ILLUSTRATIVE CASE

Sepsis Due to Superinfected Varicella? A Case of a Challenging Rash

Case: A 6-year-old boy with no significant medical history and up-to-date immunizations presented to the emergency department (ED) with diffuse rash, leg swelling, and respiratory distress. Five days before presentation, the patient twisted his ankle while playing soccer and developed mild swelling. The following day he developed a fever and was brought to his pediatrician; he was diagnosed with an ankle sprain and a viral illness and was managed with ibuprofen and supportive care. On the day of presentation, he developed a vesicular rash that started on his forehead and spread over his entire body. In the ED, he was febrile (temperature: 102°F), tachypneic (respiratory rate: 42 breaths per minute), tachycardic (heart rate: 155 beats per minute), hypotensive (80/50 mm Hg), and lethargic. His physical examination was notable for a tense and swollen lower left leg from 2 cm below the knee to the dorsum of the foot, with decreased but palpable pulses. He also had diffuse 2- to 4-mm pink, umbilicated vesicles involving his face, trunk, and extremities (Figs 1 and 2). Although inconsistent with the patient’s history, these lesions raised concern for varicella.

In the ED, the patient was started on intravenous ampicillin-sulbactam and vancomycin because of his toxic appearance and the presence of skin lesions. Chest radiography revealed reticulonodular densities throughout the lungs bilaterally as well as small bilateral pleural effusions. Results of admission laboratory tests were pertinent for a complete blood cell count with depressed cell lines and elevated inflammatory markers. His white blood cell count was 1.2 K/μL, hemoglobin was 9.2 g/dL, and platelets were 36 K/μL. His C-reactive protein level was 24.5 mg/dL, and creatine kinase was 349 U/L. Results of coagulation studies were within normal limits, but fibrinogen and d-dimer levels were elevated (738 mg/dL and 15.6 μL/mL, respectively). The initial working diagnosis was sepsis, possibly due to superinfected varicella.

Question: What are the possible sequelae of varicella infection?

Discussion: At first, this case of sepsis was believed to be a result of superinfected varicella. Although varicella infections are usually relatively benign and self-limited, there is a wide spectrum of associated complications. Viral-related sequelae include arthritis, hepatitis, encephalitis, myocarditis, and pneumonia. Other complications occur as a result of bacterial entry through a defective skin barrier and a transient, varicella-induced disrupted cellular immunity. Bacterial superinfection and disseminated disease usually occur within 14 days of primary varicella infection, although there have been cases reported as late as 6 weeks after initial infection. In a retrospective chart review, 73% of children hospitalized...
with varicella had superficial infections (eg, cellulitis, abscesses, impetigo), and 27% had deep-seated infections (eg, necrotizing fasciitis, osteomyelitis, pneumonia, sepsis).³ In another retrospective chart review of 417 children hospitalized with complications of varicella, 6% required operative treatment.⁴ Group A streptococci and Staphylococcus aureus are the most commonly isolated pathogens. In 1 review, 59% of bacterial isolates were group A streptococci and 28% were S aureus.³ However, these percentiles differ in other reports.⁵

Case Continuation: The dermatology service was consulted due to the unusual character of the rash. The initial examination revealed well-demarcated, 2- to 4-mm umbilicated pink vesicles, scattered widely on the face, trunk, and extremities. Most lesions were in the same stage of evolution. However, numerous small erosions localized to areas of pressure (eg, the back), and focal hemorrhagic crusts covered the forehead. Fragile vesicles contained a clear fluid when manually ruptured for Tzanck smears and herpesvirus direct fluorescent antibody specimens. Although the direct fluorescent antibody was reported as negative, a Tzanck smear showed multinucleated epithelial cells. Clinical findings and a positive Tzanck smear suggested varicella, but the immunization history and negative direct fluorescent antibody specimen seemed contradictory. Because enteroviruses, such as Coxsackie and echovirus, may cause blisters simulating varicella, immune titers were obtained that proved negative on testing. The odd confluence of bacterial sepsis and a possible viral eruption in a previously healthy, immunocompetent child led us to perform a skin biopsy.

The patient was brought to the operating room because of concerns about compartment syndrome involving his leg. He underwent a fasciotomy, compartment release, and incision and drainage of distal tibial osteomyelitis. Multiple wound and blood cultures grew community-acquired methicillin-resistant S aureus (CA-MRSA).

The skin biopsy specimen disclosed a subcorneal vesicle containing gram-positive cocci, consistent with disseminated MRSA. The patient had a prolonged hospital course, complicated by persistent fevers and bacteremia, repeat incision and drainage of osteomyelitis, and focal pulmonary necrosis and cavitation requiring chest tube placement. He ultimately improved with intravenous clindamycin. The patient’s final diagnosis was osteomyelitis and sepsis secondary to disseminated CA-MRSA.

Question: What is the etiology of this unusual manifestation of MRSA infection?

Discussion: Staphylococcus species cause a wide variety of skin and soft tissue infections, including impetigo, folliculitis, cellulitis, abscesses, furuncles, and carbuncles, as well as staphylococcal scalded skin syndrome and toxic shock syndrome. Staphylococcal skin disorders rarely present as umbilicated vesicles, as in this patient. Nonetheless, previous case reports have identified varicella-like eruptions due to staphylococcal septicemia.⁶,⁷ In a study by Gonzalez et al⁶ of 14 adolescents who had severe CA-MRSA sepsis, 11 developed skin lesions ranging from hives to erythema multiforme simulants. Two of the 14 children in the report developed papulopustular eruptions comparable to our case. Another series describes 3 patients with staphylococcal septicemia presenting with opalescent vesicles on the face.⁷ Such cutaneous manifestations of severe bacterial infections develop due to dissemination of bacteria, the action of their toxins, or because of immune-mediated mechanisms.⁸ S aureus causes vesicles and blisters through the production of an exfoliative toxin that binds to a desmosomal protein called desmoglein-1. This toxin causes cleavage of desmoglein’s extracellular domain, leading to acantholysis within the epidermal granular layer. This process is seen both in bullous impetigo as well as in staphylococcal scalded skin syndrome.⁹ In bullous impetigo, the exfoliative toxins are restricted to the area of infection. In contrast, staphylococcal...
scalded skin syndrome is caused by exfoliative toxins that are hematogenously spread from a localized source, causing widespread epidermal damage at distant sites. In the clinical case presented here, gram-positive cocci were seen within a subcorneal vesicle, raising the hypothesis that the MRSA had disseminated to the skin and caused a vesicular eruption via exfoliative toxin production.

**Question:** What are other possible manifestations of MRSA infections?

**Discussion:** *S. aureus* is the most common pathogen causing pediatric osteomyelitis, reported in 25% to 60% of culture-positive cases, with the incidence of MRSA infections increasing 10-fold in 1 study. Although both MRSA and methicillin-sensitive *S. aureus* (MSSA) osteomyelitis may present with a similar clinical picture of fever, pain, and loss of function of the affected limb, studies have demonstrated that MRSA infections are generally more severe and have greater associated morbidity. Higher fevers, lower hematocrit levels, higher degree of leukocytosis, and higher C-reactive protein levels have been shown to be independent predictors of MRSA infection compared with MSSA in a retrospective review of 129 children with *S. aureus* osteomyelitis. Other studies have shown a statistically significant difference in the length of hospitalization, fever duration, rate of pyomyositis, and occurrence of subperiosteal abscess requiring ≥1 surgical drainage with MRSA osteomyelitis compared with MSSA. One proposed virulence factor partially responsible for the higher morbidity of MRSA is the Panton-Valentine leukocidin factor, which increases the adherence of MRSA to collagen.

In addition to skin and bone infections, CA-MRSA reportedly causes invasive disease, which may occur spontaneously after a skin and soft tissue infection, or occur secondary to metastatic spread after an episode of osteomyelitis. Cases of such invasive disease in older children who had no significant risk factors were initially reported by Shulman and Ayoub in the 1970s. They described 9 previously healthy adolescent patients who presented with severe staphylococcal septic shock and multisystem involvement, including multifocal osteomyelitis or septic arthritis, deep venous thrombosis, pulmonary manifestations such as septic emboli, necrotizing pneumonia with diffuse airspace disease, cardiovascular disease with vegetations, renal failure, and rash. The aforementioned case series by Gonzalez et al presented adolescents who had manifestations starkly similar to those in the current clinical case presentation.

As with these previous cases, the patient in the current report had no significant medical history or underlying immunologic deficiency but went on to develop severe, disseminated disease. His clinical findings were similar to previously reported cases, including bone/joint involvement (osteomyelitis), pulmonary involvement (necrotizing pneumonia with empyema and effusions), and disseminated skin lesions. As this case demonstrates, rapidly developing vesicles in a morbidity febrile child should alert the clinician to possible fulminant staphylococcal septicemia.

**Conclusions:** The incidence of MRSA osteomyelitis has been increasing, and the disease is associated with higher fevers and inflammatory markers, longer hospitalization duration, and worse overall morbidity and mortality than MSSA osteomyelitis. Although unusual, disseminated staphylococcal infection can present with vesiculopustular lesions mimicking varicella. Invasive disease caused by CA-MRSA can occur in otherwise healthy children who have no significant risk factors.

**REFERENCES**


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