Cerebral vasculitis and *Cardiobacterium valvarum* endocarditis

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We present a case of aortic and tricuspid native valve endocarditis in which *Cardiobacterium valvarum* was isolated from the blood culture of a 65-year-old man. *Cardiobacterium valvarum* is a fastidious, Gram-negative bacillus. The genus *Cardiobacterium* encompasses two species – *Cardiobacterium valvarum* and *Cardiobacterium hominis*. Although both species rarely feature as the aetiological agent of endocarditis, *Cardiobacterium hominis* has a higher incidence than *Cardiobacterium valvarum*. For this causative organism, we believe this is the first report of fatality prior to surgical intervention and the first clinical course to be complicated by cerebral vasculitis. Native valve endocarditis caused by Gram-negative bacilli is extremely rare and identification of isolates may require the use of reference laboratories with molecular identification techniques.

**Case report**

A previously fit and well 65-year-old male was admitted with an 8 month history of intermittent back pain, worsening abdominal distension and non-specific symptoms of malaise, fatigue, slowed mobility and weight loss. He had not visited his general practitioner for over 30 years and had no known past medical or drug history. The patient was an occasional drinker and ex-smoker, having stopped 25 years previously. He had no history of recreational drug use. His dentition was extremely poor and abdominal radiographs. Laboratory results revealed a normal electrocardiogram and chest radiograph. The patient was catheterized and commenced on strict fluid monitoring. Prostate specific antigen was 1.6 µg l⁻¹ (normal <4 ng ml⁻¹) and rectal examination revealed a benign, normal-sized prostate. Antibiotic therapy (co-amoxiclav 1.2 g intravenously three times per day) was administered for the presumed inflammatory pulmonary nodules (Fig. 1a). A follow-up CT scan was performed on day 14 to assess response to antibiotics. This showed evolution of the lung pathology into multifocal airspace abnormalities (Fig. 1b).
Three days after admission, the microbiology laboratory reported growth of Gram-negative bacilli isolated from the aerobic bottle of the blood culture taken in the emergency department; the organism was subsequently reported as sensitive to amoxicillin, cefuroxime and levofloxacin, but resistant to trimethoprim. The organism was difficult to identify and referred to the Health Protection Agency Reference Laboratory in Colindale, London.

The mid-stream urine taken on admission grew *Citrobacter koseri* and showed a pyuria >100 × 10⁶ l⁻¹ and a bacterial count >100 × 10⁶ l⁻¹; this was treated with intravenous gentamicin and oral trimethoprim.

**Subsequent progress**

Despite catheterization, repeat bloods showed worsening renal function in addition to hyperkalaemia (potassium 6.2 mmol l⁻¹) and worsening anaemia (Hb 7.3 g dl⁻¹). In view of deteriorating renal function, a renal ultrasound was performed on day 8. This showed no urinary obstruction; however, it did reveal hepatosplenomegaly, ascites and multiple gallbladder stones. Immunological screen showed a polyclonal rise in IgG to 27.2 g l⁻¹ (normal range 6–16 g l⁻¹) and rheumatoid factor less than 10. Autoantibody tests including anti-nuclear antibody, anti-glomerular basement membrane antibody, anti-mitochondrial antibody, gastric parietal cell antibody, anti-liver–kidney microsome antibody and smooth muscle antibody were all negative. Repeat electrocardiography on day 10 showed a prolonged PR interval.

Possible diagnoses included infective endocarditis (IE), vasculitis with secondary renal failure or bacteraemia arising from the urinary tract or from a respiratory source. Renal biopsy and echocardiogram were booked to explore these differential diagnoses. On day 16 following admission, prior to these investigations being carried out, the patient experienced a vacant episode. Examination revealed receptive and expressive dysphasia, a dense hemiplegia, facial weakness and Babinski’s sign on the right side. A CT scan of the head indicated evolving ischaemic change. Magnetic resonance (MR) scan of the brain showed an acute left mid-cerebral artery infarct indicated by the arrow in Fig. 2(a). The MR scan of the brain also demonstrated multiple stenosis and beading of anterior circulation arteries and cerebellar arteries, consistent with cerebral vasculitis, as shown in Fig. 2(b). Intravenous methylprednisolone (2 g) and stroke management were initiated.

An urgent bedside echocardiogram performed following the vacant episode revealed aortic and tricuspid endocarditis. The images showed a 10 mm aortic valve vegetation with severe aortic regurgitation, a 23 mm vegetation on the anterior leaflet of the tricuspid valve with severe tricuspid regurgitation, and a ventricular septal defect (VSD) demonstrated in Fig. 3(a–d). The patient was deemed unfit for acute surgical intervention. Antibiotics were subsequently changed to intravenous gentamicin and piperacillin–tazobactam, and the methylprednisolone was discontinued. His renal function continued to deteriorate. Intensive care unit assessment after a worsening of his general status concluded that escalation of care would be inappropriate. He died shortly after, following a 24 day inpatient stay. Post-mortem was not performed. On the day of death, the admission blood culture was identified as *Cardiobacterium valvarum*. Three subsequent blood cultures, taken on day 16 and 17 of admission (after commencement of antibiotic therapy), were all negative.

**Microbiology tests**

The organism grew slowly, with subculture from the blood culture bottles onto Oxoid Columbia blood agar and chocolate agar. Growth was faintly visible on chocolate agar after 48 h incubation, but the isolate failed to grow on blood agar and was not X or V factor dependent.
The Reference Laboratory identified the organism as *Cardiobacterium valvarum* using partial sequencing of the 16S rRNA gene. The API NH profile was 1134 and in phenol red broth base sugars the isolate was glucose-, sucrose-, sorbitol- and mannose-positive and lactose-, maltose- and mannitol-negative. The isolate was catalase-negative, oxidase-positive and indole-negative.

**Discussion**

The genus *Cardiobacterium* encompasses two species – *Cardiobacterium valvarum* and *Cardiobacterium hominis*. Although both species rarely feature as the aetiological agent of endocarditis, *Cardiobacterium hominis* has a higher incidence than *Cardiobacterium valvarum* (Han et al., 2004). *Cardiobacterium valvarum* is a fastidious, Gram-negative bacillus and is a member of the HACEK group [Haemophilus species, *Aggregatibacter actinomycetemcomitans* (formerly *Actinobacillus actinomycetemcomitans*), *Aggregatibacter aphrophilus* (formerly *Haemophilus aphrophilus* and *Haemophilus paraphrophilus*), *Cardiobacterium hominis*, *Eikenella corrodens* and *Kingella* species] (Health Protection Agency, 2011). It was first identified in 2004 from the blood culture from a 37-year-old male (Han et al., 2004). The patient had presented following rupture of a mycotic cerebral aneurysm which was later found to be a complication of IE. He was afebrile on admission. Risk factors for this patient included dental work 2 weeks prior to presentation and a congenital bicuspid aortic valve. The patient made a full recovery following aneurysm repair, antibiotic administration and aortic valve replacement. Histological analysis of the aortic root and valve showed acute and chronic inflammation (Han et al., 2004). Blood cultures became positive after an incubation period of 3 days. Utilizing 16S rRNA gene sequencing and phylogenetic analysis, Han et al. (2004) proved the organism to be unique, but most closely matched to *Cardiobacterium hominis*.

Following this case, further research was conducted which resulted in the characterization of four oral *Cardiobacterium* strains from the Culture Collection of the University of Goteborg in Sweden. Analysis using 16S rRNA gene sequences showed these strains were most genetically akin to *Cardiobacterium valvarum* (>99% match for all four strains), suggesting a causal relationship between periodontal diseases and *Cardiobacterium valvarum* IE (Han & Falsen, 2005).

To date, fewer than 10 cases of *Cardiobacterium valvarum* infection have been published worldwide (see summary in Table 1). From the cases reported so far, several common themes have emerged in relation to the epidemiology, risk factors, presentation and prognosis of *Cardiobacterium valvarum* endocarditis. The affected patients were often male and relatively young, ranging from 23 to 63 years of age. Recent dental work or poor dentition and congenital cardiac disease were commonly associated risk factors. Initial presentation of previous patients was often insidious, non-specific and without fever. Blood cultures were mostly negative at 48 h with an incubation period ranging from 3 to 5 days. Echocardiogram images showed large, devastating vegetations in the majority of cases. Heart failure and/or neurological sequelae often occurred. The organisms could not be isolated or cultured from the explanted valves from the first six previously published cases. This indicates sensitivity to the β-lactam antibiotics used in each case (Vanerková et al., 2010).

Our patient had a large vegetation burden on echocardiography. Additionally, a VSD was evident, which was highly likely a result of aggressive infection-related tissue destruction. Far less likely, the VSD was a congenital lesion predisposing to IE, which would constitute a minor
criterion of Duke criteria of IE. The pulmonary lesions and cerebral infarction are both highly likely to be related embolic phenomena, with the pulmonary lesions showing dramatic evolution. The finding of a vasculitic rash was also noted. The patient met the Duke criteria (Durack et al., 1994) on one major (echocardiography) and three minor (blood culture, embolic and immunological phenomena) criteria. The combination of the gross echocardiogram findings, the rapidly progressive pulmonary lesions and cerebral vasculitis all pointed to a particularly aggressive manifestation of IE.

Unusually, this case demonstrated evidence of cerebral vasculitis on MR angiography. Cerebral vasculitis has previously been described in severe endocarditis (van de Beek et al., 2008); although an unrelated vasculitic process is possible, this seems less likely. Our patient was briefly treated with intravenous corticosteroid therapy prior to the echocardiogram. Although the impact on the clinical outcome can only be conjecture, it remains an interesting point for debate as to the appropriateness of immunosuppressive therapy in patients with IE but life-threatening cerebral vasculitis.

The delay in requesting the diagnostic investigation (echocardiography) may have been significant. In retrospect, it is possible to relate some of the initial clinical presentation to endocarditis; however, many of the symptoms were non-specific. Moreover, the initial presentation was dominated by renal failure, obstructive uropathy and urosepsis. Even electrocardiographically derived PR interval prolongation (often taken as a sign of aortic root abscess) may be associated with systemic small vessel vasculitis rather than IE (Iqbal et al., 2005).

Drawbacks of this case include the difficulty in obtaining multiple blood cultures prior to antibiotic usage and failure
to obtain post-mortem valvular tissue samples for culture or PCR sampling. Although the patient did satisfy the Duke criteria for endocarditis, these may have strengthened the diagnosis of IE. The initial presentation was that of an ill man with renal failure and urinary sepsis. Despite having a cardiac murmur, other clinical features had dominated, leading to a delay in his diagnosis. This clearly highlights the importance of clinical vigilance.

Conclusions

To our knowledge, this is the second case of bi-valve endocarditis caused by Cardiobacterium valvarum, and the first case in which surgical intervention could not be explored resulting in fatality. Cardiobacterium valvarum is a rarely described cause of endocarditis, but previous cases have confirmed high morbidity and mortality with this organism. As this case also demonstrates, common features include a large vegetation burden with concomitant tissue destruction, heart failure and neurological sequelae.

Endocarditis should always be considered as a differential diagnosis in any patient displaying signs of systemic immunological and embolic phenomena, noting that instigation of definitive treatment is a clinical imperative.

Acknowledgements

We thank the Health Protection Agency Reference Laboratory in Colindale, London.

References


Table 1. Summary of the first six published cases of Cardiobacterium valvarum infection

<table>
<thead>
<tr>
<th>Reference</th>
<th>Age</th>
<th>Sex</th>
<th>Presentation</th>
<th>Risk factors</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Han et al. (2004)</td>
<td>37</td>
<td>M</td>
<td>Insidious; aphasic/left facial droop secondary to subarachnoid haemorrhage due to a ruptured mycotic cerebral aneurysm</td>
<td>Dental treatment 2 weeks prior to admission</td>
<td>Survived</td>
</tr>
<tr>
<td>Hoover et al. (2005)</td>
<td>46</td>
<td>M</td>
<td>Insidious; 1 month history of exertional dyspnoea and fatigue</td>
<td>Congenital bicuspid valve</td>
<td>Survived</td>
</tr>
<tr>
<td>Bothelo et al. (2006)</td>
<td>51</td>
<td>M</td>
<td>Insidious; 2 month history of anorexia, weight loss and asthenia Febrile at 38 °C</td>
<td>Congenital bicuspid aortic valve</td>
<td>Survived</td>
</tr>
<tr>
<td>Geissdörfer et al. (2007)</td>
<td>71</td>
<td>M</td>
<td>Several weeks of psychometric slowing, generalized weakness, fever, chills, pedal oedema and petechiae</td>
<td>Congenital bicuspid aortic valve</td>
<td>Died</td>
</tr>
<tr>
<td>Hoffman et al. (2010)</td>
<td>28</td>
<td>F</td>
<td>3 month history of soaking night sweats</td>
<td>Poor dentition</td>
<td>Survived</td>
</tr>
<tr>
<td>Vanerková et al. (2010)</td>
<td>63</td>
<td>M</td>
<td>Febrile on readmission 1 month history of shortness of breath at rest</td>
<td>Repaired truncus arteriosus</td>
<td>Survived</td>
</tr>
<tr>
<td>This case</td>
<td>65</td>
<td>M</td>
<td>Malaise, back pain</td>
<td>Nil congenital</td>
<td>Died</td>
</tr>
</tbody>
</table>