A 10-year-old Girl being Evaluated for Cardiomegaly

Robert Listernick, MD

This 10-year-old girl was transferred from an outside hospital for evaluation of cardiomegaly. She had been well until several weeks before admission when she started complaining of increasing fatigue and dyspnea on exertion. Three days before admission, she developed a dry cough and left-sided chest pain, without any fever or viral symptoms. Review of systems was otherwise unremarkable. Past history and family history were unremarkable.

On exam, she was an alert, healthy-appearing, somewhat anxious girl. Weight was in the 50th percentile, and height was in the 15th percentile. Pulse was 104, respiratory rate 35, blood pressure 106/45, pulse oximetry 99% in room air. She was not dysmorphic. HEENT exam was unremarkable. Lungs had good aeration bilaterally with bibasilar crackles. S1 and S2 were normal without murmurs, rubs, or gallops. Abdomen was soft without masses or organomegaly. She was Tanner I. Pulses were 2+ bilaterally. Neurologic exam was unremarkable.

Chest X-ray revealed cardiomegaly with increased interstitial markings. Echocardiogram demonstrated severely depressed biventricular systolic function, a moderately dilated left ventricle, severely dilated left atrium, moderate to severe mitral regurgitation, and moderate tricuspid regurgitation. The origins of the coronary arteries were normal. EKG showed normal sinus rhythm, left atrium enlargement, T wave inversion in II, III, and AVF.

Dr. Listernick: How do you distinguish between the two?

Dr. Gossett: With the information at hand, it can be very difficult. A family history of early cardiac disease could be a clue to familial cardiomyopathy. History of a recent febrile illness might suggest myocarditis. Elevated serum troponin or inflammatory markers, such as C-reactive protein, are more typical of an acute process, such as myocarditis. Also, you always want to make sure that there isn’t an anomalous origin of a coronary artery leading to depressed cardiac function.

Ben Katz, MD, pediatric infectious disease physician: Any number of viruses can cause myocarditis, particularly the enteroviruses. Although tuberculous myocarditis is rare, we would place a PPD if there was any chance of exposure. We also recommend respiratory and stool viral cultures in the appropriate clinical settings, but the yield is low.

Dr. Listernick: What’s the role of endocardial biopsy in establishing the diagnosis?

Dr. Gossett: We often perform a biopsy to help guide therapy. We look for a lymphocytic infiltrate, suggestive of an active viral process. We will also do PCR to try
to identify viral nucleic acid. However, even in those cases, where we strongly suspect active myocarditis because of the presence of fever or elevated inflammatory markers, we’re only able to identify an organism in fewer than 50% of the cases.

Pauline Chou, MD, pediatric pathologist: The other problem is that the lymphocytic infiltrate in cases of myocarditis may be patchy and missed on biopsy. It’s often impossible on a small biopsy specimen to determine histologically whether we missed the inflammatory cell component or whether the biopsy represents a “burned out” myocarditis in which the active inflammatory process occurred months earlier. Some of the familial dilated cardiomyopathies are often unremarkable histologically.

Wayne Franklin, MD, pediatric cardiologist: Another potential etiology for dilated cardiomyopathy could be primary arrhythmia, such as atrial tachycardia leading to cardiomyopathy. Treating the arrhythmia might lead to return of normal ventricular function. The findings on EKG may be subtle, such as abnormal P waves.

Dr. Listernick: What are the diagnosable genetic causes of cardiomyopathy?

Barbara Burton, MD, geneticist: First, it’s important to make sure that the patient has normal stature, normal intelligence, and is not dysmorphic because there are malformation syndromes, such as Noonan syndrome, that have been associated with cardiomyopathy. Next, there are a number of metabolic disorders associated with cardiomyopathy, including late-onset forms of the long chain fatty acid oxidation disorders and propionic acidemia to name a few. We would review the medical history for evidence of previous metabolic crises involving hypoglycemia or acidosis. We would always perform an acylcarnitine profile, plasma carnitine, and urine organic acids. Because mitochondrial disorders can present in this way, a serum lactic acid would be important.

Dr. Listernick: What about the primary familial cardiomyopathy syndromes?

Dr. Burton: About 50% of dilated cardiomyopathy in children is presumably genetic in origin. The most common mode of inheritance is autosomal dominant, so obtaining a family history is very important. More than 20 genes have been identified, many highly variable in the age of onset of cardiac dysfunction. We routinely recommend performing echocardiograms in all first-degree relatives, some of whom may have an asymptomatic cardiomyopathy. Finally, there’s a “dilated cardiomyopathy chip,” which tests for the known genetic mutations.

Dr. Listernick: I noticed that this patient had a cardiac magnetic resonance imaging (MRI) study.

Elfriede Pahl, MD, pediatric cardiologist: This modality is new and not well-studied yet. However, we’ve found it helpful in identifying an inflammatory component, as one might see in myocarditis.

Dr. Listernick: Once you’ve gathered all the initial information, how do you approach treatment?

Dr. Pahl: If we believe that there’s an active inflammatory process, we may try giving the patient intravenous immunoglobulin. Some programs will try corticosteroids; occasionally both are used. There are even some programs who have advocated the use of extracorporeal membrane oxygenation in very sick children with myocarditis. We try to avoid listing a child for transplant who has active myocarditis as we don’t want to provide that degree of immunosuppression to someone with an acute infectious process. Biopsy is often helpful in those situations where we want to do our best to exclude active myocarditis so that we can proceed rapidly to transplantation.

Dr. Listernick: What’s the long-term outcome of myocarditis?

Dr. Pahl: One-third of patients completely recover, greater than another one-third develop dilated cardiomyopathy leading to transplantation or death, and the rest have stable cardiomyopathy. When she came in, even though she had significant congestive heart failure, it wasn’t initially clear which direction she would go. Her biopsy did not show active myocarditis, and she initially responded to the cardiac inotropic agents. However, it soon became clear that we were
not going to be able to wean her off these agents easily, so she was listed for cardiac transplantation.

Dr. Listernick: Are there any absolute contraindications to transplantation?

Dr. Pahl: There are few, such as the presence of malignancy, active fungal infection, an overwhelming uncontrolled systemic disease, and significant systemic neurologic disorders.

Dr. Listernick: All the initial data suggested that she had a primary cardiomyopathy. One month after admission, she received a heart transplant. For several days before receiving the transplant, she had complained of abdominal pain. On the third post-transplant day, she became febrile and had an episode of hypotension requiring intravenous fluid resuscitation and escalation of her inotropic support. She started having increased amounts of diarrhea while remaining febrile and intermittently hypotensive, despite fluid resuscitation. Broad spectrum antibiotics for possible sepsis were started. Her abdomen became distended and tense, making assessment of the intraabdominal organs difficult. On the fifth postoperative day, she continued to have diarrhea despite negative stool cultures, but she was found to be positive for Clostridium difficile toxin in the stool. At that time, white blood count was 73,000/mm³ with 71% neutrophils, 10% bands, 11% metamyelocytes, and 5% myelocytes.

What is the significance of finding C. difficile toxin in the stool?

Dr. Katz: A small percentage of the general population carries C. difficile in the stool asymptomatically. Classical risk factors for the development of colitis due to this organism are exposure to antibiotics and prolonged hospital stays.

Stanford T. Shulman, MD, pediatric infectious disease physician: Recently, an extremely virulent strain of C. difficile has been identified, called NAP1, which appears to produce a much more potent toxin than the traditional strains. The NAP1 C. difficile strain has become an increasingly significant pathogen in pediatric and adult intensive care units and specifically in transplant populations.

Dr. Listernick: What is the treatment for routine C. difficile colitis?

Dr. Katz: Normally, we would recommend metronidazole. However, if a child is extremely ill or if there’s a concern about a NAP1-associated organism, there is evidence that oral vancomycin is more effective. This child had multiple risk factors for the presence of severe disease, including a lengthy stay in the intensive care unit, her physical examination, and the high white blood cell count. Furthermore, she was not getting better while receiving metronidazole.

Tara Benton, MD, pediatric critical care physician: Over the space of several hours, her abdomen became increasingly distended, tense, and tender. We were very concerned about the development of an abdominal compartment syndrome. Although it is well-recognized in the extremities, the possibility of an abdominal compartment syndrome has only recently become recognized. Intra-abdominal hypertension can cause

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Key Learning Points

1. Enteroviruses are the most common cause of acute myocarditis.
2. Identifiable causes of dilated cardiomyopathy include malformation syndromes, muscular dystrophies, metabolic disorders, including late-onset forms of the long chain fatty acid oxidation disorders, mitochondrial diseases, and more than 20 primary dilated cardiomyopathy genetic disorders with single gene mutations.
3. Potential treatment for myocarditis could include intravenous immunoglobulin or corticosteroids, although neither has been proven to be of benefit.
4. Initial treatment for C. difficile colitis should be intravenous or oral metronidazole. Severe cases should be treated with oral vancomycin.
5. The highly toxigenic NAP1 C. difficile strain has become an increasingly significant pathogen in pediatric and adult intensive care units and specifically in transplant populations.
decreased tissue perfusion and respiratory insufficiency from decreased diaphragmatic excursion, decreased venous return leading to poor cardiac output, and tissue hypoperfusion leading to kidney and other end organ damage. You can even measure bladder pressure as a proxy for intraabdominal hypertension. Her bladder pressures were significantly elevated.

Erin Rowell, MD, pediatric surgeon: When I first saw her, she appeared gravely ill. There was no need for further imaging, and we immediately took her to the operating room. When we opened her abdomen, serous fluid came out under extreme pressure. The small intestines appeared entirely normal. The colon appeared thick and boggy but didn’t appear ischemic. A surgeon could be easily fooled that the colon was viable. However, it needs to be understood that C. difficile colitis is a mucosal process and that when a patient achieves this degree of illness with a toxic megacolon, the treatment is total colectomy, which is what we performed. The adult literature is quite clear that a surgeon cannot predict which parts of the colon are viable in toxic megacolon by examination.

Dr. Listernick: What exactly did you do?

Dr. Rowell: We performed a total colectomy and created a terminal ileal stoma. We also left the distal rectum intact and gave her metronidazole enemas to try to combat any remaining inflammation in the rectum. Assuming she does well, we would hope to re-anastomose her ileum to the remaining rectum in 3 to 6 months. Hopefully, the small amount of rectum that we left will allow her to have formed stools.

Elaine Cham, MD, pediatric pathologist: If only to reinforce what Dr. Rowell suspected, the colon was markedly dilated and had diffuse severe mucosal inflammation.

Dr. Pahl: It’s worth mentioning that a recent report from Innsbruck of 40 solid organ transplant patients who had C. difficile colitis identified five patients with toxic megacolon of whom three required colectomy.

Dr. Listernick: Thank you, everybody.