

## CLINICAL CASE OF THE MONTH

# Recurrent Pneumonia in a Middle-aged Woman

Paul Niolet, MD; Carlos Vital, MD; Dayton Daberkow, II, MD;  
Scott L. Beech, MD; Prem Kumar, MD; Sanjay Kamboj, MD  
and Fred A. Lopez, MD, Article Editor

A middle-aged woman presented to the emergency department with chief complaints of cough productive of yellow sputum and progressive dyspnea on exertion for one week. She also reported fever, chills, fatigue, myalgias, and right sided pleuritic chest pain. The patient denied night sweats, weight loss, or nausea. One month earlier, she had presented to the hospital with similar symptoms, and a diagnosis of right-middle-lobe pneumonia was made. Blood cultures were positive for *Streptococcus pneumoniae*. She was treated with levofloxacin for 2 weeks with resolution of her symptoms.

The patient's past medical history was significant for a chronic productive cough and recurrent sinus infections since childhood. At 20 years of age, she was diagnosed with asthma. She also had a 10-year history of 6-8 episodes per year of intermittent watery, nonbloody diarrhea, usually lasting 1-2 weeks and resolving spontaneously. Her mother had a history of hypertension, and her father died of a myocardial infarction at 55 years of age. She denied any history of smoking or ethanol use. At the time of presentation, she was taking loratadine 10 mg daily, mometasone 50 mcg/spray intranasally daily, fluticasone 44 mcg metered dose inhaler daily, albuterol

2.5 mg metered dose inhaler, as needed, 2 drops of olopatadine 0.1% in each eye twice daily, and a daily multivitamin. She reported itching and a rash after taking sulfa-based drugs and urticaria after taking penicillin. She received the polysaccharide pneumococcal vaccine 1 year ago and an influenza vaccine in each of the previous 2 years.

Vital signs included a temperature of 38 degrees Centigrade, blood pressure of 136/72 mmHg, heart rate of 92 beats per minute, 22 respirations per minute, and a pulse oximetry of 97% while breathing air. She had coarse breath sounds bilaterally with crackles and egophony in the right middle and lower lung fields. Laboratory studies included a white blood cell count of 21,100 cells/ $\mu$ L (6,000-11,000/ $\mu$ L) with 45% neutrophils and 49% bands. The blood urea nitrogen was elevated at 41 mg/dL (7-18 mg/dL), and the creatinine was 1.3 mg/dL (0.6-1.2 mg/dL). A chest radiograph revealed alveolar infiltrates in the right middle and upper lobes with a parapneumonic effusion (Figure 1; Figure 2). She was admitted to the hospital and received cefotaxime 1 gram IV every 12 hours and levofloxacin 500 mg IV daily. Blood cultures were negative. A HIV ELISA test was negative. The patient improved and was discharged home to complete a 14

### CME INFORMATION

#### TARGET AUDIENCE

The November/December Clinical Case of the Month is intended for family physicians, general internists, medicine subspecialists, general practitioners, obstetricians-gynecologists, emergency medicine physicians, pediatricians, dermatologists, radiologists, and psychiatrists.

#### EDUCATIONAL OBJECTIVES

The Clinical Case of the Month is a regular educational feature presented by the Louisiana State University Department of Medicine in New Orleans. Medical students, residents, postdoctoral fellows, and faculty collaborate in the preparation of these discussions. After reading this article, physicians should be better able to identify and to understand the pathophysiology, clinical presentation, diagnosis, and treatment of common variable immunodeficiency.

#### CREDIT

The LSMS Educational and Research Foundation designates this educational activity for a maximum of one (1) category 1 credit toward the AMA Physician's Recognition Award. Each physician should claim only those hours of credit that he/she actually spent in the educational activity.

#### DISCLOSURE

Dr. Niolet has nothing to disclose.  
Dr. Vital has nothing to disclose.  
Dr. Daberkow has nothing to disclose.  
Dr. Beech has nothing to disclose.  
Dr. Kumar has nothing to disclose.  
Dr. Kamboj has nothing to disclose.  
Dr. Lopez discloses that he is a member of the LSMS *Journal* Board and the LSMS *Journal* Editorial Board.

#### ORIGINAL RELEASE DATE

12/1/2004

#### EXPIRATION DATE

12/31/2005

Estimated time to complete this activity is 1 hour.



Figure 1.

**Figures 1 and 2.** Right upper and middle lobe pneumonia. PA (Figure 1) and lateral (Figure 2) views of the chest reveal consolidation of the posterior segment of the right upper lobe and an infiltrate in the right middle lobe. A parapneumonic effusion accounts for the blunted costophrenic angle and flattened appearance of the right hemidiaphragm.



Figure 2.

day course of antibiotics. During a follow-up clinic visit five months after the hospitalization, immunoglobulin levels were drawn which revealed an IgG level of 11 mg/dl (680-1530 mg/dl), IgA less than 6.4 mg/dL (75-374 mg/dL), IgM 9.9 mg/dL (47-188 mg/dL), and IgE less than 7 mg/dL (0-99 mg/dL). These labs were repeated, and similar results were obtained (as well as documentation of poor antibody response to pneumococcal polysaccharide immunization) confirming the diagnosis of common variable immunodeficiency (CVID).

## DISCUSSION

CVID is characterized by recurrent sinopulmonary bacterial infections, decreased serum immunoglobulin levels, and abnormal antibody responses. Described in 1953 by Janeway et al, CVID is also known as "acquired" hypogammaglobulinemia, dysgammaglobulinemia, or idiopathic late-onset immunoglobulin deficiency.<sup>1</sup> The incidence of CVID is equal among men and women, can occur at any age, and (excluding specific IgA deficiency) is the most common primary immunodeficiency with a prevalence of approximately 1 in 50,000-80,000 persons.<sup>2</sup> Affected individuals are predisposed to recurrent bacterial infections, diarrhea, and various autoimmune diseases and malignancies.

## CLINICAL PRESENTATION

Symptoms may present at any age, but the peak incidence is seen in the second and third decades of life.<sup>3</sup>

The diversity of the clinical manifestations of CVID often delays the diagnosis, a delay which can result in complications including irreversible lung damage.<sup>4</sup> Humoral defects render these patients particularly susceptible to encapsulated bacterial infections with organisms such as *S. pneumoniae* and *Haemophilus influenzae*.<sup>6</sup> The majority of patients suffer from sinopulmonary infections and have histories of recurrent pneumonia, bronchitis, sinusitis, pharyngitis, conjunctivitis, and otitis.<sup>5</sup> Invasive complications including sepsis and meningitis can occur. Bronchiectasis may develop from chronic respiratory infections and is an important factor contributing to mortality.<sup>4</sup>

In some patients, the initial presentation may be an autoimmune process or gastrointestinal disease. Approximately twenty percent of patients develop autoimmune diseases such as hemolytic anemia, pernicious anemia, rheumatoid-like arthritis, endocrinopathies including hypothyroidism, and idiopathic thrombocytopenia.<sup>2,5</sup> There is an increased incidence of gastrointestinal disturbances particularly chronic diarrhea and malabsorption.<sup>6</sup> Chronic diarrhea due to *Giardia lamblia* is a characteristic infection in these patients.<sup>6</sup>

The incidence of neoplasms is elevated in CVID.<sup>7</sup> Among these, lymphoid malignancies, especially B-cell non-Hodgkin's lymphoma (NHL) and Hodgkin's disease, are prevalent.<sup>5,8</sup> The risk of NHL increases with advancing age and is a major cause of mortality in this population.<sup>5</sup> Of note, benign lymphadenopathy or splenomegaly can be present in approximately one-third of patients.<sup>3</sup> Up to a 50-fold increase in the incidence of

gastric carcinoma has also been observed.<sup>6</sup> Lastly, skin cancers are more likely in this patient population than in the general population.

## PATHOGENESIS

No specific molecular defect has been identified as the cause of CVID. Various mutations result in hypogammaglobulinemia secondary to failure of B-lymphocytes to differentiate into plasma cells.<sup>9</sup> Although B-cell defects have been identified, current evidence suggests that many patients also have various T-lymphocyte defects.<sup>9</sup> Approximately sixty percent of patients have a decreased proliferative response when T cells are stimulated.<sup>9</sup> Increased suppressor T cell activity resulting in down regulation of B-cells and decreased production of immunoglobulin has been proposed as a likely cause in some cases of CVID.

Although most cases of CVID are sporadic, 20% of these patients have autosomal dominant inheritance patterns with variable penetrance.<sup>10</sup> Cases in which several family members have CVID or selective IgA deficiency have been described, supporting the hypothesis that the two diseases may be related genetically.<sup>11</sup>

## DIAGNOSIS

A high clinical suspicion of CVID is necessary to make the diagnosis. Patients often present to various physicians depending on the specific manifestation of their disease. A careful history which reveals recurrent infections of the respiratory tract and chronic diarrhea often alerts the clinician to the possibility of CVID.

The diagnosis of CVID requires onset after 2 years of age in order to exclude children who present with an array of primary immunodeficiencies.<sup>12</sup> Primary hypogammaglobulinemic states to be considered include X-linked agammaglobulinemia (XLA), hyper-IgM syndrome, and IgA deficiency. XLA is caused by the complete absence of B-cells and must be differentiated with genetic tests from CVID in young men who may also have decreased B-cell populations (although B cell numbers are normal in most cases of CVID). The hyper-IgM syndrome is characterized by neutropenia, IgG deficiency, and elevated IgM levels in the serum. IgA deficiency may also present with recurrent sinopulmonary infections, but these patients have selected IgA deficiency while other immunoglobulin levels are normal. Secondary causes of hypogammaglobulinemia such as drugs (especially anticonvulsants), infections (Ebstein-Barr virus, cytomegalovirus, human immunodeficiency virus, and parvovirus B19, for example), protein losing gastroenteropathy, nephrotic syndrome, and lympho-proliferative disease must be ruled out.<sup>3</sup> The criteria for diagnosis also include a reduced total serum IgG at least 2 standard deviations (SD) below the mean and a reduced total IgA and/or IgM 2 SDs below the mean.<sup>12</sup> Normal values

specific for sex and age should be applied to individual cases. Patients may have normal IgG immunoglobulin levels but may have IgG subclass deficiencies. These patients also have low or absent titers of protective antibodies when administered pneumococcal or diphtheria vaccines.

## MANAGEMENT

The treatment for CVID is lifelong intravenous immunoglobulin (IVIG). IVIG has been shown to decrease the incidence of pneumonia and hospitalization.<sup>13, 14</sup> Maintaining serum IgG levels above 500 mg/dL with the regular (approximately monthly) administration of IVIG (typically 300-400 mg/kg/month and titrated according to serum levels) is a means of providing protection against infections and improving quality of life.<sup>15</sup> The complications of IVIG therapy include anaphylaxis, fever, myalgias, aseptic meningitis, acute renal failure, and thrombotic episodes (cerebrovascular accident, acute myocardial infarction).

Bronchiectasis and other chronic lung diseases, such as chronic obstructive pulmonary disease and asthma, which occur in CVID can be monitored with spirometry and high resolution CT scanning.<sup>4</sup> Moderate enlargement of mediastinal lymph nodes on CT scan occurs in over 50% of patients with CVID; thus, serial CT scans need to be performed.<sup>16</sup> Changes in size of lymph nodes and/or development of associated symptoms of fever, night sweats, or weight loss warrant targeted work-up for the possibility of lymphoproliferative disorders.

## CONCLUSION

CVID is a heterogeneous syndrome characterized by recurrent infections secondary to panhypogammaglobulinemia. A high clinical suspicion from an appropriate history can hasten the diagnosis and treatment, preventing infections and progression of pulmonary disease.

## REFERENCES

1. Janeway CA, Apt L, Gitlin D. Agammaglobulinemia. *Trans Assoc Am Phys* 1953;66:200-202.
2. Kainulainen L, Nikoskelainen J, Ruuskanen O. Diagnostic findings in 95 Finnish patients with common variable immunodeficiency. *J Clin Immunol* 2001;21:145-149.
3. Eisenstein EM, Sneller MC. Common variable immunodeficiency: diagnosis and management. *Ann Allergy* 1994;73:285-291.
4. Thickett KM, Kumararatne DS, Banerjee AK, et al. Common variable immune deficiency: respiratory manifestations, pulmonary function and high-resolution CT scan findings. *Q J Med* 2002;95:655-662.
5. Cunningham-Rundles C, Bodian C. Common variable immunodeficiency: clinical and immunologic features of 248 patients. *Clin Immunol* 1999;92:34-48.

6. Sneller MC. Common Variable Immunodeficiency. *Am J Med Sci* 2001;321:42-48.
7. Cunningham-Rundles C, Siegal FP, Cunningham-Rundles S, et al: Incidence of cancer in 98 patients with common varied immunodeficiency. *J Clin Immunol* 1987;7:294-299.
8. Zenone T, Souquet PJ, Cunningham-Rundles C, et al. Hodgkin's disease associated with IgA and IgG subclass deficiency. *J Int Med* 1996;240:99-102.
9. Emedicine. Park CL: Common variable immunodeficiency: <<http://www.emedicine.com/ped/topic444.htm>> (accessed 08 September, 2004).
10. Spickett GP. Current perspectives of common variable immunodeficiency (CVID). *Clin Exp Allergy* 2001;31:536-542.
11. Vorechovsky I, Zetterquist H, Paganelli R, et al. Family and linkage study of selective IgA deficiency and common variable immunodeficiency. *Clin Immunol Immunopathol* 1995;77:185-192.
12. Abonia JP, Castells MC. Common variable immunodeficiency. *Allergy Asthma Proc* 2002;23:53-57.
13. Busse PJ, Razvi S, Cunningham-Rundles C. Efficacy of intravenous immunoglobulin in the prevention of pneumonia in patients with common variable immunodeficiency. *J Allergy Clin Immunol* 2002;109:1001-1004.
14. Garcia MAM, De Rojas HF, Manzur N, et al. Respiratory disorders in common variable immunodeficiency. *Resp Med* 2001;95:191-195.
15. Buckley RH, Schiff RI. The use of intravenous immune globulin in immunodeficiency diseases. *N Engl J Med* 1991;325:110-117.
16. Curtin JJ, Murray JG, Apthorp L, et al. Mediastinal lymphadenopathy and splenomegaly in primary hypogammaglobulinaemia. *Clin Radiol* 1995;50:489-491.

---

**Dr. Niolet** is a member of the Internal Medicine-Pediatrics house staff at the Louisiana State University School of Medicine in New Orleans. **Dr. Vital** is a postdoctoral fellow in the Department of Medicine at Louisiana State University School of Medicine in New Orleans. He is also a member of the Board of Governors for the Louisiana State Medical Society. **Dr. Beech** is Associate Professor of Clinical Medicine in the Department of Radiology at Louisiana State University School of Medicine in New Orleans. **Dr. Daberkow** is Associate Professor of Clinical Medicine in the Department of Medicine at Louisiana State University School of Medicine in New Orleans. **Dr. Kumar** is Professor of Medicine in the Department of Medicine at Louisiana State University School of Medicine in New Orleans. **Dr. Kamboj** is Clinical Instructor of Medicine in the Department of Medicine and Section of Allergy and Immunology at Louisiana State University School of Medicine in New Orleans. **Dr. Lopez** is Associate Professor of Medicine at the Louisiana State University School of Medicine in New Orleans.

The **Clinical Case of the Month** is a regular educational feature presented by the Louisiana State University Department of Medicine in New Orleans. Medical Students, residents, postdoctoral fellows, and faculty collaborate in the preparation of these discussions.

## CME QUESTIONS

To earn CME credit, read the preceding CME article and complete the registration, evaluation, and answer form on page 336. Mail or fax the registration, evaluation, and answer form to the Educational and Research Foundation. Answers must be postmarked or faxed prior to December 31, 2005. Participants must attain a minimum score of 75% to receive credit.

For each question, choose the one answer that is most correct.

1. The following are associated with CVID:
  - a) Recurrent sinopulmonary bacterial infections
  - b) Decreased serum immunoglobulin levels
  - c) Chronic diarrhea
  - d) Lymphoid malignancies
  - e) All of the above
2. True or False. Chronic diarrhea due to *Cryptosporidium parvum* is a characteristic infection of patients with CVID.
3. True or False. CVID is due exclusively to B cell defects.
4. All of the following statements are true except:
  - a) CVID is the most common primary immunodeficiency syndrome.
  - b) The hyper-IgM syndrome is characterized by neutropenia and deficiency of IgG.
  - c) The treatment for CVID is lifelong intravenous immunoglobulin (IVIG).
  - d) Complications of IVIG therapy include anaphylaxis, fever, aseptic meningitis, acute renal failure, and thrombotic episodes.