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Association between common variable immunodeficiency and collagenous infiltrative disorders of the gastrointestinal tract: A series of four patients

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Abstract

Hypogammaglobulinemia/common variable immunodeficiency (CVID) may lead to disruption of the gut mucosal immune barrier. Collagenous infiltrative disorders of the intestinal tract (colitis, gastritis, sprue) constitute a relatively new spectrum of gastrointestinal disorders. Our aims were (1) to determine the association between immunoglobulin deficiency state like CVID and collagenous infiltrative disorders of the gut and (2) to study the clinic-pathologic characteristics and treatment outcomes in these patients. A retrospective search was conducted to identify cases with concurrence of these two conditions at an academic center from 2007 to 2013. Four such patients were identified from our database: three with collagenous colitis and one with collagenous gastritis. All patients with collagenous colitis had normal colonic mucosa while the patient with collagenous gastritis had nodular gastric mucosa. Only one patient out of four had decreased plasma cells in the submucosa as expected in low immunoglobulin states. All patients had improvement in their symptoms on immunoglobulin therapy with considerable remission on budesonide. Literature search revealed reporting of four similar patients. In conclusion, (1) the association between collagenous infiltrative disorders of the gut and CVID and its prompt response to immunoglobulins with effective maintenance with budesonide are novel findings. Our study also shows that the presence of plasma cells should not rule out the possibility of CVID. (2) In patients with chronic diarrhea, hypogammaglobulinemia and collagenous colitis/sprue should be considered for the available effective treatments such as immunoglobulins and budesonide.

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Compliance with ethical standards

Conflict of interest RM, ALB, AJD, SR, and SC declare that they have no conflict of interest.

Ethics statement The study was performed in a manner to conform to the Helsinki Declaration of 1975 as revised in 2000 and 2008 concerning Human and Animal Rights, and the authors followed the policy concerning informed consent as shown on Springer.com.

Keywords

Collagenous colitis; Collagenous gastritis; Collagenous sprue; Common variable immunodeficiency; Hypogammaglobulinemia

Introduction

The recent recognition of common variable immunodeficiency disease (CVID) in a patient with difficult to manage collagenous colitis prompted this evaluation of a possible association between these two conditions. CVID is an immunological disease characterized by hypogammaglobulinemia, diminished ability to produce antibody in response to vaccines or infections, and a propensity for infection [1].

Patients with hypogammaglobulinemia or CVID may have various pathologic conditions in the intestine [2, 3]. The gastrointestinal (GI) manifestations are variable and mimic celiac disease, inflammatory bowel disease, or pernicious anemia, but usually with distinct microscopic features [4]. Hypogammaglobulinemic sprue has also been increasingly recognized entity causing chronic diarrhea and GI infections [5]. Based on the previously published studies, there is a high prevalence of inflammatory, malignant, and infectious GI disorders in patients with CVID or IgA deficiency [3].

Collagenous infiltrative disorder of the gut is a relatively new spectrum of disease characterized by deposition of collagen band in the mucosa of the GI tract. They include collagenous colitis, collagenous sprue, and collagenous gastritis. The etiology of this type of inflammation is unknown. Collagenous infiltrative disorders categorized as primary immunodeficiency/CVID have been rarely described. Our aims were (1) to determine the association between immunoglobulin deficiency state like CVID and collagenous infiltrative disorders of the gut and (2) to study the clinicopathologic characteristics and treatment outcomes in these patients.

Methods

A retrospective search was conducted to identify the cases of hypogammaglobulinemia/CVID and collagenous colitis, collagenous sprue, or collagenous gastritis from 2007 to 2013 at Thomas Jefferson University Hospital. The pathological database was queried for the diagnosis: CVID, hypogammaglobulinemia, collagenous colitis, collagenous sprue, and collagenous gastritis. For each subject identified, medical, endoscopy, and biopsy reports, treatment administered, and outcomes were reviewed. The study design and data collection methods were approved by the institutional review board of Thomas Jefferson University Hospital.

Significantly low or levels below detectable limits in the serum of one or more immunoglobulin(s) (IgA, IgG, and IgM) were the basis for diagnosis of hypogammaglobulinemia. The diagnosis of CVID was based upon finding of a decrease below two standard deviations in serum immunoglobulin G (IgG) and/or low levels of IgA and IgM, impaired antibody production in response to infection and/or vaccines, and

exclusion of other causes of immunodeficiency [1]. Collagenous infiltration of the GI mucosa was defined as collagen deposition with thickness of more than 10 μm /high power field following the standard criteria [6].

Results

A retrospective search of the data from 2007 to 2013 at Thomas Jefferson University Hospital revealed four patients (three patients having collagenous colitis and one patient with collagenous gastritis) with underlying or subsequent diagnosis of low immunoglobulins consistent with hypogammaglobulinemia or CVID. The data are summarized in Table 1.

The levels of immunoglobulins were less than two standard deviations from the central value described. The level of IgG was less than 400 mg/dL (normal range 723–1685 mg/dL) in first three patients. The total level of all immunoglobulins was very low in the fourth patient, with high albumin/globulin ratio (3.2; normal range 1.0–2.1) consistent with hypogammaglobulinemia. The levels of various immunoglobulins of the patients described are shown in Fig. 1. Patients 1, 2, and 3 with collagenous colitis had evidence of CVID based on severely low immunoglobulins with history of recurrent infections and impaired antibody production in response to infection. The reports of their humoral responses to vaccines were not available for review. Patient 4 with collagenous gastritis did not have recurrent infections till date. Humoral response to vaccine was not evaluated. But, the patient's levels of immunoglobulins were low enough to characterize it as hypogammaglobulinemia per our criteria.

All three work up for associated conditions or secondary causes of low immunoglobulin (nephrotic syndrome, chronic steroid use, intestinal lymphangiectasias, celiac disease, HIV, lymphoproliferative disorders) were negative. Gastrointestinal infections were ruled out by stool studies for ova and parasites and bacteria. Small intestinal bacterial overgrowth was ruled out by hydrogen breath test using glucose. The criterion for small intestinal bacterial overgrowth (SIBO) was increase in breath hydrogen by more than 12 ppm from baseline. The results of the three patients were no significant increase in breath hydrogen from baseline.

The most common presenting symptom of collagenous colitis was diarrhea followed by weight loss and abdominal pain. The presenting symptom of collagenous gastritis was abdominal pain.

In our study, three out of four patients were subsequently diagnosed of low immunoglobulin states after the diagnosis of collagenous inflammation.

The endoscopic findings in collagenous colitis consisted of normal mucosa, with stiff colon noticed under air insufflation during colonoscopy. Nodular mucosa was the characteristic pattern observed in collagenous gastritis (Fig. 2). The histological findings consisted of collagen layer of more than 10 μm with confirmation with Masson's trichrome stain (Figs. 3 and 4). Basal cell apoptosis was seen in all the mucosal biopsies. Interestingly, plasma cells in the mucosa were significantly decreased in only one patient while other patients revealed an increase in distribution of such cells in the mucosa (Fig. 5).

The patients in our study group having collagenous colitis had significant improvement on administration of intravenous monthly immunoglobulins (with an aim to maintain the level of serum IgG above 800 mg/dL) followed by considerable remission on budesonide.

Discussion

The present retrospective study describes a novel association between hypogammaglobulinemia/common variable immunodeficiency and collagenous infiltrative disorders of the GI tract via case series.

Up to 60 % of untreated patients with CVID develop diarrhea. Small intestinal involvements include sprue like disease, bacterial overgrowth, giardia infection, lymphoid nodular hyperplasia, and small bowel lymphoma [4]. Associated infection and infestation are quite commonly seen in patients with CVID in tropical countries. A recent Indian study described 12 patients with hypogammaglobulemic sprue with diarrhea and malabsorption with associated infection and infestation [5].

Collagenous infiltrative inflammation of the GI mucosa tract was first described in small intestine as collagenous sprue, then in large intestine as collagenous colitis and recently in stomach as collagenous gastritis [7]. Association between collagenous infiltrative disorder of the GI tract and CVID/hypogammaglobulinemia is not recognized. Our review of the literature revealed only four such patients reported in the literature having collagenous inflammation of the GI tract with underlying immunoglobulin deficiency, Table 2.

Two out of four patients described in the literature had a prior diagnosis of CVID.

There were three patients (two patients with collagenous colitis and one patient with collagenous sprue) with CVID in a recent clinicopathologic study of 20 patients with CVID [12]. However, no other specific clinical details were reported.

All the four patients described in Table 2 had poor response to the routine initial treatment for collagenous colitis which includes loperamide, cholestyramine, and mesalamine. One patient was treated with antibiotic without any symptomatic relief. However, all the patients responded with significant improvement in the symptoms on treatment with budesonide in either oral or suppository form. In one patient, symptoms were improved on bismuth citrate and immunoglobulins without any trial of budesonide.

The nature of immunoglobulin deficiency described in this study is primary immunodeficiency: CVID in three cases while hypogammaglobulinemia in one case from our database, while two patients had CVID and one each had IgA deficiency and IgG deficiency in reported cases in the literature. Five out of eight patients described here were subsequently discovered of low immunoglobulins state/CVID from recurrent infections or suspicion of CVID. We believe that the collagenous infiltration is possibly the manifestation of CVID by disruption of the gut mucosal barrier. It is less likely that the immunoglobulin deficiency is secondary to mucosal disease as collagenous gastritis and colitis do not have any effect on the absorption of proteins.

Paucity of the plasma cells in the intestinal submucosa is usually a characteristic finding in CVID (about 2/3 of cases). However, there is a marked increase in plasma cells in the intestinal submucosa in typical collagenous colitis. In our series, biopsy studies revealed that three patients had increased plasma cells and only one patient had paucity of plasma cells. This reflects the heterogeneity of this immunodeficiency disorder which comprises many clinical phenotypes [13, 14].

Classic collagenous colitis usually occurs in 6th or 7th decades of life. In contrast, the patients in our study as well as those reported in the literature were considerably younger. We speculate a possible mechanism for collagenous infiltrative disorders in CVID is increased predisposition to gut infection or immune dysregulation resulting in epithelial damage, leading to epithelial lymphocytosis with subsequent villous atrophy, followed by progression to subepithelial collagen deposition.

In our experience from series of patients, one patient had a rare form of gastritis, collagenous gastritis. We were able to report this rare disorder which is in search of a disease [15].

In our review of reported cases as well as cases from our study, initial regimented therapies with either cholestyramine or mesalamine failed to resolve the symptoms. Data reveal a novel therapeutic modality of a good temporary initial resolution of symptoms with immunoglobulin therapy. These studies demonstrate a satisfactory response to budesonide for maintenance of remission. It is noteworthy that there were no additional secondary infectious complications reported in our patients in a follow up period of 6 months to 1 year.

The major limitation of this study is the small sample size of only four patients. It is also important to note that collagenous colitis itself is not a frequently encountered disease.

Although, GI symptoms are common in CVID, this is the first original report that demonstrates an association of collagenous infiltrative disorders of the gut and hypogammaglobulinemia/CVID via in-depth study of case series. In conclusion, (1) an association between collagenous infiltrative disorders of the gut and CVID, its prompt response to immunoglobulins with good maintenance with budesonide, and increased plasma cells in mucosa are all novel findings and (2) while it is typical to see paucity of plasma cells in GI pathologic conditions in CVID, increased plasma cells seen in collagenous colitis is atypical. Collectively, we propose that in patients with antibody deficiency and chronic diarrhea, collagenous colitis should be considered for the available and effective treatment.

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Fig. 1. Scatter plot graph showing serum levels of IgG, IgA, and IgM in the first three patients respectively. *Dotted rectangles* indicate normal range of these immunoglobulins with two standard deviations from central value. *Black line* in the graph indicates mean value

Fig. 2. Esophagogastroduodenoscopy. There is a nodular appearing gastric mucosa prominent in the gastric body and antrum. These nodules are well demarcated

Fig. 3. Biopsy of colon in a patient with common variable immunodeficiency (CVID) (H&E at 40×). The biopsy shows classic features of collagenous colitis including thickened subepithelial collagen band, entrapped subepithelial capillaries, and an increased lymphoplasmacytic infiltrate in the lamina propria. This case demonstrates that not all patients with CVID have a paucity of plasma cells in their gastrointestinal biopsies, reflecting the variability in the pathogenesis of the disease

Fig. 4.
Biopsy of colon in a patient with common variable immunodeficiency (Trichrome at 20×).
The subepithelial collagen band is stained light blue and is abnormally thick (60 µm)

Fig. 5.

Colon biopsy in a different patient with common variable immunodeficiency (CVID) (H&E at 40×). The biopsy shows a markedly thickened subepithelial collagen band and entrapped subepithelial capillaries; however, there is no increased lymphoplasmacytic infiltrate in the lamina propria as usually seen in collagenous colitis. The paucity of plasma cells should be a red flag to strongly consider the diagnosis of collagenous colitis in a patient with CVID

Table 1

Retrospective case review of patients with hypogammaglobulinemia/common variable immunodeficiency and collagenous inflammation of the gut (2007–2013)

	Patient 1	Patient 2	Patient 3	Patient 4
Age (years)	69	32	51	19
Sex	M	F	F	M
Symptoms	Diarrhea, weight loss	Diarrhea	Diarrhea, abdominal pain	Abdominal pain, constipation
Symptom duration	6 months	1 year	6 months	6 months
Prior diagnosis of low Ig	No	Yes	No	No
Ig levels	↓↓IgG, IgM, IgA	↓↓IgG, IgM, IgA	↓↓IgG. Low normal IgM, IgA	↓↓IgG, IgM, IgA
Immunodeficiency	CVID	CVID	CVID	Hypogammaglobulinemia
Endoscopy findings	Stiff colon	Stiff colon	Stiff colon	Nodular gastric mucosa
Histology findings	Collagenous colitis	Collagenous colitis	Collagenous colitis	Collagenous gastritis
Basal cell apoptosis	Present	Present	Present	Present
Plasma cells in mucosa	Increased	Increased	Decreased	Increased
Therapy	Immunoglobulins followed by budesonide	Immunoglobulins followed by budesonide	Mesalamine and balsalazide. After immunodeficiency diagnosis, immunoglobulins followed by budesonide	Fiber supplement, miralax
Response to treatment	Excellent response on immunoglobulins with resolution of symptoms, fair response to budesonide	Good response to immunoglobulins, moderate to fair response to budesonide	Poor response to mesalamine and balsalazide Initially transient response to immunoglobulins and budesonide, later good maintenance response to budesonide	Symptoms improved in spite of worsening thickness of collagen in follow-up biopsy

CVID common variable immunodeficiency

Table 2

Reported cases in the literature having hypogammaglobulinemia/common variable immunodeficiency and collagenous colitis/sprue/gastritis

	Patient 1 [8]	Patient 2 [9]	Patient 3 [10]	Patient 4 [11]
Age (years)	27	35	37	53
Sex	F	F	F	M
Symptoms	Diarrhea	Diarrhea	Diarrhea	Diarrhea
Duration	10 years	10 years	3 years	2 months
Diagnosis	Collagenous colitis	Collagenous colitis	Collagenous colitis	Collagenous colitis
Immune disorder	CVID	CVID	IgA deficiency	IgG deficiency
Associated conditions	None	None	Graves' disease, atrophic gastritis	Prior Yersinia gastroenteritis 1 month back
Initial therapy	No response on metronidazole	Initial temporary improvement on cholestyramine	No response to loperamide and cholestyramine	Could not tolerate cholestyramine. Partial response to mesalamine
Treatment	Improvement on bismuth subcitrate and immunoglobulins with remission on monthly immunoglobulins	Significant improvement on oral budesonide maintenance dose	Improvement with salazosulfapyridine and betamethasone enemas	Complete improvement on oral budesonide

CVID common variable immunodeficiency