A 2-Year-Old Male with Persistent Fever and Pneumonia

Robert Listernick, MD

A 2-year-old male was initially seen for fever and rhinorrhea 7 days prior to admission to our hospital. Two days later, he was seen by his primary care physician and was rapid-strep positive, for which he was started on amoxicillin. Due to persistent fever, he returned to an outside emergency department where chest X-ray demonstrated left lower lobe pneumonia. He was admitted and started on intravenous ceftriaxone. The following day his blood culture became positive for what was ultimately identified as methicillin-resistant Staphylococcus aureus (MRSA) and the antibiotic was changed to clindamycin. Despite the treatment with clindamycin, he remained persistently febrile for a total of 6 days in the hospital, although repeat blood cultures were negative.

His medical history is remarkable for having had a buttock abscess 1 year ago. Family history is only remarkable for the father’s diagnosis of ankylosing spondylitis.

On admission to the outside hospital, his temperature was 39°C, pulse was 130 beats per minute, respiratory rate was 36 breaths per minute, and blood pressure was 100/60 mm Hg. His weight and height were in the 70th percentile. Lungs were clear. Cardiac exam was normal. Abdomen was soft without organomegaly. Neurologic exam was normal.

Initial laboratory evaluation had the following results: Chem-14 normal save for albumin 2.6 mg/dL; hemoglobin 10 g/dL with a borderline low mean corpuscular volume (73); white blood cell count 20,000/mm³ with 77% neutrophils and 13% immature neutrophils; sedimentation rate 61 mm/hour; and C-reactive protein 16 mg/dL. Initial chest X-ray had bilateral lower lobe infiltrates.

Robert Listernick MD, moderator: Comments?

Stanford T. Shulman, MD, pediatric infectious disease physician: Although children under the age of 3 years can get streptococcal pharyngitis, the standard recommendation in low-risk countries is not to test children under the age of 3 years for streptococcal pharyngitis because they’re not at risk for the development of rheumatic fever. In addition, if a child at any age is diagnosed with streptococcal pharyngitis and is treated with an appropriate antibiotic but the fever persists, then physicians should be concerned that the strep was a “red herring” and the child is a streptococcal carrier with some other illness causing fever.

Dr. Listernick: What would you be thinking when the blood culture starts growing gram-positive cocci in clusters?

Dr. Shulman: Gram-positive pneumonias in healthy children often seem to present following a viral illness. In addition, there’s a past history of what could have been a MRSA infection. His X-ray is unimpressive (the infiltrates are small and there is no pleural effusion or pneumatocele), but I’d still be concerned about a staph pneumonia and I think the treatment with clindamycin was appropriate.

Dr. Listernick: So what would you be thinking now that this child has persistent fever with negative repeated blood cultures?

Dr. Shulman: We certainly can see prolonged fever with staphylococcal infections despite adequate therapy, assuming it’s a clindamycin-susceptible MRSA (which we now know that it is). After 5 days of treatment, I would begin to worry that he had seeded another site and has a metastatic infection, most commonly involving a bone or joint. We see staphylococcal endocarditis, but I would expect persistently positive blood cultures.

Ellen Chadwick, MD, pediatric infectious disease physician: I’m not sure when the most recent chest X-ray was obtained, but I would want to reevaluate for the possibility of the development of a large pleural effusion requiring drainage.

continued on page 8
Mary Wyers, MD, pediatric radiologist: Over the course of his illness, he had four chest X-rays. A small pleural effusion did develop. However, the most dramatic finding on the most recent radiograph was the development of a right paraspinial mass near the diaphragm that definitely wasn’t present on the previous X-rays. It clearly required further radiologic evaluation.

Dr. Listernick: Differential diagnosis?

Dr. Wyers: It was very puzzling as it was a real finding and was definitely new.

Dr. Listernick: How did you proceed?

Dr. Wyers: A computed tomography (CT) scan was performed that revealed a large low-density mass adjacent to the abdominal aorta. The contrast study revealed contrast extravasating from the aorta into a large pseudoaneurysm. The “walls” of the pseudoaneurysm appear to be comprised of thrombus.

Dr. Listernick: Amazing, if for no other reason he’s alive! So, he’s still at our sister institution even though our radiologists are reading the study. What needs to be done next?

Osama Eltayeb, MD, pediatric cardiothoracic surgeon: The first question is how we get him here safely. His vital signs were normal but this was obviously a scary situation. The decision was made to transport him immediately by helicopter. When he arrived, he looked like any other healthy child, sitting up and playing. The attending physician at the intensive care unit looked sicker than the abdominal aorta.

Dr. Listernick: Preoperative concerns?

Dr. Wyers: The first question is how we get him here safely. His vital signs were normal but this was obviously a scary situation. The decision was made to transport him immediately by helicopter. When he arrived, he looked like any other healthy child, sitting up and playing. The attending physician at the intensive care unit looked sicker than the abdominal aorta.

Dr. Listernick: How did you get him here safely?

Dr. Wyers: A computed tomography (CT) scan was performed that revealed a large low-density mass adjacent to the abdominal aorta. The contrast study revealed contrast extravasating from the aorta into a large pseudoaneurysm. The “walls” of the pseudoaneurysm appear to be comprised of thrombus.

Dr. Listernick: Amazing, if for no other reason he’s alive! So, he’s still at our sister institution even though our radiologists are reading the study. What needs to be done next?

Osama Eltayeb, MD, pediatric cardiothoracic surgeon: The first question is how we get him here safely. His vital signs were normal but this was obviously a scary situation. The decision was made to transport him immediately by helicopter. When he arrived, he looked like any other healthy child, sitting up and playing. The attending physician at the intensive care unit looked sicker than the child did.

Dr. Listernick: Why didn’t he die, given that he has a ruptured aorta?

Dr. Eltayeb: The bleeding was contained within the retroperitoneal structures, which allowed for thrombus formation and “plugging up” a big leak. The hemorrhage appeared to be rather acute.

Dr. Shulman: However, his low serum albumin suggests to me that the inflammatory process was somewhat chronic.

Dr. Listernick: Did he go straight to the operating room?

Mjaye Mazwi, MD, cardiac intensive care unit physician: Preoperative management involved confirmation of the concerns of the referring hospital and assessment of blood pressure. If the child were hypertensive we would want to control his blood pressure with a rapid-acting drug such as esmolol or nitropresside. Echocardiography confirmed there were no vegetations and that cardiac function was normal.

Michael Monge, MD, pediatric cardiothoracic surgeon: Just prior to surgery, he had another CT scan with three-dimensional reconstruction. This was quite helpful in planning the operative procedure. We can see the aneurysm arising from the right side of the aorta between the celiac and superior mesenteric arteries. Based on these findings, we thought that using cardiopulmonary bypass would be the safest approach and we decided that a midline incision would give us the most options. The other problem with its location is that the pancreas lies directly over the pseudoaneurysm. We mobilized the spleen and performed a Mattax maneuver in which the left colon, spleen, and kidney are mobilized and the viscera are rotated medially to expose the entire length of the abdominal aorta.

Dr. Listernick: How long can a child have his aorta clamped before risking distal ischemia?

Dr. Monge: It depends upon the exact placement of the clamp and which vessels are compromised. We were also afraid about complete rupture because this was a pseudoaneurysm. First, we obtained control distal to the lesion at the iliac artery, followed by opening the chest and the pericardium posteriorly so as to obtain proximal control of the aorta. We found a 1-cm hole in the aorta that had a pseudo-aneurysmal sac filled with purulent material. This entire segment of aorta was excised.

Dr. Listernick: How did you reconstruct the aorta?

Dr. Monge: We were concerned about putting a Dacron graft into a potentially infected area; in addition, it wouldn’t grow with the child. Instead, we chose to use an aortic homograft, which is a piece of aorta from a cadaver.

Dr. Listernick: What were the postoperative concerns?

Nguyenvu Nguyen, MD, cardiac intensive care unit physician: Blood pressure management is important in this case, both in the pre- and postoperative periods. Before surgical intervention, hypertension can lead to worsening of dissection of the aneurysm; after surgery, normotension is key in protecting extensive sutures lines. The patient was extubated and maintained on two oral antihypertensives. In the early postoperative stage, we were vigilant in monitoring for signs of significant inflammatory responses and end organ damage.

Dr. Eltayeb: Another concern was that the homograft patch could become infected with breakdown of a suture line. He had several ultrasound examinations and another CT scan to monitor for this prior to discharge.

Dr. Listernick: Can we see the pathology?

Jonathan Bush, MD, pediatric pathologist: We found evidence of both acute and chronic inflammation in the wall of the aorta as well as evidence of both old and new thrombus formation. Gram stain revealed occasional gram-positive cocci. All of this was very consistent with the clinical
diagnosis of infective aortitis with a mycotic aneurysm. The culture grew clindamycin-susceptible MRSA.

Dr. Listernick: Is it possible looking at the histology that he has an underlying connective tissue disease that has led to disruption of the aortic wall and subsequent infection?

Dr. Bush: There’s definitely disruption of the elastin fibers. That could be secondary to infection, but a primary collagen disorder should certainly be part of the differential diagnosis.

Dr. Listernick: So let’s talk pathophysiology.

Dr. Shulman: Classically, we see mycotic aneurysms in individuals who have infective endocarditis. Infected microemboli implant in the vasa vasorum (the blood vessels that feed the arterial walls) and establish an infection in the wall of an artery, leading to a weak spot that undergoes aneurysmal dilation.

Dr. Bush: We weren’t able to identify any of the vasa vasorum vessels.

Dr. Eltayeb: We didn’t provide the pathologists with much tissue.

Dr. Listernick: My first thought when I heard about this case was whether he had a disorder of collagen such as Marfan syndrome. Comments?

Barbara Burton, MD, pediatric geneticist: This would be an extraordinarily unusual presentation of a connective tissue disorder. In general, abdominal aortic aneurysms are much less likely to be associated with connective tissue disorders than are thoracic aortic aneurysms. We certainly see extension of aortic disease in patients with Marfan syndrome into the descending aorta, but we don’t typically see it beginning there. It’s conceivable that this could occur in isolation in children who have the vascular type of Ehlers-Danlos syndrome (EDS).

Dr. Listernick: Can you elaborate a bit?

Dr. Burton: Children who have EDS type IV, vascular type, have translucent skin and easy bruising. They are prone to develop vascular dissections or gastrointestinal perforation. Pregnant women may develop uterine rupture. It’s caused by a mutation in the COL3A1 gene. However, given how unusual this child’s presentation was, one certainly would carefully examine him for other manifestations of a connective tissue disorder.

Dr. Listernick: Which are you likely to see in a 2-year-old male?

Dr. Burton: The child might have a Marfanoid body habitus. In children with EDS, one might see easy bruising, skin hyperextensibility, or unusual scarring. Certainly you would want to take a very careful family history, looking for these findings in other family members.

Dr. Listernick: What about genetic testing?

Dr. Burton: We sent a panel of 20 genes that cause both Marfan syndrome and a number of other Marfan-like disorders of collagen, including such diseases as Loeys-Dietz syndrome types 1-4 and Ehlers-Danlos syndromes type I-IV. He was found to have a “variant of unknown significance” in the SMAD3 gene, which causes Loeys-Dietz syndrome type III. Individuals who have a SMAD3 variant may also develop severe early-onset arthritis as well as vascular aneurysms.

Dr. Listernick: How do you decide whether this is a pathogenic mutation or simply a benign genetic variation?

Dr. Burton: First, you can try to determine if the mutation changes the amino acid sequence. If it doesn’t, then
it’s probably a benign polymorphism. If it changes the amino acid sequence, you can look to see if this predicts a change in the protein’s function. Next, you look at the incidence of the variant in the healthy general population; in this case it’s rarely seen. In the case of this child, we’ll test the parents. If a parent is clinically normal and he or she has the mutation, then it’s almost certainly a benign variant.

**Dr. Listernick:** It will be interesting if the father has the mutation, as he carries a diagnosis of ankylosing spondylitis. Should this child have any other vascular imaging given the potential diagnosis?

**Dr. Burton:** Given the potential diagnosis of Loeys-Dietz syndrome type III, it would be very reasonable to perform magnetic resonance angiography of the brain. He’s already had imaging of his aorta and abdominal vessels.

**Dr. Monge:** I would state a word of caution. He had a “pseudoaneurysm.” In connective tissue disorders, we generally see diffuse uniform dilatation of the aortic wall, a finding he did not have. I would be surprised if he had one of these disorders based on the surgical findings.

**Dr. Listernick:** What should his length of treatment be?

**Dr. Shulman:** An endovascular infection with *Staphylococcus* is generally treated for 6 weeks, perhaps even longer in this child to make sure that the infection doesn’t persist on the prosthetic material.

**Dr. Listernick:** Thanks everyone.