Chronic Diarrhea in Hypogammaglobulinemia: A Case Report of Immunodeficiency

Abstract

Introduction: Common variable immunodeficiency (CVID) or acquired hypogammaglobulinemia is the most common primary antibody deficiency which leads to lymphocytic dysfunction. CVID is not related to gender and can affect the person at any age, but the peaks of onset are the first and the third decades of life. CVID presents with various manifestations, which can obscure the proper diagnosis of the disease based on broad non-specific presentations. In this report, we describe a case of refractory chronic diarrhea secondary to underlying CVID disease without recurring bacterial infections.

Case Presentation: A 31 year old woman with a chief complaint of persistent diarrhea and weight loss for five years. She did not complain of any symptoms until the age of 26 when she started having several episodes of semi-solid diarrhea per day. Despite dietary and additional interventions, symptoms were persistent during a 5 year course of the disease and worsened in the last 2 months, with significant increase in volume and frequency of diarrhea and associated weight loss of 10 kilograms. Several work-ups were inconclusive and she was referred to us for evaluation of CVID enteropathy.

Discussion: Chronic diarrhea is considered one of the most common clinical manifestations of CVID. More than half of patients present with diarrhea and 10% develop idiopathic malabsorption associated with weight loss. This case report presents gastrointestinal manifestation of CVID as the only presentation during 5 years, which led to exhaustive diagnostic studies without definitive diagnosis or effective management. This report signifies the importance of early diagnosis of CVID, and the need to improve physicians' general awareness of manifestations of the disease.

Keywords: Common variable immunodeficiency; Hypogammaglobulinemia; Chronic diarrhea; Celiac disease

Case Report

Volume 4 Issue 1 - 2016

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Received: September 09, 2016 | **Published:** September 27, 2016

Abbreviations: CVID: Common Variable Immunodeficiency; GI: Gastrointestinal; Ig: Immunoglobulins; TNFα: Tumor Necrosis Factor Alpha

Introduction

Common variable immunodeficiency (CVID) or acquired hypogammaglobulinemia is the most common primary antibody deficiency which leads to lymphocytic dysfunction. Prevalence of CVID differs according to previous studies and ranged between 1 per 10,000 to 1 per 50,000 inhabitants [1,2]. CVID is not related to gender and can affect the person at any age, but the peak of onset are the first and the third decades of life [3,4]. Unfortunately, the pathophysiology of CVID does not lead to a simple and reliable method of diagnosis. CVID can present different signs and symptoms, but typically presents with recurrent bacterial infections [4].

The approach to such cases seems straight forward as recurrent bacterial infections bring the attention to an underlying immunodeficiency disease. The challenge begins when there is no obvious recurrent infection associated with immunodeficiency. Other manifestations of CVID includes: autoimmune diseases, respiratory complications, neoplasias, granulomatous diseases and gastrointestinal (GI) diseases [4]. Among these manifestations, gastrointestinal symptoms are broadly represented and therefore do not immediately bring the suspicion to CVID.

Below, we report a patient with underlying CVID who presented with diarrhea and poor quality of life. This case report is an example of sophisticated route to the final diagnosis of CVID with initial single GI manifestation and the need of appropriate physician awareness regarding CVID manifestations.

Case Presentation

A 31 years old woman was referred to our hospital with chief complaint of persistent diarrhea and weight loss. She did not have any complains until the age of 26 when she started having several episodes of semi-solid diarrhea per day. During these episodes, her diarrhea was associated with cramping abdominal pains. Daily number of defecations and their amount was variable during

the course of the disease. The initial evaluations excluded the probable role of bacteria, virus or parasites in the natural history of the disease. After ruling out of common possible etiologies of chronic diarrhea, the patient was considered as a possible case of Celiac disease and managed on a gluten-free diet. Despite the diet and supportive treatment, patient´s condition did not improve over the past 5 years and progressively worsened especially in the prior 2 months, with the increase in volume and frequency of diarrhea. She lost 10 kilograms during the immediately prior 2 months. The patient also complained of a new appearance of eczema-like patches on her hands and eyelids which resolved spontaneously after few weeks.

On physical examination, the patient was a cachectic young woman with normal vital signs. Physical examinations found no other abnormalities except a 5-6 cm vitiligo patch on the right side of her face. The eczema-like patches on upper extremities and eyelids which was reported previously by the patient, were not observed at the time of visit or afterwards. Laboratory findings were: white blood cells count: 8100 /mL with 73% neutrophils and 24% lymphocytes (normal range, 4000-1000), Hemoglobin: 12.7 g/dL (normal range, 12-16 gr/dL), Hematocrit: 37.5% (normal range, 36-46%), Platelet: 237000 (normal range, 140,000-400,000). Stool exam was negative for bacteria, parasite (ova, cyst or trophozoites) and occult blood. Colonoscopy and upper GI endoscopy with biopsy were performed. Serial section biopsy specimens from different parts of jejunum mucosa showed mild to moderate villous atrophy. Villous height to crypt depth ratio was 2-3/1. Focal borderline increase in the number of intraepithelial lymphocytes had been reported mainly at the tip of some of the villi reaching a number of 35 per 100 enterocytes. Focal cytoplasmic vacuolization of the epithelial cells was seen at the tip of a few intestinal villi. Intestinal glands are unremarkable. Mucosal associated lymphoid cells showed mild increase only in few areas which was composed of normal number of plasma cells and B-lymphocytes with mild increase in number of T-cells. No Giardia was seen in any of the biopsies. The pathology results, HLA typing and small bowel series ruled out diagnosis of Celiac disease, malignancies or other common well known gastro-enteric disorders. At this time, the patient was referred to our center of immunodeficiency diseases for the evaluation of CVID enteropathy. As the next step toward the final diagnosis, evaluation of patient's humoral immune system was conducted.

Serum levels of Immunoglobulins (IgG, IgA, IgE and IgM) were measured. This evaluation of humoral immune system revealed decreased levels of Immunoglobulins (IgG = 331 mg/dL, IgA = 19 mg/dL, IgM= 39 mg/dL, IgE = 1 mg/dL) compared to normal reference ranges (IgG: 768 to 1728 mg/dL, IgA: 99 to 396 mg/dL and IgM 38 to 266 mg/dL). Further measurements confirmed low levels of immunoglobulins. Based on these significant reductions in the immunoglobulins and complete prior investigations which ruled out other defined immunodeficiency states, we assigned the diagnosis of CVID [5,6] (CVID is a diagnosis of exclusion) and secondary chronic diarrhea as the sole manifestation of the underlying CVID enteropathy in this patient. IVIG was administered accordingly at the standard dosage and three months follow up revealed significant improvement in initial symptoms and general condition of the patient.

Discussion

Common variable immunodeficiency (CVID) includes a heterogeneous group of disorders characterized by hypogammaglobulinemia, defective specific antibody production, and increased susceptibility to recurrent and chronic infection. More than half of CVID patients present with diarrhea and possible risk of malabsorption and weight loss. Chronic diarrhea presents as one of the most common clinical presentation of CVID [1-4]. The present case report introduces a young woman with a chief complaint of persistent diarrhea with unknown etiology who was referred to our center for the evaluation of CVID enteropathy. She was suffering from these symptoms for the duration of five years and a history of complete work ups during this period did not reveal any specific diagnosis. Complete sequential GI investigations was reported normal findings except lymphocytic infiltration in lamina propria and interepithelial mucousa with villous atrophy in the biopsy of the small intestine, the patient having been on a gluten free diet for approximately four years.

Considering natural history of the disease, up to 60% of CVID patients present with diarrhea and 10% develop idiopathic malabsorption associated with weight loss [7]. Differentiating between diarrheas from the source of infection or inflammatory origin is difficult [8]. Some patients have small-intestine involvement with villous atrophy mimicking celiac disease, with poor response to gluten-free diet [9]. It is possible, however, that increased apoptosis, decreased plasma cells, and increased tumor necrosis factor alpha (TNFα) found in some patients, are related to dysfunction of T and B lymphocyte [10,11] related to CVID.

Typically, primary immunodeficiency diseases (PIDs) are characterized with multiple organ involvement. Involvement of a single organ would normally point to the existence of anatomical or functional disorder in that organ, but the physicians must consider other probable conditions. So, in any patient suffering from chronic diarrhea unrelated to known causes, could have primary immunodeficiency.

Secondly, this case shows that although CVID as a primary immunodeficiency disease (PID) is often identified by recurrent infection, the presence of recurrent infection is not an absolute criterion for the diagnosis, at least in the preliminary presentation of disease. As the introduced case had had no history of irregular infection (recurrent or unusual infections) since the initiation of symptoms.

H. Chapel and colleagues in a valuable cohort study on CVID patients, had described five major clinical phenotypes of CVID: Viral infections, Autoimmunity, Polyclonal lymphocytic infiltration, Enteropathy and Malignancies [5]. The initial criteria for inclusion of a patient into a specific group were described. A total of 83% of patients had only one of these phenotypes. In patients with dominant enteropathy, biopsy-proven lymphocytic infiltration in lamina propria and interepithelial mucous with villous atrophy was described, which is also consistent with our case.

Moreover, some standardized criteria for diagnosis of CVID have also been described and subcategorized based on phenotypical

characteristics [5]. These include: recurrent bacterial infections, age older than 4, serum IgG level below the lower normal limit with at list low level of one other serum Ig isotype, and exclusion of underlying causes. However, CVID should be considered even in the absence of any history of recurrent infections [12,13].

Unfortunately, CVID is often diagnosed late during the progress of the disease. Analysis of diagnostic delay on 388 patients has shown a range of 0 to 61 years for age, with 20% of the patients being diagnosed with a CVID more than 15 years after the onset of symptoms [5]. The mean diagnostic delay has been 7.46 years, and median has been 5 years, with 94.9% of the values being within 14.84 years (2 SD). The association between autoimmunity and later age at diagnosis has been shown in some studies. It may indicate lack of awareness of this association and is unexpected, since autoimmunity is usually more common in young females [2,5].

CVID and the related manifestations are rarely considered as a differential diagnosis in current clinical practice. This can bring high imposed expenditures to our medical practice, regarding excessive time and cost spend on numerous diagnostic tests for each CVID patient. Because IVIG can be an effective treatment of CVID, current standard of care may consider IVIG responsiveness in such refractory cases, as a clue to the diagnosis of the disease; especially in those centers with insufficient equipment to evaluate patients' immunologic panel.

Finally, it should be considered that CVID could present with single organ involvement, especially GI system, without any previous history of recurrent bacterial infection. This could mislead the initial diagnoses, hence, physician awareness of CVID and related heterogeneous clinical presentations should be considered seriously in common clinical practice.

Conclusion

The importance of improvement of general physicians' awareness with education on the diagnostic methods related to CVID is warranted.

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Citation: Shokuhfar T, Panah E, Aghamohammadi A (2016) Chronic Diarrhea in Hypogammaglobulinemia: A Case Report of Immunodeficiency. MOJ Immunol 4(1): 00116. DOI: 10.15406/moji.2016.04.00116