Robert Listernick, MD, and colleagues discuss hard-to-diagnose cases.

A 13-Year-Old Boy with Elevated BUN and Creatinine

Robert Listernick, MD

A 13-year-old boy was sent to our emergency department for evaluation of elevated blood urea nitrogen and creatinine following an outside hospital clinic visit. Seven weeks prior to presentation at our hospital, he was found to have a stress fracture caused by running.

It was initially thought to be a torn ligament, but the fracture was confirmed on MRI scan. His leg was placed in a cast for 4 weeks. Following removal of the cast, he was noted to have a soft tissue infection on the bottom of his foot; it was incised and drained 2 weeks prior to coming to our hospital. He was started on amoxicillin-clavulonic acid; the wound culture was negative. After 5 days he was found to have no improvement while receiving the antibiotic and was admitted to an outside hospital. At that time, complete blood count was normal, with C-reactive protein (CRP) of 1.1 mg/dL and erythrocyte sedimentation rate of 40 mm/hour.

MRI at that time demonstrated "extensive osteomyelitis with posterior medial cortical destruction with intraosseous and extraosseous phlegmon as well as several soft tissue abscesses and extensive soft tissue edema."

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He underwent extensive surgical incision and drainage that confirmed these findings. Pathology revealed "necrotizing granulomatous inflammation of bony tissue." Cultures were all negative. CT scan of the foot the day following operation revealed "diffuse subcutaneous edema throughout the plantar medial aspect of the left foot, consistent with recent postoperative change and infection, lytic lesion of the medial navicular bone with posterior and inferior cortical destruction, consistent with intraosseous abscess."

Several days later, he returned to the operating room for a second incision and drainage. Initially on this admission, he received intravenous clindamycin and vancomycin. The infectious disease service at the outside hospital was consulted and recommended intravenous (IV) cefepime for home antibiotic therapy. CRP at this time was 1.5 mg/dL.

He received IV cefepime at home for 5 days, at which time the home health nurse noted a systolic blood pressure of 140 mm Hg. The following day, he was seen at a clinic visit where his blood pressure was noted to be 150/98 mm Hg. Laboratory testing revealed blood urea nitrogen (BUN) of 97 mg/dL and creatinine level of 11 mg/dL.

Review of systems, medical history and family history were unremarkable. On physical exam, he was a well-appearing young man. Pulse was 81, respiratory rate was 18, blood pressure was 144/90 mm Hg, weight was in the 90th percentile, and height was in the 75th percentile. His physical examination was normal save for his left foot, which was wrapped in gauze. When the dressing was removed, there was a 5-cm incision extending to the plantar surface of the foot. The foot was swollen and tender in the areas surrounding the incision. There was a small fluid collection and blister at the proximal end of the wound and a hemorrhagic blister abutting the incision.

Initial laboratory testing showed hemoglobin of 8.8 g/dL; white blood cell count of 12,000/mm^3 with 79% neutrophils and 10% lymphocytes; sodium of 128 mEq/L; potassium of 4.1 mEq/L; chloride of 96 mEq/L; bicarbonate of 14.8 mEq/L; BUN of 103 mg/dL; and creatinine of 11 mg/dL. Urinalysis had 2+ protein, 10 to 20 white blood cells per high-powered field, and 6 to 10 red blood cells per high-powered field. The specific gravity was 1.009. Urine protein/creatinine ratio was 0.7.

Robert Listernick, MD, moderator: Children get stress fractures?

Eric B. Eller, MD, orthopedic surgeon: Stress fractures of the navicular bone are not uncommon in higher-level athletes. We don't have the initial X-rays or MRI to review, but the story would be reasonable except for the fact that he wasn't training excessively.

Dr. Listernick: How do you initially diagnose a stress fracture?

Dr. Eller: Typically the child has localized foot pain with initially nega-

tive X-rays. Two weeks later, the repeat X-rays will show thickened cortices suggestive of a longer-standing process. If performed, MRI would show the fracture earlier. This child's fracture was atypical. It is possible he was born with a small cortical cyst that would be prone to fracture. The casting seems reasonable; children heal faster than adults, so 4 to 6 weeks seems a reasonable amount of time.

Dr. Listernick: Do we know what it looked like when the cast was removed?

Larry K. Kociolek, MD, pediatric infectious disease physician: He had a large blister on the medial aspect of the foot with underlying erythema with an ulceration on one end. Initially, it was felt to be a superficial cellulitis without underlying bone infection.

Dr. Listernick: What about the choice of augmentin to treat the cellulitis?

Dr. Kociolek: It is adequate for treatment of infection with methicillin-sensitive *Staphylococcus aureus*, but inadequate for methicillin-resistant *S. aureus*. We would have chosen clindamycin, which provides coverage for both organisms.

Dr. Listernick: Moving forward, the patient is diagnosed with osteomyelitis. Is this acute or chronic osteomyelitis?

Dr. Kociolek: Usually, if symptoms have been present for more than 2 weeks, we consider the infection chronic. This distinction is important because the duration of therapy would be much longer in chronic osteomyelitis and the need for surgical debridement would be much higher. For chronic osteomyelitis, we generally recommend 6 weeks of IV antibiotics followed by 4.5 months of oral antibiotics.

Dr. Listernick: How important is it to identify an organism?

Stanford T. Shulman, MD, pediatric infectious disease physician: We always welcome the opportunity to identify a causative organism in acute osteomyelitis. Ideally, the blood culture would be positive, but this occurs in a minority of cases. We try to educate orthopedic residents that whenever these children go to the operating room it is extremely helpful to aspirate the blood and place a sample in a blood culture bottle, which helps dilute the host substances that prevent us from recovering a pathogen. We rarely can identify an organism in chronic osteomyelitis.

Dr. Listernick: Why is his CRP so low?

Dr. Kociolek: In acute osteomyelitis, there is a very brisk inflammatory response from both the direct effect of the organism as well as tissue destruction from the host's immune response that ultimately leads to ischemia and bone infarction. The end result is a chronically infected sequestrum with no blood supply; the systemic inflammatory response disappears.

Dr. Listernick: Moving forward, he has renal failure. What's going on? Short of having an earlier BUN or creatinine test, how can you determine whether it is acute or chronic?

Kavita S. Hodgkins, MD, pediatric kidney disease physician: His growth had been normal and there was no previous history of elevated blood pressures. His initial hemoglobin at the time of his first operation was normal. We thought it much more likely that this was acute renal failure. In addition, several days later, we discovered an earlier BUN and creatinine test that showed levels were normal.

Dr. Listernick: What was your differential diagnosis?

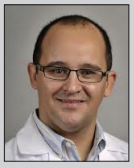
Dr. Hodgkins: The most obvious explanation was that it was due to any one of the antibiotics he received. Certainly, the vancomycin is nephrotoxic, and many of the cephalosporins have been implicated in the development of interstitial nephritis. Another possibility is postinfectious glomerulonephritis, particularly if the original organism was *Streptococcus pyogenes*. In trying to distinguish between glomerular and interstitial kidney disease, the specific gravity can be quite helpful. In acute interstitial nephritis, the urine specific gravity will be 1.010 or a bit lower, whereas it generally will be quite high in acute glomerulonephritis. In addition, although you didn't give the values, the urine microalbumin and the beta-2 microglobulin were quite high. These are markers of tubular function, and the elevated values are quite suggestive of tubular dysfunction. Putting it all together, the most likely explanation for his kidney failure is acute interstitial nephritis secondary to one of the antibiotics.

Dr. Shulman: I should point out that post-streptococcal glomerulonephritis is common following skin infections with group A streptococcus but quite rare after

Panelists

Robert Listernick, MD
Moderator

Eric B. Eller, MD
Orthopedic surgeon



Larry K. Kociolek, MD,
Pediatric infectious disease physician

Stanford T. Shulman, MD
Pediatric infectious disease physician:

(Not pictured: Kavita S. Hodgkins, MD, pediatric kidney disease physician; and Rupal M. Patel, PharmD)

All panelists practice at The Ann and Robert H. Lurie Children's Hospital of Chicago, IL, where this discussion, part of a weekly series, was recorded and transcribed for *Pediatric Annals.*

deeper infections with that organism.

Dr. Listernick: He had normal antinuclear antibody and complement levels. Without going into the values, 96 hours after his last vancomycin dose, he had an extremely high vancomycin level. The level was even higher 24 hours later. Can the vancomycin be removed by dialysis?

Dr. Hodgkins: No. The indications for dialysis are the same with any child with acute kidney injury — symptomatic uremia, electrolyte abnormalities uncontrollable with medical management, or intractable hypertension.

Dr. Listernick: Is there any treatment available for severe interstitial nephritis?

Dr. Hodgkins: There are no randomized controlled trials looking at the efficacy of corticosteroid treatment for acute interstitial nephritis, but there are case reports that suggest that it is beneficial and may lead to a more rapid decline in BUN and creatinine levels and resolution of the symptoms. Before we started corticosteroids, we thought a kidney biopsy was important to determine the extent and severity of the injury. The glomeruli were intact and there was extensive mononuclear cell infiltration into the tubular intersitium. On closer view, there were a number of eosinophils. All of these findings are consistent with a diagnosis of acute interstitial nephritis.

Dr. Kociolek: While all this was occurring, we were surprised that the vancomycin level was rising. We were even more surprised when X-rays of the infected foot revealed three round, radiopaque objects. Those beads were impregnated with gentamicin. In addition, the orthopedic surgeon took a vial of vancomycin and sprinkled it on the beads before implanting them.

Dr. Eller: It's a common practice among orthopedic surgeons who treat adults. These are not premade beads with a defined amount of antibiotic. Rather, we make the beads ourselves and pack them in the soft tissue to get a high local concentration of antibiotic. Usually, all of the antibiotic is absorbed after 6 weeks and we then remove the beads. The systemic absorption is supposed to be very low. However, we don't use them in any adult who has any degree of renal insufficiency.

Rupal M. Patel, PharmD, pharmacist: We don't use them at our hospital. There are several case reports in adults of kidney failure due to these methylmethacrylate polymers that are mixed with antibiotics. Their use is not regulated and, obviously, the local concentration of antibiotic is highly variable.

Dr. Shulman: It turns out that the material to make the beads comes with gentamicin and is fairly standardized. The package insert specifically states not to use vancomycin when beads are implanted, and beads are not to be used in children.

Dr. Eller: From our standpoint, this was a very low number of beads. We may use 50 such beads in adults.

Dr. Hodgkins: We did wonder whether the interstitial nephritis started with one of the earlier antibiotics and was exacerbated by the inability to excrete the vancomycin. But this was conjecture. He underwent 2 days of hemodialysis and gradually we saw his BUN and creatinine levels improve. He was discharged, and 2 weeks later his BUN is 30 mg/dL and creatinine 0.8 mg/dL. He is still definitely at risk for long-term kidney injury.

Dr. Listernick: As the late-night television commercials say, "But wait, there's more!" Several days into his admission here, cultures from his foot grew fungus.

Dr. Kociolek: This was not a complete surprise to us. We knew that the original biopsy of the lesion performed at the outside hospital showed necrotizing granulomas, which was very suggestive of fungal or mycobacterial disease. Coupled with the negative bacterial cultures, we thought it quite likely that he had a fungal infection, in particular blastomycosis. Blastomycosis is endemic in northern Illinois and Wisconsin. In fact, the patient previously had traveled to Eagle River, WI, which is a hotbed of blastomycosis. Ultimately, the cultures were positive for blastomycosis.

Dr. Listernick: How does blastomycosis classically present?

Dr. Kociolek: The triad of pulmonary, skin, and osteoarticular disease is highly suggestive of disseminated blastomycosis. We actually started itraconazole prior to giving the corticosteroids because of the concern that he could worsen while receiving the large doses of steroids. He had a normal chest X-ray. He will probably receive it for a total of 12 months. ■

Key Learning Points

1. Stress fractures may occur in children who are higher-level athletes. Typically, the child has localized foot pain with initially negative X-rays. Two weeks later, the repeat X-rays will show thickened cortices suggestive of a longer-standing process.
2. If a child with a bone infection has symptoms present for more than 2 weeks, the infection should be considered chronic. This distinction is important because the duration of therapy is much longer in chronic osteomyelitis and the need for surgical debridement much higher. A course of 3 to 6 months of intravenous antibiotics is generally recommended for treatment of chronic osteomyelitis.
3. In acute interstitial nephritis, the urine specific gravity will be close to 1.010, whereas it generally will be quite high in acute glomerulonephritis.
4. The triad of pulmonary, skin, and osteoarticular disease is highly suggestive of disseminated blastomycosis.