A previously healthy 4-year-old boy presented with left shoulder pain. Two nights prior to admission he was sleeping in bed with his grandmother and awoke complaining that his left arm hurt. Although he went to school the next day, he left early due to arm pain caused by trying to put on his jacket. That night, he couldn’t sleep due to persistent fever and pain, so he was taken to an emergency department. His past history is unremarkable. Family history and development were normal; immunizations were up-to-date.

On presentation he was afebrile. His growth parameters were normal. He was alert and he was crying during the examination. His general physical examination was normal. His right arm was normal. The left arm was held flexed at the elbow and kept rigid. His clavicles were intact. He had mild fullness or edema of the left anterior shoulder compared to the right. He was tender to palpation over the left anterior shoulder without warmth or erythema. He moved his wrist and all his fingers without pain. Distal pulses were normal. Neurologic examination was normal.

The initial laboratory evaluation was hemoglobin 11.8 g/dL, white blood cell count 12,000/mm³ with 72% neutrophils, and platelet count 450,000/mm³. Erythrocyte sedimentation rate (ESR) was 94 mm/hour and C-reactive protein (CRP) was 4.3 mg/dL. His shoulder X-ray was normal. Ultrasonography revealed left shoulder joint effusion with internal debris with a volume of roughly 4 cm³. The joint effusion was predominantly located posteriorly. There was mild hyperemia of the surrounding tissues.

Aspiration of the shoulder joint performed by interventional radiology yielded 4 cm³ of turbid fluid with white blood cell count of 200,000/mm³ with 98% neutrophils. Ultimately, both the joint culture, and subsequently a blood culture from the outside hospital, grew methicillin-sensitive Staphylococcus aureus (MSSA). Magnetic resonance imaging performed 3 days later showed findings suggestive of left septic joint with small effusion and synovitis and marrow edema with enhancement involving the epiphysis of the proximal right humerus concerning for osteomyelitis. A peripherally inserted central catheter was placed and he started receiving intravenous cefazolin every 8 hours to be given for 4 to 6 weeks.

Robert Listernick, MD, moderator: Why would this child have osteomyelitis of the shoulder? This seems like an unusual location.

Larry Kociolek, MD, pediatric infectious diseases physician: Hematogenous osteomyelitis usually presents in the metaphysis of long bones, in this case the humerus, because blood flow is highest at the ends of long bones. Osteomyelitis contiguous to joints in young children often ruptures into the joint leading to a secondary septic arthritis. This is much more likely the case than having a primary septic arthritis lead to secondary osteomyelitis.

Dr. Listernick: OK, now I can ask a question that has been bugging me for a long time. Why does everyone seem to order both ESR and CRP when looking for inflammatory processes, one of which would be a bone or joint infection?

Dr. Kociolek: Simultaneous use of both ESR and CRP is helpful for monitoring treatment response in bone and joint infections, which may not be the case in other infectious and inflammatory conditions. In bone and joint infections, CRP rises early and declines with the resolution of infection, whereas ESR tends to resolve more slowly. Normalization of CRP is an excellent marker of initial response to therapy in osteomyelitis. Some physicians use normalization of ESR to guide long-term response to...
therapy and help determine treatment duration.

Robert Liem, MD, pediatric hematologist: ESR is falsely elevated in anemia; the lower the hemoglobin, the higher the ESR despite a lack of inflammation.

Dr. Lister nick: I know that I’ve seen discrepant values in other conditions, such as Kawasaki disease, but I agree with Larry that’s there’s sparse evidence, other than their use in osteomyelitis, to support ordering both. Next, what is the general treatment regimen for osteomyelitis?

Dr. Kociolek: Standard treatment regimens vary among institutions and even among physicians at the same institution. We tend to treat acute osteomyelitis parenterally for several weeks before switching to oral antibiotics. Treatment duration for acute osteomyelitis is approximately 4 weeks of therapy, although it can vary from 3 to 6 weeks depending on the site and severity of infection. Physicians at other children’s hospitals may switch to oral therapy much sooner, although randomized trials are lacking.

Dr. Lister nick: My corollary question is why not use ceftriaxone to which the MSSA was sensitive? It’s a once-a-day drug.

Anne Rowley, MD, pediatric infectious diseases physician: The minimum inhibitory concentration of ceftriaxone for MSSA will never be as good as that of first general cephalosporins. In addition, ceftriaxone has such a broad spectrum of action that you’re more likely to eradicate the “good” intestinal flora. Use of a first-generation cephalosporin, albeit one that needs to be administered three times daily, is a more sensible choice.

Leena Mithal, MD, pediatric infectious diseases physician: Our patient improved very slowly. His CRP was still elevated when he was discharged; we planned for at least 4 weeks, if not 6 weeks, of therapy based on his slow response.

Dr. Lister nick: He did well for his first 19 days of treatment. On day 20, he developed a fever that persisted for the next 8 days. On day 21, he developed an erythematous macular nonpruritic rash on his right arm that spread diffusely over the next few days. He was seen twice at an outside emergency department; blood cultures drawn both times were negative. He was diagnosed as having a viral exanthem. Following these visits, he developed intermittent abdominal pain, increased abdominal distention, and decreased oral intake.

On presentation to our emergency department he was irritable and had a temperature of 40°C. Pertinent findings on physical examination included (1) abdominal distention without appreciable fluid wave, (2) firm liver border palpated 6 cm below the costal margin, (3) palpable spleen 3 cm below the left costal margin, and (4) multiple hyperpigmented, slightly erythematous patches and macules on the face, trunk, and extremities but sparing the palms and soles. There was no mucosal involvement. Initial complete blood count was hemoglobin 11.3 g/dL, white blood cell count of 4300/mm$^3$ with 12% eosinophils, and platelets 192,000/mm$^3$.

My initial question is does this child have Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)?

Anthony Mancini, MD, pediatric dermatologist: Obviously, one must think about a drug reaction in a child who has been on an antibiotic for a period of time who then develops a new rash. The most common drug rashes will be morbilliform or urticarial in morphology. Morbilliform eruptions tend to be type II cytotoxic reactions that occur within days to a week of starting the drug; there is generally no reason to stop the drug. The classic example is the morbilliform “amoxicillin rash.” Urticarial eruptions are
type I immunoglobulin E (IgE)-mediated processes that occur within hours to a couple of days of starting a medication. These have the potential to progress to anaphylaxis. Exanthsms that occur later than the two previously described rashes may be due to DRESS. The classic timing for DRESS is 2 to 4 weeks after starting a drug.

Dr. Listernick: Which classes of drugs commonly cause DRESS?

Dr. Mancini: Most commonly anticonvulsants, primarily phenytoin, phenobarbital, carbamazepine, and lamotrigine. Any antibiotic may cause DRESS, but minocycline and sulfonamides are the biggest culprits. However, any medication has the potential to trigger DRESS.

Dr. Listernick: What is the classic clinical syndrome of DRESS?

Dr. Mancini: The rash is polymorphous, ranging from macules and papules to intensely erythematous urticaria. These urticarial lesions usually don’t come and go within hours as seen in typical urticaria. They may be fixed for days to weeks. The rash can be so severe that on biopsy it can mimic cutaneous T-cell lymphoma with a dense lymphohistiocytic infiltrate in the dermis. Peri-orbital edema is a very characteristic finding in children with DRESS. Other organ systems can be involved, leading to hepatitis, pneumonitis, nephritis, myositis, and even thyroiditis. Transient hypothyroidism can be a late finding in these patients.

Dr. Listernick: Treatment?

Dr. Mancini: Obviously, elimination of the offending agent is most important. We typically recommend treatment with corticosteroids for severe progressive hepatitis. Anecdotally, intravenous immunoglobulin has been tried, although I don’t believe that there is any convincing evidence of its efficacy.

Dr. Listernick: What does this mean for his ability to use cephalosporins in the future?

Ramsay Fuleihan, MD, pediatric immunologist: There are experimental in vitro assays that expose the patient’s activated lymphocytes to various drugs in an attempt to predict which are safe. These assays are not commercially available so we will generally ask the patient to avoid all drugs in the potential offender’s class. In our patient, we will recommend avoidance of both cephalosporins and penicillins.

Dr. Listernick: Moving forward a bit, is splenomegaly common in DRESS?

Dr. Fuleihan: It’s not a finding we generally see.

Estella Alonso, MD, pediatric hepatologist: I would speculate that in the setting of activated CD8 lymphocytes as seen in DRESS, infiltration of the liver by these lymphocytes might cause acute portal hypertension and splenomegaly. This wouldn’t be true in acute viral hepatitis, which leads to liver cell death and necrosis but not obstruction of portal venous flow.

Dr. Listernick: These are the results of further testing upon admission: aspartate aminotransferase (AST) 12,800 IU/L; alanine aminotransferase (ALT) 1428 IU/L; total bilirubin 2.4 mg/dL; direct bilirubin 1.6 mg/dL; gamma-glutamyl transferase 370 IU/L (markedly elevated); albumin 3.2 mg/dL; ammonia 98 mcg/dL (elevated); prothrombin time 60 seconds (international normalized ratio 4.6); partial thromboplastin time 61 seconds (elevated); fibrinogen <70 mg/dL (markedly depressed); and markedly elevated fibrin degradation products (FDP). Estella, please walk us through the meaning of these results.

Dr. Alonso: First, this child meets criteria for acute liver failure with markedly abnormal coagulation tests and elevated ammonia. However, it’s striking that the bilirubin is relatively very low. This suggests that either the underlying insult is impairing liver function without killing a lot of hepatocytes or that the injury is very zonal. Zonal injury around the central vein, the area most susceptible to oxidant stress, leads to marked release of AST with minimal release of ALT. This pattern is very consistent with acetaminophen toxicity, which we know that this child doesn’t have. Other possibilities for this mismatch of AST and ALT are that the AST is actually coming from some other tissue such as muscle (myositis) or red blood cells (hemolysis). Theoretically, an infiltrative liver disease could also produce these results. Finally, the markedly elevated FDP are evidence of disseminated intravascular coagulation on top of everything else.

Dr. Listernick: Just to throw another monkey wrench into the mix, his serum ferritin was greater than 100,000 ng/mL. This raised the specter of hemophagocytic lymphohistiocytosis (HLH).

Dr. Liem: There are certainly reports of HLH associated with DRESS. There is definitely a growing concern that HLH is underdiagnosed. Early diagnosis is extremely important for instituting appropriate therapy. We are beginning to define an institutional protocol developed by the various stakeholders (oncology, rheumatology, hepatology) who can coordinate a diagnostic algorithm and treatment in suspect cases.

Marisa Klein-Gitelman, MD, pediatric rheumatologist: We have to be careful about relying on such nonspecific markers as serum ferritin. Although the literature suggests that serum ferritin greater than 10,000 ng/mL is highly specific for HLH, there is no literature regarding ferritin levels or some of the other HLH markers (e.g., soluble interleukin-2 (IL-2) receptor levels) in DRESS.

Dr. Listerpink: We’ve spoken many times about HLH. I’ll briefly list the diagnostic criteria (5 of 8 are necessary for diagnosis): (1) fever ≥38.5°C; (2) splenomegaly; (3) blood cytopenias with at least two of the following—hemoglobin <9 g/dL, platelets <100,000/mcL, or
absolute neutrophil count <1,000/mcL; (4) hypertriglyceridemia (fasting triglycerides >265 mg/dL) and/or hypofibrinogenemia (fibrinogen <150 mg/dL); (5) hemophagocytosis in bone marrow, spleen, lymph node, or liver; (6) low or absent natural killer (NK) cell activity; (7) ferritin >3,000 ng/mL; and (8) elevated soluble IL-2 receptor level. Alternatively, a child could have homozygosity or compound heterozygosity for mutations of one or more of the known HLH genes.

Our patient had mildly elevated soluble IL-2 receptor, normal NK cell function, and no major cytopenias. Despite the massively elevated ferritin, he really didn’t meet clinical criteria for HLH. The dilemma was whether to treat him as if he has DRESS or HLH.

Dr. Liem: Everyone felt comfortable with the use of corticosteroids, which is the treatment for DRESS and part of standard treatment for HLH. The question was whether to add etoposide for treatment of HLH.

Dr. Klein-Gitelman: His liver enzymes actually started improving once the cefazolin was stopped. He continued to improve dramatically after the steroids were started. It wasn’t clear to me which of these two treatments was more effective.

Dr. Listernick: I believe that there’s increasing evidence that some cases of HLH may occur in people who are heterozygous for any one of the mutated HLH genes. Perhaps he should still undergo testing for these disorders. For the moment, let’s say that he has DRESS. Thanks everyone.

**Key Learning Points**

1. Hematogenous osteomyelitis usually starts at the metaphysis of long bones because that area has the highest concentration of blood vessels. Osteomyelitis contiguous to joints in young children often ruptures into the joints, leading to a secondary septic arthritis.
2. Urticarial eruptions are type I immunoglobulin E-mediated processes that occur within hours to a couple of days of starting a medication. Cessation of the drug and its future avoidance are necessary.
3. Morbilliform drug eruptions tend to be type II cytotoxic reactions that occur within days to a week of starting the drug; there is generally no reason to stop the drug.
4. Symptoms of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) generally occur 2 to 4 weeks after starting a drug. The rash is polymorphous, ranging from macules and papules to intensely erythematous urticaria. Multiple organ systems may be affected, most notably the liver. Elimination of the offending agent is key, but corticosteroid treatment is crucial in the setting of severe progressive hepatitis