CASE REPORT

Common variable immunodeficiency associated enteropathy: A diagnostic enigma in developing countries

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Abstract

Common variable immunodeficiency (CVID) is the most prevalent primary immunodeficiency disorder with different phenotypes and aetiologies. It is characterised by hypogammaglobulinaemia, defects in specific antibody response, erroneous activation and proliferation of T cells, leading to increased risk of recurrent infections. In CVID, "Variable" refers to the heterogeneity of clinical presentations, which include recurrent infections, autoimmunity, enteropathy, and increased risk of malignancies. This wide spectrum of disease manifestations and being a diagnosis of exclusion poses a diagnostic challenge. It is pertinent to mention that CVID along with associated complications is the commonest symptomatic primary antibody deficiency but is scarcely mentioned in local literature. The main aim of presenting this case is to impress upon the importance of systematic immunological workup in cases of suspected immunodeficiency to prevent morbidity and mortality.

Keywords: Common Variable Immunodeficiency, Enteropathy, Primary Immunodeficiency.

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Introduction

The term "Common variable immunodeficiency" (CVID) was conceived by a World Health Organisation committee in 1971 to distinguish ill-defined antibody deficiency conditions from the one's with more coherent clinical criteria and genetic linkage.

Cases of CVID are usually sporadic but infrequently familial clustering has been reported.[1] The frequency of CVID varies from 1:10,000 to 1:50,000 and equally affects males and females. This disease may be diagnosed at any age but is more common between 20–45 years of age. CVID is broadly classified into four clinical phenotypes which include infections, autoimmunity, lymphoproliferative disease, and enteropathy.[2,3] The clinical presentation is variable as patients may have only one of these phenotypes or may present with overlapping manifestations. The main aim of presenting this case is to impress upon the importance of systematic immunological workup in cases of suspected immunodeficiency to prevent morbidity and mortality.

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Case Report

The case of a 16-year-old male patient is presented who was wrongly diagnosed as a case of seronegative coeliac disease. This caused a diagnostic delay of his primary immunodeficiency disease, CVID-associated enteropathy. The child was the first born of non-consanguineous parents. The presenting complaints were persistent diarrhoea for the last 10 years, recurrent sinopulmonary infections, and failure to thrive. The patient underwent diagnostic evaluation in March 2022 at the Armed Forces Institute of Pathology, Rawalpindi, Pakistan. There was no family history of primary immunodeficiency or autoimmune diseases in first degree relatives. He was vaccinated as per extended programme of immunisation. General physical examination revealed a thin emaciated boy with Glasgow Coma Scale (GCS) 15/15.[4] His anthropometric measurements revealed that his height and weight were well below the third centile for age-specific range and his BMI was less than the first centile for age-specific range. He had mild pallor. There was no hepatosplenomegaly or lymphadenopathy and tonsils were present. Laboratory investigations including blood complete picture which showed Hb 10 g/dl (RR: 12-17 g/dl), TLC 6.1x10^9/L (RR: 4-11x10^9/L) with platelet count of 210 x10^9/L (RR: 150-450x10^9/L). His serum urea, creatinine and coagulation profile were within normal limits. The work-up to rule out any bacterial or viral infections, blood culture, mycobacterial culture, serological tests for HIV, toxoplasmosis, parvovirus, cytomegalovirus, brucella and hepatitis were negative. On Chest X-ray and HRCT there were no signs of mediastinal lymphadenopathy, emphysema, and bronchiectasis. His coeliac serology including anti-tissue transglutaminase IgA and IgG, anti-endomysial IgA and IgG, anti-deamidated gliadin peptide antibodies IgA and IgG, anti-reticulin IgA, and anti-gliadin IgA antibodies were also negative. Although the serology for coeliac disease was negative, duodenal endoscopy and biopsy were carried out to investigate unexplained weight loss and persistent diarrhoea. Histopathological

examination of duodenal biopsy was suggestive of coeliac disease. On the basis of biopsy findings, he was diagnosed as a case of seronegative coeliac disease and was advised gluten free diet but his symptoms did not resolve. To rule out any underlying primary immunodeficiency, the patient was advised estimation of serum immunoglobulin levels, which were found low: IgG<1.6 g/L (RR: 5.3- 16.5 g/L), IgA <0.3 g/L (RR: 0.8-4.0 g/L) and IgM <0.1 g/l (RR: 0.5-2.0 g/L). His serum IgE antibodies were also low: < 1 IU/ ml. Blood grouping showed A+ while his isohaemagglutinin titre was absent. Flow cytometry of the peripheral blood displayed absolute lymphocyte count to be 3,160 cells/ul and absolute CD3+ T cell count to be 2,939 (93%), CD3+CD4+ T cells=999 (34%), CD3+CD8+ T cells=1,645 (56 %), reversed CD4+/CD8+ T cells ratio: 0.6, CD19+ B cells=158 (5 %) and CD 16+CD 56+NK cells=88 (3%). The HLA-DQ 2 and HLA-DQ 8 were noted to be absent which ruled out coeliac disease. To investigate functional antibody response against ubiquitous organisms, anti-*E. coli* and anti-Candida antibody titre were checked by indirect immuno-fluorescence technique and were observed to be negative. To determine post immunisation response, anti-tetanus and anti-diphtheria antibody titre were checked by third generation enzyme-linked immunoassay (ELISA) and were noted to be deficient. Keeping in view the immunological investigations, exclusion of secondary causes of hypogammaglobulinaemia, and histopathological findings, the patient was diagnosed as a case of CVID-associated enteropathy with almost absent serum immunoglobulins and reduced B lymphocytes. The patient was treated with immunoglobulin replacement therapy at a dose of 400-600 mg/kg/month. He was also given steroids (Prednisolone) orally starting with a dose of 0.1 mg/kg/day. After two months his diarrhoea and recurrent infections were well controlled, he started to gain weight and is experiencing significantly improved quality of life. Assent and consent of the patient and his parents was obtained prior to reporting this case for publication.

Discussion

CVID is a diagnosis of exclusion and clinical heterogeneity of this condition makes it a diagnostic enigma. Furthermore, specialised immunological investigations are required to reach a definitive diagnosis which are not usually available in routine diagnostic labs. However, early recognition of warning signs of immunodeficiency and careful investigation of past medical history are the early steps for the diagnosis, followed by relevant immunological workup. Detailed past medical history, including duration of illness, frequency of recurrent infections, and other associated symptoms such as autoimmune and allergic manifestations, should be documented. Dietary habits and nutritional status of the patient should be evaluated as failure to thrive in children and unexplained weight loss in adults is a relatively common symptom in CVID. Family history is of utmost importance in such cases, possible occurrence of immunodeficiency or autoimmunity in relatives must be inquired. As per the International Consensus (ICON) guidelines 2016[1], for diagnosis of CVID, five criteria are required: age more than four years; presence of at least one of the characteristic clinical presentations (infection, autoimmunity, enteropathy and lymphoproliferation); reduced IgG levels on two repeated measurements three weeks apart, either a low IgA or IgM; poor immunisation response; and exclusion of secondary causes of hypogammaglobulinaemia. Molecular investigations are not required for diagnosis but can be helpful for genetic counselling in familial cases.[1,5]

Common underlying causes of gastrointestinal manifestations of CVID include viral infections, amoebiasis, chronic giardiasis, intestinal malabsorption, and atrophic gastritis with pernicious anaemia. The symptoms range from mild dis-comfort, bloating, and diarrhoea to more severe profuse diarrhoea, malabsorption, and weight loss. CVID associated enteropathy is characterised as a biopsy-proven lymphocytic infiltration in lamina propria and intraepithelial mucous and villous atrophy. While these findings resemble coeliac sprue, several key differences are apparent between the villous flattening of CVID and coeliac disease. In coeliac disease, there is plasma cell infiltra¬tion accompanied by increased levels of IgA and IgM. CVID-related enteropathy can be differentiated from coeliac disease on the basis of the absence of pathognomonic antibodies (Anti-tissue transglutaminase, anti-endomysial, anti-gliadin, and anti-reticulin antibodies), absence of response to gluten withdrawal, and absence of HLA DQ 2 and 8.[6] This is a very rare case of CVID-associated enteropathy with nearly absent serum immunoglobulin levels and significantly reduced B lymphocytes. Due to chronic diarrhoea and villous atrophy in intestinal biopsy, the patient was misdiagnosed with coeliac disease and placed on gluten free diet which further resulted in weight reduction. Many cases of CVID have been reported in Pakistan but CVID-associated enteropathy is being reported for the first time. It is pertinent to mention that a similar case of enteropathy with multiple immunodeficiencies had already been reported in local literature in which a previously diagnosed case of seronegative coeliac disease was later diagnosed as a case of refractory CD with IgA, IgG, and classical NK cell deficiency.[7] Early diagnosis and prompt management can lead to improved quality of life and better prognosis. Immunoglobulin replacement therapy either by an intravenous or subcutaneous route, usually in doses of 400 to 600 mg/kg/month is the mainstay of treatment in CVID.

Immunoglobulin replacement significantly improves symptoms and allows patients to live a near normal life.[8] Immunoglobulin replacement therapy alone is not effective in CVID-related enteropathy and oral steroids are also recommended in such cases.

Conclusion

A high level of suspicion must be raised in all patients presenting with warning signs of primary immunodeficiency. Systematic immunological workup in cases presenting with chronic diarrhoea and features of primary immunodeficiency can lead to early diagnosis and reduce morbidity and mortality in such cases.

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MAH: Concept, data interpretation.
MH, MOR: Drafting, revision.
DA: Revision, final approval.
MZA: Data acquisition, interpretation.