Gastrointestinal Presentations of Common Variable Immunodeficiency

Hiding in Plain Sight

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Primary immunodeficiency disorders typically have an onset in childhood. The suspicion for these conditions usually arises from a history of recurrent respiratory, gastrointestinal, or cutaneous infections with a history often dating back to infancy or early childhood. However, adults can also be affected. Common variable immunodeficiency, which usually has an onset/diagnosis in adulthood, is the most common symptomatic primary immunodeficiency. However, as its presentation could be manifold, its diagnosis is often delayed. The gastrointestinal tract is the second most affected system after the respiratory tract; symptoms associated with the gastrointestinal tract are often intractable. As patients with common variable immunodeficiency are often misdiagnosed, a high index of suspicion and clinical correlation is required for the appropriate diagnosis of this potentially debilitating condition.


Common variable immunodeficiency (CVID) is a heterogeneous and complex clinical syndrome that is secondary to a defective production of immunoglobulins. The deficiency is usually due to an abnormality in the differentiation of B cells, although occasional T-cell abnormalities may also be present.1 It is important to note that CVID is a mixed bag of several immunoglobulin deficiencies, all presenting with a common clinical syndrome characterized by low serum immunoglobulins and recurrent infections.1 As this condition is often underdiagnosed, the determination of the actual incidence and prevalence of this condition is difficult. Estimated figures put the prevalence at between 1:10,000 and 1:50,000.2,3 Although it is known that CVID shows no gender or racial predilection, the majority of patients with CVID are white (from Europe and North America), with rare cases among Asians and blacks.2–5 Patients typically begin to experience symptoms by the third decade of life, with 20% of patients presenting before the age of 20 years, but diagnosis is often delayed until the fourth decade of life.1–5

PATHOGENESIS/ETIOLOGY

Although the exact pathogenesis of CVID remains unknown, certain patients harbor mutations of genes related to the impairment in the development and differentiation of B cells. The most common mutation described in patients with CVID (seen in approximately 8%–10% of cases) is that involving TNFRSF13B, a gene that encodes for the transmembrane activator and calcium modulator and cyclophilin ligand interactor (TACI).6,7 TACI is a tumor necrosis factor–like receptor selectively expressed on B cells, especially on memory B cells (CD27-positive subset).7 The B-cell–activating factor receptor (BAFFR) and B-cell maturation antigen (BCMA) are other important receptors involved in B-cell maturation. A series of complex reactions between B-cell receptors (such as TACI, BAFFR, and BCMA) and B-cell–maturation regulatory molecules (such as B-cell–activating factor [BAFF] and a proliferation-inducing ligand [APRIL]) is important in the development and maintenance of B cells and consequently humoral immunity (Figure 1).7 Other identified mutations include autosomal-recessive mutations in BAFFR, CD20, CD19, CD81, CD21, and inducible T-cell costimulator (ICOS).7 Although CVID patients with TNFRSF13B mutations show normal total peripheral B-cell numbers, these patients have a diminished CD27-positive memory B-cell population, with a severe decrease in the switched memory B-cell compartment (CD27+ immunoglobulin D [IgD]+) B-cell population (Figure 1).7 This impairment in class switching may explain the inability of these patients to make adequate amounts of immunoglobulins despite a normal total B-cell count (Figure 1). Although abnormalities have been described primarily in B cells, chronic activation and expansion of CD8-positive T-cell populations have also been found in some patients.8

It is thought that B-cell abnormalities and resulting immunoglobulin deficiency (especially IgA) are responsible for the increased incidence of gastrointestinal infections, small intestinal bacterial overgrowth, and lymphoid hyperplasia in patients with CVID. However, the occurrence of more unusual infections (fungal and viral) suggests that T-

Accepted for publication February 23, 2018.
Published online November 16, 2018.
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The authors have no relevant financial interest in the products or companies described in this article.
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cell abnormalities also contribute to the increased frequency of infectious gastrointestinal diseases seen in these patients.\textsuperscript{8} The pathogenesis of inflammatory bowel disease (IBD) in CVID is not well understood, but it is thought that an increase in the number of the so-called innate lymphoid cells in the mucosa of the bowel and T-cell dysfunction may be responsible.\textsuperscript{8}

**PRESENTATION**

The majority of CVID patients present with recurrent, acute, or chronic respiratory tract infections such as sinusitis, bronchitis, and pneumonia. These patients may also present with conjunctivitis and otitis media. The pathogens are typically encapsulated bacteria, including *Haemophilus influenzae*, *Streptococcus pneumoniae*, and atypical bacteria such as *Mycoplasma* spp. Unencapsulated bacteria and viruses have also been rarely implicated.\textsuperscript{2} Many of the patients who have recurrent lung infections go on to develop chronic lung disease.\textsuperscript{5}

Gastrointestinal manifestations occur in about 10% to 20% of patients with CVID, and may be the initial or sole presentation. Patients often present with a history of transient or persistent diarrhea with malabsorption and weight loss.\textsuperscript{2,6–12} Epigastric discomfort, postprandial fullness, and anemia have also been described as presenting symptoms.\textsuperscript{13}

Diarrhea in patients with CVID is mostly of infectious origin. *Campylobacter jejuni*, *Salmonella*, *Cryptosporidium parvum*, and *Norovirus* are commonly implicated organisms, and typically cause transient infections. On the other hand, *Giardia lamblia* and *Cytomegalovirus* have been associated with transient and persistent infections.\textsuperscript{2,3,14} The incidence of *Helicobacter pylori* infection is also higher in CVID when compared with immunocompetent hosts.\textsuperscript{2,4,15} Noninfectious gastrointestinal diseases presenting with diarrhea and weight loss can also occur in CVID. These include IBD-like disease, sprue-like disease, granulomatous disease, bacterial overgrowth, protein-losing enteropathy, and nonspecific malabsorption.\textsuperscript{9} Inflammatory bowel disease–like disease is the most common noninfectious gastrointestinal manifestation of CVID, but the exact pathogenesis of this condition in patients with CVID is unknown. The clinical presentations of IBD-like and sprue-like diseases in CVID are similar to that seen in their immunocompetent counterparts. A possible link between CVID and monomorphic epitheliotropic intestinal T-cell lymphoma has recently been described.\textsuperscript{16}

**LABORATORY TESTING**

Routine laboratory tests such as complete blood counts, complete metabolic profile, and urinalysis usually show no abnormality in patients with isolated CVID. If an infection is present, C-reactive protein and erythrocyte sedimentation rate may be elevated. Culture of the appropriate specimen may help in ascertaining the nature of the infection.

Measurement of serum immunoglobulin levels is important in the evaluation of patients with CVID. Serum levels of IgG and IgA are usually below the lower limit of normal, whereas the concentration of IgM may be normal or decreased. In a study by Quinti et al,\textsuperscript{5} the mean concentrations of IgG, IgA, and IgM were 258 mg/dL (normal reference range, 768–1728 mg/dL), 28 mg/dL (normal reference range, 99–396 mg/dL), and 40 mg/dL (normal reference range, 38–266 mg/dL), respectively. Many patients with CVID have nondetectable serum immunoglobulin levels.

The serum immunoglobulin measurements are best done when the patient is in his or her usual state of health. It should be noted that chronic systemic glucocorticoid therapy may decrease serum IgG levels. If testing reveals low immunoglobulin levels, repeat testing should be done to confirm the deficiency.

To date, there are no universally accepted criteria to diagnose CVID. The criteria for a clinical diagnosis of CVID, proposed by the European Society for Immunodeficiencies Registry,\textsuperscript{17} are based on immunoglobulin deficiency, abnormal B-cell function, age of diagnosis, and the exclusion of...
both T-cell disorders and secondary causes of immunoglobulin deficiency, among other considerations (Table).

**ENDOSCOPIC FINDINGS**

The colon is the most commonly affected portion of the gastrointestinal tract. In an endoscopic study of patients with CVID by Khodadad et al., 4 of 5 patients (80%) who underwent colonoscopy had friable mucosae and abnormal vascular patterns similar to those seen in IBD. Seventeen patients underwent esophagogastroduodenoscopy, and 4 (24%) had moderate distal esophagitis in the absence of acid reflux. Eight patients (47%) had apparent gastritis. Only 2 of these 17 patients (12%) had small bowel abnormalities, namely macroscopic nodularity in the duodenum and erosion in the duodenal bulb.

**HISTOPATHOLOGY**

The spectrum of morphologic abnormalities seen in the gastrointestinal tract is far ranging. The patterns overlap with a multitude of diseases such as IBD, graft-versus-host disease, lymphocytic colitis, lymphocytic gastritis, collagenous enterocolitis, celiac disease, and Whipple disease. However, the diagnostic features of these entities are not fully present.8,15

A common finding in patients with CVID is the conspicuous paucity or absence of plasma cells in the lamina propria of the gastrointestinal tract, which is usually confirmed with negative immunohistochemistry staining for CD138, a marker for plasma cells (Figure 2, A and B).8,15 The colon is the most frequently affected site within the gastrointestinal tract, with severe disease ranging from microscopic colitis (more common) to severe colitis with ulcerations.14 Histologic findings in the colon may include crypt destruction and architectural distortion (Figure 3, A and B), Paneth cell metaplasia in the left colon (Figure 3, C), nonnecrotizing granulomas (Figure 3, D), prominent lymphoid aggregates, and intraepithelial neutrophils. Malamut et al.8 found that chronic gastritis with/without pernicious anemia in the gastric mucosa and microscopic colitis in the colonic mucosa were the most frequent histopathologic observations in the gastrointestinal tract in CVID patients. They reported moderate increase in small intestinal intraepithelial lymphocytes (75.6%) and villous atrophy/blunting in 51% of their study set. In a study of 34 consecutive dyspeptic patients with CVID, Zullo et al.10 found that chronic active gastritis (involving both antrum and body) and multifocal atrophic gastritis were especially common in patients with H pylori infection. Other findings described in literature include esophageal intraepithelial lymphocytosis and neutrophils; poorly formed granulomas in the gastric and colonic mucosa; apoptotic bodies and lymphocytes in crypts of the stomach, small bowel, and colonic mucosa; duodenal mucosal atrophy; CD8-predominant intraepithelial lymphocytosis; prominent lymphoid aggregates in the small bowel; and colonic neutrophilic infiltration and crypt distortion.8,15,19 Diffuse nonnecrotizing granulomas are typically seen in granulomatous disease.8 Foamy histiocytes in the small intestinal lamina propria and nodular hyperplasia complicated by lymphoma of the small bowel have also been reported.8 Regardless, the disease should be suspected in mucosal biopsies that show paucity or complete absence of plasma cells.

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**European Society for Immunodeficiencies Diagnostic Criteria for Common Variable Immunodeficiency**

AT LEAST ONE of the following:
- Increased susceptibility to infection
- Autoimmune manifestations
- Granulomatous disease
- Unexplained polyclonal lymphoproliferation
- Affected family member with antibody deficiency

PLUS all of the following:
- Marked decrease of IgG and marked decrease of IgA with or without low IgM levels (measured at least twice; <2 SD of the normal levels for age);
- Poor antibody response to vaccines (and/or absent isohemagglutinins); that is, absence of protective levels despite vaccination where defined or low switched memory B cells (<70% of age-related normal value)

Age older than 4 years at diagnosis (even if symptoms may have been present before)

Exclusion criteria:
- Secondary causes of hypogammaglobulinemia
- No evidence of profound T-cell deficiency

Abbreviation: Ig, immunoglobulin.
Celiac disease is a close differential for CVID enteropathy, with both entities showing intraepithelial lymphocytosis and villous blunting. Human leukocyte antigen (HLA) DQ2 and/or DQ8 genotypes that are typically associated with celiac disease have also been identified in CVID patients with intestinal intraepithelial lymphocytosis. However, small intestinal biopsies in CVID typically show profound depletion of plasma cells and follicular lymphoid hyperplasia, morphologically distinguishing it from celiac disease.

Although histopathologic features of CVID are mostly similar to those seen in IBD, colonic biopsies in CVID typically show a lack of plasma cells in the lamina propria. Also, CVID lacks the prominent mucosal eosinophilia seen in cases of IBD. In contrast to Crohn disease, which shows transmural skip inflammatory lesions, the inflammatory lesions in CVID are diffuse but superficial in extent, that is, not extending beyond the lamina propria. By sharing histopathologic features such as apoptotic bodies and lymphocytes in crypts, gastrointestinal findings in CVID may be histologically indistinguishable from acute graft-versus-host disease. However, these 2 entities are easily distinguished by a history of transplantation in the latter.

Chronic colonic infections may share similar histopathologic features with CVID. Uncomplicated *Clostridium difficile* colitis may show the characteristic pseudomembranes. Findings in giardiasis include the identification of the binucleated pear-shaped organism between the villi, variable villous blunting, and an inflammatory infiltrate. *H pylori* organisms are spiral shaped and cause gastritis, which may manifest as surface epithelial degeneration or acute neutrophilic and/or chronic inflammation depending on the duration of infection. In non-CVID patients with any of these infections, plasma cells are easily identifiable in the lamina propria on mucosal biopsies.

Common variable immunodeficiency may present with complications including autoimmune disease, granulomatous disease, and malignancies. Findings in chronic atrophic gastritis and/or pernicious anemia particularly involving the gastric body and fundus include atrophy of the mucosal glands, diffuse lymphoplasmacytic inflammation extending into the lamina propria, pseudohypertrophy of the parietal glands, and intestinal metaplasia. Autoimmune hepatitis in CVID typically shows liver parenchyma with inflammatory infiltrate and variable fibrosis. Common variable immunodeficiency patients have an increased incidence of lymphomas, and these are typically Epstein-Barr virus-related.

**Figure 3.** Colon in common variable immunodeficiency (CVID) showing partial (A) and complete (B) crypt destruction. The left colon in CVID (C) showing Paneth cell metaplasia in the glands consistent with chronic mucosal injury. The colon in CVID (D) showing a poorly formed nonnecrotizing granuloma (hematoxylin-eosin, original magnifications ×400 [A through C] and ×630 [D]).
Barr virus–negative, extranodal non-Hodgkin B-cell lymphomas, particularly mucosa-associated lymphoid tissue lymphoma and marginal zone lymphoma.12,23,28 The incidence of gastric adenocarcinoma, usually the intestinal type, is also increased in CVID and occurs on a background of chronic gastritis, diffuse intestinal metaplasia, and paucity of plasma cells in the lamina propria.1,21,22

**TREATMENT AND PROGNOSIS**

The treatment of CVID consists primarily of intermittent immunoglobulin replacement therapy. This is usually done by periodic infusion of intravenous immunoglobulin, which is usually effective in reducing the incidence of respiratory tract infections. In contrast, diarrhea in CVID—with the exception of that caused by *C. difficile*—does not usually respond to immunoglobulin therapy. Corticosteroids, especially budesonide, are effective in reducing inflammation and restoring mucosal architecture.14,23,24 Immunomodulatory agents, such as azathioprine, 6-mercaptopurine, and tumor necrosis factor α inhibitors (eg, infliximab), in conjunction with corticosteroids have been found to be effective in the treatment of the various gastrointestinal manifestations of CVID.25,26 The efficacy of newer medications such as anti–IL-12/IL-23 therapy (ustekinumab) and anti αβ7 integrin (vedolizumab) is still a subject being studied.8

If an infectious agent such as *Giardia* or cryptosporidium is identified, then appropriate treatment should be instituted. Treatment of bacterial overgrowth with a nonabsorbable broad–spectrum antibiotic such as rifaximin may be helpful. In patients with malabsorption, vitamin and mineral replacement should be commenced as needed. Clinical improvement and partial villous recovery have been reported in some patients with villous atrophy following the introduction of a gluten-free diet.14

A considerable number of patients with CVID develop one or more autoimmune phenomena affecting the gastrointestinal tract, including pernicious anemia, chronic atrophic gastritis, IBD, celiac sprue, and autoimmune hepatitis. These patients also tend to have other autoimmune conditions involving the hematologic system, skin, thyroid, and musculoskeletal system.1,2,6,7

Incidence of malignancies, including those of the gastrointestinal tract, has been found to be higher in patients with CVID relative to otherwise healthy immunocompetent hosts. B-cell non-Hodgkin lymphoma (usually mucosa-associated lymphoid tissue lymphoma) is the most common malignancy associated with CVID, typically occurring between the fourth and seventh decades of life.1,2,5,6 As up to 20% of patients with CVID develop lymph hyperplasia, differentiation of atypical lymphoid hyperplasia from a low-grade lymphoma such as mucosa-associated lymphoid tissue lymphoma may be particularly challenging.22

Common variable immunodeficiency patients with pernicious anemia, chronic atrophic gastritis, and/or extensive intestinal metaplasia are at increased risk of developing gastric adenocarcinoma.21,23,28 Although there is no clear association between CVID and colorectal carcinoma, Quinti et al5 reported that 2 of 14 CVID patients with malignancies had colorectal carcinoma.8 Proposed mechanisms that drive carcinogenesis in CVID include recurrent infections with impaired clearance of oncogenic pathogens, immune dysregulation, and genetic factors.29

Although the pharmacologic treatment of the IBD seen in CVID is essentially the same as that used in Crohn disease, ulcerative colitis, bowel inflammation is significantly more difficult to control in CVID. Although there is no definitive evidence that the use of monthly immunoglobulin infusions in patients with CVID is effective in treating the associated IBD, it is definitely effective for the reduction of morbidity (from recurrent infections) and slowing the progression of CVID. Therefore, it is important to distinguish between CVID and other causes of IBD. Also, gastrointestinal infections in CVID are often difficult to eradicate, and recognition of the syndrome alerts physicians to the possibility of the need for prolonged/repeat courses of antibiotic therapy.9,20,28

Overall survival in patients with CVID has significantly improved over the years, especially with the introduction of intravenous immunoglobulin and other pharmacologic therapy, with the mortality rate decreasing from about 29% to 15%.5,25,30 The most predominant causes of death include malignancy and chronic lung disease.25

**CONCLUSIONS**

Common variable immunodeficiency is often misdiagnosed in clinical and pathology settings because of its myriad clinical and pathologic presentations. Gastrointestinal complaints are a common presentation, and suspicion for the disease should be raised in the setting of significantly decreased or absent plasma cells in the lamina propria of gastrointestinal tract. Subsequent clinical and laboratory correlation should be sought. The gastrointestinal manifestations of CVID are the most difficult to treat, causing significant morbidity and mortality. Although CVID is a diagnosis of exclusion requiring a thorough search for alternative diagnostic considerations, keen observation by an astute pathologist may be all that is required to initiate a cascade of events that would lead to a potential stabilization of this chronic debilitating disease.

Stefan Pambuccian, MD, of the Department of Pathology at the Loyola University Medical Center (LUMC), provided critical review and considerable editorial assistance (including the figures and table) during the preparation of this manuscript. Kathy Palumbo, AA, also of the Department of Pathology at LUMC, provided additional proofreading of the manuscript.

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