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A 34-year-old man with facial droop and dysarthria

A 34-YEAR-OLD MAN is referred with sudden-onset left facial droop and dysarthria. He reports a 3-week history of flulike symptoms and episodes of chills and temperature of 101 to 103°F (38.3–39.4°C) for 2 weeks. He took azithromycin for 5 days with no improvement.

The patient has a 20 pack-year history of smoking but has no history of alcohol abuse or injection drug use. He works in the construction field and lives with his wife. Home medications include cyclobenzaprine, atenolol, chlorthalidone, and occasionally ibuprofen.

His blood cultures grow methicillin-sensitive *S aureus*

Physical examination

The patient appears ill; temperature 101°F, pulse 126, and blood pressure 164/77 mm Hg. His neck is supple, his funduscopic examination is normal, and his lungs are clear.

Heart: 2/6 holosystolic murmur, best heard at the left sternal border; 2/6 diastolic decrescendo murmur at the right base. Normal electrocardiogram.

Skin: multiple erythematous, nontender, macular lesions on the distal parts of his fingers and toes, distal petechial lesions under his nails, and multiple psoriatic lesions on the groin and buttocks.

Neurologic examination: central-left facial nerve palsy and dysarthria. Review of a computed tomographic (CT) scan of his brain, which had been performed at another hospital, is normal.

Blood studies

- White blood cell count 20.9 × 10⁹/L (normal 4.0–11.0), neutrophils 93% (normal 40%–70%)
- Creatinine 2.1 mg/dL (normal 0.7–1.4)
- Potassium 3.1 mmol/L (normal 3.5–5.0)
- International normalized ratio 1.36 (normal 0.77–1.17)
- Lyme disease serologic tests (immunoglobulin G [IgG] and immunoglobulin M [IgM] antibody titers) negative.

Lumbar puncture for cerebrospinal fluid

- White blood cells 34/μL (normal 0–5), neutrophils 50% (normal 0)
- Glucose 65 mg/dL (normal 50–75)
- Protein 50 g/dL (normal 20–50).
- Bacterial, fungal, mycobacterial, and viral cultures are normal.

DIFFERENTIAL DIAGNOSIS

1 What is the *least* likely diagnosis?

- ❑ Brain abscess
- ❑ Septic emboli to the brain
- ❑ Central nervous system vasculitis
- ❑ Aseptic meningitis

Aseptic meningitis is the least likely diagnosis. Although all the other conditions are considerations in a patient presenting with a febrile illness and focal neurologic deficits, aseptic meningitis usually does not present with focal deficits such as dysarthria and facial droop.

Case continued

The patient's blood cultures grow methicillin-sensitive *Staphylococcus aureus*. Magnetic resonance imaging (MRI) of the brain shows multiple embolic infarctions (**FIGURE 1**), and a transthoracic echocardiogram shows aortic and tricuspid valve vegetations, raising the possibility of infective endocarditis.

Infective endocarditis: Acute and subacute

Infective endocarditis can be classified as

Embolic brain infarction

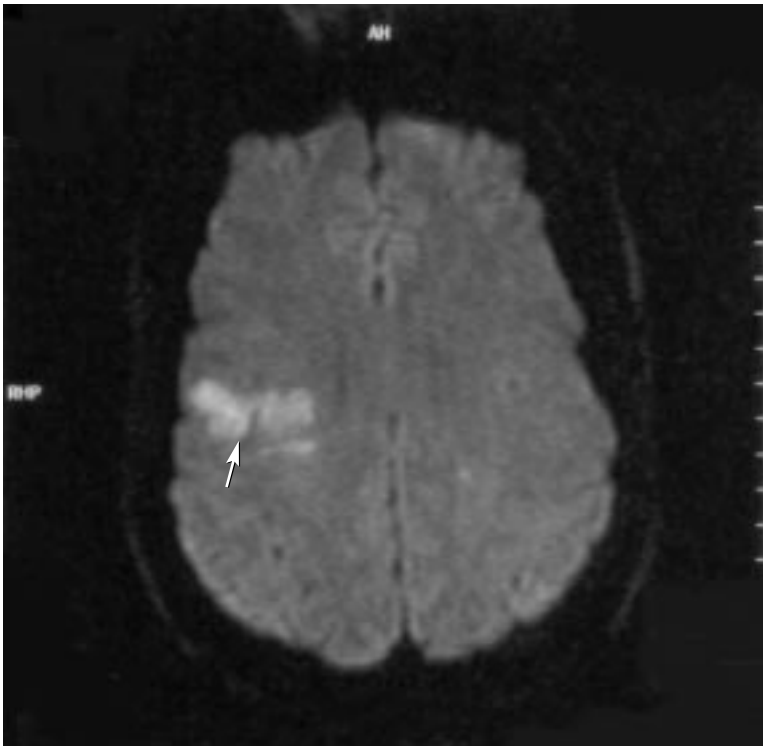

FIGURE 1. Magnetic resonance image of the brain showing multiple foci of acute infarction involving different vascular territories and suggesting an embolic source. The largest of the infarcted areas is in the caudal aspect of the right precentral gyrus (arrow).

acute or subacute, depending on the presentation of illness and the time that elapses until death.

Acute infective endocarditis presents as a hectic febrile illness with cardiac damage and extracardiac embolization. The course usually spans days to weeks. The cause is a virulent organism that infects a normal valve.

Subacute infective endocarditis presents more indolently with slow cardiac damage and, rarely, metastatic disease. It is caused by a less virulent organism that infects a diseased valve.[1] Fever may often be absent: this is a simple way to differentiate acute and subacute infective endocarditis.[2]

RISK FACTORS FOR INFECTIVE ENDOCARDITIS

2 All of the following are risk factors for infective endocarditis *except* which one?

- ❑ HIV infection
- ❑ Prior episodes of infective endocarditis
- ❑ Injection drug use
- ❑ Low socioeconomic status
- ❑ Prosthetic valves
- ❑ Congenital heart disease

Low socioeconomic status is not a risk factor for infective endocarditis, but many other conditions are. For example:

Prior infective endocarditis is a well-recognized risk factor, with a 4% recurrence rate within the first 5 years of the initial episode.[3]

Prosthetic valves, whether mechanical or bioprosthetic, carry a 0.5% yearly incidence of infective endocarditis.[3,4]

Injection drug use confers a 60-fold higher risk for infective endocarditis compared with the risk for the general population, with a predilection for the right-sided heart valves.[3]

Older age. Elderly persons have a potentially higher incidence of infective endocarditis because of their higher prevalence of degenerative valvular disease, rheumatic heart disease, valve prosthesis implantation, and skin fragility (which provides a potential portal for bacterial entry).

HIV infection is a newly recognized risk factor that is mostly attributed to comorbidities such as injection drug use and mucositis.

Congenital heart disease, especially complicated anomalies such as tetralogy of Fallot, can lead to infective endocarditis at an earlier age (median 43 years). Early surgical repair can prevent the risk.[3]

Our patient has none of these risk factors, which sometimes is the case in persons with acute infective endocarditis.

CAUSATIVE ORGANISMS

3 What is the most common organism causing infective endocarditis?

- ❑ *Streptococcus* species
- ❑ *Enterococcus* species
- ❑ *Staphylococcus* species
- ❑ *Haemophilus* species, *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella kingae* (HACEK organisms)
- ❑ *Candida albicans*

Streptococcus species are the most common cause of infective endocarditis. However, the prevalence of *Staphylococcus* endocarditis is increasing along with the growing use of prosthetic valves and intravenous catheters and with increasing injection drug use in the general population.[5]

TABLE 1 outlines the differences in the microbiology of native and prosthetic valve endocarditis.[6]

Prosthetic valve endocarditis

Prosthetic valve endocarditis can present either early (onset within 60 days of valve replacement) or late after valve surgery.

In early prosthetic valve endocarditis, the sewing ring, sutures, and adjacent tissues have not yet endothelialized and are covered with host proteins. Microorganisms, which gain direct access intraoperatively or during the first days or weeks postoperatively, can adhere to these proteins and cause infection.

Early prosthetic valve endocarditis usually is not accompanied by peripheral stigmata. It also has a higher incidence of perivalvular lesions, which cause valvular dysfunction and conduction defects.[7]

Late prosthetic valve endocarditis occurs after there has been complete endothelialization of the valve and adjacent tissues. Thus, microorganisms lack adherence sites and access to host tissues; in this way, the microbiologic factors of late prosthetic valve endocarditis resemble those of native valve endocarditis.

Bioprosthetic valves differ from mechanical valves in that they age faster, creating more sites for bacterial adherence. Therefore, the incidence of prosthetic valve endocarditis in bioprosthetic valves, unlike mechanical valves, increases with time.

Prosthetic valve endocarditis almost always requires removal of the valve for cure.

DUKE CRITERIA FOR ENDOCARDITIS

4 What constitutes a major Duke criterion in our patient?

- ❑ Embolic stroke
- ❑ Fever
- ❑ Elevated sedimentation rate
- ❑ Echocardiographic finding of a valvular lesion or vegetation
- ❑ Leukocytosis
- ❑ Heart block

TABLE 1

Predominant organisms in infective endocarditis

Native valve endocarditis
- Not acutely ill
  - Viridans streptococci
  - HACEK organisms (*Haemophilus* species, *Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens, Kingella kingae*)
- Acutely ill
  - *Streptococcus pneumoniae*
  - *Staphylococcus aureus*
- Injection drug users
  - *Staphylococcus aureus*
  - *Pseudomonas aeruginosa*

Prosthetic valve endocarditis
- Early (< 60 days)
  - *Staphylococcus epidermidis*
  - *Staphylococcus aureus*
- Late (> 60 days)
  - Viridans streptococci
  - *Staphylococcus epidermidis*
  - *Staphylococcus aureus*

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Valvular vegetation is the only major Duke criterion in this list.[8]

In 1981, Von Reyn et al[9] proposed the initial diagnostic criteria for infective endocarditis. These criteria relied mostly on histopathologic diagnosis and did not account for echocardiographic findings or organism virulence. In 1994, these deficits led Durack et al[8] to propose new criteria, known as the Duke criteria (TABLE 2).

Even though the Duke criteria have a high sensitivity (80%), specificity (99%), and negative predictive value (92%),[10–12] they have inherent limitations that led to the following revisions in 2000, proposed by Dodds et al[12]:

- Transesophageal echocardiography (TEE) became standard in patients with suspected prosthetic valve endocarditis or complicated infective endocarditis, or both.
- The category of complicated infective endocarditis was added, eg, with perivalvular

TABLE 2

abscess formation.

- A single positive blood culture for *Coxiella burnetii* or a bacterial IgG antibody titer greater than 1:800 was added to the two classic major criteria.
- *S aureus* bacteremia was added to the major criteria.

The revised Duke criteria still need to be validated in prospective studies.

Our patient has two major Duke criteria that support the diagnosis of acute infective endocarditis: documented staphylococcal bacteremia and valvular vegetations on echocardiographic examination.

AFFECTED HEART VALVES

5 Which heart valves are most likely to be affected by infective endocarditis?

- ❑ Mitral
- ❑ Pulmonary
- ❑ Tricuspid
- ❑ Aortic

The mitral and aortic valves are most commonly affected.[5] Multivalvular involvement (more than two valves) occurs in 15% to 20% of cases of infective endocarditis.[3]

The left-sided, high-pressure chambers are affected more often than the low-pressure, right-sided chambers; the exception is in injection drug users, in whom involvement of the tricuspid valve is predominant; valve damage from impurities and bacteria injected with illicit drugs is the main reason right-sided valves are more often affected in this population.

Although mitral valve endocarditis is associated with the highest rates of systemic embolism, aortic valve endocarditis usually results in the most adverse hemodynamic consequences.[3]

Isolated right-sided infective endocarditis has a more benign course; cure rates are 90% to 100%, and surgical intervention is rarely needed. The tricuspid valve accounts for most of the cases of right-sided infective endocarditis, followed by the pulmonary valve and right-sided pacemaker wires.[3]

SYSTEMIC EMBOLIZATION

6 Which of the following statements about systemic embolization as a complication of infective endocarditis are true?

- ❑ Most central nervous system emboli involve the middle cerebral artery territory
- ❑ The risk of emboli remains constant throughout the treatment period
- ❑ The site of valvular involvement does not predict embolization risk
- ❑ Large vegetations do not increase the risk of embolization

Embolization occurs in 22% to 50% of cases of infective endocarditis.[13] Sixty-five percent of emboli involve the central nervous system; the remainder involve other major arterial beds, such as the lungs, coronary arteries, spleen, bowel, and extremities.[14] Ninety percent of central nervous system emboli involve the middle cerebral artery.

Systemic embolization usually occurs within the first 2 to 4 weeks, with a dramatic decrease in incidence after the first 2 weeks of antibiotic therapy (from 13 to < 1.2 embolic events per 1,000 patients).[15]

As stated previously, mitral vegetations are associated with higher embolization rates than aortic vegetations (25% vs 10%), regardless of their size.[16]

Central nervous system embolization usually features septic meningitis; the cerebrospinal fluid findings in our patient were unusual. An exception is endocarditis caused by viridans streptococci, in which the emboli are bland and cause aseptic meningitis.

Studies using transthoracic echocardiography demonstrated higher embolization rates in left-sided vegetations greater than 1 cm in diameter. Predictive accuracy for embolism with large mitral vegetations (> 1 cm) approaches 100%.[14,17]

Case continued

Our patient undergoes aortic valve replacement with homograft and tricuspid valve debridement and repair on the third day after admission. Postoperatively, he complains of persistent dull abdominal pain accompanying his persistent fever. CT scans of his abdomen and pelvis show large left renal and splenic infarcts (**FIGURE 2**).

We start the patient on a regimen of vancomycin, gentamicin, and rifampin. We later switch vancomycin to oxacillin after blood cultures grow methicillin-sensitive *S aureus*.

ANTIMICROBIAL MANAGEMENT

7 All of the following statements are true regarding appropriate antimicrobial management in this patient *except* which one?

- ❑ Gentamicin should be used because of its synergy with penicillin and its potent bactericidal effects
- ❑ Rifampin has good penetration into vegetations
- ❑ Antibiotic treatment should continue for 2 weeks after documented negative blood cultures or valve surgery
- ❑ At least three sets of blood samples should be drawn (with at least 1 hour between the first and the last sets) for culture before antibiotic treatment is started

Splenic infarction

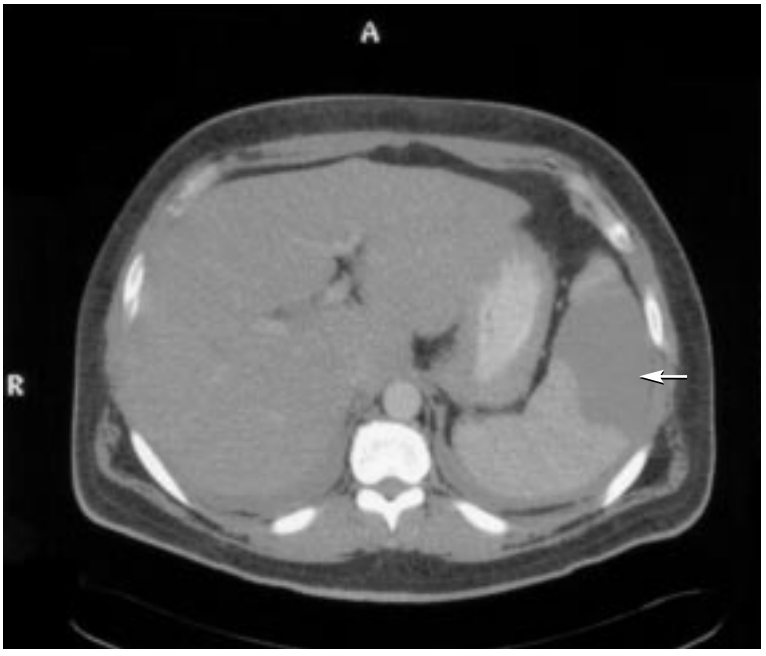

FIGURE 2. Computed tomographic scan of the abdomen showing a large area of low attenuation within the superolateral spleen with sharp, wedge-shaped borders, likely representing splenic infarction (arrow).

In infective endocarditis, 2 weeks of anitibiotics is not enough

A 2-week antimicrobial course usually is not enough. Wilson et al[13] reported a 98% cure rate in patients treated with a 2-week regimen of penicillin plus an aminoglycoside. However, these were cases of uncomplicated infective endocarditis involving mostly highly penicillin-sensitive streptococci. Our patient has multifocal embolization, and limiting him to a 2-week course of antibiotics is inappropriate.

SURGICAL INTERVENTION

8 When is surgical intervention appropriate in infective endocarditis?

- ❑ Perivalvular abscess

Sacroiliac joint infection

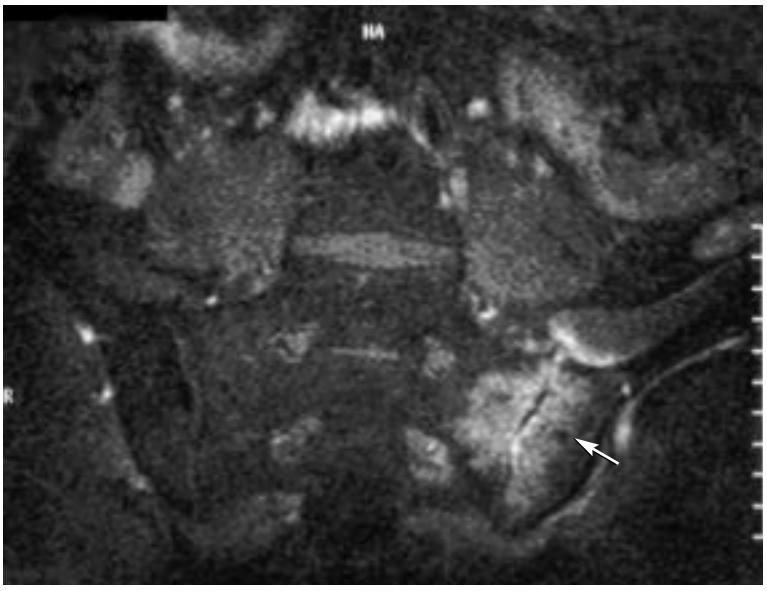

FIGURE 3. Magnetic resonance image of the pelvis showing areas of edema and soft-tissue swelling around the sacroiliac joint (arrow), with increased uptake consistent with infection.

- ❑ Fungal endocarditis
- ❑ Acute valvular regurgitation and congestive heart failure
- ❑ Complete heart block
- ❑ Major embolization phenomenon
- ❑ All of these

Musculoskeletal manifestations occur in up to 44% of cases of infective endocarditis

All of these conditions require surgical intervention to prevent embolization and other potentially life-threatening complications. Because of the increased embolic risk in the first 2 weeks of antibiotic treatment, the maximum benefit achieved from surgical intervention is seen early.

The site and extent of valvular vegetations determine the technical feasibility of debridement and repair rather than valve replacement. It is acceptable to perform valve debridement and repair if the vegetation can be removed with a 2-cm margin without disturbing the integrity of the valve (especially in right-sided endocarditis with a more benign course).[18]

Case continued

Our patient is discharged to his home to complete a 6-week course of intravenous oxacillin and oral rifampin. He presents 6 weeks later with pain in his low back and left hip joint, which is worse with movement and better with rest.

MUSCULOSKELETAL MANIFESTATIONS

9 What is the most likely source of this new pain?

- ❑ Osteoarthritis
- ❑ Infective arthritis
- ❑ Bone metastasis
- ❑ Plasma cell carcinoma

Musculoskeletal manifestations occur in up to 44% of cases of infective endocarditis.[19] They usually are monoarticular or oligoarticular and include arthralgia (most common), arthritis, low back pain, myalgia, disc space infection, nail clubbing, and Achilles tendonitis. Avascular necrosis is a rare manifestation. These manifestations are more likely the result of circulating immune complexes than of septic embolism.[20]

Sapico et al[21] reported a 24% incidence of musculoskeletal manifestations with infective endocarditis. Two thirds of patients in this series had documented osteoarticular infection, and all those with osteoarticular infections were injection drug users; none in the non-drug-using group had osteoarticular infection. This suggests that injection drug users are more likely to have osteoarticular complications. The most common infection sites were the vertebrae and the sternoclavicular, sacroiliac, and wrist joints. Both immunologic and septic musculoskeletal complications improved with appropriate antibiotic therapy.[21]

Our patient undergoes MRI of the pelvis, which reveals edema and soft-tissue swelling in the left sacroiliac joint consistent with infection (FIGURE 3). He is treated with an extension of the oxacillin and rifampicin course to total 9 weeks. His symptoms improve significantly after the extended antibiotic course. He is then treated with a long-term course of oral doxycycline.

CONCLUSIONS

Acute bacterial endocarditis is potentially fatal. With persistent controversies in the diagnosis and management of the disease,

infective endocarditis is still a challenge. Our patient had been healthy before he presented with a wide spectrum of serious complications of bacterial endocarditis. A high index of suspicion that led to early diagnosis and treatment was key to his favorable outcome.

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