A 9-Year-Old Girl with Recurrent Infections

Robert Listernick, MD

A 9-year-old girl was seen for evaluation of recurrent infections. Since 18 months of age, she has had numerous episodes of otitis media; bilateral myringotomy tubes had been placed twice. In addition, she had four to five pneumonias that were confirmed by chest X-ray at least three times, as well as five episodes of clinically diagnosed sinusitis. There were no unusual infections, such as thrush or cutaneous abscesses.

Her medical history was remarkable for diagnosis of asthma. She has had intermittent chronic cough since infancy. No physician has ever heard wheezing and she has never been admitted for asthma, but she has been receiving inhaled albuterol and a corticosteroid intermittently. She had a history of eczema during the first 4 years of life. Her mother suspected that the child was allergic to milk because her otitis media resolved on a dairy-free diet, although the coughing persisted. She had chronic diarrhea from 2 months of age until the age of 5 years; dairy was stopped at that time and the diarrhea disappeared. Her birth and family history were unremarkable. She had received all her immunizations.

On physical examination, she was a healthy-appearing girl. Weight and height were in the 35th percentile. Blood pressure was 110/60 mm Hg. Head, ears, eyes, nose, and throat (HEENT) exam was unremarkable. There were bilateral scars on her tympanic membranes. Her lungs were clear without wheezing or crackles. S1 and S2 were normal without murmurs. Her abdomen was soft and nontender without masses or organomegaly. There was no digital clubbing.

Robert Listernick, MD, moderator: How many infections are “too many”?

Ellen G. Chadwick, MD, pediatric infectious disease physician: I assume you’re asking when should one worry about an undiagnosed immunodeficiency or another problem leading to recurrent infections. Certainly any child who has an infection with an “unusual” organism should be evaluated for immunodeficiency. For example, lymphadenitis caused by Serratia marcescens should raise the possibility of chronic granulomatous disease (CGD). It’s unlikely that a child who has recurrent upper respiratory infections or nonspecific febrile illnesses has an underlying problem. On the other hand, two or more radiographically documented pneumonias should raise suspicion.

Susanna A. McColley, MD, pediatric pulmonologist: One should be careful about the designation “recurrent pneumonia.” More often than not, children labeled as having recurrent pneumonias have small areas of atelectasis when the X-rays are reviewed and their actual diagnosis is asthma. Physicians should always insist on seeing the X-rays when evaluating such children.

Melanie M. Makhija, MD, pediatric allergist: This is more controversial than you might imagine. The Jeffrey Modell Foundation, which promotes understanding and research of immunodeficiency syndromes, has 10 “warning signs” of immunodeficiency. Among them are 1) four or more new ear infections within 1 year; 2) two or more serious sinus infections within 1 year; and 3) two or more pneumonias within 1 year. Although it is important to identify children with immunodeficiency as early as possible, the specificity of these criteria is low.

Robert R. Tanz, MD, general academic pediatrician: I know it sounds overly simplistic, but I’m worried when I’m worried. Sometimes strict guidelines are not helpful. The majority of children with recurrent ear infections probably do not have an underlying immunodeficiency, but the stakes are raised if they have concurrent sinusitis or radiographically documented pneumonias. Complicating the situation is that sinusitis is dramatically overdiagnosed in children despite American Academy of Pediatrics (AAP) guidelines.

Dr. McCollery: Agreed. The AAP clinical practice guideline on sinusitis defines acute sinusitis as occurring in children with upper respiratory tract symptoms (nasal discharge, daytime cough that may be worse at night) that are either persistent (lasting longer than 10 to 14 days) or severe (temperature of at least 39°C and purulent nasal discharge for at least 3 days in a child who appears ill).

Dr. Listernick: Once you’ve decided a child requires evaluation for immunodeficiency, how do you proceed?

Dr. Makhija: If the history or physical exam points to a specific immunodeficiency syndrome, such as CGD, I will do targeted...
testing. If not, I generally will perform the first “level” of testing to evaluate all parts of the immune system and subsequently dig deeper depending upon the initial tests. If children are older than 6 months, I look at humoral immunity with quantitative immunoglobulins (Ig) and total white blood cell count. It should be remembered that IgA levels may not be maximal until at least 4 years of age. Flow cytometry will give us a good look at the numbers and types of B cells, T cells, and natural killer cells that are present. Total hemolytic complement is a good functional assessment of the complement cascade. If a child has had a full set of primary immunizations, we can measure antibody titers to any immunizations the child has had, including tetanus, diphtheria, and pneumococcus, to assess the child’s ability to make functional antibody. Occasionally, we will immunize a child to the 23-valent pneumococcal vaccine and measure pre- and post-immunization titers.

Dr. McColley: As far as targeted evaluations go, if a child has recurrent sinopulmonary infections, including otitis media, we will perform testing for primary ciliary dyskinesia. This diagnosis is often difficult to establish because the diagnostic gold standard is ciliary biopsy, generally from the inferior turbinate of the nose; however, the epithelial cells of the nasal mucosa of these patients often undergo squamous metaplasia, which prevents acquisition of an adequate specimen. In addition, 10% to 15% of children with cystic fibrosis have normal pancreatic function and may present with significant sinopulmonary disease.

Dr. Listernick: Because of chronic abnormalities seen on review of all her chest X-rays, a computed tomography (CT) scan of the lungs was performed.

Mark E. Haupt, MD, pediatric pulmonologist: Normal bronchi will progressively narrow as we move to the distal parts of the lung parenchyma. On her CT scan, we see that many of the distal airways are unusually wide. This is bronchiectasis. The pattern of bronchiectasis might be helpful in suggesting a diagnosis. If it were restricted to a single segment, it might be a post-obstructive phenomenon due to a bronchial foreign body. If exclusively in the posterior segments in infants, it would suggest chronic aspiration. Her bronchiectasis was fairly diffuse, reinforcing the possibility of a primary immunodeficiency syndrome, cystic fibrosis, or primary ciliary dyskinesia.

Dr. Listernick: Continuing with her evaluation, spirometry revealed moderate airway obstruction that improved following bronchodilation. The following tests were normal: complete blood count with differential, IgG, IgA, and total hemolytic complement. Tetanus toxoid antibody titers were on the very low end of normal. IgM and *Haemophilus influenza* antibody titers were low. Flow cytometry revealed a slight decrease in the number of T cells and T-cell subsets, but normal B-cell numbers. She did not have an adequate antibody response when vaccinated to the 23-valent pneumococcal vaccine.

Dr. Makhija: Putting this all together, we can make a tentative, but definitely not conclusive, diagnosis of common variable immunodeficiency (CVID). CVID is not a single disease; it is a diverse group of disorders. As such, it is made by clinical diagnosis and genetic diagnosis is not possible. The clinical criteria include: 1) low serum IgG levels with variably low IgA and IgM levels; 2) presence of B cells; 3) poor response to immunizations; and 4) the absence of any other specific immunodeficiency syndrome such as X-linked agammaglobulinemia. Her diagnosis is tentative because her IgG level is normal.

Dr. Listernick: How does CVID generally present?

Dr. Makhija: As in this girl, with recurrent sinopulmonary infections. In addition, patients with CVID have a 30% to 40% incidence of associated autoimmune disease such as autoimmune hemolytic anemia or thrombocytopenia. Less commonly, they may develop chronic diarrhea, malabsorption symptoms, or frank inflammatory bowel disease. Finally, there is a definite increased risk of malignancy, most commonly lymphoma.

Anjali Sharathkumar, MD, pediatric hematologist: If children with autoimmune hemolytic anemia or thrombocytopenia have an atypical course or present at an older age (usually older than 10 years), we always assess antibody levels looking for CVID.
Dr. Listernick: Treatment?

Dr. Makhiya: Treatment is intravenous immunoglobulin (IVIG) every 3 to 4 weeks. If it’s tolerated, we often switch to weekly subcutaneous administration.

Dr. Listernick: Although her IgG level was not low, she definitely did not respond to repeat immunizations, so a diagnosis of CVID was made. The family did not want her to receive IVIG and they were lost to follow-up. Three years later, at age 12 years, the patient was referred for evaluation of pneumonia and splenomegaly. One month prior to the visit, she started complaining of left shoulder and back pain. Eventually she became febrile, and a chest X-ray revealed pneumonia, for which she received antibiotics. Due to persistent fever and repeat physical examination that noted splenomegaly, she was referred here. Her interim history was remarkable for having had sinus surgery.

Physical exam was remarkable for bilateral lung crackles and a spleen palpable 9 cm below the left costal margin almost to the pelvic brim. Hemoglobin was 8.8 g/dL with normal mean corpuscular volume, white blood cell count was 4,600/mm³ with 55% lymphocytes, 36% neutrophils, and 5% eosinophils; platelet count was 133,000/mm³. A Chem-14 test, including serum transaminases, was normal. Direct and indirect Coombs’ test were negative.

Dr. Chadwick: Although she was admitted to the infectious disease service, we thought that a primary infection was quite unlikely given the massive splenomegaly. We did perform serology for Epstein-Barr virus and cytomegalovirus, which was negative. We wondered about the possibility of hemophagocytic lymphohistiocytosis (HLH) or a malignancy, particularly in the face of a pre-existing diagnosis of CVID. Another possibility we considered is hypersplenism, given the pancytopenia. However, we had no evidence of chronic liver disease that would lead to portal hypertension and hypersplenism.

Dr. Sharathkumar: Although HLH is a reasonable thought, she had no hepato-megaly or biochemical hepatitis. In addition, her coagulation profile, including fibrinogen, was normal. Finally, one fact that didn’t come across on the physical examination was that, in addition to being huge, her spleen was rock-hard. In the oncology world, the two conditions that present with huge spleens are chronic myelogenous leukemia (CML) and lymphoma. The median white blood cell count in CML is 100,000/mm³, with a differential that has all forms of neutrophils from the least to the most mature. Therefore, lymphoma was high on our list.

Dr. Listernick: It obviously doesn’t fit the clinical scenario given the CVID, but Gaucher’s disease is another condition that could present with massive splenomegaly and thrombocytopenia. Moving forward, her spleen progressively enlarged while her medical evaluation was in progress and her hemoglobin dropped, necessitating further transfusion. Ultimately, she underwent splenectomy. As I understand it, the preliminary pathologic diagnosis showed marked nodular lymphoid proliferation with Castleman’s disease-like changes.

Daniel Choi, MD, pediatric oncologist: Castleman’s disease is a lymphoproliferative disorder that may be localized (unicentric or multicentric). Unicentric disease generally presents as an asymptomatic cluster of lymph nodes that may be incidentally found on imaging. Surgical resection is curative, although there appears to be an associated risk of lymphoma. Multicentric Castleman’s disease generally presents with fever and constitutional symptoms such as weight loss, night sweats, and fatigue. There’s a strong association with HIV infection. These patients almost always have anemia, hypoalbuminemia, hypergammaglobulinemia, and elevated inflammatory markers. Levels of circulating cytokines, in particular interleukin-6, may be markedly elevated. Our patient’s interleukin-6 level was quite high.

Dr. Listernick: However, my understanding is that cytogenetics revealed a different diagnosis.

Dr. Choi: Yes. Translocation involving the BCL6 gene on chromosome 3 and the IGH gene on chromosome 14 coupled with the clinical and pathologic presentation led to the diagnosis of marginal zone lymphoma. It’s a rare form of non-Hodgkin’s lymphoma. In children, the more common types of non-Hodgkin’s lymphoma are Burkett’s lymphoma and diffuse large B-cell lymphoma.

Dr. Listernick: Treatment?

Dr. Choi: In adults, this tumor is exquisitely sensitive to the monoclonal antibody rituximab. Although splenectomy is often curative, adult oncologists generally don’t resort to this operation unless the patient is very symptomatic. We are very reluctant to treat her with rituximab given her underlying diagnosis of CVID. Her blood counts have normalized following splenectomy, so we will just follow her without further treatment.

Dr. Listernick: Thank you, everyone.