Common Variable Immunodeficiency Enteropathy and Its Unpredictable Biopsy Findings: Not Everything Is Black and White

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Abstract

Common variable immunodeficiency syndrome (CVID) is a diverse entity characterized by hypogammaglobinemia and a propensity for recurrent infections. Involvement of the gastrointestinal tract has a variable manifestation ranging from asymptomatic involvement to florid signs and symptoms. Due to these incongruous findings, multiple concurrent biopsies are to be done for tissue diagnosis. Here, we present two cases diagnosed with CVID on the basis of clinical findings, lab investigations, and morphological features on biopsy.

Keywords:
Common variable immunodeficiency syndrome, Enteropathy, Hypogammaglobulinemia, Infection

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Introduction

Common variable immunodeficiency syndrome (CVID) is a primary immunodeficiency syndrome characterized by a defect in B cell function.[1] As a result, there is hypogammaglobulinemia, leading to a diminished ability to produce antibodies in response to infections. CVID enteropathy is a challenging entity, due to the varied disease course and heterogeneous biopsy findings, along with variable distribution of plasma cells throughout the gastrointestinal (GI) tract. Patients with CVID are often misdiagnosed; hence a high index of suspicion and clinicopathological correlation are required for the correct diagnosis of this potentially debilitating condition.

Case Report

Case 1

A 38-year-old man had a prolonged history of loose stools (15-20 episodes per day) over the last 4 months. This was associated with intermittent colicky abdominal pain. There was a history of significant weight loss of more than 7 kg in the past 3-4 months duration. There was no history of fever or bloody stool. His symptoms started 4 years back, and he was given anti-tubercular therapy in some other hospitals. The symptoms subsided for around 9 months but again recurred with

an on-and-off presentation. On physical examination, the patient had a poor build and low body mass index (BMI) with pallor. Laboratory studies showed moderate anemia with low serum iron and ferritin levels. Other investigations revealed serum protein 48 g/L, serum albumin 26 g/L, and serum globulin 18 g/L. Tissue transglutaminase IgA (tTG-IgA) levels were normal. Stool examination showed mucus with 10-15 WBCs/hpf. Stool biofire multiplex PCR for organisms revealed giardia lamblia and isospora. Computed tomography (CT) enterography revealed thickening in the lower common bile duct (CBD) along with dilatation of CBD and intrahepatic biliary radicals with mild prominence of ileal folds compatible with cholangiopathy. Upper GI endoscopy showed no abnormal findings. Colonoscopy showed ileal nodularity (Figure 1a). Three biopsy samples (duodenal, jejunal, and ileal) were taken, and histological features are summarized in Table 1. Considering the history of low globulin levels, opportunistic infections, and the absence of plasma cells on biopsies, the possibility of CVID was suggested. The serum immunoglobulin levels were then evaluated and were found to have low levels of IgG, IgM, and IgA. The CD4 counts were normal. H*uman immunodeficiency virus enzyme-linked immunosorbent assay* (HIV ELISA) was negative. The patient was thus diagnosed as having CVID. He was treated with intravenous (IV) immunoglobulins. The symptoms subsided, and the patient gained weight on follow-up.

Case 2

A 34-year-old man with no previous co-morbidities presented with complaints of vomiting after food intake. The vomiting was non-projectile, non-bilious in nature, and was associated with abdominal discomfort, bloating, and diarrhea (3-4 episodes per day) over the last 2 years. He also complained of weight loss (8-10 kg) in the last 3 years. He was evaluated at a local hospital. A routine stool examination showed the presence of giardia. Laboratory studies showed hemoglobin 100 g/L, folic acid 11.3 nmol/L, vitamin B12 121.7 pmol/L, serum iron 3.93 µmol/L, and ferritin 0.009 nmol/L. D-xylose and hydrogen breath tests were normal. IgA, and IgM serum immunoglobulin levels were decreased, but IgG was normal. ELISA tests for HIV, hepatitis B surface antigen (HBsAg), and hepatitis C virus (HCV) were negative. CT enterography showed no abnormality. Duodenal and ileal nodularity was noted on endoscopy and colonoscopy, respectively. In view of the clinical findings, two biopsy samples (duodenal and ileal) were taken, and histological features are discussed in Table 1. The patient was diagnosed with CVID enteropathy and was further treated with IV

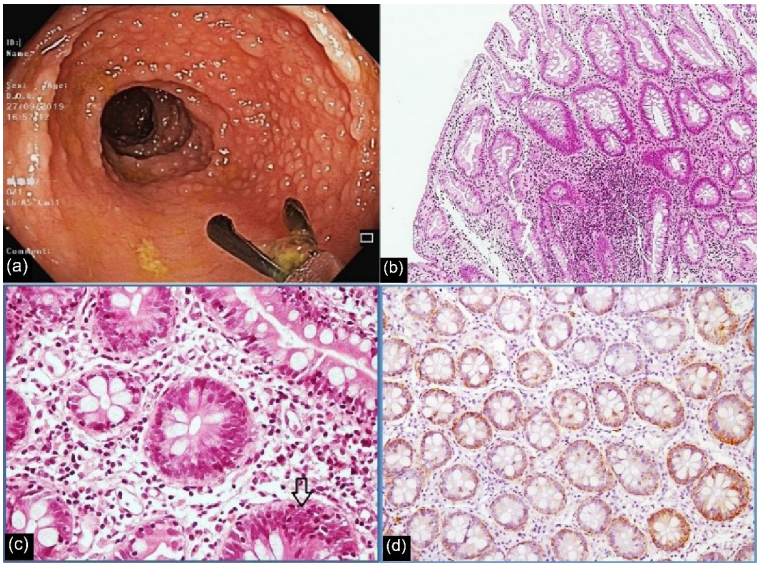

Figure 1. (a) Colonoscopy image showing ileal nodularity; (b) Duodenal biopsy showing moderate blunting of villi (H&E 100x); (c) Jejunal biopsy showing mild increase in intraepithelial lymphocytes (arrow) with marked reduction of plasma cells in the interstitium (H&E 200x); (d) CD138 IHC stain: Jejunal biopsy showing marked reduction in plasma cells (200x)

Table 1. Comparative analysis of biopsy findings of the two cases

Histopathological parameters	Duodenal biopsy		Jejunal biopsy		Ileal biopsy	
	Case 1	Case 2	Case 1	Case 2	Case 1	Case 2
Villous height	Tall villi	Mild to moderate blunting (Figure 1b)	Mild blunting	-	Mild blunting, focal ulceration of the mucosa	Mild focal blunting
Villous to crypt ratio	Normal	Normal	Reduced	-	Reduced	Reduced (focal)
Intraepithelial lymphocytes	Not increased	Mildly increased	Mildly increased (Figure 1c)	-	Normal	Increased
Cryptitis	Absent	Absent	Present (focal)	-	Present (focal)	Eosinophilic cryptitis
Inflammatory cells						
Lymphocytes	Increased	Mildly increased	Increased	-	Normal	Increased
Eosinophils	Normal	Mildly increased	Increased	-	Normal	Normal/ Increased
Plasma cells (H & E stain with CD138 IHC)	Normal	Reduced	Reduced (Figure 1d)	-	Variable (patchy areas showing normal number while few areas showed marked reduction) (Figure 2c,d)	Reduced (Figure 2b)
Lymphoid follicles (H & E stain with CD20 IHC)				-	Hyperplastic (Figure 2a)	Hyperplastic
Granuloma	Absent	Absent	Absent	-	Absent	Absent
Bacterial colonies	Absent	Absent	Absent	-	Absent	Present
Parasite	Absent	Absent	Absent	-	Absent	Absent
Viral inclusions	Absent	Absent	Absent	-	Absent	Absent

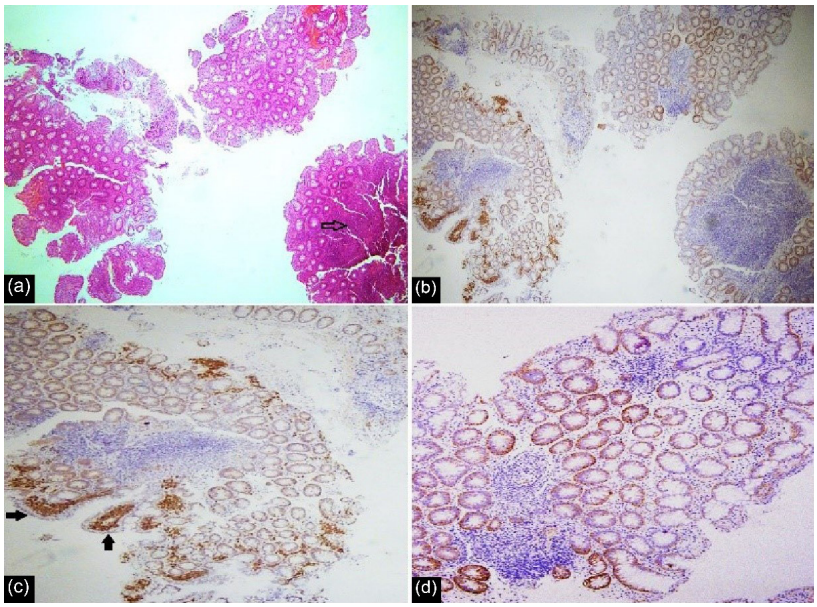

Figure 2. (a) Ileal biopsy showing hyperplastic lymphoid follicle (arrow) (H&E 40x); (b) CD138 IHC stain: Ileal biopsy showing variable number of plasma cells (40x); (c) Higher magnification highlighting the increased plasma cells in the lamina propria (arrows) (CD 138 IHC 100x); (d) Biopsy from same site showing complete absence of plasma cells in another fragment (CD 138 IHC 100x)

fluids, antibiotics, and other supportive measures. The symptoms subsequently subsided, and the patient is doing fine in a 2-year follow-up.

Discussion

Although CVID can present at any age, it is usually diagnosed between 20-40 years of age.[2] The classic presentation of CVID involves recurrent and chronic bacterial infections. This propensity to develop infections occurs due to deficient antibody production. Nearly all the patients present with recurrent respiratory infections (bronchitis, sinusitis, pneumonia) followed by involvement of the gastrointestinal tract (9-20%).[3,4] The diagnosis is challenging when they present with only GI symptoms. CVID can present with a spectrum of clinical manifestations, and the histopathological finding can simulate many conditions. Clinically, patients may be asymptomatic or may present with vague abdominal discomfort, bloating, chronic diarrhea, malabsorption, weight loss, rarely intestinal obstruction, and even malignancy. The most important diagnostic clue (but not sine qua non) for CVID in a biopsy is the paucity of plasma cells. However, that is also not a constant finding, and the number is variable in different parts of the GI tract. Daniels and colleagues evaluated 132 GI biopsies of 20 patients over 26 years and found the reduction of plasma cells in 63-68% of biopsies in various parts of the intestine.[2] Other histological findings were lymphoid aggregates, increased apoptosis, increased intraepithelial lymphocytes, villous blunting, thickened collagenous bands, granulomas, intraepithelial neutrophils, crypt distortion, superadded infections, and malignancy in various proportions. An understanding of the range of histologic features associated with this disease is required to avoid misdiagnosis. CVID can mimic various other conditions in the biopsy, too, like celiac disease, graft versus host disease, inflammatory bowel disease, sarcoidosis, and collagenous sprue, to name a few. In the published European study comprising 252 patients with CVID, giardia *lamblia* was the most common GI pathogen.[5] Repeated antigenic stimulation leads to lymphoid hyperplasia; hence, numerous tiny polypoidal nodules are seen in the small and large intestines on endoscopy/colonoscopy.[2] Because of the heterogeneous clinical and pathological features, there is often a delay in diagnosis ranging from 5 years to 10 years.[6] Better understanding of epidemiological, clinical, and histopathological features may reduce the time lapse in diagnosis, thereby reducing the severity and clinical complications. There are studies that report a shorter diagnostic delay in patients with CVID in recent years after a better understanding of the disease process.[7] European Society of Immunodeficiencies formulated a diagnostic criterion for CVID in 1999, which was updated in 2014.[8,9] The cases are categorized either as 'probable CVID' or 'possible CVID' as per the diagnostic criteria and are treated with IV immunoglobulins accordingly. Our first case developed cholangiopathy. Although the exact etiology was not identified, it was believed to be an outcome of opportunistic infection. Crotty and others in their study, reviewed a cohort of 26 hepatic CVID biopsies and found two cases showing features of primary biliary cholangitis , including florid duct lesions and prominent bile duct injury, and suggested this biliary pathology as one of the many autoimmune manifestations of CVID.[10] It is important to keep patients with CVID on long-term follow-up as the chances of developing granulomatous diseases, lymphoproliferative disorders, and malignancies are high.[11,12] Prompt recognition and conscientious treatment of opportunistic infections with timely replacement of immunoglobulins are the mainstays of therapy. These patients need close clinical follow-up and continuous antimicrobial prophylaxis unless they undergo stem cell transplantation.

Conclusion

To conclude, CVID is often misdiagnosed in clinical and pathological settings because of myriad clinical and histological presentations. Diagnosis cannot be given in isolation and has to be correlated with clinical and laboratory findings. Although the absence/paucity of plasma cells is considered the best diagnostic clue in GI biopsies, the heterogeneous presence, and distribution of plasma cells mandates the need for multiple concurrent biopsies. Clinicians should be aware of this fact and should take multiple biopsies from various sites and ask for other appropriate investigations for correct diagnosis. The possibility of this entity should be kept in mind by the reporting

pathologist as well, especially if there is a history of recurrent intestinal infections or malabsorption-like symptoms. Keen observation by a pathologist can go a long way to avoiding a delay in diagnosis and preventing serious sequelae, including malignancy, end organ damage, or even death.

Conflict of Interest

The authors declare no conflict of interest related to this work.

Ethical Approval

There is nothing to be declared.

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