Non-bacterial Thrombotic Endocarditis

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A 63-year-old man presented with cachexia and confusion. He was found to have culture-negative endocarditis affecting his aortic valve. Despite treatment with broad-spectrum antibiotics and extensive investigation for an underlying cause, he suffered a large cerebral infarct and died. At post-mortem he was found to have non-bacterial thrombotic endocarditis and a metastatic signet-ring carcinoma.

Introduction

A 63-year-old man presented to the Accident and Emergency Unit with a 2-month history of increasing confusion, anorexia and weight loss. He was a heavy smoker and consumed in excess of 50 units of alcohol weekly. He had been treated for hypertension and moderate obstructive airways disease (COAD).

On examination, he looked cachectic. He was normotensive, apyrexial, and had no peripheral signs of infective endocarditis. Cardiovascular examination was unremarkable, and respiratory examination showed signs of COAD and some crepitations in the left base. Neurological examination revealed fluent dysphasia, perseveration, inappropriate behaviour and a widely swinging mood. He was orientated in person but not in time or place. He had generalized hyper-reflexia, but Babinski responses were negative.

Investigations showed hyponatraemia (Na+ 128 mmol/l) with high urine osmolality, normal serum creatinine and liver function tests. He had a neutrophil leukocytosis, mild normocytic anaemia and normal clotting. A computerized tomogram (CT) of the brain with contrast showed two abnormal areas in the right posterior parietal lobe with rim enhancement but no mass effect. Cerebrospinal fluid (CSF) examination was entirely normal, including cytology and polymerase chain reaction (PCR) for Herpes viruses. An electroencephalogram revealed diffuse, frequent slow wave abnormalities predominantly in the temporal regions, with absent alpha rhythm. The C-reactive protein was 10 mg/l at presentation, but rose to 110 mg/l the following day. Multiple blood cultures remained sterile. A magnetic resonance scan of the brain was attempted twice but proved impossible, even with sedation. Thyroid function, B12 and folate measurements, autoimmune and porphyria screens, syphilis serology, serum protein electrophoresis, tumour markers, and sputum examination were all negative. Bone marrow examination showed reactive changes only. Oesophago-gastro-duodenoscopy showed oesophageal candidiasis, gastritis and duodenitis. CT scan of the thorax and abdomen showed very small pleural effusions and ascites, as well as extensive emphysematous changes. A repeat CT brain scan showed two additional small areas of low attenuation. Carotid Doppler scans were normal. Screening for disseminated intravascular coagulation (DIC) showed mild to moderate thrombocytopenia, unremarkable blood film, and mild abnormalities of fibrinogen levels and fibrin degradation products.

The patient was commenced on high-dose intravenous aciclovir and cefotaxime pending results of investigations, as well as on thiamine and nutritional supplements. An echocardiogram was performed to investigate possible thromboembolism in the presence of raised inflammatory markers (Fig. 1A–E). Following this, he was treated empirically for culture-negative endocarditis, cefotaxime being replaced with intravenous vancomycin and gentamicin. The progress of the inflammatory markers during this period is shown in Figure 2. There was a minor initial improvement in the patient’s condition, but 6 weeks later he suddenly developed aphasia.

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and right hemiplegia. A CT scan performed on that same day was unchanged. Despite supportive therapy, he developed pneumonia and died 1 week later.

At post-mortem, no macroscopic lesions were noted in the mediastinum. Histology of mediastinal lymph nodes, however, showed evidence of a metastatic signet ring adenocarcinoma. Although a primary tumour could not be identified, a bronchogenic or gastric source were felt to be most likely. There was also widespread atheromatosis and thrombotic occlusion of multiple cerebral, renal and splenic arterial branches. Histologically, these appeared to be most likely to represent \textit{in situ} thrombosis. The brain showed multiple infarcts. Superficial sterile vegetations, consisting largely of thrombotic material, were found on two of the aortic valve leaflets, in keeping with the diagnosis of non-bacterial thrombotic endocarditis in association with metastatic adenocarcinoma.

\section*{Discussion}

Non-bacterial thrombotic endocarditis (NBTE) has been reported in 0.3–9.3\% of autopsies\cite{1} and predominantly affects patients with co-existent malignancy, sepsis, burns, or DIC. Vegetations occur on the contact margins of valvular leaflets, predominantly on the atrial surface of the mitral valve and the ventricular surface of the aortic valve. Microscopically, the lesions are

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure1}
\caption{Transoesophageal echocardiogram showing vegetations on left and non-coronary cusps of the aortic valve. Long-axis (A–C) and short-axis (D–E) views of the aortic valve. A small amount of aortic regurgitation is seen in C.}
\end{figure}
superficial and consist largely of fibrin and platelet thrombi with no inflammatory changes. A proposed scheme for the pathogenesis of NBTE is shown in Figure 3. A recent animal study has reported a close association between circulating tissue factor activity, as well as expression of tissue factor by macrophages in cardiac valves, and the development of NBTE[2].

Murmurs are unusual, perhaps due to the superficial nature of the vegetations. Systemic thromboembolism, however, is very common, occurring in 50% of patients, most commonly in the cerebral, coronary, renal, or mesenteric circulations[3]. Neurological manifestations are extremely common, and may include confusion or focal deficits. It is often difficult to differentiate clinically between emboli and arterial thrombi forming as a result of a coexisting hypercoagulable state[4]. The diagnosis, which is predominantly echocardiographic, requires a high index of suspicion in any patient with a disease process associated with NBTE, especially in the presence of neurological abnormalities or systemic embolism, even in the absence of a murmur. The differential diagnosis in a patient with vegetations and sterile blood cultures includes culture-negative bacterial endocarditis (eg. Brucella, Legionella, Coxiella, Chlamydia), fungal endocarditis, syndromes associated with the presence of antiphospholipid antibodies, and cardiac tumours[5].

Treatment is often difficult. Treatment of the underlying disease is of paramount importance, whenever possible. If there are no contraindications, the patient

Figure 2. Changes in C-reactive protein (mg/l) during the patient’s illness. (●) CRP.

Figure 3. Proposed scheme for the pathogenesis of non-bacterial thrombotic endocarditis[2,4]. It is believed by some sources that formation of a sterile vegetation is also an important step in the pathogenesis of infective endocarditis (bottom right).
should be anticoagulated. Warfarin may be ineffective in this setting\(^6\), necessitating therapy with unfractionated, or low-molecular weight\(^7\) heparin. There is no consensus regarding indications for surgery in patients with NBTE. The advantages of such treatment are at least partly counterbalanced by the high risk of cardiac surgery in patients with a coexistent major illness. Moreover, it is often extremely difficult to in differentiate clinically between embolism and \textit{in situ} thrombosis. However, removal of the vegetation does remain an option for patients at high risk of embolism, such as those with large vegetations (>1 cm) or a previous history suggestive of embolism.

References


