

Recurrent diarrhea in a 26-year-old man

Troy W. Baker, D.O., Shayne Stokes, M.D., Jacob Clawson, M.D., Todd Garrett, M.D., Josh J. Sacha, D.O., and Erika Gonzalez-Reyes, M.D.

ABSTRACT

This is a case report of a 26-year-old healthy man with chronic diarrhea for 2 years. He was initially believed to have irritable bowel syndrome by his primary care physician after all stool studies yielded negative results. His symptoms persisted, which prompted a referral to a gastroenterology specialist. The patient's esophagogastroduodenoscopy revealed variable villous blunting and a paucity of CD 138 plasma cells, which helped reveal the final diagnosis. This case illustrates a unique presentation of a common primary immunodeficiency that allergy/immunology specialists, along with primary care specialists, will likely encounter.

(Allergy Asthma Proc 32:482–485, 2011; doi: 10.2500/aap.2011.32.3471)

CASE PRESENTATION

Chief Complaint

Chronic diarrhea for 2 years.

History of Present Illness

A 26 year-old white male military aviator presented with a 2-year history of progressively worsening, non-bloody diarrhea. He denied any nausea, vomiting, abdominal pain, fever, chills, sweats, fatigue, or weight loss and had not traveled outside the United States in the previous year. His initial workup by his primary care physician included stool studies (bacterial culture, intestinal parasites, and occult blood), a complete metabolic panel, and a complete blood count. All initial studies were normal with the exception of a mildly decreased serum total protein level. The patient was subsequently given a diagnosis of irritable bowel syndrome. On follow-up, he continued to be symptomatic and was referred to a gastroenterology specialist for additional evaluation.

Medical History

The patient had a history of recurrent otitis media in childhood that required bilateral myringotomy with

pressure equalization tube placement. He also had a history of recurrent pharyngitis resulting in tonsillectomy but denied any history of additional upper or lower respiratory tract infections. He denied any medication use and all age-appropriate vaccinations were up to date and verified by shot records. His family history was negative for any primary immunodeficiencies, unexplained early deaths, or consanguinity.

Physical Examination

This patient was a well-nourished, normal appearing adult man in no acute distress with normal vital signs. Head, eyes, nose, throat, and lymph nodes were unremarkable. Bilateral tympanosclerosis was noted. His cardiac and pulmonary exams were normal. His abdominal exam revealed no organomegaly, masses, or tenderness to palpation. Skin exam was normal.

QUESTION 1

Based on the history, what is the differential diagnosis for this patient with chronic diarrhea?

- Irritable bowel syndrome
- Inflammatory bowel disease (*i.e.*, Crohn's disease or ulcerative colitis)
- Malabsorption syndrome (*i.e.*, celiac disease or chronic pancreatitis)
- Chronic bacterial or parasitic infections (*i.e.*, *Campylobacter*, *Giardia*, or *Cryptosporidium*)
- Primary or secondary immunodeficiency

Laboratory and Other Diagnostic Findings

A limited vitamin evaluation was performed that revealed normal vitamin B12 and folate levels. Screening antibodies for celiac disease to include antien-

From the 59th MDG/SG05A, Lackland Air Force Base, Texas
The authors have no conflicts to declare pertaining to this article
The opinions or assertions herein are the private views of the authors and are not to be construed as reflecting the views of the U.S. Department of the Air Force or the U.S. Department of Defense
Address correspondence and reprint requests to Troy W. Baker, D.O., 59th MDG/SG05A, 2200 Bergquist Drive, Suite 1, Lackland Air Force Base, TX 78236
E-mail address: troy.baker2@afncr.af.mil
Copyright © 2011, OceanSide Publications, Inc., U.S.A.

Table 1 Laboratory results

	Result	Reference Range
Complete blood count		
WBC	6.1	4.8–12 k/ μ L
Hgb	14.7	14–18 g/dL
Hct	43.9	39–50%
Plts	201	140–340 k/ μ L
Neutrophil (%)	62.5	35–71%
Lymphocyte (%)	28.6	25–45%
Monocyte (%)	7.5	0–10%
Eosinophil (%)	1.1	0–6%
Neutrophil, absolute	3.8	1.8–7.0 k/ μ L
Lymphocyte, absolute	1.7	1–4.8 k/ μ L
Eosinophil, absolute	0.1	0–0.5 k/ μ L
Quantitative immunoglobulins		
IgG	124	649–1634 mg/dL
IgA	<5	73–358 mg/dL
IgM	7	53–2512 mg/dL
Flow cytometry		
WBC	6.1	4.8–12 k/ μ L
Lymphocytes (%)	28.6	17–44%
Total lymphocytes	1.74	1.0–4.8 k/ μ L
CD3 ⁺ (%)	80.5	55–82%
Total CD3 ⁺	1.40	0.70–2.10 k/ μ L
CD4 ⁺ (%)	18.3	28–57%
Total CD4 ⁺	0.32	0.56–2.70 k/ μ L
CD8 ⁺ (%)	59.4	12–35%
Total CD8 ⁺	1.04	0.10–0.44 k/ μ L
CD4/CD8	0.31	0.9–3.9
CD19 ⁺ (%)	9.9	9–29%
Total CD19 ⁺	0.17	0.10–0.50 k/ μ L
CD56 ⁺	8.8	5–22%

Hct = hematocrit; Hgb = hemoglobin; Plts = platelets; WBC = white blood cell count.

domysial IgA and antitissue transglutaminase IgA were negative (Table 1). Amylase and lipase levels were normal. Serum protein electrophoresis was ordered and revealed low serum total protein, albumin, and γ -globulin levels. Quantitative immunoglobulins were subsequently obtained and showed low IgG and IgM levels with an undetectable IgA level. A 24-hour urine protein level was normal but the patient was found to have an elevated stool α -1-antitrypsin level.

Further review of the patient's medical record revealed that on accession into the military and before the patient's initial presentation, routine vaccine titers had been performed. At that time, his titers were protective for rubeola but negative for rubella, varicella, hepatitis B, and mumps, despite confirmed prior vaccination and/or natural disease. Additional vaccine titers were subsequently drawn and showed undetect-

able levels against tetanus and *Streptococcus pneumoniae* (patient had no prior history of pneumococcal vaccination). Antidiphtheria IgG levels were obtained and found to be protective.

Concurrent with the aforementioned laboratory evaluation, esophagogastroduodenoscopy was performed and showed prominent duodenal nodularity with histopathological examination showing marked villous blunting, increased intraepithelial lymphocytosis, scattered active inflammation, and a paucity of plasma cells. A colonoscopy was also performed and showed scattered nodularity with histopathological examination showing reactive lymphoid hyperplasia and a paucity of plasma cells. Repeat stool and biopsy studies were negative for infectious organisms.

QUESTION 2

Based on the information obtained from additional laboratory and endoscopy evaluation, what is the differential diagnosis for this patient with chronic diarrhea, diffuse intestinal nodularity, marked villous blunting, a paucity of plasma cells, and hypogammaglobulinemia?

- Malabsorption syndromes (*i.e.*, celiac disease and chronic pancreatitis)
- Primary or secondary immunodeficiency
- Gastrointestinal lymphoma
- Protein losing enteropathy

QUESTION 3

What additional laboratory data or investigations would be helpful in obtaining the diagnosis?

- Repeat endoscopy with biopsy after a gluten-free diet
- Small bowel biopsies looking for malignancy
- Human immunodeficiency virus (HIV) DNA polymerase chain reaction
- Specific antibody production after vaccine challenge

Additional Diagnostic Evaluation

An initial diagnosis of celiac disease was considered given this patient's presentation with chronic diarrhea. After the initial endoscopy, he was placed on a gluten-free diet for 6 weeks after which he was reevaluated by esophagogastroduodenoscopy and colonoscopy. Additionally, antitissue transglutaminase IgG was performed and found to be negative. His repeat endoscopic exam and histopathological findings remained unchanged, making the diagnosis of celiac disease unlikely (see Figs. 1 and 2). Repeat histopathological evaluation was also negative for malignancy and infectious organisms, further helping to narrow the differential diagnosis. Initial evaluation of celiac disease generally begins with serological evaluation for antitissue trans-

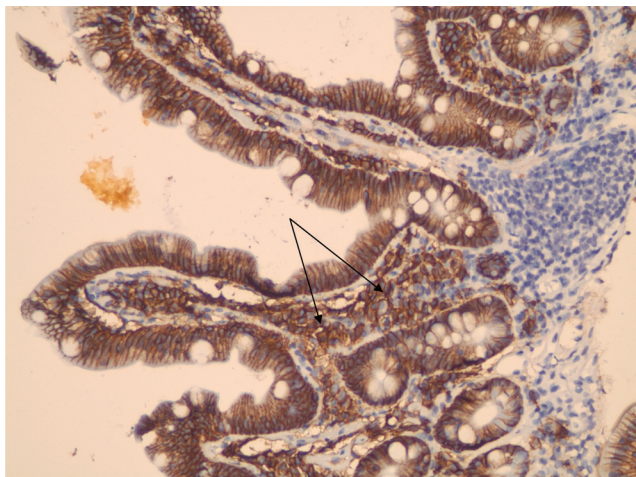


Figure 1. Photomicrograph of representative normal small intestine mucosa with normal villi and lamina propria. Membranes of the plasma cells stain brown (black arrows).

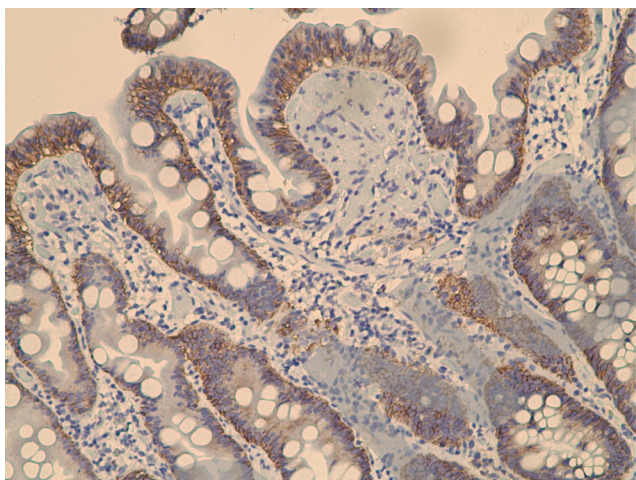


Figure 2. Photomicrograph of the subject case at 200× magnification showing variable villous blunting and lack of plasma cells in lamina propria (no brown staining). Staining materials are the same as mentioned in Fig. 1.

glutaminase IgA and antiendomysial IgA antibodies. These assays each have sensitivities and specificities exceeding 90%.¹ However, patients with concomitant celiac disease and IgA deficiency can be missed using IgA-specific tests. In such patients, testing for antitissue transglutaminase IgG antibodies, antiendomysial IgG antibodies, and/or antigliadin IgG antibodies should be performed and if positive, confirmed with small bowel biopsies.

HIV infection was also considered as an etiology of this patient's symptoms. The patient is an active duty military member where periodic HIV screening is required. Before symptom onset, he had two negative HIV screening tests using enzyme immunoassay. Although symptomatic, a third HIV enzyme immunoassay was obtained and was negative. Given his profound hy-

pogammaglobulinemia, HIV DNA polymerase chain reaction was subsequently ordered and was likewise negative.

The patient was also given Pneumovax (Merck Sharp and Dohme Corp., Whitehouse Station, NJ) to assess his polysaccharide antigen responsiveness. Postvaccination titers obtained 4 weeks after vaccination showed undetectable titers to all serotypes tested. Serum isohemagglutinin studies would be noncontributory because of the patient's AB blood type.

Immunization with bacteriophage phiX174 was not performed but has also been used as a tool to both diagnose and monitor various primary and secondary immunodeficiencies. Patients with T-cell or T/B-cell interaction deficiencies (*i.e.*, adenosine deaminase deficiency and HIV disease) characteristically have diminished or absent amplification of antibody titers and limited antibody isotype switching from IgM to IgG after repeated immunizations with bacteriophage phiX174.² Computed tomography scans of his sinuses and chest were normal, and he continued to have no evidence of infection during his workup. Pulmonary function tests were normal.

Final Diagnosis

The patient's clinical presentation of chronic diarrhea with associated low total serum protein; hypogammaglobulinemia; impaired production of specific antibodies; and gastrointestinal findings of diffuse nodularity, marked villous blunting, increased intraepithelial lymphocytosis, reactive lymphoid hyperplasia, and paucity of plasma cells supports the diagnosis of common variable immune deficiency (CVID).

Clinical Course

The patient was started on monthly i.v. immunoglobulin (IVIG) replacement. Despite proper IVIG dosing, his serum total IgG trough level remained very low. In addition, a repeat stool α -1-antitrypsin level continued to be elevated. Although his hypogammaglobulinemia persisted, his diarrhea fully resolved and he remained infection free and otherwise completely asymptomatic. Quantitative immunoglobulins drawn 2 weeks after an IVIG infusion were found to be protective. Ongoing loss of immunoglobulins was assumed to be a function of CVID enteropathy. Current consultation with a gastroenterology specialist for consideration of treatment options for CVID-associated protein losing enteropathy is ongoing. In addition, the options of IVIG replacement every 2 weeks or a trial of subcutaneous immunoglobulin replacement were considered. The patient was recently started on weekly subcutaneous immunoglobulin replacement with planned follow-up of his IgG levels to monitor efficacy.

DISCUSSION

CVID, first described by Janeway and colleagues,³ is the most common symptomatic primary antibody deficiency that physicians will encounter. CVID is a heterogeneous disorder of atypical B-cell maturation and occasionally T-helper lymphocyte dysfunction, resulting in impaired plasma cell differentiation and antibody production. Because of its variable (and sometimes subclinical) manifestation, the true incidence of CVID is unknown but is estimated to affect between 1/25,000 to 1/50,000 white subjects.⁴ It is most often diagnosed between the ages of 20 and 40 years but can be found in all age groups.⁵

Immunologic evaluation characteristically shows low serum IgG with low IgA and/or IgM.^{6,7} Confirmation of impaired antibody production showed by poor responses to protein and/or polysaccharide vaccine challenges is also an essential part of the diagnosis.⁴ Protein vaccine responses are usually assessed with tetanus or diphtheria toxoids; haemophilus conjugate; and/or measles, mumps, and rubella vaccines while polysaccharide response can be assessed with the administration of either pneumococcal polysaccharide vaccine or meningococcal polysaccharide vaccine.

Several rare, recessive gene mutations have been implicated in a handful of patients with CVID including inducible costimulator,⁸ CD19,⁹ the receptor of B-cell activation factor,¹⁰ and CD20 and CD81 mutations.^{11,12} Interestingly, mutations in the gene encoding TACI,¹³ a transmembrane activator and calcium-modulating ligand interactor (TNFRSF13B) expressed on mature B cells, have been found in ~8–10% of patients.¹⁴

Up to 10% of CVID patients have no history of serious or recurrent infections⁵ with ~20% manifesting gastrointestinal symptoms without an infectious cause.¹⁵ The main gastrointestinal manifestation of CVID is transient or persistent diarrhea, which can be found in up to 57% of patients.⁴ Symptoms of CVID enteropathy include diarrhea, malabsorption, and weight loss with some patients presenting with frequent watery stools without any other systemic effects.

Villous blunting in the small intestine is a common manifestation of CVID and appears to be an immune-mediated/inflammatory phenomenon resembling what is seen in celiac disease. The villous blunting can lead to diarrhea, protein losing enteropathy, and weight loss. Several features can help distinguish the villous blunting seen in celiac disease from that seen in CVID. Plasma cells are absent or decreased in patients with CVID whereas in classic celiac disease they are typically increased. In addition, removal of gluten from the diet typically causes no clinical or histopathological improvement if the underlying cause is CVID. Inflammation of the small and large intestine can also be seen in up to 13% of patients with CVID. The management of inflammatory bowel disease

occurring in patients with CVID is generally the same as for immunocompetent patients, although gastrointestinal inflammation in patients with CVID can be more difficult to control.¹⁶

CONCLUSIONS

This case illustrates one of the varied and less common presentations of CVID. Although patients with CVID frequently report a history of recurrent sinopulmonary infections, physicians should also consider CVID in individuals presenting with isolated gastrointestinal manifestations and hypogammaglobulinemia, in particular in patients who have findings consistent with celiac disease who do not respond to a gluten-free diet and have biopsy findings showing a paucity of plasma cells.

REFERENCES

1. Rostom A, Dubé C, Cranney A, et al. The diagnostic accuracy of serologic tests for celiac disease: A systematic review. *Gastroenterology* 128:S38–S46, 2005.
2. Fogelman I, Davey V, Ochs HD, et al. Evaluation of CD4[^{sup}+] T cell function in vivo in HIV-infected patients as measured by bacteriophage phiX174 immunization. *J Infect Dis* 182:435–441, 2000.
3. Janeway CA, Apt L, and Gitlin D. Agammaglobulinemia. *Trans Assoc Am Phys* 66:200–202, 1953.
4. Cunningham-Rundles C. How I treat common variable immune deficiency. *Blood* 116:7–15, 2010.
5. Cunningham-Rundles C, and Bodian C. Common variable immunodeficiency: Clinical and immunological features of 248 patients. *Clin Immunol* 92:34–48, 1999.
6. Bonilla FA, Bernstein IL, Khan DA, et al. Practice parameter for the diagnosis and management of primary immunodeficiency. *Ann Allergy Asthma Immunol* 94:S1–S63, 2005.
7. Notarangelo LD, Fischer A, Geha RS, et al. Primary immunodeficiencies: 2009 Update. *J Allergy Clin Immunol* 124:1161–1178, 2009.
8. Grimbacher B, Hutloff A, Schlesier M, et al. Homozygous loss of ICOS is associated with adult-onset common variable immunodeficiency. *Nat Immunol* 4:261–268, 2003.
9. Van Zelm MC, Reisli I, Van der Burg M, et al. An antibody-deficiency syndrome due to mutations in the CD19 gene. *N Engl J Med* 354:1901–1912, 2006.
10. Warnatz K, Salzer U, Rizzi M, et al. B-cell activating factor receptor deficiency is associated with an adult-onset antibody deficiency syndrome in humans. *Proc Natl Acad Sci USA* 106:13945–13950, 2009.
11. Kuijpers TW, Bende RJ, Baqrs PA, et al. CD20 deficiency in humans results in impaired T cell-independent antibody responses. *J Clin Invest* 120:214–222, 2010.
12. Van Zelm MC, Smet J, Adams B, et al. CD81 gene defect in humans disrupts CD19 complex formation and leads to antibody deficiency. *J Clin Invest* 120:1265–1274, 2010.
13. Castigli E, Wilson SA, Garibyan L, et al. TACI is mutant in common variable immunodeficiency and IgA deficiency. *Nat Genet* 37:829–834, 2005.
14. Bachelli C, Buckridge S, Thrasher AJ, et al. Translational mini-review series on immunodeficiency: Molecular defects in common variable immunodeficiency. *Clin Exp Immunol* 149:401–409, 2007.
15. Yong PFK, Michael T, Ignatius C, et al. Common variable immunodeficiency: An update on etiology and management. *Immunol Allergy Clin North Am* 28:367–386, 2008.
16. Agarwal S, and Mayer L. Pathogenesis and treatment of gastrointestinal disease in antibody deficiency syndromes. *J Allergy Clin Immunol* 124:658–664, 2009. □

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.