) as well as five minor criteria: bicuspid AV, fever of 38°C , metastatic embolisation (splenic and renal infarcts), ICH and a positive RF. A systemic vasculitis was initially suspected, but the rest of the autoimmune serology was negative including normal C3 and C4, and a negative cryoglobulin screen. Thrombophilia and antiphospholipid syndrome screens were, likewise, negative. Although sarcoidosis can present with the same systemic symptoms, the absence of clinical and/or radiological signs of relapse of pulmonary disease suggested from the outset that an alternative diagnosis was more likely. The vasculitic skin rash did not conform to any of the classic skin manifestations of sarcoidosis. Serum ACE level was

Video 3 TTE showing an abnormal aortic valve (AV) with a vegetation (left) and aortic regurgitation (right) (case 2).

normal. Neurological complications of sarcoidosis are rare, occurring in 5% of cases only and do not typically include ICH, although this has been reported in the literature.^{3 4} The temporal relationship of the ICH to the patient's symptoms in the absence of other features of active sarcoidosis was strongly in favour of IE as a unifying diagnosis.

TREATMENT

Case 1

The patient initially received empiric antibiotic therapy for septic arthritis and possible meningitis pending cerebrospinal fluid (CSF) analysis. Following detection of pneumococcal bacteraemia and diagnosis of IE, she was continued on a 6-week course of intravenous benzyl penicillin and subsequently had a mitral valve repair.

Case 2

The patient completed 6 weeks of intravenous benzyl penicillin therapy, with synergistic gentamicin for the first 2 weeks. He

subsequently underwent a tissue aortic valve replacement; however, an aortic root abscess was found intra-operatively and he required a further 4 weeks of intravenous antibiotics.

OUTCOME AND FOLLOW-UP

Both patients made a full recovery with antibiotic therapy and subsequent cardiac surgery. They remained well at follow-up 6 months and 1 year post surgery.

DISCUSSION

IE can present acutely or insidiously with non-specific systemic symptoms and/or variable organ pathologies owing to complications from septic embolism, haematogenous seeding, immunological phenomena and, rarely, vasculitis, in addition to its cardiac manifestations. Clinical diagnosis is based on the Modified Duke's criteria: two blood cultures positive for a microorganism typical of IE (or two cultures drawn 12 h apart positive for other microorganisms consistent with IE or a single blood culture or serology consistent with *Coxiella burnetii*

Video 4 Transoesophageal echocardiogram (TOE) showing a vegetation on an abnormal (bicuspid) AV (left) and moderately severe aortic regurgitation (right) (case 2).

infection), together with evidence of endocardial involvement (2 major criteria). Alternatively, various minor criteria, of which 5, or 3 with 1 of the 2 major criteria, are considered diagnostic. Endocarditis is considered possible if 1 major criterion and 1 minor criterion or 3 minor criteria are found.⁵ There are a few caveats concerning the reliability of Duke's criteria. Prior antibiotic therapy, inadequate microbiological techniques or infection with highly fastidious bacteria or fungi may be associated with culture-negative endocarditis. In addition, failing to draw more than a single culture due to initial lack of suspicion of IE, while giving empiric antibiotic therapy, may result in subsequent negative cultures after an organism has been isolated. In the two cases that we report here, the initial presentations of intracerebral haemorrhage and oligoarthritis in the absence of fever did not raise the suspicion of endocarditis in the first instance.

Neurological complications occur in 20–40% of IE cases and are the presenting features in approximately half of these patients.^{2 6 7} Intracerebral haemorrhage due to IE is rare, generally occurring only in 3–7% of patients, and can be due to septic arteritis, secondary haemorrhagic transformation of a cardioembolic infarct or a ruptured mycotic aneurysm.^{2 8 9} More commonly associated with staphylococcal endocarditis, ICH with streptococcal endocarditis has been rarely reported.¹⁰ As well as intracranial spread of infection in the form of meningitis or metastatic abscess formation, non-specific encephalopathy has also been described in cases of IE in the literature.^{2 11 12}

Osteoarticular manifestations are a well known complication of IE,^{13 14} although the pathogenesis of joint involvement is poorly understood. Septic arthritis with culture positive synovial fluid is rare.^{15 16} More commonly, sterile fluid is aspirated from affected joints.¹⁴ Wofsy described culture-negative septic arthritis due to IE, where synovial biopsy culture was positive in a patient with sterile synovial fluid.¹⁷ Therefore, both septic seeding and immunological phenomena may be responsible.^{13 18} In our splenectomised patient who had pneumococcal endocarditis, a sterile abscess was found around the ankle joint. Spinal cord abscesses have been reported rarely in association with streptococcal endocarditis;^{19 20} however, the finding of an extra-axial periarticular abscess in infective endocarditis has not, to our knowledge, been previously reported. Pneumococcal endocarditis is rare and splenectomised patients are at increased risk.^{21 22} It may be associated with pneumococcal arthritis and has also been described as part of the Austrian syndrome of pneumococcal pneumonia, meningitis and endocarditis.^{23–26}

Cutaneous purpura is the most common skin manifestation of IE; nonetheless, it is infrequently seen and was found in 8% of IE cases in an observational prospective French study.²⁷ Its pathogenesis is thought to be a hypersensitivity immune-mediated (leucocytoclastic) vasculitis, and in some case reports has been biopsy-proven, as in our second patient.²⁸ Antineutrophil cytoplasmic antibody (ANCA) positivity in IE is increasingly recognised and care must be taken to distinguish IE as a systemic vasculitis mimic from authentic ANCA-associated vasculitis.^{29–32} Similarly, the occurrence of non-infective endocarditis in a patient with ANCA-associated vasculitis or systemic lupus erythematosus may be a source of confusion.^{33–35} Histological examination, commonly of skin or renal tissue, as appropriate, may be required to aid in the diagnostic process, particularly in difficult cases or in the absence of blood cultures fulfilling the criteria for IE.

Learning points

- ▶ Infective endocarditis (IE) remains a challenging diagnosis in many patients, due to the heterogeneity of its presentations and various pathogenetic mechanisms. Identification of those with suggestive clinical signs and/or predisposing risk factors is essential for early diagnosis and treatment. As well as traditional risk associations, the long-term risk of pneumococcal endocarditis and septicaemia in splenectomised patients should not be overlooked.
- ▶ Auscultation of heart sounds is a crucial part of physical examination; the detection of a murmur can be the initial trigger for a diagnostic work up of IE and prompt initiation of antibiotic therapy.
- ▶ Fever is not universal in IE and its absence should not rule out the diagnosis or deter the physician from obtaining blood cultures and initiating therapy in the presence of other features that may be attributable to IE and are otherwise unexplained.
- ▶ When suspecting or excluding autoimmune disease and vasculitis, endocarditis should be considered in the differential diagnosis. The distinction between non-infectious systemic vasculitis and IE is an important one to make in order to avoid inadvertent immunosuppression in patients with IE, or vice versa, to inappropriately delay immunosuppression in a patient with non-bacterial thrombotic (marantic) endocarditis associated with connective tissue disease.

Contributors SM was involved in planning, collection of clinical data, literature search, writing, amending and submission of manuscript. PO'C took part in critical appraisal of intellectual, linguistic and clinical content of article, editing and approval of final version.

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