A 14-Year-Old Girl with Fatigue, Weakness, and Pallor
Robert Listernick, MD

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his 14-year-old previously healthy girl presents with a 6-week history of increasing fatigue, weakness, and pallor. She was well until 6 weeks before admission when she went on a 2-week Mediterranean cruise with her family. During the cruise, she started having nasal congestion and rhinorrhea. Upon returning home, she was prescribed a 10-day course of Augmentin for possible sinusitis by one of her parents who is a nurse practitioner, which was said to have helped the symptoms. She then went to sleep-away camp, during which time she began to feel fatigued and developed persistent rhinorrhea. In addition, she had been experiencing temperatures ranging from 100 to 101.5°F. For the last week, she has complained of thigh and knee pain while walking and “purplish-red bumps” on her feet, ankles, knees, and wrists. On review of systems, she complained of intermittent epistaxis whenever she “blows her nose hard.” She has had occasional aphthous ulcers and intermittent abdominal pain during this time.

Her travel history includes a mission trip to Kentucky 2 weeks before admission, the Mediterranean cruise, and sleep-away camp in Michigan.

There was no history of TB or animal exposure. Past medical and family histories were unremarkable.

On exam, she was pale but otherwise healthy-appearing. Her pulse was 108, respiratory rate 20, blood pressure 116/72, temperature 36.8°C. Her weight and height were in the 25th percentile. On HEENT exam, she had nasal congestion bilaterally with dried, dark secretions in both nares. There was no active epistaxis. She had a shallow ulcer on her left lateral tongue. Neck was supple without significant adenopathy. Lungs were clear. Cardiac exam was normal. Abdomen was soft and nontender without masses or organomegaly. She was Tanner IV. She had full range of motion of all her extremities without pain. There were purpuric 3 mm papules over both wrists, the dorsum of her hands, both ankles, and the left knee. There were petechiae on multiple toes with a painful nodule on her left big toe.

Robert Listernick, MD, moderator: Do you treat your own children?

Julie Kim Stamos, MD, pediatric infectious disease physician: I let my son stay home from school yesterday because he wasn’t feeling well, if that counts. Seriously, on vacation I looked in his ears when I thought he might have an ear infection. Beyond that, it clearly isn’t appropriate or wise.

Dr. Listernick: OK. What’s your gestalt of our patient?

Dr. Stamos: Given the subacute course, aphthous ulcers, arthralgias and what sounds like a “vasculitic” rash, I’d put some form of vasculitis at the top of the list.

Dr. Listernick: There are too many juicy potential red herrings that deserve comment. What about...
the Mediterranean cruise, Appalachia, and Kentucky?

Stanford T. Shulman, MD, pediatric infectious disease physician: Her illness seems to be too protracted for any common viral infection. The absence of splenomegaly mitigates against chronic bacterial diseases (eg, typhoid fever, brucellosis) that she might have picked up in certain Mediterranean ports depending upon what she drank or ate or chronic parasitic diseases (eg, ehrlichiosis), which is highly prevalent in Tennessee and Arkansas. I’m with Julie and vote for vasculitis, as much as I would like her to have an infectious disease for me to treat.

Dr. Listernick: Here is some of her laboratory evaluation: hemoglobin 8.7 g/dL, white blood cell count 29,000/mm³ with 91% neutrophils, 4% lymphocytes; platelet count 345,000/mm³. Sodium 122 mEq/L, potassium 5.6 mEq/L, chloride 89 mEq/L, bicarbonate 14 mEq/L, BUN 131 mg/dL, creatinine 11 mg/dL, albumin 2.5 g/dL. Urinalysis revealed a specific gravity of 1.010, 2+ protein, and 10-15 red blood cells per high powered field. Comments?

Richard Cohn, MD, pediatric kidney diseases specialist: The first thing to try to determine is whether the kidney failure is acute or chronic. Nothing in the history suggests chronic disease. There was no history of linear growth arrest. It would be helpful to know whether she ever had a previous urinalysis or blood pressure measurement. She is anemic but that could either be from long-standing kidney failure or an acute process causing hemolysis or blood loss. Parathyroid hormone levels don’t rise acutely; a PTH value above 300 pg/mL suggests chronicity. Decreased urine output is generally not a symptom of chronic kidney failure, whereas children who have acute kidney failure are often oliguric or anuric. I agree that vasculitis seems quite likely. I would perform ultrasonography of the kidneys immediately to look at kidney size and to exclude obstructive uropathy.

Tamar Ben-Ami, MD, pediatric radiologist: There’s a great deal of ascites present. Her kidneys were greater than the 95th percentile in size with diffuse increased echogenicity. This is a non-specific finding but suggestive of a variety of pathologic processes including some of the vasculitides. There was no obstruction noted.

Marisa Klein-Gitelman, MD, pediatric rheumatologist: I know that everyone is thinking about lupus as the most likely culprit, given her palpable purpuric rash and the kidney failure.

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Kavita Hodgkins, MD, pediatric kidney diseases specialist: The history is even more interesting than that. During the summer, her pediatrician had treated her numerous times for sinusitis. She had received multiple courses of antibiotics for her chronic cough, and her mother had actually pointed out the deformity of her daughter’s nasal bridge the day before she was admitted here.

Dr. Klein-Gitelman: This physical finding is quite specific for either of two diseases in pediatrics — Wegener’s granulomatosis (WG) or relapsing polychondritis. Relapsing polychondritis is a severe inflammatory disease that affects the cartilage, primarily of the ears, nose, and tracheobronchial tree. Although cutaneous vasculitis has been reported occasionally, kidney disease would be extremely rare. WG is clearly at the top of the list with this clinical presentation.

Dr. Shulman: Let’s not forget syphilis and leprosy as causes of nasal cartilage destruction.

Dr. Klein-Gitelman: As we immediately suspected WG, there are a number of laboratory tests we would want, but the most specific diagnostic test for WG is measurement of anti-neutrophil cytoplasmic antibodies (ANCA).

Dr. Listernick: Additional laboratory testing revealed erythrocyte sedimentation rate 82, normal C3, low C4, negative ANA and anti-DNA antibodies, normal quantitative immunoglobulins. ANCA was abnormal with a c-ANCA pattern, negative
myeloperoxidase and a highly positive PROT-3. Immediate interpretation from an expert is necessary.

**Dr. Klein-Gitelman:** First, low C4 is not unusual in healthy individuals. It’s quite common for an individual to have one abnormal C4 gene, leading to a low serum C4 level without any clinical consequences. As long as the C3 and total hemolytic complement levels are normal, low C4 is of no significance.

**Kim Watts, MD, pediatric pulmonologist:** Even if a newly diagnosed child with WG is asymptomatic, as many as 30% have evidence of pulmonary disease if investigated by computerized tomography (CT). We also look for evidence of abnormal diffusion capacity on pulmonary function testing.

**Dr. Ben-Ami:** The initial chest X-ray showed streaky nonspecific bibasilar opacities. However, 2 days later, she developed a diffuse alveolar pattern that resembled either pulmonary edema or pulmonary hemorrhage. CT scan revealed a small pleural-based cavitary lesion that appeared to have developed during the first week of hospitalization.

**Dr. Cohn:** We need to know how aggressive to be about treatment; if her kidney disease is acute and potentially reversible, aggressive immunosuppressive therapy is indicated. Once she was stabilized and underwent hemodialysis for one week, we performed a kidney biopsy that showed an active, crescentic glomerulonephritis. There were no chronic changes in the interstitium, which provided us with some hope that it was, at least in part, reversible.

**Dr. Listernick:** At what point would you deem the kidney failure irreversible?

**Dr. Cohn:** Three months following institution of therapy.

**Dr. Klein-Gitelman:** The ENT physicians examined her nasal passages at the time of the kidney biopsy. They saw many ulcerations and opened up the blocked airway. In addition, there were multiple tracheal erosions and signs of pulmonary hemorrhage. Her disease was extremely aggressive. She was treated with high-dose corticosteroids and oral cyclophosphamide.

**Dr. Cohn:** The dose of cyclophosphamide had to be adjusted due to her kidney disease. We also placed her on Bactrim, as there is anecdotal evidence that it has a therapeutic effect. Bactrim also provides prophylaxis against the development of Pneumocystis pneumonia.

**Megan Curran, MD, pediatric rheumatologist:** There is anecdotal evidence that Bactrim can be used to eradicate staphylococcal carriage. Staphylococcal antigens are thought to drive some of the inflammatory response in WG.

**Wayne Franklin, MD, pediatric cardiologist:** There’s a 1.6-cm mass attached to the left ventricular wall with mildly decreased systolic function. The mass is just underneath the aortic valve causing intermittent aortic outlet obstruc-
tion. Her electrocardiogram was normal. This is important information because patients with WG can develop inflammation of the conduction system leading to arrhythmias or heart block. Although my initial thought was that this represented an unusual form of infective endocarditis, review of the literature suggests that patients with WG rarely develop inflammatory, noninfectious cardiac masses.

Dr. Listernick: Could an interventional cardiologist remove this mass?

Dr. Franklin: Definitely, if it were on the right side of the heart. A left-sided mass would be very risky. Surgery is actually the safest course.

Dr. Curran: The mass was removed by the cardiovascular surgeons without incident. It was comprised of granulation tissue with infiltration by neutrophils and eosinophils, without specific features. Once we were sure that this wasn’t an infected mass, we started Remicade, which anecdotally has been very helpful in patients who have had this complication of WG. The combination of remicade and cyclophosphamide is quite controversial because it greatly increases her immunosuppression with the ensuing increased risks of both opportunistic infections and malignancy. Both of these points were carefully discussed with the family. In addition, because remicade can contribute to the development of heart failure, we have to monitor her cardiac function very closely.

Dr. Listernick: Hopefully all will go well. Thank you, everybody.

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Key Learning Points

1. Saddle nose deformity is highly characteristic of Wegener’s granulomatosis (WG).
2. Anti-neutrophil cytoplasmic antibodies (ANCA) should be measured in any patient suspected of having WG. A positive c-ANCA, or classical ANCA, is almost always associated with WG, microangiopathic angiitis, or Churg-Strauss disease.
3. Common sites of involvement in WG include the lungs (necrotizing pneumonia), kidneys (rapidly progressive glomerulonephritis), skin (vasculitic rash) and sinuses. Constitutional symptoms, including fever, weight loss, arthralgias and fatigue, are also common.