Robert Listernick, MD

A 14-Year-Old Girl with Weight Loss and 22q11.2 Deletion

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A 14-year-old girl was admitted for evaluation of a 30-pound weight loss over the past 5 weeks. Approximately 5 weeks earlier, she developed a cough and started feeling tired. Her mother thought that she just had a cold and was not eating because she didn’t feel well, without any other symptoms. One week prior to admission, she started complaining that she couldn’t go to school because she was having abdominal pain. She was seen by her physician and was found to have a documented 27-pound weight loss over the previous 5 weeks.

Her medical history is remarkable in that she was diagnosed as having both atrial and ventricular septal defects (VSD) at birth. At approximately age 5 years, due to articulation problems, she was seen by a geneticist and found to have a submucous cleft palate. Subsequently, she was found to have a 22q11.2 deletion. She had one episode of pneumonia at age 4 months. She has a history of learning disabilities. She also had a tooth extracted 10 weeks ago.

On examination, she was overweight but appeared well. Her height was in the 95th percentile and her weight was in the 80th percentile. Body mass index was in the 95th percentile. Her pulse was 100 beats per minute, respiratory rate was 18 breaths per minute, blood pressure was 108/68 mm Hg, and temperature was 37°C. Head, ears, eyes, nose, and throat (HEENT) exam was unremarkable. Neck was supple without significant lymphadenopathy. Lungs were clear. S1 was normal and S2 was physiologically split. There was a III/VI holosystolic murmur without rubs, clicks or gallops heard best at the right middle sternal border. There were strong pulses bilaterally. Abdomen was soft without masses or organomegaly. She had Tanner 4 breasts and genitalia. She had full range of motion of all her extremities. There were no rashes. Neurologic exam was normal.

Laboratory evaluation was as follows: hemoglobin 8.5 g/dL, mean corpuscular volume (MCV) 70, and red blood cell distribution width (RDW) 14.8; white blood cell count 11,000/mm³ with 71% neutrophils, 23% lymphocytes, and 4% monocytes; platelet count 128,000/mm³. The smear had 3+ hypochromia, 3+ microcytosis, and 2+ teardrop cells. Reticulocyte count was 1.5%. Serum chemistries were normal. Erythrocyte sedimentation rate (ESR) was 43 mm/hour and C-reactive protein (CRP) was 3.3 mg/dL.

Robert Listernick, MD, moderator: This seems like a very late diagnosis of the 22q11.2 deletion syndrome, formerly known as DiGeorge syndrome.

Barbara K. Burton, MD, pediatric geneticist: The 22q11.2 deletion syndrome is an example of a contiguous gene deletion syndrome in which a variable portion of the long arm of chromosome 22 is deleted. The phenotype is extremely broad. Many of the children with this syndrome have very subtle facial features that aren’t obvious at birth. Obviously, infants with conotruncal defects (interrupted aortic arch, truncus arteriosus, Tetralogy of Fallot), hypocalcemia, or severe T-cell deficiency and unusual infections will be identified early. However, this child had what is called “velocardiofacial syndrome,” which is a particular articulation disorder, submucous cleft palate, and heart disease.

Dr. Listernick: What is the articulation disorder?

Dr. Burton: They have very nasal speech that doesn’t respond to speech therapy due to velopharyngeal insufficiency with or without a cleft. Learning disabilities are very common and occasionally we see a child who is severely developmentally disabled. As the patients age, there’s a higher incidence of psychiatric disorders such as obsessive-compulsive disorder and schizophrenia.

Dr. Listernick: Is this deletion inherited?

Dr. Burton: About 90% of the cases are de novo, the other 10% familial. Although the phenotypic variability is, in part, related to the extent of the deletion, there is phenotypic variability within families.

Dr. Listernick: What testing is appropriate if you suspect 22q11.2 deletion syndrome?

Dr. Burton: If you have a strong suspicion, I would send fluorescent in situ hybridization (FISH) testing specifically looking for the deletion. If the phenotype were less specific, I would order whole genome microarray.

Dr. Listernick: Did she need an immunologic evaluation at diagnosis?

Dr. Burton: Because she hadn’t had...
a history of recurrent infections by age 5 years, I wouldn’t perform any testing.

**Dr. Listernick:** So, what’s your gestalt of her present condition?

**Robert R. Tanz, MD, academic general pediatrician:** I’m sure many of us are wondering whether she might have an eating disorder. But I wouldn’t even begin to consider that diagnosis until excluding organic causes. She has a mild microcytic anemia and thrombocytopenia with an inappropriately low reticulocyte count and mildly elevated inflammatory markers. As a start, I’d wonder about inflammatory bowel disease.

**Steven J. Kindel, MD, pediatric cardiologist:** I should point out that her cardiac examination is consistent with a simple small VSD. The loudness of the murmur is going to be directly related to the pressure gradient across the hole. Small VSDs make the loudest murmurs.

**Donald Zimmerman, MD, pediatric endocrinologist:** I should point out that occasionally children with 22q11.2 deletions may develop hyperthyroidism, which can clearly lead to unexplained weight loss.

**Dr. Listernick:** When she was initially seen in the emergency department, they consulted hematology because of the complete blood count (CBC) results.

**Robert I. Liem, MD, pediatric hematologist:** Her CBC is complicated. She has a microcytic anemia so you might think that she was iron deficient, particularly because she is a menstruating adolescent; however, the RDW is normal (it should be elevated in iron deficiency anemia).

**Dr. Listernick:** What about the anemia of chronic disease?

**Dr. Liem:** Usually that causes a normocytic anemia. However, over time, the anemia of chronic disease might become microcytic.

**Dr. Listernick:** Can you distinguish between iron deficiency anemia and the anemia of chronic disease?

**Dr. Liem:** Serum ferritin is a good reflection of total iron stores. Unfortunately, it is also an acute phase reactant that will be elevated in chronic inflammation. In these situations, probably the best test is soluble transferrin receptor, which is elevated in iron deficiency but normal in chronic inflammation.

**Dr. Listernick:** What about her mild thrombocytopenia?

**Dr. Liem:** Normally, we see thrombocytosis in iron deficiency, occasionally with platelet counts greater than 1,000,000/mm3. In addition, when we examined the smear, we noted that she had large platelets. This generally suggests peripheral destruction such as in immune thrombocytopenic purpura. We tracked down a CBC from 9 years previously that had a platelet count of 110,000/mm3. Bernard Soulier syndrome is a congenital bleeding disorder characterized by large platelets and mild thrombocytopenia; it has been associated with 22q11.2 deletion syndrome. A gene in the 22q11 deletion region controls the coding region for one of the subunits of the glycoprotein on the surface of the platelets that is involved with binding von Willebrand factor, which is necessary for primary hemostasis.

**Dr. Listernick:** That’s all very interesting, but I believe the primary service consulted you about the possibility of cancer?

**Dr. Liem:** Probably the one pediatric malignancy that can present with constitutional symptoms and the anemia of chronic inflammation is Hodgkin’s lymphoma, and less commonly non-Hodgkin’s lymphoma. I don’t believe there’s an increased risk of malignancy in 22q11.2 deletion syndrome.

**Dr. Listernick:** What about the other abnormalities on the peripheral smear?

**Dr. Liem:** Occasionally, teardrop cells indicate marrow infiltration but their presence is often artifactual.

**Dr. Listernick:** The other initial consultant was gastroenterology. Considering the weight loss, elevated inflammatory markers, and microcytic anemia, there was a major concern for inflammatory bowel disease. However, testing for fecal occult blood and calprotectin was negative. Calprotectin is a protein found in large amounts in the cytoplasm of neutrophils and is a sensitive and
specific marker of intestinal inflammation.

**Dr. Listernick:** We’re not making any headway. What next?

**Dr. Tanz:** I know that she has had minimal fever, but given her heart disease, I’d consider the possibility of endocarditis. If she hasn’t yet had blood cultures obtained, that should be the next step.

**Dr. Listernick:** To make a long story short, one blood culture had been obtained that started growing gram-positive cocci in chains ultimately identified as *Streptococcus mitis.*

**Dr. Kindel:** Only 80% to 90% of patients who have infective endocarditis (IE) will have a history of fever. Her heart disease, unrepaired restrictive ventricular septal defect, is a high-risk lesion for the development of IE due to the very high velocity left-to-right-jet that leads to endothelial damage, which allows for bacteria to take hold. She absolutely needs a trans-thoracic echocardiogram (TTE) looking for vegetations.

**Ellen G. Chadwick, MD, pediatric infectious disease physician:** Once she has a positive blood culture, she clearly needs a TTE. However, once subacute bacterial endocarditis (SBE) is suspected, the first step should be to obtain multiple blood cultures. I’d also point out that SBE with low-pathogenicity organisms might cause proteinuria and microscopic hematuria may be seen in as many as 50% of cases.

**Dr. Kindel:** Anemia and elevated inflammatory markers are common. Rheumatoid factor, which is an indirect marker for circulating immune complexes, may be found. Proteinuria and microscopic hematuria may be seen in as many as 50% of cases.

**Dr. Listernick:** We’ve alluded to it, but what’s the role of echocardiography in diagnosing SBE?

**Dr. Kindel:** In small, thin children, TTE is almost as sensitive as transesophageal echocardiography (TEE). The aortic valve and aortic outflow tract are not seen quite as well. In obese teenagers or adults, TEE is a much more sensitive test. However, I would always start out with TTE; if it’s positive, it’s positive. Her TEE was negative.

**Dr. Listernick:** Are there established criteria for the diagnosis of IE?

**Benjamin Z. Katz, MD, pediatric infectious disease physician:** The modified Duke Criteria assist us in categorizing cases into definite or possible infective endocarditis. They easily can be found on the Internet. In short, definite endocarditis can be diagnosed when you find histologic evidence of vegetation or if you have histologic or microbiologic evidence of a pathogen from an intracardiac or embolized vegetation. In addition, the combination of two major criteria (1. identification of a typical organism in two or more separate blood cultures or persistently positive blood cultures; and 2. echocardiographic evidence of endocardial disease, including evidence of new valvular regurgitation); five minor criteria (predisposing heart condition, fever, embolic vascular phenomena, immunologic phenomena, and a positive blood culture); or one major and three minor criteria are necessary for the diagnosis of definite endocarditis.

**Dr. Listernick:** What is *Streptococcus mitis?* She had multiple positive blood cultures with this organism.

**Dr. Katz:** It’s one of the group of viridans streptococci found in the oral cavity, with viridans streptococci being one the most common cause of IE.

**Dr. Listernick:** Treatment?

**Dr. Katz:** Classic therapy would be a beta-lactam antibiotic such as penicillin or ampicillin in combination with an aminoglycoside for at least 2 to 4 weeks, depending on the degree of penicillin susceptibility of the specific organism.

**Dr. Listernick:** Thank you, everyone.