Therapy-Resistant Diarrhea due to *Giardia lamblia* in a Patient with Common Variable Immunodeficiency Disease

M. Sawatzki^a S. Peter^b C. Hess^c

^aMedical Outpatient Department, ^bGastroenterology Unit, ^cDepartment of Internal Medicine, University Hospital Basel, Basel, Switzerland

Dear Sir,

Numerous disorders are associated with chronic diarrhea. The prevalence of specific disorders depends upon the socioeconomic status of the studied population. In developed countries the most common causes of chronic diarrhea are irritable bowel syndrome, inflammatory bowel disease and malabsorption syndromes such as lactose intolerance and celiac disease. In developing countries chronic diarrhea is most often caused by bacterial, mycobacterial, and parasitic infections. Of the parasitic infections, *Giardia lamblia* causes abdominal pain, nausea, watery diarrhea and malabsorption, but can sometimes be asymptomatic. Therapy-resistant infection is uncommon and should raise suspicion of an underlying cause.

Case Report

A 48-year-old man presented to our Medical Outpatient Department complaining of diffuse abdominal pain and non-bloody diarrhea that persisted despite treatment of *G. lamblia* infection 6 months earlier. At the time he had received sequential metronidazole (1.5 g daily for 5 days) and albendazole (800 mg daily for 3 days). On examination we found an afebrile, obese patient (BMI 37.3 kg/m²) who appeared well. His physical examination was

normal. Eosinophils, liver function tests, albumin concentration, lipid status, serum glucose levels and glycosylated hemoglobin (HbA1c) were all within the normal limits. The stool examination was repeated, and *G. lamblia* cysts were detected. A second course of treatment with metronidazole (1.5 g daily for 5 days) followed by albendazole (1.2 g daily for 3 days) was ineffective. Gastroduodenoscopy and colonoscopy detected no pathology. Well-controlled diabetes and arterial hypertension, and stable psychiatric disease made malcompliance an unlikely cause for the persistent *Giardia* infection. Relevant pharmacological interactions of metronidazole and/or albendazole with the patient's medication for diabetes, high blood pressure and psychiatric condition could not be identified. We therefore assumed therapy-resistant *G. lamblia* infection, which prompted us to search for underlying immunodeficiency. Screening tests for HIV-specific antibodies and p24 antigen were repeatedly negative, largely excluding HIV-induced immunodeficiency. Immunoglobulin subclass analyses revealed decreased levels of IgA (0.067, range 0.7–3.8 g/l), IgG2 (1.29, range 1.5–6.4 g/l), IgG4 (<0.04, range 0.08–1.4 g/l), and IgM (<0.08, range 0.50–2.60 g/l). Lymphocyte subset analyses identified a moderate reduction in CD8+ and CD4+ T cells (CD4+ T cells

655, normal range 700–1,100/μl; CD8+ T cells 319, normal range 500–900/μl; CD19+ cells 196, normal range 200–400/μl, and NK cells 130, normal range 200–400/μl). These laboratory anomalies, confirmed on more than one occasion, were most consistent with the diagnosis of a common variable immunodeficiency syndrome (CVID), malignant lymphoma being a concern. A CT scan of the abdomen detected mild mesenteric lymphadenopathy and splenomegaly (16 × 13 × 5 cm). Both lymphadenopathy and splenomegaly are frequently observed in CVID patients. The differential diagnosis, however, remained malignant lymphoma (CVID to some extent continues to be a diagnosis of exclusion) and, in this specific patient, reactive inflammatory enlargement of lymph nodes and spleen vis-à-vis a chronic *G. lamblia* infection. On the background of an established, most likely primary, immunodeficiency, a course of high dose albendazole (1.2 g daily for 5 days) in combination with ornidazole (1.5 g daily for 2 days) was initiated. Upon completion of this treatment the patient became asymptomatic, and no *G. lamblia* cysts were detected in repeat stool examinations and on duodenal biopsy. A control CT scan of the abdomen was scheduled and, reassuringly, both lymphadenopathy and splenomegaly had regressed.

Discussion

Therapy-resistant *G. lamblia* infection is uncommon and should raise suspicion of an underlying immunodeficiency. Immunodeficiency may be acquired or, much less frequently, primary. Among the primary immunodeficiency syndromes, selective IgA deficiency is the most common (1 in 400–800 individuals), but usually passes unnoticed. The pattern of immunoglobulin deficiency is highly variable in CVID patients, ranging from only marginally decreased total IgG levels or isolated subclass deficiency, to very low total IgG levels across all subclasses, absence of IgA and low or undetectable IgM [1]. Characteristically there is accompanying, mostly mild, lymphopenia, typically with reduced numbers of CD4+ and CD8+ T cells. Lymphadenopathy and (hepato)-splenomegaly are common, and close observation must be maintained for the development of malignant disease (lymphoma and also gastric cancer), which has an up to 40 times higher incidence in patients with CVID. The usual presentation of CVID is recurrent bacterial infections [1].

Aside from chronic, recurrent (and often destructive) respiratory infections, chronic gastrointestinal infections and particularly infection with *G. lamblia* are common in CVID [1–3]. Among a cohort of 248 CVID patients, 3.2% had a history of *Lamblia* enteritis, at least 1.2% a history of *Campylobacter* or *Salmonella* enteritis [4].

Strict site selectivity of infections, as also seen in our patient, is intriguing yet

not unusual. Partially, such site selectivity reflects the fact that various immunoglobulin classes and subclasses differ in their efficiency to neutralize and/or opsonize different pathogens, and in their ability to activate complement. Also, immunoglobulin classes and subclasses vary in their concentration at different anatomical sites. Other factors, such as the extent of the accompanying cellular immunodeficiency in a given CVID patient, are likely to contribute to the pattern of infection(s) observed.

Splenomegaly and/or lymphadenopathy are found in up to 30% of CVID patients [5]. In our patient, mesenteric lymphadenopathy and splenomegaly regressed 4 months after successful treatment of *G. lamblia* infection, and was interpreted as being largely reactive due to longstanding *Giardia* infection. Given the high incidence of lymphoma in CVID patients, biopsy of (persistently) enlarged lymph nodes, as well as a careful clinical follow-up are mandatory [6, 7].

Nitroimidazoles (such as metronidazole or tinidazole) and albendazole are the drugs of choice for treating *G. lamblia* both in the immunocompetent and in the immunocompromised host [8]. High-dose combined antiparasite therapy eventually was successful in eliminating the gastrointestinal parasitosis in our patient with underlying CVID. The lack of success of prolonged, high-dose treatment with antiparasite drugs would have justified a trial of concomitant substitution with intravenous immunoglobulins. The effectivity of intravenous immunoglobulins in the

treatment of *G. lamblia* in CVID patients has been described in case reports [2, 3].

References

- 1 Sneller MC: Common variable immunodeficiency. *Am J Med Sci* 2001;321:42–48.
- 2 Daniel R, Debonne JM, Klotz F: Common variable hypogammaglobulinemia. A rare cause of chronic diarrhea. *Presse Med* 1993; 22:1696–1698.
- 3 Onbasi K, Gunsar F, Sin AZ, Ardeniz O, Kokuludag A, Sebik F: Common variable immunodeficiency (CVID) presenting with malabsorption due to giardiasis. *Turk J Gastroenterol* 2005;16:111–113.
- 4 Cunningham-Rundles C, Bodian C: Common variable immunodeficiency: clinical and immunological features of 248 patients. *Clin Immunol* 1999;92:34–48.
- 5 Sneller MC, Strober W, Eisenstein E, Jaffe JS, Cunningham-Rundles C: NIH conference. New insights into common variable immunodeficiency. *Ann Intern Med* 1993;118: 720–730.
- 6 Kinlen LJ, Webster AD, Bird AG, Haile R, Peto J, Soothill JF, Thompson RA: Prospective study of cancer in patients with hypogammaglobulinaemia. *Lancet* 1985;1:263–266.
- 7 Mellemkjaer L, Hammarstrom L, Andersen V, Yuen J, Heilmann C, Barington T, Bjorkander J, Olsen JH: Cancer risk among patients with IgA deficiency or common variable immunodeficiency and their relatives: a combined Danish and Swedish study. *Clin Exp Immunol* 2002;130:495–500.
- 8 Farthing MJ: Treatment options for the eradication of intestinal protozoa. *Nat Clin Pract Gastroenterol Hepatol* 2006;3:436–445.