The Diagnostic Challenge of Infective Endocarditis: Cutaneous Vasculitis Leading to the Diagnosis of Infective Endocarditis

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Background: **Signs and symptoms of infectious endocarditis are protean. They result from destruction of cardiac endothelium, metastatic embolization, hematogenous seeding, and immune complex deposition. Embolic manifestations of infectious endocarditis can mimic several other pathologic conditions and make the diagnosis of infectious endocarditis difficult.**

Methods: **We describe a case of cutaneous vasculitis leading to the diagnosis of infectious endocarditis. A review of the literature highlights the variable clinical presentations and key diagnostic strategies in the evaluation of infectious endocarditis.**

Results and Conclusion: **Infective endocarditis has protean clinical symptoms and signs and can be a challenging diagnosis. Being alert to the condition is crucial, and where a high clinical probability exists despite a negative transthoracic echocardiogram, diagnostic evaluation with transesophageal echocardiograph is required. (J Am Board Fam Pract 2001;14:451–6.)**

Infective endocarditis, characterized by microbial infection of the endothelial surface of the heart, can have numerous symptoms and signs. Typically they include fever, chills, a new or changing heart murmur, and bacteremia. Infective endocarditis can appear in an atypical manner and pose in a diagnostic challenge. In such cases, initial signs and symptoms might be those from a complication, such as pneumonia, meningitis, congestive heart failure, osteomyelitis, septic arthritis, glomerulonephritis, endophthalmitis, splenic infarction, or vasculitis. The differential diagnosis of a bacteremic patient with one of these conditions should include infective endocarditis. Delays in diagnosis and treatment increase mortality. We describe a case in which the diagnosis of infective endocarditis was established after the patient developed a cutaneous vasculitis.

Methods

We describe a case of cutaneous vasculitis leading to the diagnosis of infectious endocarditis. A MEDLINE review of the literature was performed using the key words "infective endocarditis," "vasculitis," and "diagnosis." Findings highlight the variable clinical presentations and key diagnostic strategies in the evaluation of infectious endocarditis.

Case Report

A 64-year-old woman came to the emergency department with a complaint of weakness and confusion. Her medical history was notable for diabetes mellitus, hypertension, chronic renal failure for which she was receiving hemodialysis, and a remote history of breast cancer. She had a history of mild-moderate left ventricular dysfunction but no valvular heart disease. On review of systems the patient denied chest pain, headache, photophobia, neck stiffness, cough, sore throat, or abdominal pain. On further questioning it was found that 2 days earlier she underwent an unsuccessful declotting procedure of her dialysis graft site and placement of a left internal jugular intravenous catheter for temporary dialysis access.

The patient was an obese woman in moderate distress. She was oriented only to name and place. Her temperature was 103.9°F, blood pressure was 142/70 mm Hg, heart rate was 96 beats per minute, and respiratory rate was 32/min. When examined, she had normal head, ear, eye, neck, and throat findings and basilar crackles at the left lung field. A

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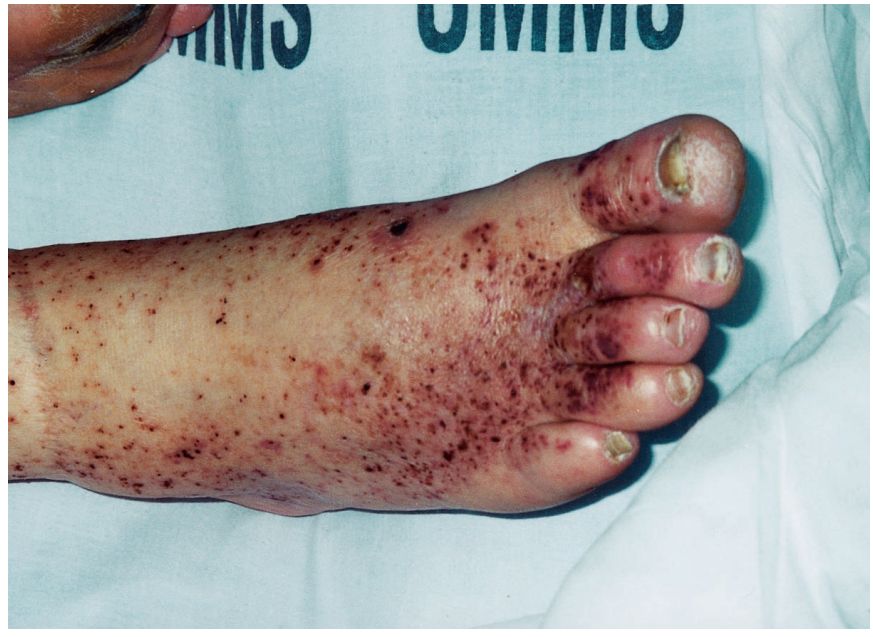

Figure 1. Prupuric rash on right ankle and foot.

3/6 systolic murmur heard best at the left sternal border was unchanged from her baseline. Her abdomen was soft and nontender. Bowel sounds were present; abdominal palpation found no hepatosplenomegaly. Her extremities showed no edema, clubbing, or cyanosis, and pulses were 2+ and symmetrical. There was no thrill or bruit from her graft. She had 5/5 strength in all four extremities, deep tendon reflexes were 1+, and sensation was mildly decreased over both feet. There were no skin lesions, and the left internal jugular catheter site was clean with no erythema noted.

In the emergency department laboratory studies disclosed the following values: white cell count $15 \times 10^3/\mu L$ with 22% band cells, hemoglobin 12.2 g/dL, hematocrit of 31.6%, and platelet count $230 \times 10^3/\mu L$. Blood urea nitrogen was 86 mg/dL, and creatinine was 9.8 mg/dL, similar to her baseline renal function studies. Findings on a chest radiograph and a computed tomographic head scan were normal. Lumbar puncture showed no cells, glucose and protein values were normal, and stains were negative. Blood, urine, and cerebrospinal fluid specimens were sent for culture.

The patient was admitted to the hospital with a presumptive diagnosis of sepsis resulting from her recent graft instrumentation, and she was given empiric antibiotic therapy (vancomycin and gentamicin). On hospital day 2, six of eight blood culture bottles grew gram-positive cocci in clusters. A transthoracic echocardiogram showed left ventricular global dysfunction, an ejection fraction of 25% to 30% (similar to her baseline), and no vegetations. On hospital day 3, the organism was identified as methicillin-resistant *Staphylococcus aureus*. Vancomycin and gentamicin were continued and, although her temperature returned to normal, she remained bacteremic. She began to complain of abdominal pain. Findings on her abdominal examination were normal, her stool was negative for occult blood, and a computed tomographic abdominal scan was unremarkable. A procedure to declot her graft was unsuccessful, and on hospital day 6 the graft was removed along with her left internal jugular line. Findings on a repeat transthoracic echocardiogram were unchanged from the previous one.

The patient's blood cultures became negative on hospital day 9, and a right internal jugular line was inserted. She remained on vancomycin, but the gentamicin was discontinued. Her abdominal pain continued. On hospital day 10, the patient developed a purpuric rash on her right ankle that appeared to be vasculitic. During the next 3 days the rash became distributed over her lower extremities to her thighs (Figures 1 and 2). Differential diagnoses that were considered included infection, drug reaction, Henoch-Schönlein purpura, underlying cancer, and connective tissue disease. Laboratory studies were ordered. Her erythrocyte sedimenta-

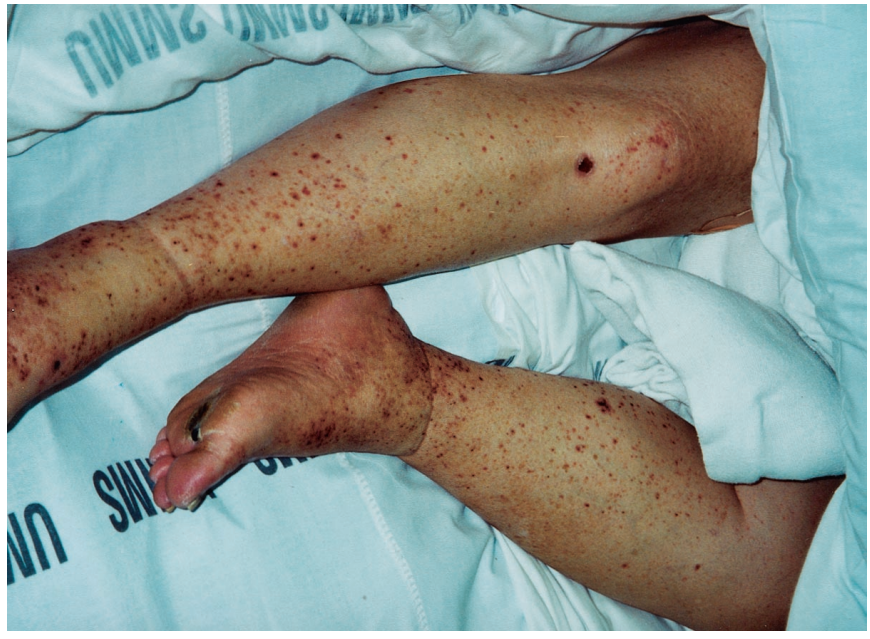

Figure 2. Rash distributed over her lower extremities within 3 days.

tion rate was 54 mm/h. Tests for antinuclear antibody, human immunodeficiency virus, rheumatoid factor, hepatitis, and cryoglobulins were negative. A biopsy of the rash with immunofluorescent staining for immune complexes was negative. Histopathologic findings were consistent with a leukocytoclastic vasculitis, and biopsy cultures grew methicillin-resistant *S aureus*. On hospital day 17 a transesophageal echocardiogram showed a small, mobile echodensity on the mitral valve. The patient's condition was diagnosed as infective endocarditis.

Discussion

Epidemiology

The overall incidence of infective endocarditis is 1.7 to 4.0 per 100,000 population.[1] In patients older than 50 years, the incidence of infective endocarditis exceeds 15 per 100,000 population.[2] In addition to age, other risk factors include male sex, congenital and rheumatic heart disease, mitral valve prolapse, prosthetic valves, previous occurrence of infective endocarditis, intravenous drug use, and nosocomial instrumentation.[2]

Numerous microbial organisms with variable virulence can cause infective endocarditis. *S aureus* is the most common etiologic organism in the United States.[1] Predisposing risk factors for infective endocarditis caused by *S aureus* are prolonged intravascular catheterization, intravenous drug use, mitral valve prolapse with valve redundancy, and prosthetic valves.[3] Complications, including metastatic abscesses, are common. The risk of death increases with the occurrence of complications,[4] and mortality rates as high as 40% are observed with *S aureus* infective endocarditis.

Clinical Characteristics

Signs and symptoms of infective endocarditis result from either local destructive effects of the cardiac endothelial surface, metastatic embolization of infected fragments to distant sites, hematogenous seeding of other sites, or antibody formation and deposition of immune complexes in tissues. Typical clinical features of infective endocarditis are constitutional symptoms of fever, chills, and malaise with persistent bacteremia and a new or changing heart murmur. In up to 40% of patients, infective endocarditis caused by *S aureus* is associated with embolic complications.[3,5]

Embolic complications can occur as neurologic abnormalities, arthralgias, or vasculitis and can focus attention away from the underlying cardiac cause.[3] Such complications initially might obscure the diagnosis of endocarditis, as in our patient's case. Moreover, infective endocarditis as a cause of vasculitis is uncommon; of 172 adults with vasculitis, only 4 (2.3%) had endocarditis.[6] Our case high-

Table 1. Definition of Infective Endocarditis by Pathologic and Clinical Criteria.

Diagnosis	Characteristic
Definite infective endocarditis	
Pathologic criteria	Microorganisms found by culture or histology in a vegetation that has embolized, or an intracardiac abscess, or
	Pathologic lesions: vegetation or intracardiac abscess confirmed by histology showing active endocarditis
Clinical criteria	1. 2 major criteria, or
	2. 1 major and 3 minor criteria, or
	3. 5 minor criteria
Major criteria	1. Positive blood culture for infective endocarditis
	a. Typical microorganisms from 2 separate blood cultures, or
	b. Persistently positive blood cultures
	2. Evidence of endocardial involvement
	a. Positive echocardiogram for infective endocarditis
	i. Oscillating intracardiac mass on valve supporting structures, in path of returgitrant jets, or on implanted material, or
	ii. Abscess, or
	iii. Dehiscence of prosthetic valve, or
	b. New valvular regurgitation (change in preexisting murmur not sufficient)
Minor criteria	1. Predisposing heart condition or intravenous drug use
	2. Fever ≥ 38.0°C (100.4°F)
	3. Vascular phenomena: major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, Janeway lesions
	4. Immunologic phenomena: glomerulonephritis, Osler nodes, Roth spots, and positive rheumatoid factor
	5. Microbiologic evidence: positive blood culture but not meeting major criterion or serologic evidence of active infection with organism consistent with infective endocarditis
	6. Echocardiogram consistent with infective endocarditis but not meeting major criterion
Possible infective endocarditis	Findings consistent with infective endocarditis that fall short of "definite" but not "rejected"
Rejected	1. Firm alternate diagnosis for manifestations of endocarditis, or
	2. Resolution of manifestations of endocarditis with antibiotic therapy for ≤ 4 days, or
	3. No pathologic evidence of infective endocarditis at surgery or autopsy after antibiotic therapy for ≤ 4 days

Adapted and reprinted from the American Journal of Medicine, vol 96, Durack DT et al. New criteria from the diagnosis and treatment of infective endocarditis, pp 202–3, 1994. With permission from Exerpta Medica, Inc.

lights the importance of being alert for infective endocarditis when patients have fever, bacteremia, and evidence of embolic phenomena.

Diagnosis

Diagnosis in our patient was complicated. Although the diagnosis of infective endocarditis was initially considered because of her prolonged bacteremia from intravascular instrumentation, we prematurely discounted this diagnosis because of two negative transthoracic echocardiograms. When she subsequently developed abdominal pain and a purpuric rash, a workup for vasculitis was initiated, which ultimately led to the correct diagnosis.

The differential diagnosis of vasculitis is extensive. Historically, vasculitic syndromes were classified by their clinical and pathologic characteristics. Newer classification systems are based on clinical, pathologic, and immunologic features.[7] One such classification system[7] divides vasculitis into the follow categories:

1. Polyarteritis nodosa group, involving serious necrotizing vasculitis (eg, classic polyarteritis nodosa, Churg-Strauss disease)
2. Hypersensitivity vasculitis (eg, Henoch-Schönlein purpura, infection-associated vasculitis,

vasculitis associated with neoplasm or connective tissue disease)
3. Granulomatous vasculitis (eg, Wegener granulomatosis, giant cell granuloma, lymphoid granulomatosis)
4. Other vasculitic syndromes (eg, Kawasaki disease, Behçet syndrome, thromboangiitis obliterans).

Our patient's condition was diagnosed as a hypersensitivity vasculitis affecting the small vessels. Histopathologic examination showed leukocytoclastic vasculitis resulting from neutrophils that infiltrated in and around the involved vessels. Typically, this vasculitis causes lesions in the lower extremities or dependent areas, such as the sacrum.

Initial consideration was given to the diagnosis of Henoch-Schönlein purpura. This syndrome consists of palpable purpura, arthralgias, gastrointestinal symptoms, and glomerulonephritis. Our patient had some of these signs and symptoms, but glomerulonephritis was difficult to evaluate because of her underlying renal disease. Although more common in children, Henoch-Schönlein purpura can occur in adults of any age.[8] Histopathology was our tool for diagnosis. Direct immunofluorescent staining for immune complexes was negative, making the diagnosis of Henoch-Schönlein purpura unlikely. Such diseases as systemic lupus erythematosus, rheumatoid arthritis, mixed cryoglobulinemia, and other connective tissue diseases can all cause cutaneous vasculitis, but they usually also produce manifestations of the underlying disease. Laboratory tests for these diseases were negative in our patient. Infection was the leading diagnosis and was confirmed by a positive tissue culture for methicillin-resistant *S aureus*. This finding pushed infective endocarditis back to the forefront of our diagnosis.

This case illustrates the difficulty of diagnosing infective endocarditis. Durack et al[9] describe the use of carefully defined clinical criteria for making the diagnosis of infective endocarditis (Table 1). According to these criteria, our patient initially met the definition for possible infective endocarditis when the transthoracic echocardiogram failed to show vegetations. In this setting of high clinical probability for infective endocarditis, a transesophageal echocardiogram was indicated. Because the transesophageal echocardiogram has been shown to be more sensitive than the transthoracic echocardiogram,[10–12] when a transthoracic echocardiogram is negative for infective endocarditis, a transesophageal echocardiogram should be performed.

Summary

Infective endocarditis has protean manifestations. Diagnosis can be challenging. When the patient described in this report was first examined, we considered the diagnosis of endocarditis. This diagnosis was excluded, in hindsight prematurely, after the initial echocardiogram results. Ultimately a correct diagnosis was made after the patient developed a cutaneous vasculitis resulting from septic embolization. Infective endocarditis was confirmed by transesophageal echocardiogram, which showed mitral valve vegetation. Although appropriate treatment was not delayed in our patient, this case illustrates the relative insensitivity of the transthoracic echocardiogram and the importance of the transesophageal echocardiogram for the diagnosis of endocarditis. The appropriate diagnosis is important for length of treatment and proper follow-up care. Although vasculitis as a manifestation of endocarditis is not common, clinicians must consider infective endocarditis in a patient with prolonged bacteremia and vasculitis.

Eric Marshall, MD, took the photographs.

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