New Diagnosis of Common Variable Immunodeficiency in a 12-Year-Old With Pneumonia: An Illustrative Case

Case: The patient was a 12-year-old African American male who presented to our hospital from a community hospital for further care of a worsening left-sided pneumonia. His mother reported a 3-week history of intermittent cough and fever at home before his community hospital admission. She had been treating these symptoms with over-the-counter cough remedies at home but became concerned because his symptoms were not improving. The patient also had diagnoses of idiopathic bronchiectasis and selective immunoglobulin (Ig) A deficiency (reported according to history). He had required hospital admission for bacterial pneumonia several times during his life, and he was well below the 1% mark for height, weight, and BMI for his age. At the community hospital, he was treated aggressively with weight-appropriate doses of ceftriaxone and vancomycin. Despite treatment, the patient’s symptoms had not improved. Repeat imaging at the community hospital demonstrated worsening status of his pneumonia. On admission to our hospital, he was not in marked respiratory distress requiring invasive respiratory support. However, it was noted that he was extremely thin, had decreased to no air movement at the left lung base, had severe digital clubbing, and was coughing frequently with dyspnea on minimal exertion. His chest radiograph (Fig 1) and chest computed tomography scan (Fig 2) from the community hospital were interpreted by our pediatric radiologists to show a left-sided necrotizing pneumonia with concern for empyema.

Question: What is the differential diagnosis for necrotizing pneumonia?

Discussion: Necrotizing pneumonia is an increasingly recognized severe complication of community-acquired pneumonia.1,2 Presenting symptoms can include fever, productive cough, and other signs of respiratory distress. Other constitutional symptoms are seen, including vomiting, abdominal pain, and chest pain. The diagnostic finding of necrotizing pneumonia is pulmonary consolidation seen on chest radiograph and axial chest computed tomography scan, with multiple various-sized cavities indicating lung parenchymal necrosis.1,3 Bacterial pathogens have been identified via culture results in 41% to 55% of cases, and the most commonly identified bacteria are Streptococcus pneumoniae or Staphylococcus aureus (methicillin sensitive and methicillin resistant) with others identified in smaller percentages, including Pseudomonas aeruginosa, Klebsiella species, Micrococcus species, Mycobacterium tuberculosis, and other streptococcal species, such as β-hemolytic streptococci. The initial management is high-dose antibiotic therapy, first empirically then tailored based on culture results. Although it is not the standard of care for uncomplicated community-acquired pneumonia, surgical drainage, either by placement of a chest thoracostomy tube with the addition of
of fibrinolytic agents or video-assisted thoracoscopic surgery, has been documented as appropriate and effective treatment in the case of necrotizing pneumonia with either large effusions or moderate-sized effusions that are unresponsive to antibiotic treatment or consistent with empyema. Because our patient had not responded clinically to 8 days of appropriate empiric antibiotic therapy, video-assisted thoracoscopic surgery was indicated.

Case Continuation: The patient underwent a left-sided video-assisted thoracoscopic surgery with decortication soon after admission, during which a chest tube was placed. The surgery team noted a large empyema and minimal viable lung tissue inferiorly on the left side. The extent of his infection was surprising given his relatively normal C-reactive protein level and erythrocyte sedimentation rate (0.235 mg/dL and 2 mm/h, respectively) and only moderately elevated white blood cell count (24.4 thousand/mm$^3$). Due to the extensive nature of the patient’s infection and initial laboratory values, we became concerned about the possibility of another underlying process. We consulted infectious disease, oncology, and immunology specialists for opinions. After extensive evaluation, the patient was noted to have IgA (49 mg/dL) and IgG (443 mg/dL) levels >2 SDs below the mean for age but normal IgM (154 mg/dL) and IgE (5.96 kU/L) levels. He had adequate responses to diphtheria and tetanus vaccines but an inadequate response to pneumococcal vaccine and indeterminate response to rubella. Test results for other immunodeficiencies and infections (including HIV polymerase chain reaction) were negative. Based on his clinical picture and laboratory findings, an immunodeficiency disorder, such as common variable immunodeficiency (CVID), X-linked agammaglobulinemia, and hyper-IgE syndromes, was considered. Because of the patient’s low IgG level and poor response to immunizations, he was given intravenous immunoglobulin (IVIg) of 500 mg/kg twice while in the hospital. His IgG level increased from 307 to 970 mg/dL. This treatment appeared to improve his rate of recovery, and he was able to be discharged from the hospital on oral antibiotics. He was re-immunized by his primary care physician ~2 months later, and repeat vaccine titers and immunoglobulin levels were obtained 4 weeks later. Although repeat immunoglobulin levels and vaccination titers may not be accurate for up to 6 months after IVIg infusion, the patient continued to show low IgA (49 mg/dL) and IgG (443 mg/dL) and normal IgM (154 mg/dL) levels as well as *Haemophilus influenza* type b antibodies that were adequate but poliovirus and pneumococcal antibodies that were inadequate or not detectible. Considering the late onset of his apparent immunodeficiency and the variable response to immunization, CVID was believed to be the most probable diagnosis.

**Question:** What is common variable immunodeficiency or CVID?

**Discussion:** Primary immunodeficiencies are a heterogeneous group of disorders that present anywhere from early infancy to adulthood. These disorders can vary in their presentation...
from largely asymptomatic to potentially fatal bacterial and fungal infections in early life. Due to the broad spectrum of presentations of the diseases and their symptomatic similarities to certain malignancies, systemic disorders, and infectious diseases, diagnosis can be challenging. Despite this difficulty, prompt diagnosis is important for instituting appropriate treatments and thereby decreasing morbidity and mortality.5,6

CVID is a primary immunodeficiency characterized by a decrease in serum IgG levels, a decrease in either IgA or IgM, and a poor response to vaccines in a child at least 2 years of age, after excluding other causes of hypogammaglobulinemia.7 However, 1 study found that although serum IgG levels are low in CVID, more than one-half of the patients have a level that is not profoundly diminished for age.6 This finding could account for the wide variety of presentations found in patients with CVID. CVID has long been thought of as an immunodeficiency of adulthood; however, 21% to 45% of patients are diagnosed when aged <21 years.6,9,10 Although our patient’s family stated that he had a previous diagnosis of selective IgA deficiency, his low concentration of IgG made this diagnosis unlikely. The differential diagnosis between CVID and hyper-IgM type 1 can be difficult. We felt that the patient met criteria for CVID based on his decreased levels of IgA and IgG on multiple occasions and his lack of appropriate response to repeat vaccinations.

CVID is generally an acquired phenotype, but there have been some familial studies showing several susceptible genes, which could confer an additive risk to family members, primarily first-degree relatives.7 X-linked hyper-IgM syndrome is likely if a patient has a positive family history suggesting an X-linked immunodeficiency disorder, normal numbers of T cells, normal responses to mitogen stimulation, normal or increased numbers of B cells but little or no antigen-specific IgG, and unusual infections or complications, including: severe bacterial or Pneumocystis jirovecii infections in the first year of life, neutropenia, cryptosporidium-related diarrhea, sclerosing cholangitis, parvovirus-induced aplastic anemia, and absent CD40 ligand expression. Because our patient did not have problems in the first years of life, had normal antibody levels to some immunizations, normal concentrations of IgG until 9 years of age, variable IgG concentrations after 9 years that were typically only slightly below normal, and clinical malabsorption without a history of chronic diarrhea, hyper-IgM syndrome was considered less likely than CVID.

A decreased concentration of IgG and poor responses to vaccines is consistent with CVID. However, many CVID patients, such as ours, will have appropriate responses to certain protein vaccines such as diphtheria and tetanus but decreased responsiveness to pneumococcal vaccines.12 One study looked at the responsiveness to polysaccharide vaccines, and 42% of the patients showed no protective titers after vaccination with a polysaccharide vaccine.13 Interestingly, our patient responded to 1 polysaccharide-conjugated vaccine (H influenza type b) but not to isolated polysaccharides (pneumococcal). There also

FIGURE 2 Chest radiograph from the community hospital showing evidence of severe necrotizing pneumonia on left with multiple fluid collections and gas collections throughout the consolidated left lung. A large, complex pleural fluid collection is also seen with areas of gas and enhancing septations concerning for empyema.
seems to be an association between CVID patients who have a poor antibody response to the pneumococcal vaccines and development of bronchiectasis and autoimmune disorders.

**Question:** *What are some of the clinical manifestations of CVID?*

**Discussion:** Recurrent infections are the hallmark of CVID. These are most commonly infections of the respiratory tract that range from simple sinusitis or otitis media to complicated pneumonia requiring hospitalization. Althoug frequent episodes of otitis media are not uncommon in the pediatric population, multiple pneumonias requiring hospitalization and intravenous antibiotic therapy, such as in our patient, should alert the clinician that there is a possibility of an underlying immunodeficiency. Even though a primary diagnosis of immunodeficiency has been made, it is essential to be aware that CVID can evolve in a patient who has IgA deficiency.

The gastrointestinal system is the second most commonly involved organ system in CVID, and manifestations include chronic diarrhea and malabsorption. These are noted in 6% to 60% of cases of CVID, though our patient denied all gastrointestinal symptoms. An increased risk for malignancy, particularly B-cell non-Hodgkin’s lymphoma, has been documented on multiple occasions, and autoimmune diseases including thrombocytopenia, autoimmune anemia, and rheumatoid arthritis have been documented in up to 60% of cases in certain studies. There is an increased association with autoimmune diseases in children compared with adults who have CVID.

Growth failure and failure to thrive have strong associations with CVID. They have been documented in 17% to 80% of patients. Patients with CVID and bronchiectasis have been noted to be significantly shorter in height than those patients without bronchiectasis. It has been speculated that this failure to thrive is due to a lack of growth hormone because growth hormone deficiency has been noted in up to 25% of patients with CVID. Further study is required to determine if this is an occasional association or a development in the progression of CVID. If it were a progression of the disease, early diagnosis and treatment would be of great importance when attempting to prevent growth retardation in patients with CVID.

Multiple studies have found bronchiectasis associated with CVID. These patients are commonly older at diagnosis with CVID, had a delay in diagnosis, and have more respiratory infections requiring antibiotics. This delay in diagnosis could be due to the number of respiratory infections being attributed to the patient’s bronchiectasis, which can distract the clinician from investigating further.

**Question:** *What is the current recommended therapy for CVID?*

**Discussion:** IVIg is the most commonly instituted treatment of CVID. Some patients with CVID and underlying lung disease, such as bronchiectasis or persistent respiratory infections, continue to have progression of their lung disease documented after initiation of IVIg therapy. However, 1 study has noted regression or resolution of mild bronchiectasis and no further profound infections such as meningitis or sepsis after beginning IVIg therapy, which is an encouraging finding. This same study also found an 85% reduction in the number of infections requiring hospitalization and a 70% reduction in the number of antibiotics needed by patients after starting monthly IVIg infusions. When using IVIg, the infection rates become similar to that of the general population. However, it has been speculated that patients with CVID and chronic lung disease may require higher doses of monthly IVIg to obtain the same results as others with only CVID.

A delay in appropriate diagnosis can be detrimental to patients with CVID. The risk of death may increase by as much as 2.7% for every year increase in the age at diagnosis. Although overall mortality has decreased since the institution of IVIg therapy, those patients with chronic lung disease, a lower baseline IgG level, and a higher IgM level still have a lower survival rate. A delay in diagnosis and beginning IVIg therapy is also correlated with an increased incidence of bronchiectasis. This finding seems significant because the most common cause of death in CVID is respiratory failure. The age at death has been correlated with the age at symptom onset and age at diagnosis. The risk of death is 11 times higher for patients with CVID and noninfectious complications such as gastrointestinal or chronic lung disease than for patients with CVID alone. Mortality rate also increases without regular physicians’ visits and IVIg therapy. Patients have a better prognosis if they have no signs of bronchiectasis, chronic lung damage, severe autoimmune disease, or malignancy.

**Conclusions:** Good medical care requires the earliest possible diagnosis of CVID. This early diagnosis entails a high index of suspicion in any child with unusual infectious symptoms such as...
frequent respiratory infections requiring extensive treatment, chronic diarrhea with malabsorption, and growth failure. If there is a suspicion, immunoglobulin levels and immunization antibody responses should be evaluated. Clearly, the fewer disease complications manifest by a patient at diagnosis, the better his or her prognosis. Early institution of appropriate therapy will improve outcomes and decrease overall morbidity and mortality of CVID.

REFERENCES


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