A 13-Year-Old Girl with Nocturnal Chest Pain

Robert Listernick, MD

This 13-year-old girl was initially seen at an outside hospital 18 months ago for an episode of chest pain. She had been well until 5 nights before the visit, when she awoke from sleep with substernal pain that was described as an 8 on a scale of 1 to 10. This pain lasted for 1 hour and then recurred over the next 3 nights, prompting a visit to the emergency department. Although she had pain with deep inspiration, there was no history of coughing, palpitations, or syncope.

In the emergency department (ED) she was described as well-appearing but had an oral temperature of 103°F. HEENT (head, ears, eyes, nose, and throat) examination was unremarkable. Her lungs were clear and a cardiac examination was normal. Her abdomen was soft and nontender without masses or organomegaly. CBC (complete blood count) was unremarkable save for white blood cell count of 10,000/mm³ with 88% neutrophils. Serum chemistries, CPK (creatine phosphokinase), amylase, lipase, and troponin were normal. A chest X-ray and ECG (electrocardiogram) were unremarkable.

She received famotidine, ketorolac, and morphine for her pain. After several hours she was discharged with a diagnosis of gastroesophageal reflux. She was told to take lansoprazole and to make a follow-up appointment with a cardiologist.

Dr. Kindel: It is, but markedly less so when the exact same pain occurs at rest. With that said, performing an ECG is reasonable. Adult ED physicians will always perform troponin levels, although I doubt that they are necessary in most cases.

Dr. Listernick: They seemed to have covered all the bases with the amount of medication she was given.

Dr. Trainor: Since it occurred 3 nights in a row while the patient was recumbent, I suppose that gastroesophageal reflux would be a reasonable thought. We weren’t there so we don’t know if the pain was severe enough to warrant both toradol and morphine.

Dr. Listernick: Six months later, she had another episode of chest pain and fever. At that time, echocardiography demonstrated a small pericardial effusion. Laboratory testing revealed an unremarkable CBC but she had a sedimentation rate 43 mm/hour and C-reactive protein of 11 mg/dL. ANA (antinuclear antibody) was positive at 1:60. A follow-up echocardiogram 1 month later showed no pericardial effusion.

Her past medical history is remarkable for mild scoliosis and spondylolysis. She developed facial acne at the age of 12 years and now has acne on her chest and back. She is receiving topical retinoic acid. In addition, she had several “cysts” removed from behind her ears.

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They had been called sebaceous cysts. The first occurred inside her right tragus 2 years earlier and had been excised. She had subsequently had three other cysts excised from behind each ear.

Family history is remarkable for the father who has a diagnosis of adult-onset Still’s disease. At the age of 37 years, he had a 6-month episode of severe polyarticular arthritis, conjunctivitis, and fever that was treated with prednisone. He is of Irish descent. The patient’s mother is of German descent. There are two healthy younger siblings.

On examination, the patient was a very healthy-appearing young woman. Weight and height were in the 30th percentile. Blood pressure was 121/67 mm Hg. She had some mild acne on her back. There was a 7-mm subcutaneous nontender nodule behind the right ear that was not mobile and was fixed to the underlying skin. The remainder of the exam was entirely unremarkable.

**Dr. Listernick:** What is adult-onset Still’s disease?

**Michael Miller, MD, pediatric rheumatologist:** Initially the term “Still’s disease” was used to describe a group of patients whom we now label system-onset juvenile idiopathic arthritis (JIA). The term is still applied to adults who have the classic triad of high spiking fevers, evanescent salmon-colored rash, and arthritis or arthralgias. Often these individuals have signs of serositis (pleuritis, pericarditis), lymphadenopathy, and hepatosplenomegaly. The pathogenesis is unknown. Given that it is a clinical, rather than laboratory-based diagnosis, there are probably a number of etiologies that lead to the same clinical syndrome.

**Stanford T. Shulman, MD, pediatric infectious disease physician:** It seems very odd for Still’s disease that he had a 6-month long illness and has remained clinically well for many years.

**Dr. Miller:** Agreed.

**Dr. Listernick:** For the sake of discussion, let’s assume that this was her first episode of pericarditis. What kind of pain do patients with pericarditis generally describe?

**Kathryn Gambetta, MD, pediatric cardiologist:** Usually the pain is substernal and sharp. Usually it’s exacerbated when the patient is lying in the supine position and is relieved by sitting upright. A pericardial friction rub may be present that may increase by sitting upright.

**Dr. Listernick:** What are the predictive values of the presence or absence of a pericardial rub or ECG changes for predicting the presence of pericarditis?

**Dr. Kindel:** I don’t have data, but I would suspect that the negative predictive value of a pericardial rub is very low (ie, pericarditis could easily exist in the absence of an audible rub) while the sensitivity of ECG should be quite high. Initially, the ECG can show ST segment elevation with PR widening, and that can resolve over time.

**Dr. Listernick:** What are the causes of pericarditis?

**Dr. Gambetta:** In pediatrics, the most likely etiologies are infectious and rheumatologic causes such as SLE (systemic lupus erythematosus) or systemic-onset JIA. Rarely, we see children who have severe hypothyroidism or uremia present in this fashion.

**Dr. Shulman:** The lion’s share of acute pericarditis is caused by enteroviruses. Following the availability of the *Haemophilus influenzae* type b vaccine, cases of purulent pericarditis have decreased substantially. Recurrent pericarditis is almost certainly not going to be from an infectious cause and strongly points to rheumatologic disease. However, we should not forget about the possibility of rheumatic fever presenting in this fashion. Although more typically presenting with isolated valvular disease, concomitant pericarditis or myocarditis may also exist.

**Dr. Miller:** We are very slow to make
the diagnosis of systemic-onset JIA because a whole host of other diseases may mimic it, including a number of infections. Having said that, we can’t diagnose JIA without arthritis lasting at least 6 weeks. The kids with systemic JIA typically take a number of months to develop full-blown persistent arthritis.

**Dr. Listernick:** What about SLE?

**Dr. Miller:** That’s certainly a possibility in a teenage girl with recurrent pericarditis. However, her ANA titer is negligible and she doesn’t have any evidence of end-organ damage (neurologic, skin or kidney disease) or other laboratory abnormalities (hemolytic anemia, thrombocytopenia, etc).

**Dr. Listernick:** Given that her only diagnosis at this time was idiopathic pericarditis, what treatment did she receive?

**Dr. Gambetta:** She didn’t respond to the initial nonsteroidal anti-inflammatory medicines, but diclofenac did relieve her pain. If the patient is refractory to these medicines either colchicine or prednisone can be tried.

**Dr. Trainor:** I would point out that pericarditis can be a side effect of a number of medications, including the penicillins, phenytoin, and minoxidil.

**Dr. Listernick:** Moving forward, she was well until September 2011 when she developed another episode of chest pain in association with a very elevated C-reactive protein level. Although the initial echocardiogram was normal, a subsequent echocardiogram 2 days later demonstrated a small pericardial effusion. She was treated with ketorolac, which relieved the pain. The following tests were normal: ANA, antinuclear cytoplasmic antibody (ANCA), serum chemistries, C3, C4, total hemolytic complement, anti-double-stranded DNA, T4, TSH (thyroid stimulating hormone), and celiac antibody panel. Now that I think of it, we never discussed her acne and sebaceous cysts.

**Anthony Mancini, MD, pediatric dermatologist:** Acne is obviously very common and frequently found in the conchal bowl of the ear but is not generally seen in the posterior auricular creases. However, we absolutely see hidradenitis suppurativa in the posterior auricular crease. These are generally painful erythematos nodules that may drain and leave scars. Patients tend to have concomitant axillary and inguinal crease involvement.

**Dr. Listernick:** So now we have a young woman with idiopathic recurrent pericarditis.

**Dr. Miller:** Anecdotally, I’ve seen a number of these kids with recurrent pericarditis and I have a distinct impression that they tend to develop tachyphylaxis when short courses of intravenous corticosteroids are used. They seem to develop a chronic chest pain syndrome, independent of acute pericarditis.

**Dr. Listernick:** I was asked to see her. In reviewing the literature, a certain percentage of individuals who have recurrent pericarditis without any other manifestations of inflammatory disease have been found to have mutations in the gene for familial Mediterranean fever (MEFV). In addition, there have been anecdotal reports of other individuals with recurrent pericarditis who have had mutations in the gene for tumor necrosis receptor periodic syndrome (TRAPS).

I decided to send a “familial periodic fever syndrome panel,” which looks for mutations in one of seven genes that cause autoinflammatory disorders: 1) familial Mediterranean fever; 2) TRAPS; 3) neonatal onset multisystem inflammatory disorder (NOMID); 4) hyper-IgD syndrome (HIDS); 5) cyclic neutropenia, Majeed syndrome; 6) pyogenic sterile arthritis; and 7) pyoderma gangrenosum and acne (PAPA).

I was particularly interested in PAPA because of her skin disease, although I could find no cases of recurrent pericarditis in PAPA. She was found to have a mutation in the \textit{NLPR3} gene, which causes NOMID.

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**Dr. Shulman:** Probably the most common autoinflammatory disorder, although the etiology has yet to be determined, is PFAPA (periodic fevers, adenopathy, pharyngitis, and aphthous stomatitis). These children’s symptoms generally start in the second year...
of life as 3- to 5-day episodes of fever and any combination of the signs in the name of the disease that regularly occur in 3- to 6-week cycles. Eventually, this process “burns out” without progressing to anything more serious.

**Dr. Miller:** Mutations in *NLPR3* can cause several overlapping clinical syndromes. Babies with NOMID often present in the delivery room with an urticarial rash and progress to develop arthritis, chronic meningitis, sensorineural hearing loss, and uveitis. Aside from Muckle-Wells syndrome, the third phenotype is familial cold autoinflammatory syndrome, in which individuals have recurrent urticaria, conjunctivitis, and fever when exposed to a cold environment.

**Dr. Listerick:** There’s clearly a great deal of overlap of the phenotypes. For instance, I recently cared for a girl who had recurrent fever and abdominal pain who had a mutation in the *PAPA* gene.

**Dr. Mancini:** I’ve examined her; her skin lesions appear to be mild comedonal and inflammatory acne, as well as mild hidradenitis suppurativa. Nothing suggests PAPA or NOMID from what I’ve seen.

**Dr. Listerick:** I’ve spoken to the experts at the NIH (National Institutes of Health) who are skeptical that this particular mutation is pathogenic. However, remember the father’s history of a prolonged bout of Still’s disease? I tested him and he carries the same mutation as his daughter! I’m no expert, but in my mind this is too much of a coincidence not to be related. This is an autosomal dominant condition. However, the NIH will be doing functional studies to see if there are any abnormalities on the cellular level related to this girl’s mutation. What about treatment?

**Dr. Miller:** That depends on which condition you’re treating. Colchicine is the treatment of choice for FMF but apparently is ineffective in the cryopyrinopathies (NOMID, etc.) or HIDS. Etanercept, an anti-tumor necrosis factor agent, can be effective in TRAPS. Anakinra, an interleukin-1 beta-receptor antagonist, works well in NOMID but requires daily injections. This highlights why it’s critical to make a molecular diagnosis in this group of patients.

**Dr. Listerick:** Presently, she’s on diclofenac and doing well. Time will tell. Thanks, everyone.