A 4-Year-Old Girl with Dilated Cardiomyopathy

Robert Listernick, MD

This previously healthy 4-year-old girl was transferred from an outside hospital for evaluation of dilated cardiomyopathy. Four weeks prior to admission she started complaining of bilateral hip pain, which her mother attributed to “intensive sledding.” That was the first time I’ve mentioned this activity in “Firm Rounds.”

Two days prior to presentation, she had several episodes of emesis. When the emesis recurred, she was brought to an outside hospital, where she appeared very ill. She initially was treated for sepsis, but a chest X-ray demonstrated cardiomegaly. This led to the performance of an echocardiogram and an eventual diagnosis of dilated cardiomyopathy was made. In addition, she was felt to be in cardiogenic shock at the time of transfer.

Cardiogenic shock was treated aggressively and she improved. During the course of her treatment, a right ventricular thrombus was discovered and she was started on heparin; in addition, she had four episodes of supraventricular tachycardia that were treated with adenosine.

On review, she had decreased energy and fussiness for 1 week prior to admission.

The family history was remarkable for the mother’s history of migraines, hypertension, hyperlipidemia, and bradycardia. There was no family history of sudden death, drowning, single car crashes, or hearing loss.

Pertinent initial laboratory data on presentation were normal complete blood count with differential, ALT 504 IU/mL, AST 437 IU/mL, albumin 4.3 mg/dL, C-reactive protein 8 mg/dL and both extremely elevated B-natriuretic peptide and troponin. Titers of cytomegalovirus, all hepatitis viruses, human herpes-virus 6, and Coxsackie were all negative. However, parvovirus PCR (polymerase chain reaction) was positive with 12,000 copies per cc.

Initial echocardiogram here demonstrated moderate to severe tricuspid regurgitation, moderately dilated right atrium, mildly dilated right ventricle, moderately to severely depressed right ventricular systolic function, severely depressed left ventricular systolic function, and bilateral pleural effusions. In addition, there was a thrombus in the right ventricular apex.

Robert Listernick, MD, moderator: Comments?

Jeffrey Gossett, MD, pediatric cardiologist: The diagnosis of dilated cardiomyopathy has some grave implications; I wouldn’t make it at this point simply on the basis of the echocardiogram. While it is clearly in the differential diagnosis, it’s premature to definitively call it that. She simply has severe cardiac dysfunction, which has a reasonably varied differential. Only if there were a clear family history of dilated cardiomyopathy or a previous genetic diagnosis would I recommend making this diagnosis at initial presentation.

Dr. Listernick: Can one distinguish between acute myocarditis and cardiomyopathy on initial presentation in patients with signs of cardiac dysfunction?

Katheryn Gambetta, MD, pediatric cardiologist: Factors that would point to myocarditis include signs or symptoms of recent viral illness, including fever and the presence of either elevated inflammatory markers or an elevated serum troponin. Cardiac MRI can be useful in distinguishing between the two, looking for signs of inflamma-
tion or edema that would point to myocarditis or a scar, which would suggest longer-standing disease. She had most of these factors present, including an elevated parvovirus PCR. We thought she had acute parvoviral myocarditis. A recent study from Texas Children’s Hospital reported 19 cases of parvovirus myocarditis; 16 patients presented with fulminant myocarditis requiring inotropic support, and only 6 survived without requiring a transplant.

Ellen Chadwick, MD, pediatric infectious disease specialist: PCR is a relatively new technology and we do not yet know how to interpret the presence of low amounts of viral DNA. It might be that if we tested 1,000 children, we would find many with this degree of viral DNA who do not have any overt disease. Also, given the sensitivity of PCR for detecting DNA, this could easily represent contamination. We have seen many such cases.

Dr. Listernick: Assumed this is myocarditis, how do you treat it?

Dr. Gossett: Clearly we treat the cardiogenic shock regardless of whether it’s due to cardiomyopathy or myocarditis.

Dr. Listernick: Treatment?

Dr. Gossett: Also controversial. We tend to use intravenous immunoglobulin (IVIG) and sometimes consider corticosteroids, although this is not evidence-based. This child received IVIG.

Dr. Listernick: Any comments on the right ventricular thrombus?

Dr. Gambetta: It’s probably related to poor cardiac function. We give anticoagulant prophylaxis to children who have poor ejection fractions.

Dr. Listernick: Moving forward, she developed stable, second-degree AV block, and with treatment, her cardiac function improved. She had one episode of supraventricular tachycardia, and she remained heparinized to treat the right ventricular thrombus. Over the next several months, her cardiac function totally normalized. However, she continued to have intermittent abdominal pain on a daily basis, which often prevented her from eating. There was no history of vomiting or diarrhea. In addition, she continued to complain of right hip pain.

Four months after the initial hospitalization, she was seen for an outpatient visit and was found to have lost 1.6 kg over a 3-month period. Review of symptoms was remarkable for diffuse arthralgias and myalgia, including hip pain, which, if you remember, was her initial chief complaint. She seemed to have had an odd gait over the preceding several weeks. She no longer bent her knees or ankles when she walked. She was slow to get up out of the car or out of bed and was extremely cautious when she moved, as though she was nervous that movement would hurt her. There had been no change in her voice, difficulty swallowing, or red eyes.

On exam, she looked as if she were in pain. She had a faint erythematous hue to her upper eyelids, with slightly prominent capillary vessels. There was periungual erythema. There were no ulcerations of her toes or fingertips. Her skin did not feel “bound down.” There were no oral ulcers. Her palate and gums were mildly erythematous. Lungs were clear. Abdomen was soft without hepatosplenomegaly. She had limited range of motion of her neck in all directions. She had decreased range of motion of her shoulders and limited extension of the elbows with flexion contractures. There was severely limited flexion and extension of her wrists. Her fingers appeared tapered with loss of cutaneous markings over the distal interphalangeal joints. There was tenderness and limited flexion of all the joints of the hands, with flexion contractures of the middle interphalangeal joints. Muscle strength was decreased throughout. Neck flexion was 2+/5. She needed assistance to get up from the bed and had to hold onto the rails, although it’s not clear whether this was due to pain or weakness.

The most pertinent laboratory finding was her CBC: hemoglobin, 12.8 g/dL; white blood cell count, 10,000/mm$^3$ with 24% eosinophils, 39% neutrophils, 31% lymphocytes; platelet count, 460,000/mm$^3$; and sedimentation rate, 61 mm/hour.

Let’s start with the mnemonic for eosinophilia that I learned in medical school: NAACP- neoplasms, allergies, Addison’s disease, collagen vascular disease, and parasites. I can’t say that I’ve ever seen a case of eosinophilia associated with an infection.

Stanford T. Shulman, MD, pediatric infectious disease physician: Obviously you haven’t lived a full, complete life yet having lived, I believe, entirely in the Northeast and Midwest. Parasites that cause tissue invasion are most commonly associated with eosinophilia, more so than parasites that are limited to the gastrointestinal tract, such as giardiasis. For those of us who have practiced in the South, we’re used to seeing visceral larval migrans caused by *Toxocara canis*, the dog roundworm. Symptoms and signs may include fever, cough, and hepatomegaly, depending upon where the worm migrates. It can even cause monocular vision loss secondary to lar-
val invasion of the uvea or vitreous. Of course, travel to developing countries increases the risk of infection by a host of invasive parasites.

**Dr. Listernick:** What about eosinophilia and primary gastrointestinal diseases?

**Barry Wershil, MD, pediatric gastroenterologist:** This child could have a primary eosinophilic disease, ie, a disease in which the eosinophil is central to the pathogenesis. This includes disorders such as hypereosinophilic syndrome, which can affect practically any organ system including the gastrointestinal (GI) tract, or eosinophilic gastroenteritis, which predominantly affects the GI tract.

Eosinophilic gastroenteritis (EGE) is a disorder of unknown etiology in which eosinophil numbers increase in GI tissues, resulting in inflammation. Children with EGE may present with abdominal pain, hematochezia, diarrhea, or signs of a protein-losing enteropathy. There is often, but not always, an increase in the peripheral eosinophil count, reflecting increased eosinophil trafficking. Conversely, we rarely see peripheral eosinophilia in eosinophilic esophagitis, which is an allergic inflammatory condition limited to the esophagus. Infants with eosinophilic esophagitis present with irritability, vomiting, and feeding refusal, whereas older children most often have dysphagia or symptoms of esophageal obstruction secondary to food impactions.

**Dr. Listernick:** What about rheumatologic diseases?

**Megan Curran, MD, pediatric rheumatologist:** Many of the diseases we care for can be associated with eosinophilia. We definitely see it in systemic sclerosis, in which we would typically see swollen, sausage-shaped digits with “bound down” skin well beyond the metacarpophalangeal joints. She had contractures without effusions of the distal and proximal interphalangeal joints, and the skin was taut only on the fingertips.

**Dr. Listernick:** The following tests were normal: antinuclear antibody (ANA), autoantibodies to SCL-70, anti-centromere antibody, rheumatoid factor, anti-Smith and anti-ribonuclear protein antibodies, quantitative immunoglobulins, complement levels, CPK (creatine phosphokinase), anti-SCL/PM antibody, anti-Jo-1 antibody, and antiphospholipid antibodies. Can you walk us through these tests?

**Dr. Curran:** ANA is just a screening test and should only be ordered if a patient has clear signs (eg, arthritis, not arthralgias) of a rheumatologic disease. Anti-SCL-70 and anti-centromere antibodies are specific antibodies seen in systemic sclerosis; only a small percentage of pediatric patients who have systemic sclerosis are SCL-70-positive, although the specificity is very high. The anti-Smith antibody and the anti-double-stranded DNA are considered specific for systemic lupus erythematosus. Rheumatoid factor is a helpful prognostic sign when a patient has polyarticular juvenile idiopathic arthritis. Anti-ribonuclear protein antibodies are present in patients who have mixed connective tissue disease. Anti-SCL/PM antibody is seen in patients with overlap syndromes, such as those who have features of both systemic sclerosis and polymyositis.

**Dr. Listernick:** So these were not helpful. However, MRI of the lower extremity revealed edema and enhancement in the fascia of the musculature of the posterior compartment of the right thigh and pelvis without muscle involvement. Diagnosis?

**Dr. Curran:** Our clinical suspicion, confirmed by the MRI, was that she had eosinophilic fasciitis. Although eosinophilic fasciitis generally spares the
hands and feet in adults, we have seen this presentation in children.

Dr. Listernick: I’ve seen several children with eosinophilic fasciitis who have characteristic “peau d’orange” brawny thickening of the skin over the hands and wrists coupled with eosinophilia. The pathophysiology of the disease is unclear but may involve dysregulated fibroblast proliferation, leading to inflammation and fibrosis. But, although she clearly has eosinophilic fasciitis, I think that there’s much more going on. I don’t believe in coincidence. I believe that the combination of the recent “myocarditis” that responded to treatment with corticosteroids and the eosinophilic fasciitis strongly points to the presence of hypereosinophilic syndrome (HES). What do you think about this?

Rukhmi Bhat, MD, pediatric hematologist: HES is defined by 1) the presence of blood eosinophilia greater than 1,500/mm³ on at least two occasions (or of 6-month duration) or evidence of prominent tissue eosinophilia associated with 2) evidence of end organ dysfunction. In addition, the physician needs to exclude known causes of peripheral eosinophilia, such as parasitic disease or clonal bone marrow disorders generally quite responsive to treatment with corticosteroids.

Dr. Listernick: There are plans for her to have a bone marrow biopsy and to test her for the fusion protein; these have yet to be performed. Let’s come full circle and talk about the myocarditis.

Dr. Gossett: She could certainly have eosinophilic myocarditis; it would be indistinguishable clinically from other forms of immune-mediated myocarditis. Establishing the correct diagnosis is critical, since untreated eosinophilic myocarditis may lead to fibrosis and irreversible cardiomyopathy. MRI may be very useful in establishing the diagnosis of myocarditis during an active phase, although it wouldn’t define if it was an eosinophilic form. If she has another episode of cardiac dysfunction, I probably would opt to perform an endocardial biopsy. Apparently intracardiac thrombi, as seen in this child, may be seen in eosinophilic myocarditis.

Dr. Listernick: Treatment?

Dr. Curran: She received high-dose intravenous corticosteroids on this admission and had dramatic improvement in pain and range of motion.

Dr. Gambetta: Since children with eosinophilic myocarditis may develop microcirculatory abnormalities with abnormal vasoreactive coronary arteries, I believe that we should perform an MRI of her heart now, rather than wait for a second episode of symptomatic myocarditis. This is even more critical given the possibility of the ongoing development of fibrosis.

Dr. Listernick: Obviously we need a lot more information. Thank you, everyone.