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# Mitral Valve Infective Endocarditis with Intracranial Septic Emboli and Haemorrhage

## Case Report

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## Abstract

A 70-year-old man presented with fever and delirium. His past medical history included mitral regurgitation, palindromic rheumatoid arthritis, autoimmune haemolytic anaemia, and thrombocytopenia. The main positive examination findings included harsh systolic murmurs in the mitral area and at the lower sternal border.

A head computed tomography (CT) did not reveal any acute intracranial pathology, and lumbar puncture yielded normal cerebrospinal fluid (CSF). Brain magnetic resonance imaging (MRI)and transoesophageal echocardiogram (TOE)were performed with a high suspicion of infective endocarditis(IE), and the former revealed several ischaemic emboli with some haemorrhagic transformation, and the latter demonstrating small vegetations in the anterior and posterior mitral valve leaflets (5-7mm and 2-3mm in each) with a tiny perforation in the anterior leaflet. Management of this patient involved treatment with intravenous (IV) antibiotics for 6 weeks, management in the coronary care unit with joint care by an infective disease specialist, a cardiothoracic surgeon and a neurologist so as to optimise the management.

## Introduction

Infective endocarditis (IE) is a common infectious disease amongst the general population, predominantly in patients with underlying valvular heart disease. However, with regard to presentation with neurological complications (intracranial septic emboli and haemorrhage), its mortality rate is significantly higher than the primary condition itself, constituting up to one-third of IE cases, especially if timely diagnosis is not reached and management is delayed [1]. Thus, it is of paramount importance to identify IE with septic emboli promptly and accurately, and some patients need surgical intervention in a timely manner to improve the survival.

## Case Presentation

A 70-year-old man, a cattle farmer, was transferred to a regional hospital from another rural hospital where he had presented with acute confusion, fever, and chills. He did not have symptoms to suggest the source of infection.

He hadahistory of mitral regurgitation, palindromic rheumatoid arthritis, autoimmune haemolytic anaemia, and thrombocytopenia. He did not take any regular medications prior to presentation.

He was a life-long non-smoker and a social drinker. In particular, there was no history of intravenous drug use, and recent dental treatment.

On arrival, his temperature was 39.5'C and Glasgow Coma Scale (GCS) was 14/15. His heart rate was 90 bpm, oxygen saturation was 90% in room air. Cardiovascular system examination revealed normal jugular venous pressure, a harsh pansystolic murmur at the apex, and asystolic murmur over the lower sternal border, with no peripheral signs of IE such as Janeway lesions or Oslernodes, and no evidence of heart failure. Neurological system examination was limited as the patient was uncooperative in the context of delirium. The respiratory and abdominal system examinations were unremarkable.

## Investigations

On arrival at the regional hospital, an ECG was performed, which showed sinus rhythm with multiple premature ventricular complexes.

Admission blood tests showed haemoglobin (Hb) 92 g/L, white cell count (WCC) 11.75 x 109/L, platelet count 83 x 109/L, and C-reactive protein (CRP) 140mg/L. His renal and liver function tests were within the normal limits.

Brain CT and angiogram were unremarkable, with no signs of stroke, intracranial haemorrhage, or vascular pathology (Figure 1).

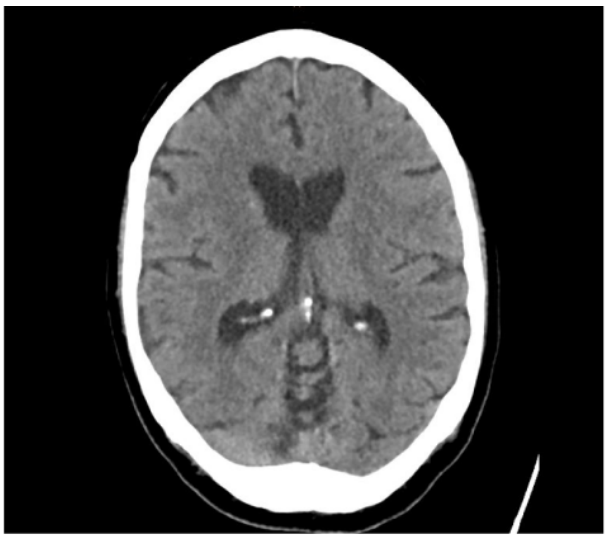

**Figure 1:** Brain CT and angiogram demonstrating no acute intracranial pathology

**Table 1:** CSF APPEARANCE

| | |
|---|---|
| Appearance | Blood stained fluid |
| Turbidity | Clear |
| Supernatant | Colourless |

**Table 2:** CSF MICROSCOPY

| | |
|---|---|
| Leucocyte count (Tube 2) | 5 x $10^{6/L}$ |
| Erythrocyte count (Tube 2) | 8420 x $10^{6/L}$ |

**Table 3**: CSF Microbiology PCR / Nucleic Acid Detection Test (NAT)

| | |
|---|---|
| Adenovirus DNA. | NOT Detected |
| Enterovirus RNA | NOT Detected |
| Herpes simplex virus type 1&2 DNA | NOT Detected |
| Neisseria meningitidis DNA | NOT Detected |
| Varicella zoster DNA | NOT Detected |
| M.tuberculosis complex DNA | NOT Detected |
| Streptococcus pneumoniae | NOT Detected |
| Listeria monocytogenes | NOT Detected |

Cerebrospinal fluid (CSF)showed acellular and sterile CSF (Tables 1-3).

Despite normal brain CT and sterile/acellular CSF results, a decision was made to proceed to brain MRI to rule out any acute brain pathology; MRI revealed several ischaemic emboli, with haemorrhagic transformation in someof them (Figure 2). Prompted by the suspicion of IE given the examination findings of two murmurs, a transthoracic echocardiogram (TTE) was performed in the rural hospital, which showed markedly dilated left atrium with mitral valve prolapse and moderate mitral regurgitation, andno vegetations. As TTE cannot rule out a small vegetation, TOE was performed, which demonstrated a tiny perforation in the anterior leaflet (Figure 3), with a 2-3mm vegetation in the posterior mitral valve leaflets and a 5-7mm vegetation in the anterior mitral valve leaflet (Figure 4). Results of blood cultures also came back positive for methicillin-sensitive Staphylococcus aureus (MSSA), which is sensitive to cefazolin di/flucloxacillin, but resistant to penicillin.In the tertiary setting, carotid doppler was performed to rule out other sources of emboli, which manifestedno atherosclerotic disease/stenosis. As the patient reported bone and joint pain, gallium scan was also performed, which ruled out any infective foci in the whole body (bones and joints).TOE was repeated in a week in the tertiary setting, revealing bileaflet mitral valve endocarditis, with an approximately 1.7cm vegetation in the posterior leaflet of the mitral valve (Figure 5) andmoderate mitral regurgitation (Figure 6). The patient was discharged with a total 6-week course of IV antibiotics, and TOE was repeated after the course of antibiotics was completed. This showed a small perforation in the

anterior mitral valve leaflet causing trivial to mild mitral regurgitation, with no evidence of vegetations (Figure 7).

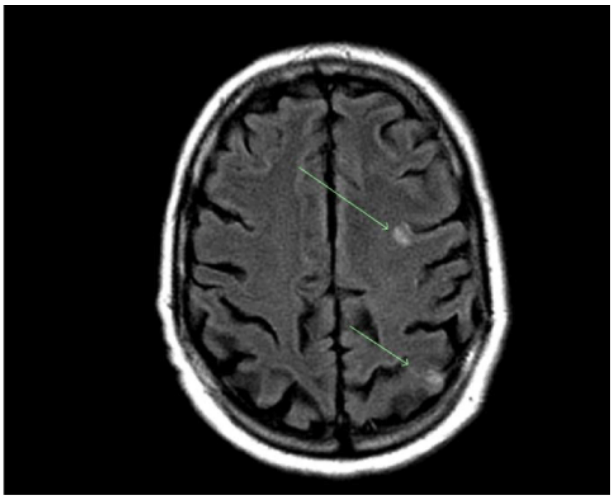

**Figure 2:** Multiplanar multiechobrain MRI demonstrating multiple ischaemic embolic phenomena, some of which are haemorrhagic (as indicated by the arrows)

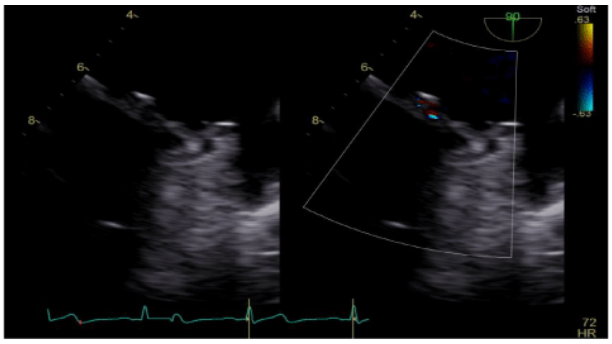

**Figure 3:** TOE 1 performed in the rural setting demonstrating tiny perforation in the anterior leaflet of the mitral valve

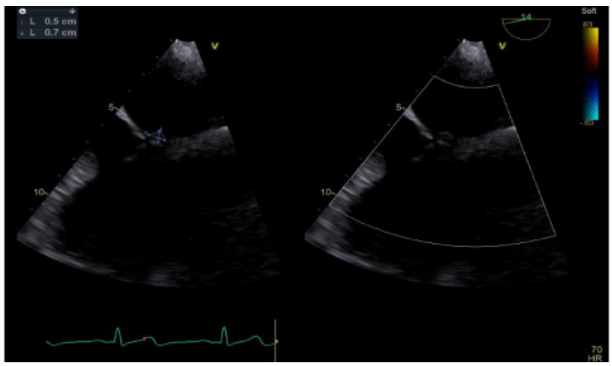

**Figure 4:** TOE 1 performed in the rural setting demonstrating small vegetation in the mitral leaflet

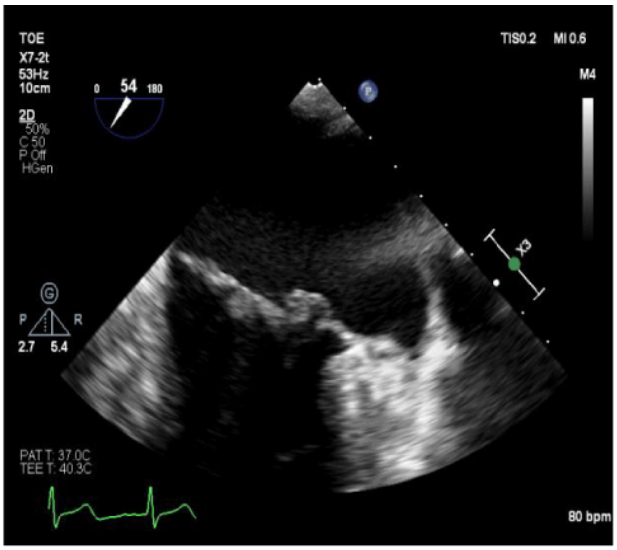


**Figure 5:** TOE 2 performed in the tertiary setting demonstrating >1cm vegetation in the mitral valve

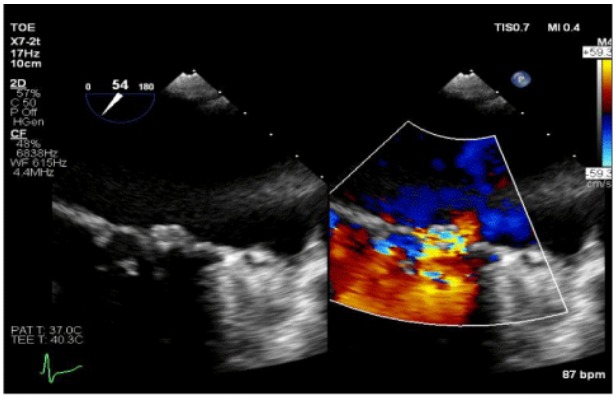


**Figure 6:** TOE 2 performed in the tertiary setting demonstrating mitral valve regurgitation

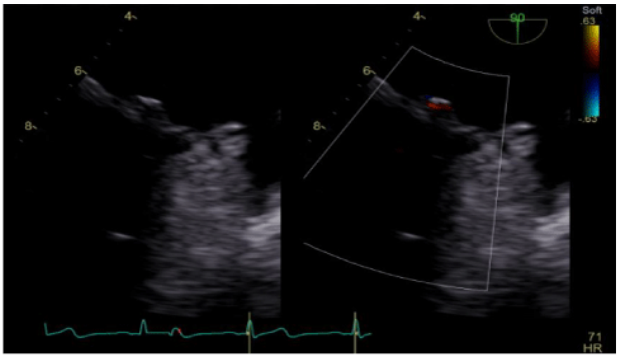

**Figure 7:** TOE 3 performed in the rural setting after 6 weeks course of antibiotic, demonstrating small perforation in the mitral leaflet but no vegetation

## Treatment

The patient was initially admitted to the medical ward of the regional hospital with fever and acute onsetof delirium. Initial sepsis screening showed no obvious source of infection.Brain CT and angiogram did not reveal acute pathology. Given the signs of presumed sepsis, the patient was initially managed with acyclovir for 72 h and broad-spectrum antibiotics (vancomycin, cefepime, amoxicillin) after consulting with an infectious disease (ID) specialist from a tertiary hospital. The patient was found to have hypotension, fever and increased confusion in the medical ward and was, therefore, transferred to the care of the high dependency unit (HDU) for intensive care and monitoring. When blood cultures came back positive for MSSA, the antibiotic was changed to IV flucloxacillin after liaising with the ID specialist. Given that MRI along with TOE findings indicated IE with intracranial septic emboli, the patient was referred for transfer to the coronary care unit (CCU) of a tertiary hospital for further management. The patient was transferred by the Royal Flying Doctor service (RFDS) to a metropolitan site.

On the arrival at the CCU, the patient's cardiac status was monitored for any deterioration, and the infectious disease team were consulted for the choice of antibiotics; they recommended continuing flucloxacillin for 6 weeks. The patient was reviewed by the cardiothoracic surgical team for the likely need of urgent surgical intervention, and the neurology team were consulted regarding intracranial septic emboli and haemorrhage. As the patient did not have any features of end organ damage and initial TOE demonstrated multiple small vegetations of <1cm with a tiny perforation in the anterior leaflet, he did not meet the absolute criteria for emergency intervention. There was a concern of increased surgical risk in the setting of intracranial emboli and haemorrhage; therefore,it had been a difficult decision regarding whether mitral valve replacement surgery should be performed during the same time window.

TOE was repeated in a tertiary hospital a week after commencement of IV flucloxacillin,which revealed a 1.7cm vegetation in the posterior leaflet of the mitral valve with moderate mitral regurgitation.As the second TOE demonstrated a >1cm vegetation, early surgical intervention versus ongoing medical therapy with close surveillance had been a debatable issue amongst the multidisciplinary team (MDT) to achieve the best plan for the patient, with the possible risk of bleeding and risk of transformation of intracranial emboli into haemorrhage engendered by intraoperative anticoagulation during cardiac surgery.After close monitoring of the patient's clinical improvement and improvement in biochemical markers, the MDT decided to continue with IV antibiotic for a total of 6 weeks, given the risk associated with surgery in the context of intracranial emboli and haemorrhage.

## Outcome and Follow-Up

With the treatment mentioned above in the metropolitan hospital, the patient was found to improve both clinically and biochemically. He was, therefore, discharged with the plan to continue IV flucloxacillin 12 gramsonce daily viaperipherally inserted central catheter (PICC) line in the regional hospital, and to undergo repeat echocardiogram as an outpatient in the regional hospital in 6 weeks.

The patient received IV flucloxacillin once daily in the rural setting with monitoring of baseline blood tests and infection markers (CRP). However,after 4 weeks of continuing IV flucloxacillin, he was found to have mild neutropenia and thrombocytopenia (platelet 118 × 109/L, WCC 3.31 × 109/L, neutrophils 1.56 × 109/L) with poorly improving CRP, which might have been due to adverse drug reaction/poor response to IV flucloxacillin, which was, therefore, switched to IV cefazolin 8 g daily and continued for 2 more weeks to complete the total 6 week course of antibiotics. Satisfactory progress with improvement of CRP was found with IV cefazolin, which was then ceased after a total of 6 weeks; however, currently, there is persistent mild to moderate neutropenia and thrombocytopenia, which will require ongoing monitoring.

TOE was repeated in a week in the regional hospital with the private cardiologist after completing antibiotic therapy, which proved that there were no vegetations, but a small perforation in the anterior mitral valve leaflet causing trivial to mild mitral regurgitation, which the cardiologist decided was of no major concern at this stage and he was arranged for a follow-up and repeated echocardiogram in 6 months and every 12 months thereafter.

## Discussion

Febrile presentation of IE is not uncommon in the emergency department (ED) [2]. Amongst myriads of clinical manifestations, approximately 90% of patients present with fever accompanied by chills, loss of appetite, and loss of weight. Fatigue, myalgia/arthralgia, sweating, dyspnoea, headache, and abdominal pain make up other

constitutional symptoms, which are also found in significant proportions of patients [3]. With regard to examination findings, cardiac murmurs are usually detected in 85% of patients. Well-known findings of IE such as petechiae on skin/mucous membranes, splinter haemorrhages (thin reddish-brown lesions underneath the nails), Janeway lesions (non-tender small erythematous macular lesions on the palms/soles), Osler nodes (tender red nodules on hands and feet), and Roth spots (haemorrhagic spots with white centre that can be seen in the retina) are in fact relatively rare manifestations.

IE is a concerning condition and if left untreated, it may cause some debilitating consequences such as septic emboli, brain abscess, and mycotic aneurysm [2]. Among the most common complications are cardiac failure, multi-organ infract (liver/spleen) secondary to septic embolization, and neurologic complications such as brain abscess, embolic stroke, meningitis, meningoencephalitis, and acute encephalopathy. Seizures can manifest as a secondary complication from abscess or infract, and embolic stroke can, in turn, cause cerebral haemorrhage if there is systematic hypertension.One important finding in our case was that the patient presented with vegetations on the mitral valve accompanied by a tiny leaflet perforation, which led to complications such as septic and haemorrhagic cerebral embolism. The incidence of these complications is further increased if the patient is an intravenous drug user, which our patient was not.

The anatomical location and size of vegetation(s) play important roles in the occurrence of neurologic complications. For example, large (>10-15mm) and mobile vegetationsor mitral valve vegetations pose a much greater risk of embolism. The causal organism is also an important factor as S. aureus leads to two to three times greater CNS involvement than any other pathogens, which is further increased depending on the sensitivity of the organism [4,5]. Studies in the literature have revealed that the mortality rate is relatively low (34.8% lower) in MSSA infection than in methicillin-resistant S. aureus (MRSA) infection. MRSA infection is strongly correlated with haemodialysis, intubation, and surgical intervention. MSSA was cultured in our case, although, unfortunately, complication with several cerebral septic emboli resulted in altered mental status. This can further lead to grave complications such as multi-organ failureand disseminated intravascular coagulation unless timely diagnosis and appropriate treatment are instigated.

Neurological symptoms may be the primary presentation of IE. Symptomatic neurologicalcomplications occur in one-third of patients,[6-13] whereas asymptomatic complications may occur in up to 80 % [14-16]. Therefore, it is more reliable to use MRI than to depend on the clinical findings to detect whether the patient has any intracranial complications.[6,16,17] In our case, the patient presented with features of delirium and fever. Even when a brain CT and an angiogram are normal, performing brain MRI as part of the initial management plan is of tremendous benefit in providing the clue to clinch the diagnosis of IE retrospectively, and this could save the patient's life. In terms of outcomes after a neurologic complication of IE, studies have revealed that patients achieved full neurological recovery in 70 % of cases with a preoperative stroke, and this percentage is reduced in patients with complicated stroke accompanied by meningitis, cerebral haemorrhage, or brain abscess [12].

## Indications for Surgery

Indications for early surgical intervention consist of heart failure; perivalvular infection with complications of abscess/fistula; multidrug-resistant pathogens; infection persisting more than 1 week after commencing appropriate antibiotic treatment; and high embolic risks such as in patients with previous recurrent emboli and enlarging vegetations despite antimicrobial therapy, mobile vegetations > 1cm, and with other relative indications such as severe valvular pathology or a history of a single embolic episode [18-21]

The optimal timing will depend on the individual case and should be decided by multidisciplinary experts after considering various factors such as indications, risks and benefits, and contraindications. Although it is mainly dependent on specialists' opinions, early surgery is recommended for silent microembolism, cerebral abscess, transient ischaemic attack, and ischaemic stroke with no haemorrhagic transformation and without severe neurological deficit [22]. As for patients with major ischaemic stroke with reduced consciousness or intracranial haemorrhage, a delay period of ≥4 weeks is suggested. Some other reasons to defer surgery are low life expectancy, multi-organ failure, and ruptured infected aneurysm.

According to the European Society of Cardiology (ESC) guidelines, emergency surgical intervention is defined as one undertaken within 24 h, urgent surgery in a few days, and an elective one after 1-2 weeks of

commencing antibiotics. The intervention known as early surgery defined by American Heart Association (AHA)/ American College of Cardiology (ACC) guidelines is one where surgery is performed before the completion of a full course of antibiotics while the patient is hospitalized [23]. However, the possibility of detrimental complications of intracranial septic emboli is reduced significantly after the initiation of appropriate antimicrobial treatment. One complication to be concerned about is the haemorrhagic conversion of an ischaemic stroke. Generally, it can occur during the first 2 weeks and stabilization can take up to 6 weeks; however, it is difficult to predict the time course for this transformation. As for cardiopulmonary bypass for patients with neurological complications, there are various opinions depending on its suitability. The need for anticoagulation during cardiac surgery may engender the haemorrhagic transformation of a silent embolic stroke. The pre-existing brain ischaemia can also be deteriorated by episodes of hypotension during the procedure [24]. Therefore, some therapeutic guidelines indicate that it is appropriate to avoid or defersurgery that requires a high level of anticoagulation such as cardiopulmonary bypass. Furthermore, coronary embolization should be appropriate in cases of left-sided endocarditis accompanied by acute coronary syndrome,as evidenced by ECG changes or laboratory values.

## Learning points

- To consider the possibility of IE on presentation of a patient with fever, delirium, and a cardiac murmur with no other signs of infective endocarditis.
- Clinical presentation with acute confusion and fever might need further evaluation with brain MRI and echocardiogram to obtain the retrospective diagnosis of IE, even if CT demonstrates no acute intracranial pathology and lumbar puncture shows sterile CSF.
- To consider the possibility of IE in the presence of a new murmur in case of known valvular pathology.
- Early diagnosis and treatment for intracranial septic emboli is of critical importance to reduce mortality rates, and management requires a multidisciplinary, multimodality therapeutic approach under the care of ICU/CCU in a metropolitan setting.
- IE complicated by intracranial septic emboli is not always an indication for urgent surgery, as highlighted in our experience with this patient.

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