Common variable immunodeficiency and isosporiasis: first report case

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ABSTRACT

We report a severe case of diarrhea in a 62-year-old female HIV-negative patient from whom Giardia lamblia and Isospora belli were isolated. Because unusual and opportunistic infections should be considered as criteria for further analysis of immunological status, laboratory investigations led to a diagnosis of common variable immunodeficiency (CVID). This is the first reported case of isosporiasis in a patient with CVID and illustrates the importance of being aware of a possible link, particularly in relation to primary immunodeficiency.

Keywords: Isosporiasis. Primary immunodeficiency. Common variable immunodeficiency.

INTRODUCTION

Isosporiasis is a parasitic disease caused by the protozoa Isospora belli and Isospora natalensis (Family, Eimeriidae; Order, Eucoccidiida; Suborder, Eimeriorina; Class, Sporozoa; Subclass, Coccidia; Phylum, Apicomplexa), the various species of which infect humans, nonhuman primates and other vertebrates (cats, dogs, foxes and pigs). Isospora belli has an anthropogenic life cycle and is transmitted through food or water contaminated with human feces; it is, therefore, not a zoonosis1.

Infection of immunocompetent individuals by the coccidia results in self-limiting acute diarrhea, and has a reported prevalence ranging between 14 and 13.1% in patients with diarrhea2. Infection of immunocompromised individuals causes severe prolonged or chronic diarrhea with simultaneous elimination of infectious microbes that represent a public health problem3. The prevalence of isosporiasis in patients suffering from human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) is variable, reflecting the frequency of the parasite in different countries; it is considered an AIDS-defining illnesses4.

Common variable immunodeficiency (CVID) is the most frequent symptomatic primary immunodeficiency, characterized by recurrent bacterial infections, hypogammaglobulinemia, and impaired antibody responses. Common variable immunodeficiency patients usually present with recurrent respiratory infections and an increased incidence of autoimmune, gastrointestinal, lymphoproliferative, and granulomatous diseases5. Although CVID is classified as an antibody deficiency, a significant number of studies have identified alterations in the phenotype and function of T cell subpopulations5.

CASE REPORT

The patient was a 62-year-old Caucasian female presenting with a 12 month history of diarrhea. She reported watery diarrhea with mucus, but without blood or purulent secretions, which was associated with loss of appetite, abdominal pain, and intermittent fever. The patient lost approximately 20kg in body weight during this period. She also reported a history of recurrent infections, including several episodes of acute rhinosinusitis over 7 years, which resulted in a sinusotomy at 59 years-of-age. At age 48, she presented with a pneumopathy and was treated for tuberculosis for 6 months. At age 50, she also presented with an acute pneumonia treated with antibiotics at home.

The patient was admitted to hospital for treatment and further investigations. During hospitalization, we confirmed that she was suffering from malabsorptive diarrhea and steatorrhea. Examination of her stools was performed, along with a colonoscopy and an endoscopy of the esophagus, stomach and duodenum. Anatomopathological analysis of a duodenal biopsy revealed the presence of Giardia lamblia and parasitological examination of the stool samples identified Isospora belli oocysts. The isosporiasis was treated with trimethoprim-sulfamethoxazole (800mg i.v. for 10 days, followed by 400mg orally for 20 days), and the giardiasis was treated with metronidazole for 14 days, resulting in a rapid improvement of the diarrhea.

An immunodeficiency was suspected because of the Isospora infection; however, HIV tests were negative. Therefore, further evaluation of the immune system was performed, including measurement of immunoglobulin dosage and lymphocyte subset analysis. The results revealed a marked reduction in B lymphocyte numbers and immunoglobulins (Table 1). A negative values of IgG against rubella and hepatitis B was found after vaccines.

<table>
<thead>
<tr>
<th>TABLE 1 - Labortorials tests to patient’s immunologic screen.</th>
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<tbody>
<tr>
<td><strong>Laboratorial tests</strong></td>
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<td>-----------------------</td>
</tr>
<tr>
<td>Anti-HIV</td>
</tr>
<tr>
<td>IgA (mg/dl)</td>
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<tr>
<td>IgG (mg/dl)</td>
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<tr>
<td>IgM (mg/dl)</td>
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<tr>
<td>CD19 cell/mm³ (%)</td>
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<td>CD3 cell/mm³ (%)</td>
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<td>CD4 cell/mm³ (%)</td>
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<td>CD8 cell/mm³ (%)</td>
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IgA: immunoglobulin A, IgG: immunoglobulin G, IgM: immunoglobulin M.
Normal levels of albumin associated with low levels of immunoglobulin are characteristic of hypogammaglobulinemia. A diagnosis of CVID was suggested and treatment with intravenous immunoglobulin (IVIg) was initiated. After 5 months of IVIg treatment (one treatment per month), the patient regained normal bowel function and gained 17kg in weight.

**DISCUSSION**

Common variable immunodeficiency (CVID) is characterized by a primary deficiency in antibodies and diagnosis is confirmed by a reduction in serum immunoglobulin G (IgG), immunoglobulin A (IgA) and/or immunoglobulin M (IgM) levels (less than two standard deviations of the reference level for age) and poor responses to vaccination with polysaccharide (Streptococcus pneumoniae and Haemophilus influenzae) and protein (tetanus and diphtheria) antigens9. Other causes of hypogammaglobulinemia must be excluded, including drugs that induce immunodeficiency, gastrointestinal or renal loss of immunoglobulins, and other primary antibody deficiencies10,11.

The basic defect in CVID is the inability of B lymphocytes to differentiate into plasma cells capable of producing the various immunoglobulin isotypes. Defective B cell development results in abnormal humoral immune responses that result in hypogammaglobulinemia, which manifests clinically as an increased susceptibility to infection7. Patients with CVID often develop acute sinopulmonary infections that can lead to chronic inflammation of the airways, such as chronic sinusitis and bronchiectasis12.

Over the last 20 years, various facets of the cellular and immunological dysfunctions present in CVID have been described; for example, abnormalities in B cell populations, a low frequency of naive CD4 T cells, and an increase in cellular activation. Other immunological defects include a reduction in the absolute number of natural killer cells and defects in dendritic cell function8. Around 30% of CVID patients develop autoimmune diseases associated with abnormalities in Treg cells, particularly hemolytic anemia and idiopathic thrombocytopenic purpura, autoimmune thyroiditis, inflammatory intestinal diseases, pernicious anemia, Sjögren’s syndrome, autoimmune hepatitis, primary biliary cirrhosis, and vasculitis5.

Chronic diarrhea in adults is considered a warning sign for immunodeficiency as described by the Primary Immune Foundation and the Jeffrey Modell Foundation9, and screening for Primary Immunodeficiency should be performed in patients with one of the signs listed in Table 2. Patients with CVID usually present with chronic diarrhea, sometimes as a consequence of an intestinal inflammatory disease; however, the presence of infectious agents should still be investigated in these patients. Several papers describe chronic diarrhea in CVID patients associated with different pathogens such as Giardia, Cryptosporidium, Cytomegalovirus and Strongyloides5,9-12; however, there are no reports of diarrhea associated with isosporiasis in CVID patients.

In conclusion, this is the first reported case of isosporiasis associated with CVID. We believe this association is common but is not often diagnosed because the investigation of isosporiasis in non-HIV patients is not standard practice and regular parasitological tests do not detect the oocysts. Common variable immunodeficiency patients with chronic diarrhea should be investigated for opportunistic and unusual pathogens as soon as they present evidence of abnormal cellular immunity. On the other hand, non-HIV patients with a diagnosis of isosporiasis must be screened for other immunological diseases, primarily CVID.

**TABLE 2 - Ten warning signs for primary immunodeficiency in adults.**

1. Two or more new ear infections within 1 year.
2. Two or more new sinus infections within 1 year, in the absence of allergy.
3. One pneumonia per year for more than 1 year.
4. Chronic diarrhea with weight loss.
5. Recurrent viral infections (cold, herpes, warts, condyloma).
6. Recurrent need for intravenous antibiotics to clear infections.
7. Recurrent, deep abscesses of the skin or internal organs.
8. Persistent thrush or fungal infection on skin or elsewhere.
10. A family history of primary immunodeficiency.

**REFERENCES**