J Microbiol Immunol Infect.
2009;42:526-529

Case Report

Severe diarrhea due to *Isospora belli* in a patient with thymoma

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Received: October 5, 2007 Revised: June 4, 2008 Accepted: October 12, 2008

Opportunistic isosporidial infection of the gastrointestinal tract is frequently encountered in patients with acquired immunodeficiency syndrome (AIDS) and is considered to be an AIDS-defining illness. Chronic severe watery diarrhea due to *Isospora belli* has also been reported in other immunodeficiency states. This report describes severe chronic debilitating diarrhea due to isosporiasis in a patient with mediastinal thymoma, a common tumor of the anterior mediastinum, originating from the epithelial cells of the thymus. Numerous oocysts of *I. belli* were detected in direct smear preparation of the diarrheic stool sample of the patient, who had an 8-month history of recurrent diarrhea. Duodenal and colonic mucosal biopsies revealed slight degrees of atrophic changes associated with infiltration of the lamina propria by an appreciable number of eosinophiles and the presence of unizoit tissue cysts of *I. belli* in the surface epithelium of the duodenal mucosa. The patient was first treated with trimethoprim-sulfamethoxazole and subsequently underwent complete thymectomy. Later, due to recurrence of the diarrhea, he was treated with ciprofloxacin.

Key words: Diarrhea; Iran; Isosporiasis; Thymoma

Introduction

Isospora belli is an obligate homoxenous intracellular protozoan responsible for human isosporiasis, a typically cosmopolitan infection, which is most frequent in tropical and subtropical regions. All the endogenous reproduction of the parasite occurs in the epithelial cells of the small intestine [1,2]. Pathologic examination of the duodenum and jejunum typically shows mucosal atrophy with crypt hyperplasia and shortened or fused villi, and infiltration of the lamina propria with eosinophils and other inflammatory cells [1,3]. *I. belli* infection usually causes a gastrointestinal illness that is characterized by loose stools or watery diarrhea and is often associated with abdominal pain, malabsorption, weight loss, and peripheral eosinophilia. Although chronic and severe illness in infants and otherwise healthy adults has been reported [3,4], in healthy hosts the illness is typically self-limiting. However, in patients with AIDS and other immunodeficient states, the illness is chronic and may be associated with severe dehydration and debilitation [1,3].

Thymoma is a rare cause of combined B- and T- cell immunodeficiency in adults. The association between the presence of a thymoma and immunodeficiency was first recognized in 1954 by Dr. Robert Good, who described a case of thymoma and hypogammaglobulinemia in an adult [5]. Immunodeficiency with thymoma is a rare condition, occurring in 7% to 13% of patients with adult onset hypogammaglobulinemia. In 80% of patients, hypogammaglobulinemia is detected within 5 years of the identification of the thymoma [6]. In a literature review of patients with thymoma, the mean age was 50 years (range, 14 to 77 years) [7]. Recurrent infectious diseases are

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the most important consequences of this syndrome, and are related to a deficiency of humoral and cell-mediated immunity. Pulmonary infections and enteric infections are frequent [6]. This report describes severe debilitating diarrhea due to isosporiasis in a patient with mediastinal thymoma.

Case Report

In December 2006, a 43-year-old man was admitted to a hospital in Tehran, Iran. He had intermittent fever, severe dehydration, vomiting, colicky abdominal pain, watery diarrhea without blood (10 bowel movements per day), and pulmonary symptoms of cough, sputum discharge, and chest pain. His diarrhea initially started 8 months previously, and was followed by several recurrences with similar macroscopical appearances. During this period, he had progressive weakness, persistant malabsorption, and weight loss of 14 kg. Physical examinations were normal.

Laboratory examination showed hemoglobin of 18.7 g/dL, leukocyte count of 5900/mm^3 (polymorphonuclear 48%, lymphocytes 35%, monocytes 6%, basophils 1%, and eosinophils 10%), aspartate aminotransferase of 49 U/L, alanine aminoitransferase of 34 U/L, alkaline phosphatase of 361 U/L, blood urea of 96 mg/dL, serum creatinine of 2.5 mg/dL, total bilirubin of 2.2 mg/dL, and uric acid of 2.2 mg/dL. Serology was negative for antinuclear and antineutrophilic cytoplasmic antibodies, as well as antigliadin antibody. The patient's serum was negative for anti-HIV antibodies by enzyme-linked immunosorbent assay. Duodenal and colonic mucosal biopsies revealed slight degrees of atrophic changes associated with infiltration of the lamina propria by appreciable numbers of eosinophiles in addition to the presence

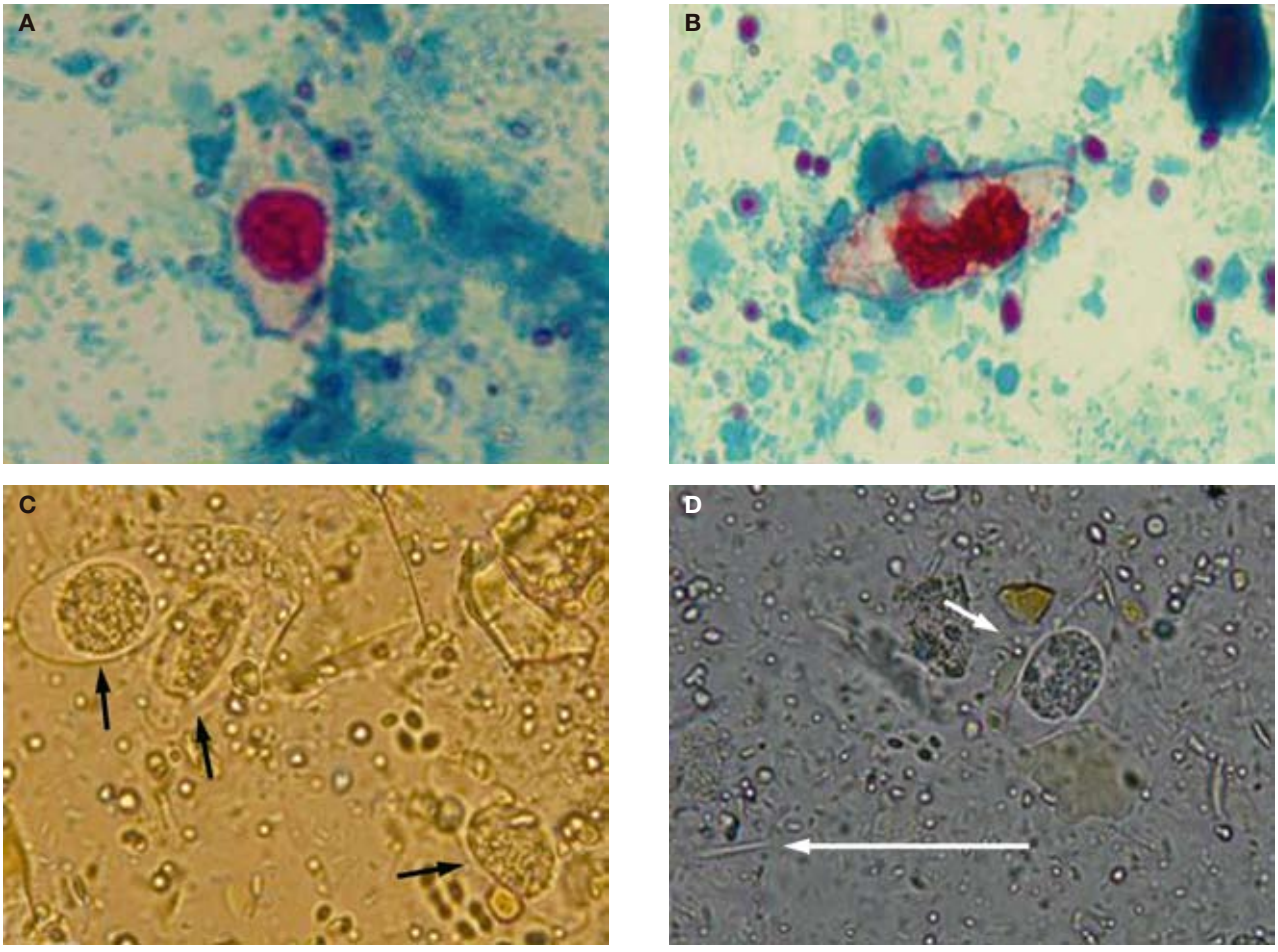

Fig. 1. Examination of the diarrheic stool sample at admission showed the presence of numerous oocysts of *Isospora belli*. Oocytes with (A) 1 sporoblast and (B) 2 sporoblasts are seen (modified Ziehl-Neelsen stain; original magnification, × 1000). Direct smears show (C) numerous oocysts (short arrows) and (D) their association with Charcot-Leyden crystals (long arrow) [original magnification, × 1000].

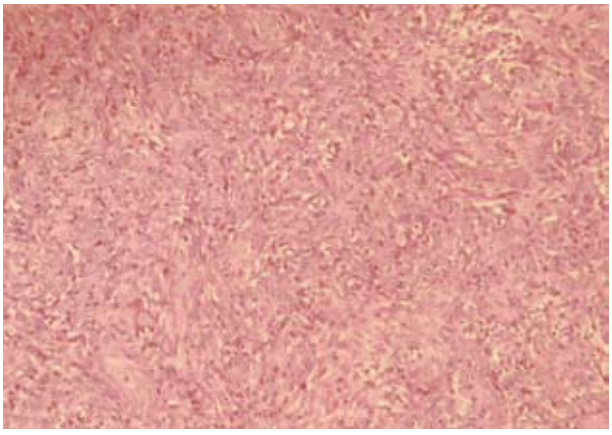

Fig. 2. Histological examination of the excisional biopsy showed a benign medullary spindle type thymoma (stage A) [hematoxylin and eosin stain; original magnification, × 400].

of unizoit tissue cysts of *I. belli* in the lamina propria. Examination of a diarrheic stool sample at the time of hospital admission showed the presence of numerous oocysts of *I. belli* and Charcot-Leyden crystals in direct smear, as well as formalin-ether concentration and modified Ziehl-Neelsen staining (Fig. 1). No other parasites or pathogenic bacteria were found by either stool examination or culture. During his hospital stay (2 months), extended clinical investigations, including chest radiography and computed tomography scan, showed the presence of an upper medastinal mass (9.0 × 4.5 cm). Histological examination of the excisional biopsy taken from this mass revealed a benign medullary spindle type thymoma (stage A) [Fig. 2].

The patient was first treated by oral cotrimoxazole (trimethoprim 20 mg/kg/day and sulfamethoxazole 100 mg/kg/day) after detection of the parasite in the stool examination, followed by complete resection of the thymoma. The diarrhea ceased within 2 days of starting chemotherapy, and the patient gained weight after discharge from the hospital following complete thymectomy. However, follow-up of the patient after discharge showed that he had 3 more episodes of diarrhea due to isosporiasis, each one about 3 weeks after finishing the relevant chemotherapy. He was given cotrimoxazole prophylaxis, and did not have any diarrhea for the following 6 months.

Discussion

Primary intrapulmonary thymic epithelial tumors are very rare lesions. These tumors can be solitary or multiple, affect both sexes, and span a broad age of distribution. The clinical course is that of a slow-growing lesion that remains asymptomatic until it reaches a size that causes problems due to local growth, such as pain, bronchial obstruction, or hemoptysis. As with mediastinal thymomas, they can be associated with paraneoplastic syndromes, such as myasthenia gravis or Good´s syndrome [7]. When present, symptoms include chest pain, shortness of breath, cough, and night sweats. Diagnosis is often made incidentally through routine radiographic examinations, as with the patient presented here. The cause of the defect in cell-mediated immunity in thymoma is uncertain, but patients usually have reduced T cell numbers, and often generalized defects in in vitro T-cell proliferation in response to mitogens and antigens [8,9]. Opportunistic infection should be suspected in these patients, even when gross indices of immune function are completely normal.

Various infections related to the immunodepression associated with thymoma have been described, with upper respiratory tract infections being the most common [10], but esophageal candidiasis and a variety of viral (cytomegalovirus, herpes) infections can occur. Diarrhea has been reported in almost 50% of patients with thymoma [6]. The causes of diarrhea in patients with Good syndrome are autoimmune enteropathy, graft versus host disease (GVHD), malabsorption [6], and enteric infections [11]. Data on parasitic diseases are scarce, with a few cases of strongyloidosis [12], toxoplasmosis [13], pneumocystosis [8], and filarial [14] infections being reported. To the best of these authors' knowledge, no report of a patient with *Isospora* infection associated with thymoma has been published.

Isosporiasis remains an important opportunistic infection in HIV-infected patients, especially in the developing countries of Africa, Asia, and Latin America [1,15]. Isosporiasis has also been observed in patients with concurrent Hodgkin's disease, non-Hodgkin's lymphoproliferative disease, human T-cell leukemia virus type 1–associated adult T-cell leukemia, and acute lymphoblastic leukemia [1]. In the patient presented here, as no other immunosuppressive condition except for thymoma was found, the association of benign thymoma with isosporiasis most probably led to a chronic debilitating diarrhea with several recurrences.

Developmental stages of *I. belli* can be identified in enterocytes in small intestinal biopsy specimens. In this patient, the unizoit cyst of *I. belli* presented in the lamina propria.

In summary, thymomas are tumors that are sometimes related to some degree of immunodeficiency,

leading to complicated infections, including parasitic infections. This unique patient is presented for clinical interest, and to highlight the possibility that the association of isosporiasis with thymoma may indicate an underlying immune dysfunction and should be considered once AIDS and malignancies are excluded in patients who present with severe diarrhea.

Acknowledgments

We thank Mr. M. H. Falakimoghadam and Mrs. Z. Sayyad Talaie for their enthusiastic cooperation with this study.

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