CASE REPORT

Gastrointestinal Complications in Two Patients with Common Variable Immunodeficiency

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ABSTRACT

Common variable immunodeficiency (CVID) is a primary immunodeficiency disease characterized by hypogammaglobulinemia and recurrent bacterial infections especially in respiratory and gastrointestinal systems. We present here 2 cases of CVID with gastrointestinal complications.

Case 1 is a 25-year-old man with a history of chronic diarrhoea from childhood. Ultrasonography revealed ascites, with liver size smaller than normal. Liver biopsy showed non-specific hepatitis. Lymphoid proliferation and Histiocytosis were reported in his ascites cytology. Moreover friability in colonoscopy due to moderate active chronic colitis was detected.

Case 2 is a 26-year-old man with chronic diarrhoea since 8 years. Abdominal sonography revealed increased liver echogenicity, increased liver size, and some enlarged lymph nodes beside pancreas. Colonoscopy revealed friability and decreased vascularity while biopsy showed moderate active chronic colitis. Lymph node biopsy showed unusual immunologic reaction. Moreover, small bowel transition test showed nodularity.

CVID should be considered in any patient with gastrointestinal manifestations especially chronic diarrhoea in association with recurrent bacterial infections in other organs. Diagnostic delay results in more morbidity and complications in untreated patients.

Keywords: Common Variable Immunodeficiency, Complications, Diarrhoea, Gastrointestinal Diseases

INTRODUCTION

Common variable immunodeficiency (CVID), the most common symptomatic primary immunodeficiency after isolated IgA deficiency, is characterized by decreased serum immunoglobulin levels and normal or decreased B cell numbers. [1-4]

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CVID patients have recurrent bacterial infections, most notably of the upper and lower respiratory tracts and gastrointestinal infections.[2-4]. Although chronic or recurrent sinopulmonary infections are the clinical hallmark of the disorder [5] many patients with CVID present with or develop chronic gastrointestinal (GI) complications, including pernicious anemia, sprue-like atrophy of the small-bowel villi, chronic giardiasis, and colitis.[6,7]

Inflammatory bowel disease, malabsorption with loss of weight, chronic gastritis associated with *Helicobacter pylori* infection and hepatitis C infection

have been reported more often in CVID patients.[8] These patients are also at increased risk for gastric adenocarcinoma and small-bowel lymphoma arising in the setting of nodular lymphoid hyperplasia.[9]

In this article we report two Iranian cases of CVID with gastrointestinal manifestations.

CASE REPORT

Case 1

A 25-year-old farmer, who lives in a rural area of Arak city in the center of Iran, had been referred to hospital because of abdominal distention of 5 years duration. He had a past medical history of chronic diarrhoea with fever from his childhood and productive cough for 10 years; also he had a history of ear surgery, lung abscess surgery and had a chest tube due to pneumonia in several hospitalizations. He smoked 5-6 cigarettes a day for the past 10 years. There was no history of alcohol or opium consumption. There was no history of any significant disease in his relatives.

Abdominal distention and dyspnea had been aggravated for the past 2 months along generalized pruritus and swelling of lower limbs during the following days. He had no complaint of bloody diarrhoea, jaundice, anorexia, and weight loss.

In physical examinations these findings were detected: Bi-temporal atrophy, collateral veins on abdomen and chest walls, diffused crackles in both lungs especially in the right side, ascites, 10 cm liver span, splenomegaly (3 cm under costal ridge), umbilical protrusion, midline abdominal scar of surgery, gynecomastia, loss of hair in lower limbs and pitting edema in both feet and legs.

Ultrasonography revealed ascites, with liver size smaller than normal but with a normal texture. The laboratory investigations showed: Total Protein= 5.6g/dl, Albumin=3.4 g/dl, Blood Urea Nitrogen= 11mg/dl, Creatinine=0.6mg/dl, AST=9 U/L, ALT= 13U/L, Alkaline phosphatase=275U/L, PT=18.1Sec; HBsAg (by ELISA) and HCV-RNA (by PCR) were negative. Liver biopsy was performed which showed non- specific hepatitis. Lymphoid prolifera-tion and histiocytosis were reported in his ascites cytology. Esophageal varices were detected in esophago-gastroscopy.

Investigations conducted for his chronic diarrhoea were as the following: friability in colonoscopy with no granuloma due to moderate active chronic colitis. Antigliadine antibody and Antiendomysial antibody were negative. Duodenal biopsy demonstrated slight superficial inflammation.

The immunological investigations were performed because of his chronic reproductive cough and diarrhoea. Immunoglubolins were assessed which showed the following results: Immunoglobulin G < 200 mg/dl (normal=800-1800), Immunoglobulin A < 50 mg/dl (normal=90-450), and Immunoglobulin M < 65 mg/dl (normal=60-250). The intravenous immuno-globulin (IVIG) therapy (300-400 mg/kg/month) was started for him due to suspicious diagnosis of common variable immunodeficiency. Moreover furo-semide (40 mg/day) plus spironolactone (75 mg/day) and Co-Trimoxazole (960 mg/day) were initiated and as a result his diarrhoea and coughs were alleviated.

Case 2

A 26-year old student with the chief complaint of chronic diarrhoea from 8 years ago had been referred to our center. He has been suffering from recurrent sinusitis and pharyngitis since 14 years. The diarrhoea was watery and sometimes bloody and had been continuous during the last 18 months. He has hypogastric pain before defecation. He also reports weight loss recently. The diagnosis of common variable immunodeficiency has been made for him according to low serum levels of IgG, IgM, and IgA 1 year ago and has been on monthly IVIG therapy since then. Now he is suffering from diarrhoea (3-4 times/day) and abdominal pain. He had no significant past medical history and does not smoke cigarettes or use alcohol or opiates. In the Laboratory data: White Blood Cell=5300/ul, Hemoglobin=12.2g/dl, Erythro-cyte Sedimentation Rate=5mm/h, and Alkaline phos-phatase=1276 U/L. Antigliadin and antiendomysial antibodies were negative; Stool Examination was normal (Total fecal fat/24h=2gr), and Anisocytosis, Ovalocytes and Poikilocytosis were detected in peripheral blood smear. Abdominal sonography revealed increased liver echogenicity, increased liver size (155 mm), normal spleen echogenicity but increased spleen size (95 * 182 mm), and some enlarged lymph nodes beside pancreas. In upper gastrointestinal endoscopy, severe nodularity in bulb was detected and biopsy showed chronic inflame-mation and marked nodular lymphoid hyperplasia. Colonoscopy revealed friability and decreased

vascularity and biopsy showed moderate active chronic colitis with no granuloma. In abdominal computed tomography scan enlargement of pancreas and dilated Gallbladder were detected. Lymph node biopsy showed unusual immunologic reaction. Small bowel transition test showed nodularity.

DISCUSSION

Although somewhat heterogeneous in clinical presentation and manifestations, CVID is recognized as the most prevalent primary immunodeficiency disease, excluding selective IgA deficiency. It is characterized by hypogammaglobulinemia and recurrent sinopulmonary infections, chronic diarrhoea, with an enhanced risk for malignancy, granulomatous disease, and joint involvement.[2,10]

The age at the onset of symptoms is variable, ranging from childhood to late adulthood, with some evidence of a bimodal distribution demonstrating peaks between 1 to 5 years and 18 to 25 years.[11] In the first case, the symptoms of chronic diarrhoea began from his childhood and in the second with recurrent sinusitis and pharyngitis, which were followed by chronic diarrhoea when he was 12 years old.

A number of disorders occur with increased frequency in patients with CVID. These include infections, chronic lung disease, autoimmune disease, liver and gastrointestinal disorders, granulomatous infiltrations, lymphoma, and solid tumors.[10,12] Acute, chronic or recurrent infections, specifically pneumonia, bronchitis, sinusitis, conjunctivitis, and otitis, are observed in practically all patients with CVID.[10,12] The first case had a history of ear surgery for chronic otitis media and the second case had a history of recurrent sinusitis and pharyngitis.

The majority of patients have at least one episode of pneumonia prior to diagnosis.[10]

Our first case had a history of pneumonia and lung abscess and had been hospitalized several times for lower respiratory tract infections. However, the incidence of bacterial pneumonia is significantly reduced in those treated with intravenous immune globulins (IVIG).[13]

Autoimmune conditions are common (22 percent) in CVID.[10] The mechanism for susceptibility to autoimmunity in CVID patients is unknown. In patients with CVID, chronic immunosuppressive therapy for these conditions should also be used with caution, as such therapy has been associated with an even higher incidence of medical complications (including overwhelming infection and neoplastic disease) in this setting.[10]

In our first case liver biopsy showed non-specific hepatitis and in both cases colon biopsy revealed chronic colitis which could be due to autoimmunity.

Approximately 10 percent of patients with CVID have significant liver dysfunction, with hepatitis B and C virus infection, primary biliary cirrhosis, and granulomatous disease.[10] Our first case had cirrhosis, ascites, esophageal varices in upper gastrointestinal endoscopy, and marked liver function abnormalities (PT=18.1s, total protein=5.6g/dl and albumin= 3.4g/dl) but the viral markers were negative and biopsy showed non-specific hepatitis. It may be due to an autoimmunity condition that has affected the liver. Our second case had no complaint showing liver dysfunction but ALP=1276U/ml and sonographic findings (higher liver echogenicity and larger size of liver and splenomegaly) might be indicators of hepatic involvement.

There is a high prevalence of inflammatory, malignant, and infectious gastrointestinal disorders in patients with CVID. These include nodular lymphoid hyperplasia (which was reported in the 2nd case's duodenal biopsy), inflammatory bowel disease (ulcerative colitis, ulcerative proctitis, or Crohn's disease) (both cases had chronic colitis with friability in colon biopsy that can be an initiating sign of IBD), sprue-like illness with flat villi, pernicious anemia, giardiasis, and non-specific malabsorption. Defects in cellular immunity, rather than antibody deficiency alone, appear to predispose patients to such illnesses.[14]

Patients may first present with atypical gastrointestinal disease, with symptoms and signs of diarrhoea, malabsorption, and weight loss.[15] Malabsorption and diarrhoea occur in 9% to 40% of patients with CVID.[16] In those with diarrhoea, an infectious organism is rarely recovered.[10] In severe cases, patients may suffer from symptoms of malabsorption, such as vitamin and electrolyte deficiencies. Malabsorption involves dietary fat, carbohydrates, vitamin B12, and folate. Small intestinal biopsies show either sprue-like histologic features, including villous shortening with increased number of lymphocytes in the epithelium and in the lamina propria, or a pattern similar to graft-vesus-host

disease. There is no response to a gluten-free diet (hypogammaglobulinemic sprue). Both of our cases had recurrent or chronic diarrhoea with normal stool exam and there was no detectable pathogen in their stools. Antigliadin antibody and Antiendomysial antibody were negative in both cases excluding celiac disease. It may indicate a sprue-like illness with malabsorption although stool exams did not prove malabsorption. In some patients with CVID, foamy macrophages are present, as found in Whipple's disease, but in contrast the macrophages do not contain periodic-acid-Schiff-positive material. In addition, nodular lymphoid hyperplasia can be detected in the GI tract in a high proportion of CVID patients and it does not correlate with the presence of malabsorption. However, the pathogenesis of most lesions in the GI tract of these patients remains unknown.[7]

It is important to consider CVID in any patient, with a history of recurrent infections in different organ systems especially respiratory and gastro-intestinal systems and such patients should undergo a full assessment of immune system. Diagnostic delay results in more morbidity and complications in untreated patients. Further studies are necessary to optimize the prevention and treatment of gastro-intestinal tract disease in CVID patients.

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