Case Report

Common variable immunodeficiency disorder - An uncommon cause for bronchiectasis

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ABSTRACT

Bronchiectasis continues to be a common respiratory problem of varied etiology. Common variable immunodeficiency disorder (CVID) is an uncommon cause for bronchiectasis. However, the prevalence of bronchiectasis remains very high in patients with CVID. This remains largely an underdiagnosed entity as primary immunodeficiency is not suspected in adults as a cause of bronchiectasis and hence, serum immunoglobulin (Ig) levels are not measured routinely. In addition to bronchiectasis, patients with CVID usually present with various extrapulmonary symptoms. I report here a case of young man who presented with bronchiectasis and multisystem complains who was diagnosed as CVID.

KEY WORDS: Bronchiectasis, common variable immunodeficiency disorder, intravenous immunoglobulin, primary immunodeficiency

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INTRODUCTION

Bronchiectasis is a common respiratory disorder of diverse etiology. Usually, extensive investigation to identify the cause of bronchiectasis is not done in routine clinical practice as it is perceived to have little influence on its management. Conventionally, in absence of an obvious cause, bronchiectasis is often considered as post-infective or idiopathic. However, establishing a specific etiological diagnosis of bronchiectasis may be significant for guiding appropriately tailored therapy in some patients with a favorable outcome.[1,2] Primary humoral immunodeficiency (PHI), an underdiagnosed entity, comprises of heterogeneous group of disorders. Common variable immunodeficiency disorder (CVID) represents the most commonly diagnosed form of PHI. CVID usually manifests as recurrent respiratory infections that often lead to bronchiectasis later on. CVID remains underevaluated as an etiology of bronchiectasis.[3] I present here a case of 34-year-old male diagnosed as CVID who presented with bronchiectasis and multisystem involvement.

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CASE REPORT

A 34-year-old male presented with fever, cough with purulent expectoration, and increased breathlessness for a week. He had mild right chest pain and occasional abdominal pain. He gave history of recurrent respiratory infections since childhood. He had recurrent diarrhea with intermittent steatorrhea and right otorrhea for last 7 years. The stool consistency was semisolid mixed with mucus but no blood. He was a farmer, married, and had two children. He had never smoked. He received empirical antitubercular therapy twice in the past in the year 1994 and 2007 for suspected smear negative pulmonary tuberculosis and empyema thoracis, respectively. He was emaciated, had pallor and clubbing. On admission his vitals were as follows: Pulse rate = 96 beats/min, blood pressure = 90/60 mmHg, respiratory rate = 32/min, and SpO_2 = 95% in room air. Auscultation revealed normal breath sound with bilateral diffuse coarse crackles. Inflammatory arthritis was noted in small joints, ankle, and knee. Blood metabolic panel, electrolytes, and hemogram were normal except for mild anemia. Repeated sputum examination for acid fast bacilli was negative. Blood, urine, and stool cultures were sterile. Stool for occult blood was negative. Stool microscopy showed hookworm ova. Chest radiograph showed patchy opacities in right lower and left upper zones [Figure 1]. High resolution computed tomography (HRCT) chest confirmed bilateral diffuse bronchiectasis [Figure 2a and b]. In view of multisystem involvement and recurrent respiratory

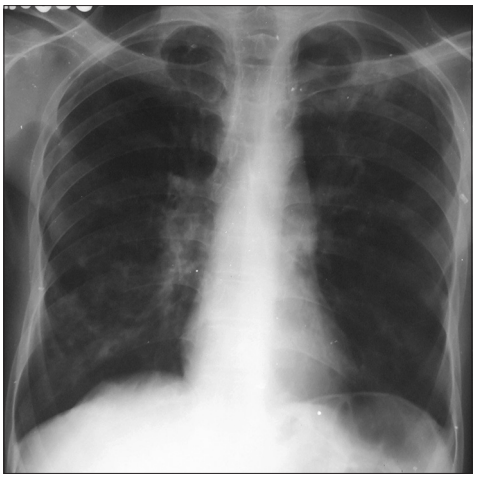

Figure 1: Chest X-ray showing nonhomogenous opacity in right lower and left upper zones

infections, serum immunoglobulin (Ig) estimation was done to rule out primary immunodeficiency. All Ig levels were significantly reduced (IgG < 1.37 g/l, IgA < 0.231 g/l, IgM < 0.17 g/l) (nephelometry) suggesting CVID. Antibody tests for human immunodeficiency virus, hepatitis B and C virus were negative. Sputum culture grew *Pseudomonas aeruginosa*. Spirometry demonstrated reversible airway obstruction. Evaluation of right otorrhea showed a small central perforation. Gastrodudonescopy was normal. Fibreoptic bronchoscopy revealed minimally inflamed airway and bronchoalveolar lavage microbiology was noncontributory. Considering the constellation of symptoms like recurrent respiratory infections/bronchiectasis, previous empyema, chronic diarrhea, suppurative otitis media, inflammatory arthritis, and low Ig levels; the diagnosis of CVID was made. He received intravenous ceftriaxone and ceftazidime for 2 weeks and recovered from the present infective exacerbation. Intravenous Ig (IVIG) therapy could not be administered as the cost was prohibitive for the patient.

DISCUSSION

PHI is a broad terminology comprising of several disorders that share defective antibody production as common abnormality. Broadly PHI is divided into two groups: One having a defined genetic linkage (e.g. X-linked agammaglobulinemia and autosomal recessive agammaglobulinemia) and one of unknown genetic base. The latter group constitutes the largest one and includes CVID, IgG subclass deficiencies, IgA deficiency, and selective antibody deficiency. The first group of diseases appear mainly during childhood and the second group appears later on.[3] Secondary immunodeficiency usually results from neoplasms like lymphoma, chronic lymphatic leukemia and myeloma, protein energy malnutrition, protein loosing enteropathy, severe trauma, corticosteroid, and cytotoxic drugs therapy and infections like human immunodeficiency virus and cytomegalovirus.[4] PHI

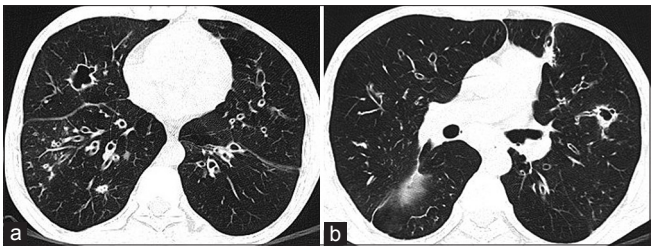

Figure 2: (a) High resolution computed tomography (HRCT) chest showing bilateral diffuse bronchiectasis with lower lobes predominance. (b) HRCT chest showing upper lobes bronchiectasis

usually manifests as recurrent respiratory infections like sinusitis, bronchitis, pneumonia, and bronchiectasis. CVID remains the most common symptomatic form of PHI diagnosed in adulthood. This is characterized by hypogammaglobulinemia, recurrent bacterial infections and autoimmune dysfunction. The reported incidence of CVID varies from 1 in 10,000 to 1 in 50,000 and equal in both sexes.[3] Familial occurrence is reported in about 20% cases. Majority present in their 2nd or 3rd decade. The average delay from the onset of symptoms to diagnosis ranges from 6 to 8 years.[5] This delay is mainly due to two reasons: (i) Primary immunodeficiency is not suspected or considered in adults and (ii) the initial symptoms are usually considered to be nonspecific. For most patients, the early symptoms of CVID are recurrent sinusitis or bronchitis. Unfortunately, serum Ig levels are not measured routinely in such cases. The fundamental immunological defect in CVID is reduced number of switch memory B cells with a failure to produce significant antibody response to specific antigens. The diagnosis of CVID is made mostly by exclusion of secondary causes of immunodeficiency and other primary immunodeficiency disorders. Though there is no consensus definition of CVID, the most agreed one as proposed by European Society for Immunodeficiencies is reduced (below 2 standard deviations of the mean) levels of IgG with reduced IgA and/or IgM, together with failure to mount a significant antibody response to vaccination, in the absence of a known cause. Functional Ig deficiency should be considered in patients who have recurrent respiratory infections and normal Ig and complement levels. These patients fail to produce measurable serological response to pneumococcal vaccine and tetanus toxoid.[3]

Bronchiectasis is a late manifestation in CVID and signatory to repeated infective insults in the past. Bronchiectasis remains the most common pulmonary pathology detected in CVID patients with a reported prevalence varying from 17 to 76%. HRCT scan is the single best imaging tool for the diagnosis and monitoring of bronchiectasis in CVID. Bronchiectasis is generally cylindrical, bilateral, and diffuse. It affects mostly the middle or lower lobes, and less commonly the upper lobes. The other pulmonary manifestations are emphysema, fibrosis, granulomatous disease mimicking sarcoidosis, and interstitial lung disease. In addition to lung, virtually any organ system can be involved in CVID. Extrapulmonary manifestations of CVID include recurrent diarrhea and malabsorption,

autoimmune disorders like idiopathic thrombocytopenic purpura and autoimmune hemolytic anemia, and malignancy like lymphoma and gastric cancer. Presence of bronchiectasis and liver disease at diagnosis carries a poor prognosis in CVID patients. Bronchiectasis is not a feature in isolated IgA or IgM deficiencies but more likely if these occur in association with selective IgG subclass deficiencies.[3,6]

The differential diagnoses those closely mimic CVID include primary ciliary dyskinesia (PCD), adult-onset cystic fibrosis (CF), alpha-1 antitrypsin deficiency, and non-tuberculous mycobacterial (NTM) infection. Male infertility is a common feature in both PCD and adult-onset CF. However, presence of rhinitis since neonatal period and a classic triad of sinusitis, situs inversus, and bronchiectasis if present (in 50% cases) will differentiate PCD from adult-onset CF, the later may present with recurrent pancreatitis. The diagnosis of PCD is established by ultrastructural study of cilia, whereas sweat chloride estimation and/or genetic analysis is required in adult-onset CF. Alpha-1 antitrypsin deficiency is usually associated with concomitant emphysema and affects the lower lobes, whereas NTM infection has a predilection for middle lobe and lingula with nodular bronchiectasis and tree-in-bud appearance.

Subjecting every patient of bronchiectasis to an array of exhaustive investigations may not be justified. However, such an approach may be rewarding in well-selected group of patients.[7-9] In a recent study, a cause for bronchiectasis was identified in 74% (122/165) of patients that influenced the management in 61 (37%). Seven had primary immune deficiency.[7] Another study involving 150 patients of bronchiectasis showed etiological diagnosis in 47% cases and this altered the management in 15%.[8] Patients with immune deficiency are younger than those with idiopathic or post-infective bronchiectasis.

IVIG remains the mainstay of therapy in CVID. The standard recommendation for IVIG is 400-600 mg/kg body weight every 3-4 weeks. An IgG trough level (the IgG level before the next infusion) of at least 5 g/l should be attained. Patients with bronchiectasis or diarrhea may require higher IVIG doses (500-600 mg/kg) to reach the mandatory trough level. The dose, frequency and route of administration of IVIG should be individualized to achieve maximum success. Antimicrobial therapy is the other main component of CVID therapy, because Ig replacement alone may not adequately prevent or treat local and/or persistent infections. Intravenous antibiotic for a longer duration (10-14 days) is recommended for control of acute infective exacerbation of bronchiectasis in CVID patients to prevent relapse. Those with recurrent infections despite IVIG therapy may benefit from suppressive antibiotic therapy especially azithromycin given three times a week. Other usual therapy for bronchiectasis like bronchodilators, inhaled corticosteroids, and airway clearance techniques should be optimized for maximum benefit. In addition, the accompanying diseases and sequel of CVID require adequate treatment. Corticosteroids and cyclosporine A are effective for granulomatous manifestations and autoimmune diseases, although long-term treatment efficacy may be limited due to side effects. Newer agents like infliximab or etanercept have been successfully used in few cases.[3,6]

In conclusion, primary immunodeficiency should be considered as a possibility for bronchiectasis in young patients who have recurrent respiratory infections and multisystem involvement. Serum Ig estimation should be done in such patients.

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