WHAT IS YOUR CALL?

Fever and multiorgan infarcts in a 35-year-old man

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A previously healthy 35-year-old man was brought to the emergency department by his family because they were concerned that he was confused. He had experienced five days of flu-like symptoms with fever, progressive swelling of his feet and hands, shortness of breath when lying down, and blurred vision. He had no history of valvular or other cardiac disease. There was no known intravenous drug use or dental or invasive procedures.

At presentation, he was febrile (38.7°C) and somnolent, but he was hemodynamically stable. He had generalized pitting edema in all extremities. His cardiac examination was normal with no murmurs, and his lungs were clear with no adventitious sounds. There was mild nonspecific abdominal tenderness on palpation. No obvious skin rashes or lesions were observed.

He had marked thrombocytopenia (platelets 14 [normal 150–400] $\times 10^9$/L), neutrophilia (neutrophils 10.7 [normal 2.0–7.5] $\times 10^9$/L) and evidence of acute kidney injury (creatinine 247 [normal 64–110] μmol/L). Two blood cultures were drawn, and Gram-positive cocci were found. Computed tomography (CT) of his head showed hemorrhage in the right occipital lobe with surrounding vasogenic edema, causing mild mass effect with slight midline shift.

What is your initial diagnosis?

a. Cerebral abscess
b. Vasculitis with cerebritis
c. Infective endocarditis
d. Illicit drug use

Given the presence of fever, bacteremia with Gram-positive cocci and cerebral hemorrhage, there was a high degree of suspicion for bacterial infective endocarditis (c) despite the absence of obvious risk factors. The lack of other systemic manifestations, as well as the presence of bacteremia, pointed away from vasculitis. Although we could not immediately exclude a cerebral abscess based on the preliminary findings, the presence of peripheral edema and orthopnea in the patient's history supported a heart failure syndrome, which is a common complication of infective endocarditis.[1] Illicit drug use should be considered in patients who present with right-sided valvular involvement, signs and symptoms of right heart failure, or septic pulmonary emboli or abscesses. In this case, clinical suspicion of intravenous drug use was low.

A magnetic resonance angiogram of the patient's head was obtained to further delineate the intracerebral hemorrhage and to rule out abscess and vascular abnormalities. It confirmed the presence of a hematoma (3.4 × 5.0 cm) in the right parieto-occipital lobe and revealed a mycotic aneurysm as the likely cause of the cerebral hemorrhage. Multifocal hemorrhagic infarcts consistent with cerebral embolism were also seen.

The patient was transferred to a tertiary care centre for his intracranial hemorrhage to be assessed by a neurosurgeon. A neurosurgical intervention was not thought to be immediately necessary because the hematoma was stable on repeat CT scans, he remained neurologically unchanged, and his perioperative risk was increased by the concomitant severe thrombocytopenia and renal insufficiency.

Empirical intravenous vancomycin therapy was started for treatment of suspected infective endocarditis. However, the antimicrobial therapy was changed to cloxacillin for methicillin-sensitive *Staphylococcus aureus*, which was grown in the first two blood cultures. Subsequent blood cultures obtained after antibiotic therapy was started were negative.

The thrombocytopenia and renal failure were believed to be related to septicemia. There was no evidence to suggest glomerulonephritis. He received a platelet transfusion and intravenous immunoglobulin (IVIg) for two days to stabilize his platelet count, while his renal function was stable without the need for dialysis. An abdominal ultrasound performed at the time of admission showed normal kidneys and spleen.

A transesophageal echocardiogram showed a bicuspid aortic valve and a vegetation measuring

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1.1 × 0.5 cm on the ventricular side of the aortic valve, thus confirming the diagnosis. There was mild-to-moderate aortic regurgitation, but the mitral valve was intact.

What is the next step in management?

a. Continue antibiotic therapy and monitor
b. Repeat the transesophageal echocardiogram in three to four days
c. Perform cardiac magnetic resonance imaging (MRI) to better characterize the size of the valvular lesion
d. Urgent replacement of the aortic valve
e. Request a follow-up neurosurgical assessment

Despite the substantial size of the vegetation, the decision was made to continue intravenous cloxacillin and closely monitor the patient's response (a) because his cerebral infarcts, hemorrhage and renal impairment would increase his operative risks from an aortic valve replacement. The goals were to control the underlying infection, prevent the formation of septic emboli and optimize his clinical status before valvular surgery.

If an initial transesophageal echocardiogram is negative but there is ongoing suspicion of infective endocarditis, repeat transesophageal echocardiography (b) is typically performed 7 to 10 days later, because an early test may miss small vegetations.[2] A follow-up transesophageal echocardiogram after an initially positive result may be indicated if the patient fails to improve during antimicrobial therapy or develops cardiac complications (e.g., heart failure, change in murmur, arrhythmia) that might require urgent surgical intervention. In our patient, a follow-up transthoracic echocardiogram showed a left ventricular ejection fraction of 40%–59% and thickened aortic cusps.

There is no evidence to support the use of cardiac MRI in infective endocarditis, which is less sensitive in detecting mobile vegetations.

An urgent neurosurgical consultation would be the appropriate next step if there was neurologic deterioration due to an enlarging hematoma or an enlarging intracranial mycotic aneurysm, which was not the case in our patient.[2] A neurosurgical intervention would not prevent further intracranial embolic or hemorrhagic events. Continued CT surveillance of our patient showed no change in the cerebral hematoma and no new areas of infarct or hemorrhage.

However, less than two weeks after antibiotics were started, the patient had an acute onset of diffuse abdominal pain and distension, accompanied by a substantial decrease in hemoglobin to less than 80 (normal 140–180) g/L. He also had persistent fevers and worsening tachypnea. A CT scan of his abdomen and pelvis with oral contrast revealed a large perinephric hematoma on the right side accompanied by intraparenchymal hemorrhage (Figure 1). At this time, there was also evidence of a new splenic infarct.

What procedure should be considered next?

a. Urgent transesophageal echocardiography
b. Renal angiography
c. Lung perfusion scanning
d. Urgent replacement of the aortic valve

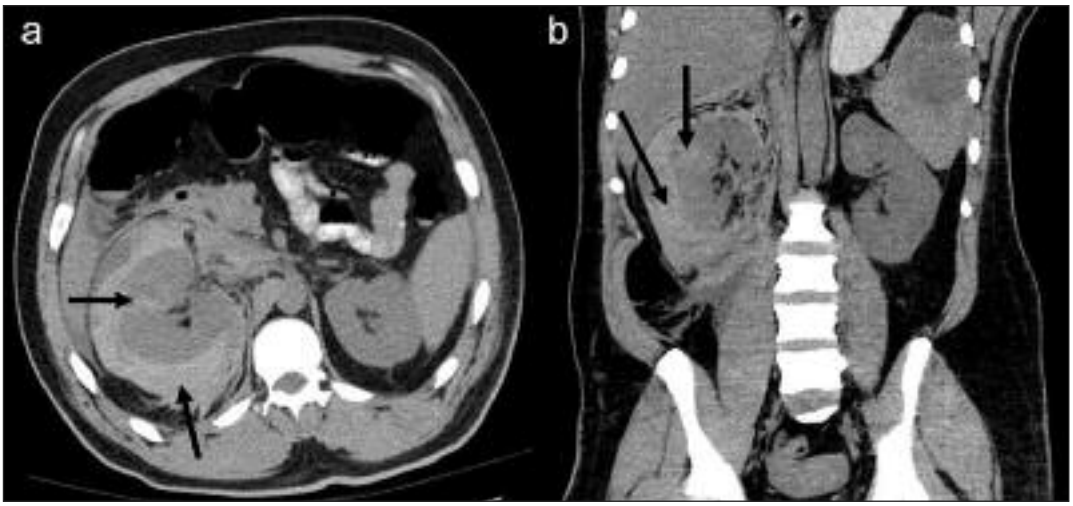

Figure 1: CT axial (a) and coronal (b) views of the patient's abdomen showing right perinephric and intraparenchymal areas of hyperdensity (arrows) consistent with hemorrhage.

In our patient's case, it was immediately necessary to first localize and control the potentially life-threatening bleed from the kidney. Renal angiography (b) was performed by an interventional radiologist; the results showed an aneurysm arising from a tertiary arterial branch as the source of the hemorrhage. This was successfully embolized (Figure 2). A lung perfusion scan (c) was also obtained to exclude the possibility of a pulmonary embolus.

Because of ongoing peripheral emboli while receiving appropriate antibiotics, the patient underwent urgent replacement of the aortic valve (d). He made a gradual recovery. Subsequent abdominal imaging revealed a stable renal infarct with resolving hematoma, and his creatinine level steadily improved. Magnetic resonance imaging of the patient's brain showed no new ischemic infarcts but suggested several mycotic aneurysms with associated microhemorrhages. He remained on intravenous cloxacillin for six weeks after surgery.

Discussion

Infective endocarditis is associated with an in-hospital mortality rate of 9%–26% because of complications from valvular destruction and septic emboli from vegetations.[3] Risk factors for infective endocarditis vary with the side of the lesion (i.e., left or right) and the clinical setting (i.e., whether it is health-care related) (Table 1).[4] A previous history of infective endocarditis is also a risk factor for recurrence.[5] *S. aureus* is the most common causative microorganism in infective endocarditis[6] and has been shown to be an independent predictor of in-hospital mortality.[6]

Systemic embolization is a common phenomenon in infective endocarditis with an incidence of 22%–50%.[2] Although antibiotic therapy reduces the rate of embolic events, the risk of embolization remains substantial at 9%–21% and is highest in the first two to four weeks of antimicrobial therapy.[2,7]

Emboli may seed any segment of the arterial vasculature. The central nervous system is the predominant site of clinically apparent septic emboli (> 50%), typically in the territory of the middle cerebral artery (> 90%).[2] Neurologic complications include embolic cerebrovascular events, intracerebral hemorrhage, ruptured mycotic aneurysm, transient ischemic attack, cerebral abscess, meningitis and encephalopathy. Neurologic complications, most commonly embolic infarcts or intracerebral hemorrhage caused by mycotic aneurysm rupture, have an estimated mortality rate of 21% to 83%.[7] Neurologic complications are the second leading cause of death in infective endocarditis after congestive heart failure.[7] The spleen is the next most common target of embolization, potentially leading to splenic abscesses. Less frequently, emboli may appear in the extremities, kidneys, lungs, heart or mesentery.[8]

The manifestations and sequelae of septic embolism range from subtle and mild to severe

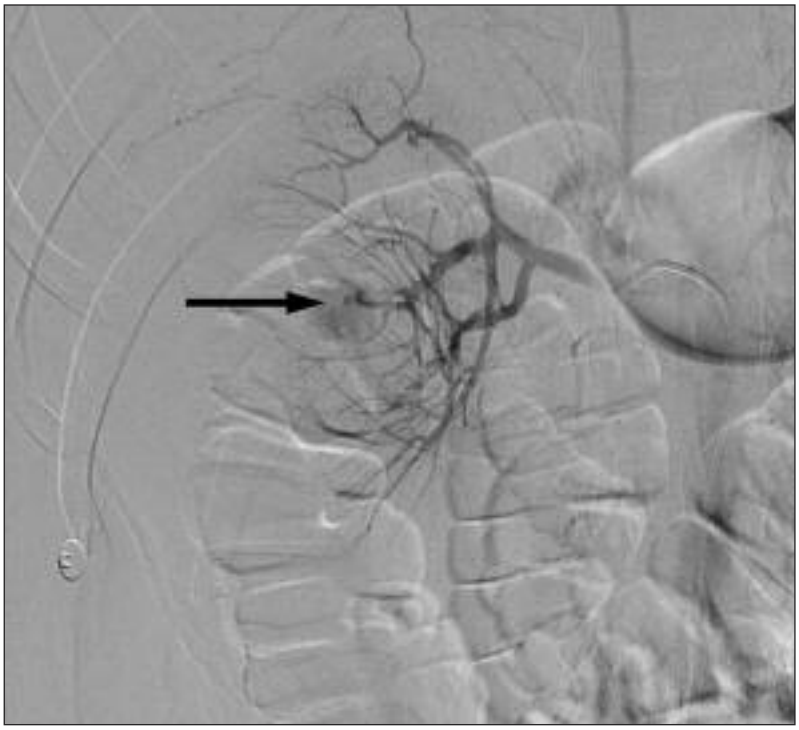

Figure 2: Angiogram of the right kidney. The catheter was advanced into the right renal artery, and the widened contrast shadow (arrow) at a tertiary midpole artery was consistent with a large aneurysm in the right midpole of the kidney. The arterial branch leading to the aneurysm was selectively embolized.

Table 1: Risk factors for infective endocarditis[5]

Type of lesions	Risk factors
Left side	Native valve
	• Congenital heart disease
	• Chronic rheumatic heart disease in developed countries
	• Mitral valve prolapse (10–100 × increased risk)
	• Degenerative valve lesions
	Prosthetic valve
Right side	Intravenous drug use (especially high risk in HIV-related immunodeficiency)
	Congenital heart disease
	Devices: pacemaker, implantable defibrillators
	Central venous catheter
Related to health care	Nosocomial
	• Invasive intravascular procedure
	• Catheter-related
	Chronic hemodialysis

and life-threatening, depending on the location and extent. About 20% of embolic events are asymptomatic, particularly in the spleen and kidneys; these events must be systematically investigated by imaging.[7] The identification of "silent" infective endocarditis has improved because of the increased use of neuroimaging, which detects clinically asymptomatic cerebral emboli.[9]

The risk of systemic embolization is highest with valvular lesions on the left side, especially those affecting the mitral valve.[2] Risk is also high with infections by *S. aureus*, *Candida*, the HACEK group of organisms and *Abiotrophia* species.[2] Large (> 10 mm) highly mobile vegetations or an increase in vegetation size are strong independent predictors of embolism during antibiotic therapy.[8,10] Thus, echocardiographic characterization of vegetations is essential when assessing the risk of septic emboli and prognosis.

Mycotic aneurysms and hemorrhage are serious complications following septic embolism. A mycotic aneurysm develops when an embolus invades through a vessel wall. It tends to occur at arterial branch points where emboli commonly lodge.[10] Mycotic aneurysms in the setting of infective endocarditis are uncommon and predominantly form in intracranial arteries (1.2%–5%).[2,7]

In infective endocarditis, intracerebral hemorrhage occurs if an enlarging aneurysm ruptures. The estimated mortality from ruptured intracranial mycotic aneurysms is 80%.[2] Therefore, patients with infective endocarditis who present with or develop headaches or neurologic deficits should undergo urgent CT or magnetic resonance angiography. These aneurysms may resolve with antibiotics in about 50% of cases,[7] but others require surgical ligation or clipping.

Pharmacologic treatment

The goal of therapy in infective endocarditis is to eradicate the causative organism from the infected tissue. Evidence-based recommendations are provided in the American Heart Association's statement for the treatment of infective endocarditis.[2]

Antibiotics are the mainstay of treatment and decrease the rate of septic embolism. The length of therapy depends on the pathogen, native or prosthetic valve involvement, and the clearance of vegetations, if present. In infective endocarditis involving native valves due to *Staphylococci*, the guidelines recommend six weeks of nafcillin or oxacillin for oxacillin-susceptible strains.[2] Cloxacillin belongs to the same family of penicillinase-resistant penicillins and provides equally effective antimicrobial coverage. Vancomycin should be used in cases of oxacillin-resistant *Staphylococci*. Recommended regimens specific for infective endocarditis involving other or resistant microorganisms or prosthetic valves, as well as cases of penicillin allergy, are provided in the American Heart Association's guidelines.[2]

There is presently no evidence for the use of anticoagulation or antiplatelet agents in infective endocarditis, unless anticoagulation is required for other conditions such as prosthetic valves.[11]

Surgical treatment

Surgical intervention is indicated in some cases of infective endocarditis of the native valves. However, the decision regarding surgery and its timing must be made individually with collaboration between cardiologists and cardiac surgeons. In accordance with the American Heart Association's guidelines,[2] recommendations for surgery exist in the following scenarios: significant mitral or aortic valve lesions causing congestive heart failure or hemodynamic compromise; periannular extension with formation of abscess, fistula or conduction block; and infective endocarditis due to fungal or highly resistant organisms. To reduce the risk of new emboli, early surgical intervention may be considered in the presence of large (> 10 mm) mobile vegetations.[7] Regardless of the characteristics of vegetations, surgery is advised if there are recurrent septic emboli despite adequate antimicrobial therapy.[2,11,12] The European Society of Cardiology further specifies the urgency of surgery for the above indications (Appendix 1, available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.111709/-/DC1).[13] In the absence of these indications, valvular surgery, if needed, may be delayed until the end of the antibiotic course.[11]

Timing

The optimal timing of surgery remains an area of uncertainty. It was previously thought that early valvular surgery in the presence of active inflammation of infected valves was associated with poorer postoperative outcomes and dysfunction of replaced valves.[14] However, with advancements in surgical techniques, early surgery (i.e., during the active phase of infection) is feasible and may be performed if there are severe cardiac complications of infective endocarditis (e.g., heart failure).

A systematic review of nine observational studies of the benefits of early cardiac surgery in 4199 patients with infective endocarditis found mixed results between studies.[14] Overall, the rate of early surgery during active infection was 23%–53%, and there were demonstrated long-term survival benefits.[15] However, these studies had substantial biases and lacked methodologic or statistical rigour. Although it is not established

that early surgery is superior for all patients, emerging studies suggest that earlier intervention may reduce the occurrence of embolic events and death. A nonrandomized, propensity-matched analysis found fewer embolic events in those with early surgery, although there were few events per group.[16] There are few randomized controlled trials of early surgery versus medical therapy for infective endocarditis; however, preliminary results of the Early Surgery versus Conventional Treatment (EASE) trial provides initial evidence supporting earlier intervention in such patients.[17] This clinical trial found reduced in-hospital death and embolic events in the early surgery group (antibiotics and surgery immediately after diagnosis) compared with the standard treatment group (antibiotics only) (i.e., 2.7% v. 23.1%; hazard ratio 0.248, 95% confidence interval 0.069–0.883).

Patients with neurologic complications

It is of paramount importance that the decision for surgical intervention take into account other factors affecting perioperative risks. In particular, the safety and timing of cardiac surgery in patients with neurologic complications are controversial. There are conflicting reports about postoperative mortality when surgery is performed within the first two weeks after a stroke.[7] Specifically, the use of cardiopulmonary bypass and perioperative anticoagulation may worsen neurologic outcomes by causing greater cerebral hemorrhage, hypotension and ischemia, as well as cerebral edema near existing areas of brain injury.[18] However, other studies have not shown poorer neurologic function from cardiac surgery after a stroke.[19] Unfortunately, there is a lack of prospective controlled studies to accurately predict neurologic outcomes and guide treatment decisions in this specific setting.

Rossi and colleagues conducted a search that included 100 published studies; they selected 20 articles as providing the best available evidence on the optimal timing of surgery in patients with neurologic complications.[18] Although the results of these studies were variable, the severity of neurologic complications and the urgency of surgery appeared to be critical determinants of the outcome.

A large, multicentre prospective study involving 109 patients with infective endocarditis and transient ischemic attacks or "silent" cerebral emboli (i.e., incidentally identified on imaging) who underwent early surgery had a good prognosis and similar mortality compared with patients who had delayed surgery.[20] In contrast, large ischemic strokes have been linked to poor neurologic outcomes after surgery. The Society of Thoracic Surgeons' clinical practice guideline on the surgical management of infective endocarditis recommends a delay in valve replacement of four weeks for patients with large ischemic strokes.[19,21]

The urgency and indication for surgery are likewise important. The overwhelming mortality associated with cardiac complications in infective endocarditis (i.e., 80% of those with severe heart failure) may outweigh the risk of early surgery in patients with a stroke. Thus, valvular surgery is indicated in the first 72 hours when infective endocarditis is complicated by congestive heart failure. In the absence of urgent surgical indications, delaying surgery by four weeks after cerebral infarction is advised.[22]

Intracerebral hemorrhage is generally associated with high postoperative mortality. Surgery should be delayed by four weeks if intracerebral hemorrhage has occurred, unless there are urgent indications for surgery as previously discussed.[18,21,22]

The treatment approach for patients with intracranial mycotic aneurysms must be individualized, given the potential for resolution with conservative treatment alone and the lack of randomized studies. However, cardiac surgery should be postponed after acute aneurysmal rupture, and some recommend delaying valvular surgery by two to three weeks after repair of a ruptured aneurysm.[19]

The European Society of Cardiology's 2009 guidelines provide recommendations for surgery for infective endocarditis in the setting of neurologic complications.[13] In the presence of urgent surgical indications, the guidelines recommend that surgery should proceed without delay in patients with a transient ischemic attack or silent cerebral emboli incidentally discovered on imaging, and for those with a stroke who do not have coma or cerebral hemorrhage on CT imaging. The presence of intracerebral hemorrhage should delay surgery for at least one month. Patients must have a brain CT or MRI to assess for hemorrhage before cardiac surgery. In all cases, multidisciplinary input from cardiology, cardiac surgery, infectious disease and neurology are recommended when determining the best course of treatment.

Conclusion

Our patient's case illustrates several important points. Septic embolization is a common complication of infective endocarditis, particularly in the central nervous system. Septic embolization should be considered and investigated in patients with suspicious symptoms. The rate of embolism is highest with infection of a left-sided valve by *S. aureus* and large vegetations, as was seen in

this case. Finally, the decision and timing for cardiac surgery must be based on the characteristics of the patient, organism and vegetations, presence of indications for urgent surgery, and the severity of embolic complications. Because our patient was hemodynamically stable and had no initial conditions that required immediate surgery, we decided to continue antibiotic therapy with close observation. However, when there was evidence of new multiorgan embolic and hemorrhagic events after two weeks of cloxacillin, aortic valve replacement was performed in accordance with current guidelines.

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