Clinical Case of the Month

A Predictable Outcome of a Preventable Disease

Sanjay Kamboj, MD; Shaminder Gupta, MD; Glenn P. Kelley, MD; Fred Helmcke, MD; and Fred A. Lopez, MD

Infective endocarditis is a systemic illness that can present with a variety of non-specific clinical symptoms. Patients with certain underlying heart valve abnormalities are at increased risk for development of infective endocarditis while undergoing minor procedures, particularly those associated with bacteremia by pathogens that typically cause infective endocarditis. We present a case of infective endocarditis that developed after a dental procedure in a patient with a previously undetected congential bicuspid aortic valve.

CASE PRESENTATION

A 35-year-old man with no past medical history presented with an extended history of fever, chills, nausea, weakness, and headache for which he had received several courses of antibiotics. His symptoms persisted and blood cultures obtained revealed the growth of viridans streptococci. Echocardiography demonstrated vegetations on the aortic and mitral valves. He was treated for infective endocarditis (IE) with a total of four weeks of penicillin (the first two weeks included the administration of an aminoglycoside) for IE. One week after discharge, he developed left upper quadrant pain, nausea, and vomiting and was transferred to this facility.

He had a root canal performed two weeks before he developed his constitutional symptoms. He works as an air conditioner repairman and is an avid hunter and fisherman. He has a five pack-year history of tobacco smoking and denies intravenous drug use (IVDU) or ethanol use. He was not taking any medications. Review of systems reveals a 40-pound weight loss over this time period.

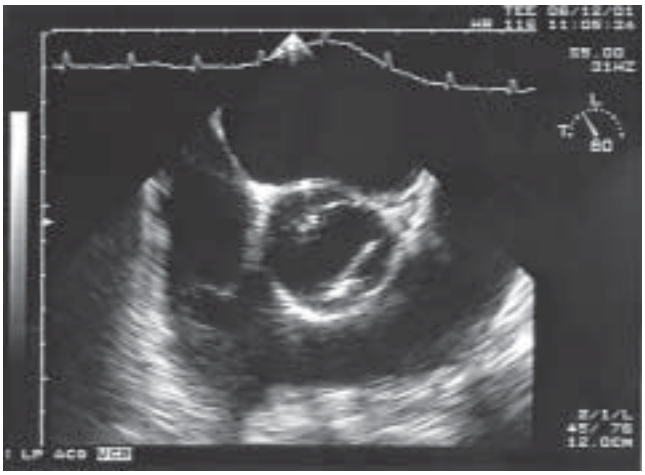

Figure 1. Still figure from transesophageal echocardiogram in systole showing partially opened bicuspid aortic valve (center). Note the moderate calcification of the valve leaflets given the patient's relatively young age.

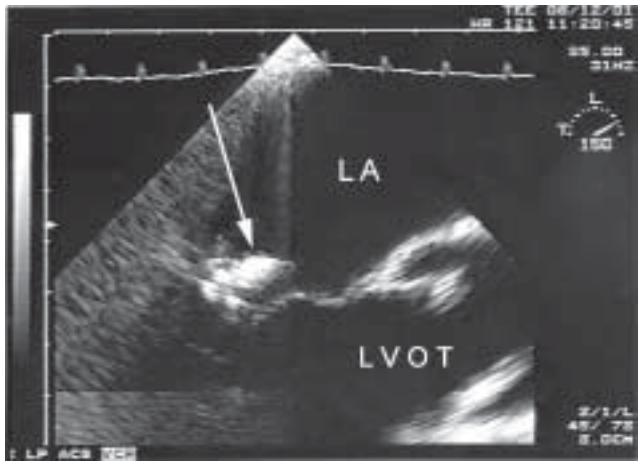

Figure 2. Still figure from transesophageal echocardiogram in systole. The vegetation is seen as a large echo-dense mass on the mitral leaflet (arrow). Left atrium (LA) and left ventricular outflow tract (LVOT).

On physical examination, he was in no distress. His vital signs were: temperature 98°F, pulse of 90 beats per minute, blood pressure of 130/60 mmHG, respirations of 22 breaths per minute, and oxygen saturation by pulse oximetry of 98% on air. Oral examination revealed multiple dental caries. Cardiovascular examination was significant for normal first and second heart sounds with a 3/6 holosystolic murmur heard at the apex with radiation to the axilla and a 3/6 diastolic murmur heard at the left sternal border, which was louder at end-expiration and with the patient leaning forward. Auscultation of the lungs revealed clear lung fields. Abdominal examination revealed diffuse abdominal tenderness without rebound or guarding. A blood chemistry and complete blood cell count revealed a thromobocytosis of 613,000/mL (150,000-400,000) and an erythrocyte sedimentation rate of 77 mm/hour (normal 0-15). A chest radiograph and twelve-lead electrocardiogram were unremarkable.

He underwent cardiac catheterization, which demonstrated severe aortic regurgitation with normal coronary arteries and an ejection fraction of 55%. Transesophageal echocardiography demonstrated mobile masses on the aortic and mitral valves (Figures 1 and 2) and the presence of a bicuspid aortic valve. On the fourth hospital day, he developed blurred vision, periorbital pain, headache, and left flank pain. Computed tomography of the abdomen revealed a splenic infarct, and magnetic resonance imaging of the brain revealed a suspected right occipital brain abscess (Figure 3). He was treated with antibiotics, which included penicillin, gentamicin, and rifampin. On hospital day 10, he had a cerebral angiogram, which demonstrated a mycotic aneurysm of the superior cerebellar artery. Neurosurgery recommended observation, and antibiotics were administered to complete a four-week course. On hospital day 11, he had a full mouth tooth extraction. On hospital day 33, he had an aortic and mitral valve replacement with porcine valves. He was discharged on hospital day number 38 and is currently doing well.

DISCUSSION

IE is a microbial infection of the endothelial surface of the heart.[1] The leaflets of the heart valves are primarily involved, but chordae tendineae, low-pressure side of a ventricular septal defect, the mural endocardium at the site of impact of a regurgitant jet of blood or an intracardiac for-

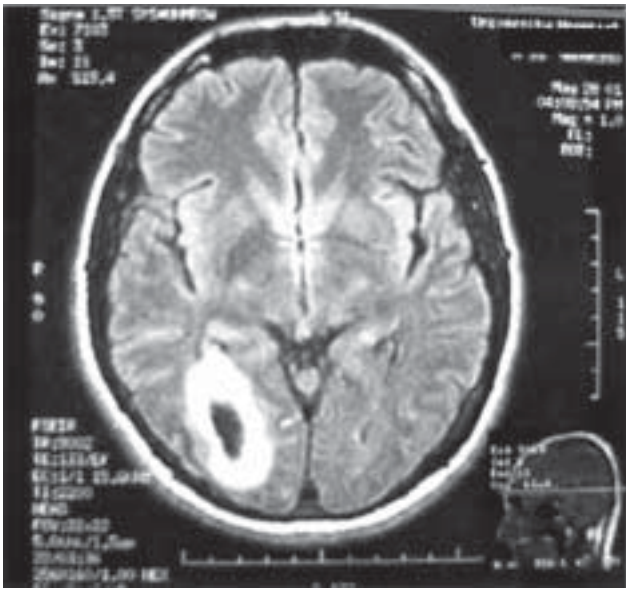

Figure 3. Axial, non-contrast, FLAIR (Fluid Attenuated Inversion Recovery) magnetic ressonance image. Ring-shaped lesion in the right occipital lobe represents an abscess. The hyperintense signal ring represents vasogenic edema within the white matter and may also contain abscess wall. The dark central area of the lesion represents fluid or purulent material within the abscess.

eign body (eg, an intravascular catheter or a pacer lead) may also be involved.

The endothelium of the heart is usually resistant to infection by blood-borne organisms. *Staphylococcus aureus* may occasionally cause infection on structurally normal valves.[2] As in our patient, IE is primarily engrafted on abnormal valves. The complex interaction among endothelium, the coagulation system, the host immune system, the structural state of the heart, the events that generate bacteremia, and specific virulence properties of bacteria result in IE.

BICUSPID AORTIC VALVE

The development of IE in the setting of a bicuspid aortic valve has been known for almost 150 years.[3] Though heretofore unknown, our patient had a bicuspid aortic valve, an abnormality that is associated with an increased overall risk for the development of IE.[4] The prevalence of bicuspid aortic valve is 1% in the general population.[3] Ten percent to thirty percent of patients with bicuspid aortic valves develop IE, and 25% of all cases of IE involve a bicuspid aortic valve. IE affecting the bicuspid aortic valve is mainly seen in children and young adults. According to one series, bicuspid aortic valve IE caused death in 55% of patients under 30 years of age and in 13% of patients aged over 70 years. IE causes severe aortic regurgitation in patients with bicuspid aortic valve in about 43% to 60% of cases and is usually a result of cusp perforation.

ETIOLOGY

Nosocomial infections are the main cause of IE in children during the initial two months of life.[2] Group B streptococcus (*Streptococcus agalactiae*), which is acquired during parturition, can also be the causative organism of IE in this group. Viridans streptococci and *S. aureus* are the main causative organisms in older children and adults. The causative agent in our patient, *S. viridans,* remains the major cause of IE among adults.[5] In patients over 60 years of age, the enterococci are the prominent causative organism of IE. IVDU is associated with a high risk for developing IE.[1] More than 50% of IVDU-associated IE cases are caused by *S. aureus*, and the right-sided heart valves are involved in more than 70% of cases. Intravenous drug users are also at risk for developing polymicrobial IE.

Blood culture-negative IE is seen in approximately 5% of patients with IE. The HACEK group of organisms (*Hemophilus aphrophilus, Hemophilus parainfluenzae, Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens* and *Kingella*) are a well established cause of blood culture-negative IE. *Bartonella* species, *Brucella* species, *Legionella* species, *Coxiella burnetii* and *Chlamydia* species are other causative organisms of blood culture-negative IE. However, the most common cause of blood culture-negative IE is the previous administration of antibiotics.

CLINICAL MANIFESTATIONS

The clinical manifestations of IE are mainly due to four major mechanisms that may involve any

organ system. These include local intracardiac complications due to infection; infected or bland embolization from vegetations; bacteremia with metastatic infection; and tissue injury secondary to circulating antigen-antibody complexes and local complement activation. The bacteremia itself causes constitutional symptoms. The main symptoms of IE, many of which were seen in our patient, are fever, chills, dyspnea, weakness, sweats, anorexia, malaise, cough, weight loss, skin lesions, myalgia/arthralgia, headaches, abdominal pain, chest pain, and back pain.[1] The main signs are fever, heart murmur, a changing or new murmur, splenomegaly, Osler's nodes, splinter hemorrhages, petechiae, Janeway lesions, clubbing, and Roth spots.[1]

DIAGNOSIS

Diagnostic criteria have been developed based on pathogenic concepts of IE, which include the microorganisms associated with this infection, acute endothelial injury and its complications, embolic phenomena, and injury secondary to immune complexes.[6] The diagnostic criteria (Duke Criteria) for infective endocarditis proposed in 1994 are now widely used.[7] Major criteria required for the diagnosis include positive blood cultures with typical organisms associated with IE, definitive echocardiographic findings such as vegetations or abscess, and a new heart murmur. Minor critera include fever, embolic phenomenon (Janeway lesions), immunologic phenomenon (for example, hematuria, Osler's nodes Ruth's Spots, or positive rheumatoid factor), minor but suggestive echocardiographic findings, predisposing heart valve abnormality, and atypical organisms. The combination of two major, one major and three minor, or five minor criteria are consistent with the clinical diagnosis of infective endocarditis.

THERAPY FOR INFECTIVE ENDOCARDITIS

The choice of parenteral antibiotics for the treatment of IE is dictated by the type of cardiac valve involved (ie, native or prosthetic). The American Heart Association has provided guidelines for antibiotic treatment of IE.[8] Suggested therapy for viridans streptococci-associated endocarditis includes the combination of intravenous penicillin G and gentamicin that our patient received. Other acceptable regimens include ceftriaxone or vancomycin (for the penicillin allergic patient). These regimens are all based on the minimal inhibitory concentration of the organism. Surgical intervention may be needed in selected patients as described below.

PREVENTION OF BACTERIAL ENDOCARDITIS

Primary prevention of endocarditis is important in individuals with underlying structural cardiac defects.[4] Some surgical and dental procedures, such as the root canal that our patient received, and instrumentations involving mucosal surfaces or contaminated tissues can result in transient bacteremia with organisms that cause IE (ie, viridans streptococci and enterococci). These blood-borne bacteria may lodge on damaged or abnormal heart valves and initiate the events that ultimately lead to IE. Patients at high risk for developing IE include those with prosthetic heart valves, previous bacterial endocarditis, and complex cyanotic congenital heart disease.[4] Moderate risk is associated with most other congenital cardiac malformations (including bicuspid aortic valve), valvular dysfunction secondary to rheumatic heart disease, hypertrophic cardiomyopathy, and mitral valve prolapse with regurgitation.[4] The American Heart Association has published recommendations for preventing bacterial endocarditis prophylaxis in high-risk and moderate-risk patients undergoing bacteremia-producing dental, oral, respiratory tract, esophageal, genitourinary and gastrointestinal procedures. According to these guidelines, a patient with known bicuspid aortic valve who undergoes extensive endodontic (root canal) instrumentation should receive amoxicillin, 2 grams orally, one hour before the procedure.[4]

COMPLICATIONS

Congestive Heart Failure

Development of congestive heart failure (CHF) has the greatest effect on prognosis in IE.[6] Acute

CHF occurs more commonly in native aortic-valve IE (29%) than with mitral (20%) or tricuspid valve (8%) IE.[6] Patients with normal ventricular function or mild CHF at initial diagnosis of IE may progress to severe CHF, usually in the initial month of therapy.

Severe CHF in IE has a poor prognosis when treated medically and is an indication for surgery. Preoperative class III or IV CHF, renal insufficiency, and advanced age are associated with a poor surgical outcome.

Risk of Embolization

Systemic embolization occurs in approximately 22% to 50% of cases of IE,[6] usually involving the major arterial beds in the lungs, myocardium, spleen, bowel, and extremities. The central nervous system is involved in approximately 65% of embolic events, and >90% of these emboli lodge in the distribution of the middle cerebral artery. Our patient had both a splenic infarct and mycotic aneurysm as a result of IE. Aortic and mitral-valve infections and infections due to *S.aureus, Candida* species, and the HACEK organisms are associated with the highest incidence of embolic complications. Most embolic events occur within the first two to four weeks of antimicrobial therapy, although they can occur anytime before diagnosis, during therapy, or after therapy is completed.

Mycotic Aneurysms

Osler coined the term mycotic aneurysm (MA) in 1885 to describe a mushroom-shaped aneurysm in a patient with subacute bacterial IE.[5] The arterial vasa vasorum or the intraluminal space are affected by septic embolization of vegetations, and there is spread of infection through the intima and outward through the vessel wall. The most common sites of MA development are arterial branching points. Intracranial arteries are most frequently involved in MAs (as in our patient), followed by visceral arteries, and arteries of the lower and upper extremities. Intracranial MAs may be managed medically with antibiotics as was done in our patient. MAs should be monitored with serial angiograms and CT scans. If enlargement or leakage (ie, bleeding) develops, surgery is indicated.

Splenic Infarct/Abscess

Our patient developed a splenic infarct without any evidence of abscess. Although splenic infarction develops in approximately 40% cases of left-sided IE, only about 5% of these patients develop splenic abscess.[1,6] Viridans streptococci and *S. aureus* are most commonly isolated (approximately 40% of cases caused by each) when splenic abscess cultures are positive; enterococci are isolated in approximately 15% of cases. Fungi and aerobic gram-negative bacilli are found in less than 5% of cases. The best tests for diagnosis of splenic infarct or abscess are abdominal CT or MRI. These imaging studies have sensitivities and specificities of approximately 90% to 95%. Splenic abscesses usually manifest as single or multiple contrast-enhancing cystic lesions. Splenic infarcts manifest as peripheral low-density, wedge shaped areas.

Antimicrobial therapy alone is rarely effective for treatment of splenic abscesses. In general, either percutaneous catheter drainage or splenectomy is required. To avoid infection of a newly implanted prosthesis, splenic abscesses should be effectively treated prior to cardiac surgery.

INDICATIONS FOR SURGERY

Valve replacement and surgical intervention are needed in addition to medical therapy in patients who develop intracardiac complications of IE. The main indications for surgery are severe congestive heart failure secondary to valve dysfunction, an unstable hypermobile prosthetic valve, patients with fungal endocarditis, uncontrolled infection despite adequate antibiotic therapy, and relapses following optimal antibiotic treatment as was the case in our patient.[10,11.12] Extension of infection into perivalvular tissue; prosthetic valve IE caused by *Pseudomonas aeruginosa*; and *S. aureus* infection of an aortic, mitral, or prosthetic valve

are relative indications for surgery. Surgery should be delayed for at least 21 days in patients who have sustained an intracranial hemorrhagic event. The central vasculature should be evaluated formally in patients who have sustained an embolic infarct. If a mycotic aneurysm is found, as was the case in our patient, the timing of cardiac surgery should be reconsidered, and prostheses that require postoperative anticoagulation should be avoided.[1]

ANTICOAGULATION

Anticoagulation, per se, is not a therapy for management of IE. In the absence of other complications, anticoagulation is contraindicated in native-valve IE because it is associated with an increased risk of intracerebral hemorrhage. Patients on maintenance anticoagulation who present with prosthetic-valve IE are usually maintained on anticoagulant therapy provided there is no evidence of a cerebral event (hemorrhage or infarction). Anticoagulation therapy should be stopped if these patients develop central nervous system complications.[2,6,9]

REFERENCES

1. Karchmer AW. Infective Endocarditis. In: Braunwald E (editor). *Heart Disease, A Textbook of Cardiovascular Medicine*, 5th edition. Philadelphia, PA: Saunders; 1997:1077-1104.
2. Karchmer AW. Infective endocarditis. In: Root RK, Waldrogel F, Corey L, et al. (editors). *Clinical Infectious Diseases, A Practical Approach.* Oxford;1999:621-642.
3. Ward C. Clinical significance of the bicuspid aortic valve. *Heart* 2000;83:81-85.
4. Dajani AS, Taubert KA, Wilson W, et al. Prevention of bacterial endocarditis, recommendations by the American Heart Association. *JAMA* 1997;277:1794-1801.
5. Bayer AS, Scheld WM. Endocarditis and intravascular infections. In: Mandell GL, Bennett JE, Dolin R (editors). *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*, 5th edition. New York, NY: Churchill Livingstone;2000:857-902.
6. Bayer AS, Bolger AF, Taubert KA, et al. Diagnosis and management of infective endocarditis and its complications. *Circulation* 1998;98:2936-2948.
7. Durack DT, Lukes AS, Bright DK. New criteria for diagnosis of infective endocarditis: utilization of specific echocardiographic findings. *Am J Med* 1994;96:200-208.
8. Wilson WR, Karchmer AW, Dajani AS, et al. Antibiotic treatment of adults with infective endocarditis due to streptococci, enterococci, staphylococci, and HACEK microorganisms. *JAMA* 1995;274:1706-1713.
9. Tarnos PR, Almirante B, Mirabet S. Infective Endocarditis due to Staphylococcus Aureus. *Arch Intern Med* 1999;159:473-475.
10. Mullany CJ, McIsaacs AI, Rowe MH, et al. The Surgical treatment of infective endocarditis. *World J Surg* 1989:13:132-136.
11. Alsip SG, Blackstone EH, Kirklin JW, et al. Indications for cardiac surgery in patients with active infective endocarditis. *Am J Med* 1985:78:138-148.
12. Dinubile MJ. Surgery in active endocarditis. *Ann Intern Med* 1982:96:650-659.

Dr Kamboj *is a House Officer in the Department of Internal Medicine at Louisiana State University School of Medicine in New Orleans, Louisiana.*

Dr Gupta *is a House Officer in the Department of Internal Medicine at Louisiana State University School of Medicine in New Orleans, Louisiana.*

Dr Kelley *is a House Officer in the Department of Internal Medicine at Louisiana State University School of Medicine in New Orleans, Louisiana.*

Dr Helmcke *is Associate Professor of Medicine, Section of Cardiology at Louisiana State University School of Medicine in New Orleans, Louisiana.*

Dr Lopez *is Assistant Professor of Medicine, Section of Infectious Diseases at Louisiana State University School of Medicine in New Orleans, Louisiana.*

The Clinical Case of the Month is a regular educational feature presented by the Louisiana State University Department of Medicine in New Orleans. Medical students, residents, postdoctoral fellows, and faculty collaborate in the preparation of these discussions.