Teenager with Fever, Petechiae, Confusion, and Weakness

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PRESENTATION

A 13-year-old previously healthy girl presents with fever (101.5°F [38.6°C]) for 3 days. It was preceded by generalized headache. The patient reports no history of vomiting, difficulty breathing, coughing, chest pain, blurry vision, speech disturbance, or trauma. The patient also has diffuse muscle pain, although no swelling of limbs or limitation of activity is reported. There is no history of any recent travel, sick contacts, or exposure to animals or insects. She does not report any intravenous drug abuse. Her dental braces were adjusted 2 weeks before admission. Our patient has no previous medical or surgical history. There is no family history of any congenital heart defects, arrhythmia, or frequent infections. She lives with her parents and has a 31-year-old brother, who is healthy.

In the emergency department she has a temperature of 102°F (38.9°C), with associated tachycardia but otherwise normal vital signs. Her physical examination shows an ill-appearing young febrile girl who is alert and oriented to time, place, and person but has trouble recalling events that happened in the past 5 to 7 days. Strikingly, there are multiple nonblanching petechial hemorrhages in the tips of her fingers and toes (Figs 1–3). In addition, tender nodes are appreciated in both palms and soles. The patient also has some weakness of all 4 limbs, but no other notable findings on clinical examination are appreciated. Importantly, auscultation of the heart reveals normal heart sounds with no murmurs. Initial laboratory data include a white blood cell count of 12,000/μL (12 × 10^9/L), a hemoglobin value of 13 g/dL (130 g/L), and a platelet count of 118 × 10^3/μL (118 × 10^9/L). The comprehensive metabolic panel is normal, but her C-reactive protein level and erythrocyte sedimentation rate are elevated at 130 mg/L (1,238 nmol/L) and 25 mm/hr, respectively. A blood culture and lumbar puncture are collected. Cerebrospinal fluid studies do not show any abnormalities. A transthoracic echocardiogram is performed that confirms the diagnosis.

DIAGNOSIS

The echocardiogram demonstrates mitral valve endocarditis and a mobile vegetation measuring 1.5 × 1 cm in the ventricular surface of the anterior leaflet of the mitral valve (Video 1). Although the patient has normal ventricular function, the vegetation causes some mitral incompetence (Video 2). The other valves are
unaffected. The blood culture is positive for methicillin-sensitive *Staphylococcus aureus*. Due to the altered mental status and weakness of extremities, magnetic resonance imaging of the brain is performed and shows multiple ischemic areas in both cerebral hemispheres as well as a punctate ischemic stroke in the left cerebellum. No midline shifting, edema, or mass effect is reported. Our patient is diagnosed as having bacterial endocarditis caused by methicillin-sensitive *S. aureus* and is treated with antibiotics.

**DISCUSSION**

**Epidemiology**

Infective endocarditis (IE) is less common in the pediatric population compared with adults. Reported incidence ranges from 0.3 cases (in older children and teenagers) to 3.3 cases (in infants) per 100,000 children per year. (1)(2) Although traditionally reported to be more common in children with congenital heart disease in developed countries, increased use of indwelling catheters is believed to contribute to a rise of IE in children without CHD. Another major pediatric population at risk for IE is newborn infants, even those with a structurally normal heart. A little more than 7% of pediatric patients with IE are neonates. There seems to be a bimodal distribution of IE with respect to age in children, peaking during infancy and again during late adolescence. (1)

The general clinical presentation is an indolent illness with nonspecific complaints such as fever, fatigue, weakness, myalgia, and sweating. This, coupled with the rarity of the condition in children, makes it a challenge to diagnose IE. (3)(4) Nevertheless, because previously healthy children without any risk factors can also develop IE (10%–20%), diagnosis requires a high degree of suspicion and a thorough physical examination. (2)(5)(6)(7)

**Causative Agents**

The most common infectious agents implicated in IE are bacteria, especially gram-positive cocci. Viridans group streptococci and *S. aureus* are the most common agents. Other causative agents include coagulase-negative staphylococci, *Streptococcus pneumoniae*, *Enterococcus* species, and HACEK (*Haemophilus* species, *Aggregatibacter* species, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella* species) organisms. Less frequently, group B *Streptococcus* species and gram-negative rods are also implicated. Fungal endocarditis, typically caused by *Candida albicans* and, rarely, *Aspergillus* species, is classically reported in children receiving parenteral nutrition.
Pathogenesis
The pathogenesis of IE has been well-studied using animal models and observational studies in humans. The initial process for developing IE involves turbulent flow-mediated valvular damage. The turbulent flow may be due to a variety of reasons, such as intracardiac devices, prosthetic valves, peripherally inserted central catheters, and congenital heart disease. This turbulent flow-mediated damage results in formation of nonbacterial thrombotic endocarditis aided by a host response involving fibrin deposition and platelet activation. An initial bacteremia in the presence of a traumatized endothelium on the valve surface forms a nidus of infection. Current research suggests that inherited variations in genes encoding for inflammatory markers and cytokines could increase the risk of IE. The initial adhesion of bacteria to the damaged endothelial surface is aided by a multitude of pathogen-dependent factors, such as adhesions and pili, and by host-derived factors, such as collagen, laminin, fibrinogen, and fibronectin. In addition, as the bacteria multiply in number they begin forming a biofilm that creates a barrier for host immune cells and antibiotics to infiltrate the vegetation.

Clinical Presentation and Diagnosis
Although most patients present with an indolent history and nonspecific complaints, the occasional child will present with fulminant bacteremia and high spiking fevers. The clinical presentation is related to bacteremia, valvulitis, immune response, and septic emboli. Valvulitis and vegetations can present as new-onset cardiac murmurs, but patients usually present without any significant cardiac findings. Heart murmurs are reported in only 10% to 20% of patients with IE. Immunologic phenomena are primarily due to immune complex deposition and manifest as glomerulonephritis, Osler nodes (tender intradermal nodules on digits), and Roth spots (small retinal hemorrhages). Septic emboli can present as
mycotic aneurysms, septic pulmonary infarcts, conjunctival hemorrhages, and Janeway lesions (painless hemorrhage on the palms and soles). Although fever is the most common presentation, symptoms such as heart failure and arthralgia, and signs such as splenomegaly, murmur, petechiae, and embolic phenomena, are noted in nearly 50% of pediatric patients. Complex and variable clinical manifestations make IE a diagnostic challenge. The Duke criteria are a validated tool to diagnose IE. The modified Duke criteria (Table) use pathological, clinical, echocardiographic, and laboratory findings to improve sensitivity. (9)

Patients with IE often have nonspecific laboratory findings, such as elevated white blood cell count, C-reactive protein level, and erythrocyte sedimentation rate and low complement levels. Blood culture is the most important investigation because it aids in diagnosis and guides treatment. Multiple blood cultures, with adequate volume for aerobic and anaerobic culture, are strongly recommended. In addition, patients should be evaluated with an echocardiogram. Although transesophageal echocardiography has better sensitivity, transthoracic echocardiography is less invasive and is usually performed first. In patients with suspicion for septic emboli, it is also ideal to obtain a magnetic resonance image of the brain.

Treatment
Antibiotics are the mainstay of treatment and should be started immediately. Broad-spectrum coverage with vancomycin and gentamicin is recommended until bacterial identification and sensitivity are established. Once sensitivity is determined, the antibiotic regimen should be narrowed and treatment continued for 4 to 6 weeks for uncomplicated infections. For patients with prosthetic valves, it is recommended to add rifampin for synergy and to treat for at least 6 weeks. Surgical intervention should be considered in patients with persistent infection and positive blood culture for more than 5 to 7 days after starting appropriate intravenous antibiotics. Infective endocarditis remains a serious condition with significant morbidity and mortality, although recent mortality is improved compared with historical data. High mortality rates are associated with neonatal IE, IE due to fungus and S aureus, and poor ventricular function. Patients with a history of IE are considered to be at high risk for another IE and require antibiotic prophylaxis for procedures associated with bacteremia of IE-associated organisms.

PATIENT COURSE
Our patient continued to have persistent fevers, for which we added rifampin, as suggested by the infectious disease consultant. Cardiothoracic surgery was performed to remove the vegetation and repair the mitral valve, after which the patient improved significantly. She received antibiotics for a total of 8 weeks and has been doing well since discharge.
TABLE. **Modified Duke Criteria for IE (Pathological Criteria Not Shown)**

**MAJOR CRITERIA**

1. Blood culture positive for IE
   
   A. Typical microorganisms consistent with IE from 2 separate blood cultures:
      
      i. Viridans streptococci, Streptococcus bovis, HACEK group, Staphylococcus aureus; or
      
      ii. Community-acquired enterococci in the absence of a primary focus; or
   
   B. Microorganisms consistent with IE from persistently positive blood cultures defined as follows:
      
      i. At least 2 positive cultures of blood samples drawn >12 h apart; or
      
      ii. All of 3 or a majority of ≥4 separate cultures of blood (with first and last sample drawn ≥1 h apart)
   
   C. Single positive blood culture for *Coxiella burnetii* or antiphase 1 IgG antibody titer >1:800

2. Evidence of endocardial involvement

3. Echocardiogram positive for IE (TEE recommended in patients with prosthetic valves, rated at least "possible IE" by clinical criteria, or complicated IE [paravalvular abscess]; TTE as first test in other patients), defined as follows:

   A. Oscillating intracardiac mass on valve or supporting structures, in the path of regurgitant jets, or on implanted material in the absence of an alternative anatomical explanation; or

   B. Abscess; or

   C. New partial dehiscence of prosthetic valve

4. New valvular regurgitation (worsening or changing or preexisting murmur not sufficient)

**Minor criteria**

1. Predisposition, predisposing heart condition, or injection drug use

2. Fever, temperature >100.4°F (>38°C)

3. Vascular phenomena, major arterial emboli; septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, and Janeway lesions

4. Immunologic phenomena: glomerulonephritis, Osler nodes, Roth spots, and rheumatoid factor

5. Microbiologic evidence: positive blood culture, but does not meet a major criterion as noted above,* or serologic evidence of active infection with an organism consistent with IE

**Definitive IE**

1. 2 major criteria; or

2. 1 major criterion and 3 minor criteria; or

3. 5 minor criteria

**Possible IE**

1. 1 major criterion and 1 minor criterion; or

2. 3 minor criteria

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*Excludes single positive cultures for coagulase-negative staphylococci and organisms that do not cause endocarditis.


Summary

- Infective endocarditis is an uncommon but serious pediatric condition that requires a high degree of suspicion to diagnose.
- Infectious endocarditis has been reported in patients without any risk factors and even in the presence of normal cardiac examination findings. Most pediatric patients present with nonspecific signs and symptoms, which further highlights the importance of a thorough physical examination in children presenting with unexplained fever.
- Blood culture and echocardiography are the most important initial diagnostic tests. Empirical treatment includes vancomycin and gentamicin (with rifampin for patients with prosthetic valves) until culture and sensitivity results are available.

References

Visual Diagnosis: Teenager with Fever, Petechiae, Confusion, and Weakness
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