CASE REPORT

A Case of Culture-Negative Infective Endocarditis with Atypical Presentation and Disseminated Multiorgan Embolism

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ABSTRACT

Infective endocarditis (IE) is associated with high morbidity and a mortality rate of 9-30% due to its life-threatening complications including systemic embolization of various organs. The complications are more common in culture-positive cases. In culture-negative IE, systemic embolism especially with multiorgan involvement occurring in a single patient is very rare. Such condition may significantly increase the hospital mortality and poses unique challenges in diagnosis and management. We present a case of a 14-year-old female who presented with a one-week history of vague left upper quadrant pain and fever. On presentation, she was fully conscious but with signs of septic shock requiring vasoconstrictor support and administration of a broad-spectrum antibiotics. There was generalised abdominal tenderness. Abdominal ultrasound showed geographic hypoechogenicity of the spleen with small bowel wall thickening. Contrast-enhanced computed tomography (CECT) abdomen confirmed splenic and renal infarction with ischaemic small bowel. Transthoracic echocardiography showed vegetation at the mitral valve. She developed a severe headache during admission. CT head and conventional cerebral angiography demonstrated a ruptured mycotic aneurysm. All her blood culture results were persistently negative throughout admission possibly due to the initiation of antibiotics prior to sample collection. Despite a negative culture, she developed disseminated embolism to various organs as described. The planned mitral valve surgery was delayed due to the intracranial bleed, and she underwent craniectomy for clot removal. Mitral valve replacement was performed one month later. During follow-up, she had good recovery with no signs of heart failure or significant impairment of quality of life.
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INTRODUCTION

Infective endocarditis (IE) is a serious, life-threatening infection of the heart's chambers and valves. Globally, the incidence of this condition is 1.5 to 11.6 cases per 100,000 person- years. There was an increase in the number of cases with the incidence of infective endocarditis reached 1,090,530 in 2019 from 478,000 in 1990. This is attributable to population growth, increased cases of degenerative valvular diseases and healthcare-associated IE caused by antibiotic-resistant hypervirulent Staphylococci (1). Rheumatic heart disease is the most common risk factor predisposing to IE particularly in the developing countries. Other risk factors include prosthetic valve and cardiac devices, congenital heart disease, mitral valve prolapse and injection drug use. In approximately 80% of IE cases, streptococci and staphylococci are identified as the causative micro-organisms.

Culture-negative IE accounted for 10% of cases mostly due to the initiation of antibiotics before a blood culture sample is collected. The immediate administration of antibiotics is warranted in cases of severe sepsis or septicaemic shock in the Emergency Department (ED) as a resuscitative measure to alleviate bacteraemia. Other causes of a negative blood culture include infection caused by fastidious and slow growing pathogens. In these cases, further assessment with polymerase chain reaction (PCR) of the valve tissue or serological testing is required for confirmation.

Septic embolism can potentially be disseminated to various organs in 12-40% of IE cases (2). Cerebral emboli can cause mycotic aneurysms with high propensity

to rupture. Emboli may occlude the arterial supply of solid abdominal organs leading to infarction. These complications are more common in culture-positive cases where there is higher burden of bacteraemia. In culture-negative IE cases, the complication of organ embolism is very rare and are only described in case reports in which a single organ is involved. To the best of our knowledge, simultaneous involvement of splenic, renal, mesenteric and intracranial circulations with ruptured mycotic aneurysm as in our case has not been reported in the literature.

CASE REPORT

A 14-year-old girl presented with left upper quadrant abdominal pain for one week duration associated with fever and intermittent non-ischaemic chest pain. She had no underlying medical conditions. She denied intravenous drug use, recent tooth extraction or throat infection. On clinical examination, she was febrile with a blood pressure of 94/55 and a heart rate of 138 beats per minute. She had generalized abdominal tenderness worst at the left subcostal region. There were no skin changes or conjunctival haemorrhage, no altered sensorium, focal neurological deficits or signs of heart failure. The abdominal radiographs were unremarkable. Point-of-care ultrasound revealed centrally located bowel wall thickening with interloop fluid and geographic heterogeneity of the visualised spleen. Bedside transthoracic echocardiography (TTE) showed mitral valve vegetation (Fig. 1). She was started on a noradrenaline infusion and intravenous ceftriaxone 2 gram was administered for septicaemic shock.

These findings raised the clinical suspicion of mesenteric ischaemia and splenic infarction due to septic emboli. Mesenteric CT angiography (CTA) was performed which demonstrated the presence of territorial, non-enhancing hypodensities involving the mid-part of the spleen consistent with infarction. A similar pattern was also seen in a lobular arterial distribution affecting both kidneys (Fig. 2). Long-segment distal jejunal wall thickening measuring up to 5mm was also noted suggestive of ischaemic bowel. However, no direct visualization of a filling defect in the respective arteries was seen to suggest acute embolism. Anti-DNase B Titre was high at 449U/mL (reference value: 0-375U/mL) indicating prior infection by group A streptococcus. Nonetheless, serial blood cultures showed no growth after five days of incubation. Serological markers and blood polymerase chain reaction were not performed due to lack of availability at our centre and patient's financial constraint to outsource the test to other laboratory facilities. She was treated as IE with multiorgan septic embolism.

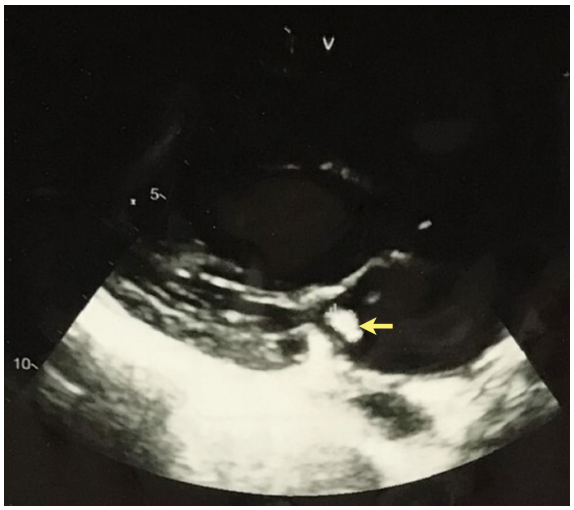

Figure 1: Parasternal long axis view of transthoracic echocardiography showing echogenic vegetation of the mitral valve leaflet (arrow)

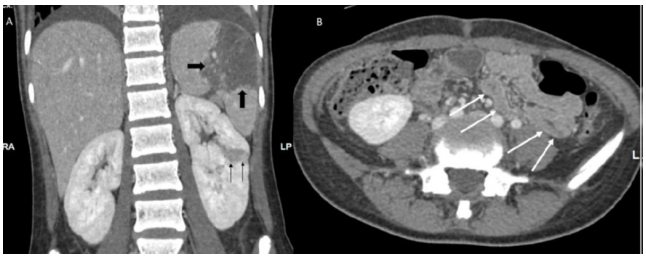

Figure 2: Contrast-enhanced CT scan of the abdomen in coronal reconstruction (A) demonstrating a wedge shaped geographic non-enhancement of the spleen (thick black arrows) and left kidney (thin black arrows) consistent with infarctions; and axial reconstruction (B) demonstrating small bowel wall thickening (white arrows) in keeping with ischaemia.

She was planned for mitral valve repair on day four of admission once she was haemodynamically stable and her sepsis was controlled. However, she experienced a severe headache followed by reduced consciousness. Cerebral CTA confirmed the presence of a ruptured saccular aneurysm at a cortical branch of the left middle cerebral artery (MCA) causing left parietal intraparenchymal bleed with minimal subarachnoid haemorrhage (SAH) component. Subsequent cerebral digital subtraction angiography (DSA) demonstrated bilobed saccular aneurysm arising from the M4 segment of left MCA (Fig. 3). The planned mitral valve surgery was postponed. She underwent craniectomy and thrombus removal with extraventricular drainage tube insertion. She was monitored in the Intensive Care Unit (ICU) and made significant clinical recovery. On discharge, she was prescribed IM benzathine penicillin 1.2 million units. She underwent mitral valve repair about one month after discharge. On follow-up, she was well with no signs of heart failure, significant neurological deficits or impaired quality of life.

DISCUSSION

Infective endocarditis refers to infection of the heart valves or endocardium by microorganisms mainly streptococci and staphylococci. The resultant vegetations can embolize to various organs. Cerebral complications are the most frequent and the most

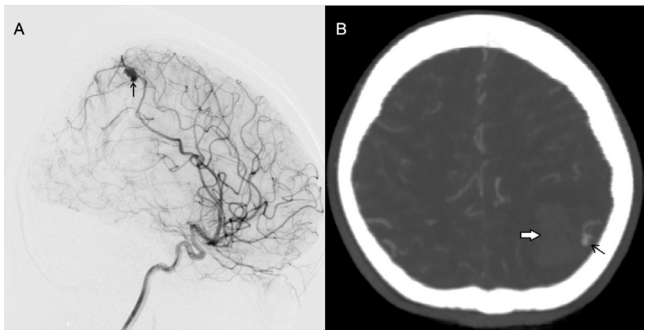

Figure 3: Cerebral Digital Subtraction Angiography (DSA) (A) showing bilobed saccular aneurysm (arrow) at a cortical branch of the left middle cerebral artery; and cerebral CT Angiography (B) showing the aneurysm (arrow) which has ruptured causing intraparenchymal haemorrhage (thick white arrow).

common initial manifestation of IE accounting for 15-20% of cases. Ischaemic and haemorrhagic stroke are the most common complications and were even found to precede the diagnosis of IE in 60% of cases (3). Other intracranial complications include transient ischaemic attack, mycotic aneurysm, cerebral abscess, and meningitis.

In the developed countries, the age group of patients affected by IE has shifted from the young population to the older population. This is due to the reduction in the incidence of rheumatic heart disease which mainly affects younger age group and an increased in the incidence of degenerative valve disease and healthcare-associated infections. However, the prevalence of rheumatic heart disease in developing countries is still high It affects the younger population in Malaysia with the latest prevalence at 14 cases per 1000 population (4). Our patient may have an undiagnosed rheumatic heart disease that predisposed her to IE based on her symptoms of fever and recurrent chest pain. Her anti-DNase B Titre was also high indicating previous Streptococci infection.

The most common cause of blood culture negative endocarditis is blood sample taken after the administration of antibiotics which reduces the sensitivity of culture compared to those taken before initiation of antibiotics. Other reasons for a negative blood culture include infection caused by fastidious and slow growing pathogens such as *C. burnetii* and *Bartonella spp*. One study shows a reduction of sensitivity due to blood culture taken as early as 50 minutes after the initiation of antibiotics (5). In our patient, antibiotics was given at the Emergency Department because the patient was in septic shock. The blood culture was taken later once patient was admitted to the ward. This contributed to the negative blood culture in this case.

Despite the negative blood culture, this patient developed complications involving multiple organs. One of the complications was mycotic aneurysms. These aneurysms are friable with a high risk of rupture resulting in severe neurological morbidity and overall mortality. The pathophysiological underpinning begins with embolism of the intracranial arteries predominantly at terminal segments at grey-white matter junction, followed by development of focus of infection at the intima breaching into the deeper vessel layers. Subsequently, the synergistic action of pro-inflammatory cytokines and neutrophils cause focal breakdown of the arterial wall creating aneurysms. These aneurysms are typically fusiform and commonly involve the anterior circulation. Rupture of these aneurysms commonly cause subarachnoid haemorrhage with or without intraparenchymal haemorrhage. Our patient developed severe headache during admission and CT scan confirmed the presence of intraparenchymal haemorrhage and SAH. Further assessment with DSA of the brain revealed saccular bilobed type of aneurysm which is atypical.

Our patient presented with vague abdominal pain which is non-specific. Without the hemodynamic instability on presentation that prompts bedside TTE examination at ED revealing mitral valve vegetation, the diagnosis of splenic and renal infarcts as the cause of the abdominal pain could be missed. Embolism to intra-abdominal organs in cases of IE commonly affects the solid organs such as spleen, liver, and kidneys. Mesenteric ischaemia is a rare complication of IE and only described in case reports. Patients with this condition usually presented with acute onset of non-specific abdominal pain partially resolved with analgesia. CT scan is required to confirm the diagnosis with the findings of bowel wall thickening with or without direct visualisation of filling defect within the mesenteric arteries to suggest embolism.

Extended parenteral antibiotics is the mainstay treatment of IE especially if left-sided cardiac valves are involved due higher bacterial density relative to right-sided vegetations. According to local guidelines, it is reasonable to delay the timing of surgical intervention in cases of IE with septic shock after 48 hours to allow hemodynamic stabilization and adequate control of sepsis with antimicrobials as cardiac surgery involving cardiopulmonary bypass carries a high intraoperative mortality if performed during septic shock. Our patient was planned for surgery on day four of admission once she was hemodynamically stable. However, she developed intracranial haemorrhage due to ruptured mycotic aneurysm and hence, the surgery was unable to proceed due to high mortality. One study reported mortality rate of 75% if surgery to be done within four weeks of acute intracranial haemorrhage.

CONCLUSION

In conclusion, this case highlights a culture negative IE associated with multiple organs complications occurring simultaneously in a previously healthy young

female. It also shows the complexity and challenges in the diagnosis and treatment of culture-negative IE especially in the areas with limited resources where rheumatic heart disease affecting younger population is still prevalent.

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