

Common Variable Immunodeficiency with Several Gastrointestinal Manifestations

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ABSTRACT

Common variable immunodeficiency (CVID) is an immunodeficiency disorder with a high incidence of gastrointestinal (GI) manifestations and an increased risk of gastric malignancy. We report a case of a CVID with mild anemia presenting with multiple GI manifestations: gastric low-grade dysplasia (LGD), enteropathy with villous atrophy, refractory *Giardia* infection, nodular lymphoid hyperplasia, and inflammatory bowel-like disease. The differential diagnosis with celiac sprue could be challenging because of CVID enteropathy with villous flattening. Gastric LGD in a patient with an increased risk for gastric malignancy makes the appropriate surveillance of gastric cancer in CVID challenging.

INTRODUCTION

Common variable immunodeficiency (CVID) is a primary immunodeficiency disorder characterized by impaired B-cell differentiation with defective immunoglobulin production.¹ It is defined by markedly reduced serum concentrations of immunoglobulin G (IgG) in combination with low levels of IgA and/or IgM, poor or absent response to immunizations and an absence of any other defined immunodeficiency state.¹ Presentation is variable and includes recurrent infections, chronic lung disease, autoimmune, granulomatous and gastrointestinal (GI) disorders, and an increased risk of malignancies, especially lymphoma, with incidence rates ranging from 2% to 10%.^{2,3} The incidence of GI manifestations is high (20–60%), and the majority of the GI disorders in CVID are thought to be caused by T-cell-mediated defects and not by the antibody deficiency.^{2,4}

CASE REPORT

A 42-year-old woman with a 2-year diagnosis of CVID after several sinopulmonary infections presented with a 2-month history of epigastric discomfort and postprandial fullness. She denied other symptoms such as diarrhea, weight loss, or fatigue. She was receiving IgG replacement therapy (400 mg/kg every 3 weeks) with normalization of IgG levels and marked improvement of sinopulmonary infections. Laboratory tests revealed iron-deficiency anemia (hemoglobin 11.2 g/dL, mean corpuscular volume 72 fL) and normal levels of albumin and inflammatory markers. Esophagogastroduodenoscopy (EGD) showed a stomach with a multifocal atrophic gastropathy and pale mucosa areas in antrum. The duodenum exhibited villous blunting, swollen and granular appearance, micronodular pattern, and exuberant ecchymotic areas (Figure 1).

Gastric biopsies showed pan-atrophic gastritis with intestinal metaplasia and low-grade dysplasia (LGD) foci in antrum and corpus. Biopsies were positive for *Helicobacter pylori*. Duodenal biopsies showed villous atrophy, presence of eosinophils, nodular lymphoid hyperplasia (NLH), and numerous parasites compatible with *Giardia lamblia* (Figure 2). The complementary study was negative for anti-tissue transglutaminase antibodies, anti-endomysial

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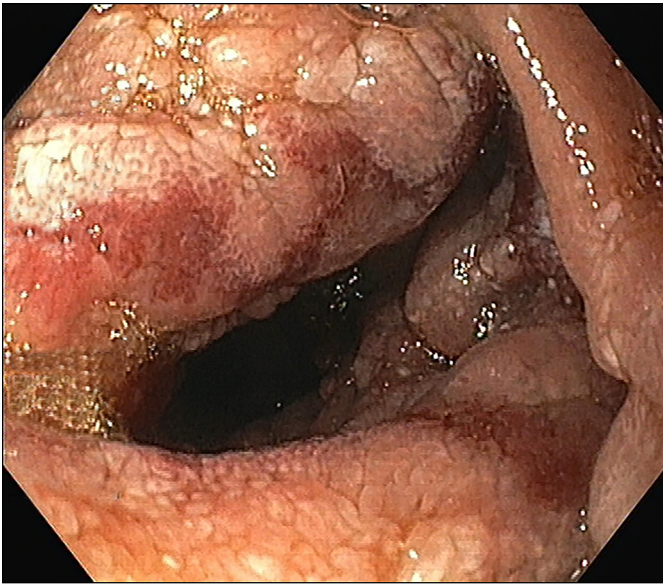


Figure 1. Duodenal villous blunting with ecchymotic areas.

antibodies, intrinsic factor antibody, parietal cell antibody, HLA-DQ2, and HLA-DQ8. Both stool culture and parasitological exam were negative. Ileocolonoscopy showed villous blunting and exuberant micronodular pattern in terminal ileum (Figure 3) and swollen friable mucosa in the right colon. Ileal biopsies showed villous atrophy, presence of eosinophils, polymorphonuclear cells, and NLH, which was also found in biopsies of the right colon.

A capsule endoscopy revealed a diffuse micronodular mucosal pattern in duodenum and ileum, a relatively spared jejunum, and uncountable ileal aphthous erosions and circular superficial ulcers (Figure 4). *H. pylori* was eradicated, and the patient was integrated into a surveillance endoscopic protocol for gastric LGD with EGD and biopsies every 6 months.

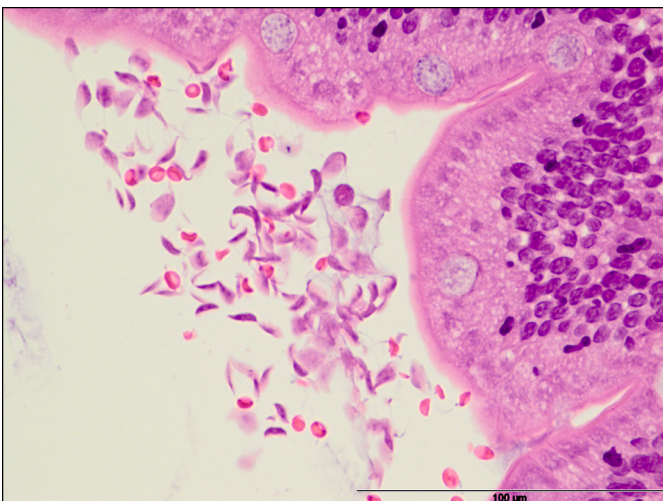


Figure 2. *Giardia lamblia* in duodenal biopsy specimens.

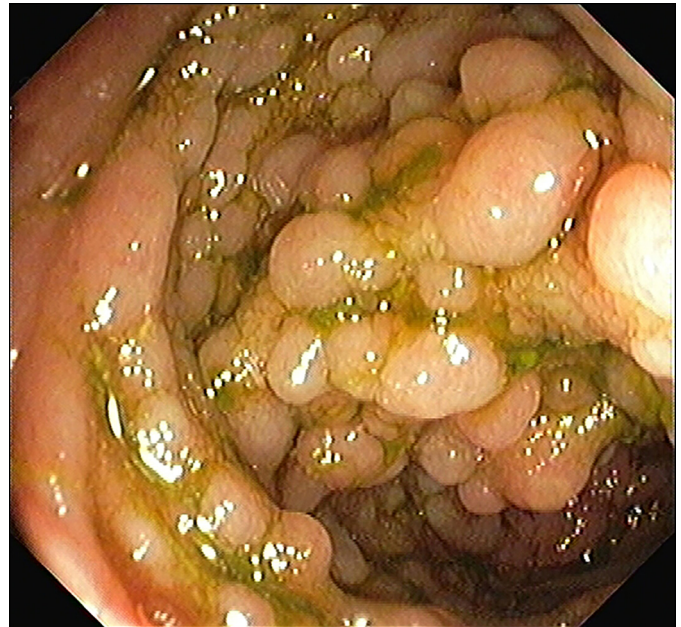


Figure 3. Micronodular ileal pattern in terminal ileoscopy.

Three different schemes were used for giardiasis treatment (metronidazole 250 mg, 3 times per day for 8 days; tinidazole 2 g in a single dose; and albendazole 400 mg/day for 5 days); all were unsuccessful, with the persistence of *Giardia* documented in duodenal biopsies. In a multidisciplinary consultation with Infectious Diseases, a decision was made not to perform any new treatment attempts.

DISCUSSION

CVID encompasses a group of heterogeneous syndromes with a common endpoint of defective immunoglobulin production and dysregulated immune responses. CVID pathophysiology remains incompletely understood. Antibody production is always disturbed, and this may be due not only to B-cell dysfunction, but also to the impairment of T-cell function and the lack of sufficient support for antibody production.⁵ The range of clinical manifestations is complex, with patients often

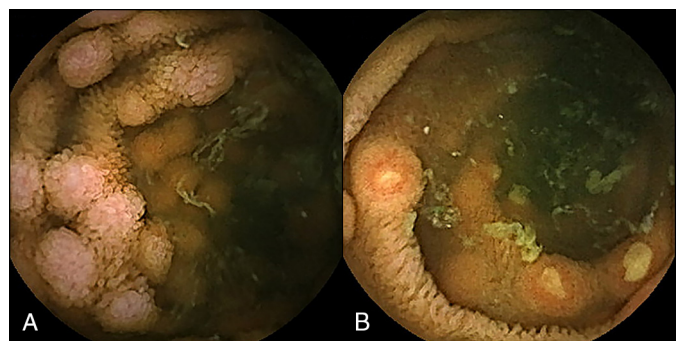


Figure 4. (A) Micronodular duodenal pattern on capsule endoscopy. (B) Ileal ulcers on capsule endoscopy.

classified into two main groups: one with only a history of infections and a second group with a history of infections and a variety of inflammatory or autoimmune conditions, with apparently stable phenotypes over time.⁶ The most common infections are sinopulmonary infections, including pneumonia, bronchitis, sinusitis, and otitis, but others such as GI infections, septic arthritis, and bacterial meningitis may also occur.^{5,7,8}

Inflammatory/autoimmune manifestations include immune thrombocytopenic purpura, autoimmune hemolytic anemia, seronegative arthritis, pernicious anemia, Sjögren syndrome, uveitis, vasculitis, thyroiditis, alopecia, vitiligo, hepatitis, primary biliary cirrhosis, or systemic lupus erythematosus.⁵ Chronic lung disease due to airway inflammation is common and may progress over time to obstructive or restrictive disease and bronchiectatic changes.⁵ All types of malignancies are more frequent in patients with CVID compared to the general population and lymphomas are the most common form of malignancy. GI manifestations of CVID are frequent and may be the initial manifestation. Specific GI disorders are bacterial, protozoal, and viral infections, enteropathy with villous blunting, inflammatory bowel disease (IBD) mimickers, NLH, gastric cancer, and GI lymphoma.^{5,6,9,10}

We present a case of multiple GI manifestations of CVID: sprue-like disease, *Giardia* infection, NLH, and IBD-like phenotype in a patient with no other organ manifestations of CVID. The presence of a gastric LGD raises questions about the appropriate surveillance, because CVID patients have a 10-fold increased risk of gastric cancer.¹⁰ Dhalla et al proposed a surveillance programme for CVID, which includes testing and treating *H. pylori* at diagnosis in all patients. EGD with biopsies should be performed in those with dyspeptic symptoms, unexplained weight loss, low vitamin B12, and urea breath test positive for *H. pylori*. Subsequent gastroenterological follow-up depends upon the histologic findings; in the presence of dysplasia, EGD should be repeated in 6–12 months.¹⁰ CVID sprue-like disease with duodenal villous atrophy is a frequent finding, and the differential diagnosis with celiac sprue could be challenging due to uselessness of antibodies, which are not detected due to poor antibody production.

Some histological features may help in differential diagnosis, as is the case of the absence of plasma cells, which are more suggestive of CVID-enteropathy than celiac disease.³ In our patient, the differential diagnosis was also supported by negative HLA-DQ2 and DQ8 haplotypes. Giardiasis is the most common GI infection in CVID and can be quite challenging to treat when comparing with immunocompetent patients.⁶ It often requires a more prolonged course, higher doses, or combination regimens.^{11–13} In our case, a decision was made not to treat because the patient was asymptomatic and had undetectable levels of IgA, which indicated a high risk of reinfection. NLH is

found in approximately 20% of adults with CVID.¹⁴ Its cause is still unknown, but it is thought to be a compensatory response to the antibody deficiency, although treatment with IgG has not been shown to correct it.¹⁵ NLH is also a risk factor for both intestinal and extraintestinal lymphoma.¹⁶ An IBD-like phenotype resembling Crohn's disease or ulcerative colitis has also been described, and its management is generally the same as for IBD in immunocompetent patients, although it might be more difficult to control in CVID.^{7,11}

It is rare to observe this multiplicity of GI disorders in a single patient, and we highlight the endoscopic abundance of findings in a patient with comparably mild symptoms.

DISCLOSURES

Author contributions: C. Atalaia-Martins wrote the manuscript and is the article guarantor. S. Barbeiro and P. Marcos collected the data and reviewed the literature. I. Cotrim and H. Vasconcelos edited the manuscript.

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