A 58-Year Old Woman With Recurrent Productive Cough and Diarrhea*

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A 58-year-old white woman with a medical history significant for hypothyroidism, hypertension, and coronary artery disease was referred for evaluation of recurrent productive cough, fever, and wheezing. During the prior 5 years, she had experienced similar episodes of respiratory illness, for which she had received 7 to 14 days of oral antibiotics and inhaled bronchodilators. In the last year, her symptoms have been associated with progressive dyspnea, and recurrent bouts of nonbloody diarrhea. She denied any hemoptysis, orthopnea, or paroxysmal nocturnal dyspnea.

Past surgeries included a coronary artery bypass 5 years ago, a cholecystectomy, and an abdominal hysterectomy. She worked as phlebotomist and had 30 pack-years of smoking but quit several years ago. She recalls being treated with isoniazid for 12 months after she tested positive for purified protein derivative while in her late 40s. Current medications included thyroxine, furosemide, nitrates, and a calcium channel blocker. Review of systems was significant for 12-lb weight loss over the last 6 months.

Physical Examination

The physical examination revealed an alert, slim, middle-aged woman in no acute distress. She weighed 51 kg. She had a BP of 110/80 mm Hg, a respiratory rate of 24 breaths/min, and a heart rate of 96 beats/min.

Head, eye, ear, nose, and throat examination was normal. The neck was supple. There was no jugular venous distention or lymphadenopathy. Lung examination revealed scattered rhonchi with occasional wheezes at end expiration. There was no rale or...
dullness on percussion. The cardiac examination was unremarkable. The remainder of the physical examination was normal except for clubbing of the fingers.

**Laboratory Findings**

The WBC count was $10.6 \times 10^3$ cells/µL, and the automated differential cell count showed 69% polymorphonuclear leukocytes, 24% lymphocytes, 5% monocytes, and 1% eosinophils. The hemoglobin level was 12.7 g/dL, and the hematocrit was 38.7%. The chemistry panel was normal, except for mild increase in creatinine to 1.5 mg/dL and alkaline phosphatase of 189 U/L (normal, 30 to 140 U/L). She had an albumin of 3.7 g/dL (normal, 3.3 to 4.7 g/dL), and a total protein of 5.5 g/dL (normal, 5.8 to 7.7 g/dL). Urine analysis was negative for hematuria and proteinuria. Antinuclear antibody, cytoplasmic and perinuclear antineutrophilic cytoplasmic antibodies (by enzyme immunoassay and fluorescence tests), rheumatoid factor, and fungal serologies (for aspergillosis, histoplasmosis, and coccidioidomycosis) were not detectable.

Spirometry showed an FVC of 1.54 L (61% of predicted), FEV₁, 1.07 L (59% of predicted); total lung capacity, 3.08 L (75% of predicted); residual volume, 1.87 L (120% of predicted); and diffusing capacity of the lung for carbon monoxide, 10.1 mL/min/mm Hg (71% of predicted). When compared to a previous pulmonary function test performed a year ago, the FVC had decreased by 270 mL (18%), and the FEV₁ had dropped by 130 mL (12%). The flow volume loop was not suggestive of an upper airway obstruction. A cardiac gated blood pool study revealed a left ventricular ejection fraction of 49%. Chest radiograph (Fig 1) and CT scan of the chest (Fig 2) are shown.

Sputum cultures revealed *Haemophilus influenzae* on two separate occasions. Flexible bronchoscopy did not reveal any endobronchial lesion, and BAL was negative for acid-fast bacilli. Cytology of bronchial washing was negative for malignancy.

Stool culture was negative for ova and parasites. Small bowel radiographic studies were normal.

**Clinical Course**

The patient responded to a 14-day course of antibiotics with significant improvement in her productive cough. Three years later, she developed a nontender cervical lymphadenopathy. A biopsy revealed non-Hodgkin’s lymphoma.

What is the likely diagnosis?
Diagnosis: Hypogammaglobulinemia secondary to common variable immunodeficiency.

Common variable immunodeficiency (CVID), also known as idiopathic, congenital non-X-linked, acquired, or late-onset hypogammaglobulinemia, is a heterogeneous disorder characterized by low serum levels of IgG, depressed levels of IgA and IgM, the inability to form antibodies to antigen, and the absence of gross defects in cell-mediated immunity. The underlying problem is a failure of B cells to differentiate into plasma cells that secrete IgG. The advanced mechanisms responsible for this failure have included an intrinsic defect in the B cell resulting in abnormal terminal differentiation, a deranged T-cell regulation with either too much suppressive activity or too little helper activity, or in rare cases, the presence of autoantibodies to T or B cells.

CVID has an incidence of 6 to 12 cases/100,000 live births. Experts agree that the defect exists most likely at birth, although CVID may develop after a fetal rubella infection or a postnatal Epstein-Barr virus infection. Patients usually present in their second or third decade, with mean age at onset of 26.9 years for men and 35.2 years for women, although patients as young as 7 years and as old as 67 years have been reported. The onset of the disease is insidious, with the majority of patients affected with CVID coming to the attention of clinicians because of recurrent respiratory tract infections, otitis, and sinusitis. The involved pathogens are typically virulent encapsulated extracellular organisms such as *H influenzae*, *Streptococcus pneumoniae*, and *Staphylococcus aureus*. Occasional infections with *Mycobacterium tuberculosis*, fungal pathogens, and *Pneumocystis carinii* may occur. The diagnosis of hypogammaglobulinemia requires a high index of suspicion, as early therapeutic intervention is critical in reducing morbidity and mortality from pulmonary disease. A discrepancy between a low total serum protein and a normal level of albumin should raise the suspicion of globulin deficiency. A serum protein electrophoresis would substantiate the diagnosis, which is confirmed usually by quantitative measurements of serum IgG.

The majority of patients report a history of recurrent pneumonia and sinusitis on presentation. Hemoptysis has been described in 15% of patients, asthmatic bronchitis in 2%, while an absence of respiratory symptoms is seen in 9%. The reason for the lack of respiratory involvement in some individuals is not well understood. Pulmonary function tests can show either an obstructive or a restrictive pattern with a reduced diffusing capacity of the lung for carbon monoxide. Diffuse bronchial wall thickening and interstitial infiltrates are the most common findings on chest radiographs. While bronchiectasis is considered a typical feature of subjects with B-cell disorders, the chest radiograph severely underestimates the extent of this abnormality. In a study of 22 patients with B-cell disorders, CT detected bronchiectasis in 15 of 19 patients (79%) compared to 7 of 19 patients (37%) on chest radiograph. The presence of hilar or mediastinal lymphadenopathy on CT scan should raise the possibility of neoplasia as the incidence of malignant lesions is increased considerably in patients with primary immunodeficiency disorders. Comparing the incidence of cancer in patients with CVID to the age-adjusted incidence in the general population, there is an eightfold increase of malignancy for male patients, and a 13-fold increase for female patients. Non-Hodgkin’s lymphoma accounts for 50% of the cases, followed by adenocarcinoma of the stomach (28%) and adenocarcinoma of the colon (18%). The peak incidence of malignancy occurs generally in the fifth and sixth decades, with an average survival of 2.4 years after diagnosis.

Other pulmonary abnormalities described in CVID include parenchymal lymphocytic infiltration and noncaseating sarcoïd-like granuloma.

Autoimmune diseases have been reported to occur in 20% of these patients, with a female predominance of 2:1. The most common autoimmune disease was idiopathic thrombocytopenic purpura (30%), followed by autoimmune hemolytic anemia (25%), and rheumatoid arthritis (20%). Systemic lupus erythematosus, primary biliary cirrhosis, pernicious anemia, and thyroid abnormalities were also described in anecdotal reports. Chronic or recurring diarrhea occurs in up to 60% of the patients. Giar-diasis and nodular lymphoid hyperplasia of the small bowel accounted for 64% and 28% of the causes, respectively.

Treatment consists of Ig replacement therapy given every 3 to 4 weeks to maintain an IgG trough level of 200 to 400 mg/dL. The average maintenance dose is 400 mg/kg and is usually adjusted to the subject’s IgG half-life and to postinfusion serum IgG levels. Serial measurements of IgG levels are recommended at day 7 postinfusion and weekly thereafter until the serum levels drop to the desired trough level, when a repeat infusion is required. The day 7 measurement is crucial because thereafter the IgG elimination rate follows an exponential order reflecting the half-life of the infused IgG. Pregnant women with hypogammaglobulinemia require a higher maintenance dose in the range of 800 mg/kg/mo due to extracellular fluid volume expansion and active placental transfer of IgG. Particular attention should be made to those recipients with no measurable serum IgA prior to IV gamma globulin infusion to decrease the possibility of anaphylactic reactions.
mediated by IgE or IgG4 antibodies directed against IgA. In those patients, a sensitive method like enzyme-linked immunosorbent assay should be done to look for anti-IgA antibody. If anti-IgA antibody is detected, Ig preparations containing low levels of IgA should be used. The current commercial IV Ig preparations licensed in the United States contain varying amounts of IgA, ranging from > 3,000 µg/mL to < 10 µg/mL. The use of “IgA-depleted” IV gamma globulin products (< 10 µg/mL) has been safely administered with minimal risk of anaphylaxis.

A low threshold for antibiotic use and aggressive bronchial hygiene are necessary adjuncts to reduce the frequency and severity of pulmonary infections and to prevent deterioration in pulmonary function. Histamine receptor blockade with cimetidine has resulted in increased production of Igs in small number of patients. Experimental therapies using retinoic acid analogs and interleukin-2 to promote B-cell lymphocyte differentiation have been promising, but await large clinical trials.

In the present patient, Ig infusion resulted in a decreased frequency of acute respiratory exacerbations and resolution of her diarrhea. A repeat pulmonary function test 2 years later revealed no significant change compared to her baseline. Following her diagnosis with non-Hodgkin’s lymphoma, the patient was started on chemotherapy. She went into remission for a relatively short period, but she relapsed and refused further treatment. Ultimately, she died of recurrent infection and respiratory failure.

**Clinical Pearls**

1. The diagnosis of common variable immunodeficiency is frequently delayed with significant morbidity and mortality.
2. The diagnosis should be suspected in individuals presenting with recurrent sinopulmonary infections, bronchiectasis, and low globulin/albumin ratio.
3. The overall frequency of neoplasia in patients with CVID is approximately 10 times greater than in normal individuals.
4. Ig replacement with preparations that contain low levels of IgA, in combination with antibiotics and aggressive chest physiotherapy, are critical in reducing the frequency of exacerbations and deterioration in pulmonary function.

**Suggested Readings**

Buckley RH. Common variable immunodeficiency. Curr Ther Allergy Immunol Rheumatol 1988; 301–304