

Case Report

Refractory Giardiasis in an Immunosuppressed Patient in Turkey

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Abstract

Giardiasis is an infection of the small intestine caused by the protozoan parasite *Giardia duodenalis*. In immunocompetent patients the infection is usually self-limited and no treatment may be needed. Immunodeficiency, however, is a predisposing factor for the development of severe *Giardia* infection. In this report, a case of recurrent giardiasis refractory to nitroimidazoles and nitazoxanides presented. A 28-year-old male patient with hypogammaglobulinemia admitted to our hospital because of chronic diarrhoea. Microscopic examination of stool revealed a high number of *Giardia* trophozoites and cysts. Treatment with higher doses and a longer course of metronidazole, trimethoprim-sulfamethoxazole, ornidazole and albendazole failed. Administration of nitazoxanide, which has been reported to be effective against *Giardia duodenalis* refractory to nitroimidazoles, was commenced, but his symptoms persisted and stool samples demonstrated *Giardia* trophozoites and cysts again.

Key words: *Giardia duodenalis*; common variable immunodeficiency; refractory giardiasis; nitazoxanide.

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Introduction

Giardiasis is a parasitic infection caused by the flagellated protozoan parasite *Giardia duodenalis* (*Giardia intestinalis*, *Giardia lamblia*) that colonises the small intestinal lumen of vertebrate hosts [1]. People generally become infected by swallowing *Giardia* cysts found in contaminated food or water. The infection is usually characterized by diarrhoea, greasy stool, abdominal cramps, bloating, weight loss, and malabsorption. Asymptomatic or self-limited infections are common in immunocompetent (IC) patients [2]. Immunosuppression, especially hypogammaglobulinemia is a risk factor for developing symptomatic *G. duodenalis* infection [3].

Hypogammaglobulinemia is a disorder that is caused by a lack of B-lymphocytes and a resulting low level of immunoglobulins (antibodies) in the blood. Common variable immunodeficiency (CVID) is the most common cause of hypogammaglobulinemia [4]. Most CVID patients suffer from an increased susceptibility to pathogens affecting mucous membranes of the upper and lower airways and the gastrointestinal tract [5]. A number of studies have shown that *G. duodenalis* is more symptomatic and

more prevalent in the stools of hypogammaglobulinemic patients [3].

Although there are a number of agents used to treat giardiasis such as nitroimidazoles (metronidazole, tinidazole, ornidazole, and secnidazole), benzimidazoles (albendazole and mebendazole), paromomycin, furazolidone and quinacrine, treatment failures have been reported with all of these drugs [6]. Nitazoxanide is a new antiparasitic agent that has been reported to be effective against a broad range of parasites, including *G. duodenalis* refractory to nitroimidazoles [7].

We report a case of a 28-year-old male who had been diagnosed with CVID for several years and presented giardiasis resistant to treatment.

Case Report

A 28-year-old male patient admitted to the Hacettepe University Department of Internal Medicine, Infectious Diseases Unit, Ankara, Turkey, presented watery, foul-smelling chronic diarrhoea, nausea and bloating, abdominal cramps and weight loss. The patient had been diagnosed with common variable immunodeficiency (CVID) and used intravenous

immunoglobulin 400 mg/kg monthly for nine years. The patient's serum levels of all major immunoglobulin isotypes (IgG, IgA and IgM) were decreased. His physical examination and other laboratory tests were normal.

Direct wet mount smear was microscopically examined for the presence of erythrocyte, leukocyte, ova, trophozoites and cysts. Formol-ether fecal concentrate smeared and stained with native iodine, trichrome and modified Ziehl-Neelsen stains for the identification of *Cryptosporidium* and other parasites. Microscopic examination of stool revealed only *Giardia* trophozoites and cysts. Stool cultures did not yield any pathogenic bacteria.

The patient underwent upper gastrointestinal endoscopy and colonoscopy. Endoscopic brush smears were collected from the small intestine and stained with Papanicolaou (Pap) and Giemsa stains. *Giardia* trophozoites and increased intraepithelial lymphocytes were seen in histological sections of the duodenum (Figure 1).

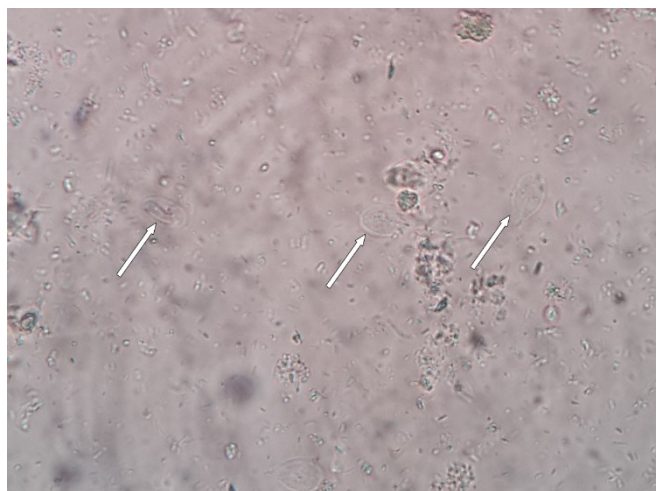
He has been prescribed metronidazole and trimethoprim-sulfamethoxazole for the last six months. Because of treatment failure with metronidazole and trimethoprim-sulfamethoxazole, administration of 2x500 mg ornidazole was commenced. Intravenous immunoglobulin replacements were continued as indicated. After a 14 day-treatment with ornidazole, *Giardia* trophozoites were still detected in stool samples. Eventually, we accepted the patient as a refractory case to standard treatment. Hence, albendazole 400mg/day was administered for 10 days. Microscopic examination of the stool samples once more yielded *Giardia* trophozoites. The patient was diagnosed as having refractory giardiasis and we applied to the Turkish Medicines and Medical Devices Association for off-label nitazoxanide treatment. After the approval, the patient was treated with nitazoxanide, which is a thiazolide antiparasitic agent, for 15 days. However, the stool examination revealed *Giardia* cysts and trophozoites again. As prolonged treatment (three months) with ornidazole or metronidazole failed to cure giardiasis, combination treatment regimens were commenced. Trimethoprim-sulfamethoxazole plus metronidazole for one month did not cure the giardiasis. Administration of a paromomycine plus nitazoxanide combination regime for 30 days once again turned out to be ineffective.

Despite all treatments the patient's symptoms persisted, and stool samples demonstrated *Giardia* trophozoites and cysts again (Figure 2).

Figure 1. *G. duodenalis* trophozoite in a histological section of the duodenum.



Figure 2. *G. duodenalis* cyst and trophozoites in a wet mount preparation.



Discussion

Parasitic infections continue to cause significant morbidity and mortality throughout the world. Although risk factors for obtaining parasitic infections are the same in both immunosuppressed (IS) and immunocompetent (IC) patients, immunosuppression can affect the presentation and severity of the infection and efficacy of treatment [3,8].

Giardiasis caused by the protozoan parasite *G. duodenalis* is one of the most common parasitic intestinal diseases in humans worldwide. *G. duodenalis* is a particularly significant pathogen for people with malnutrition or immunodeficiency. There are a number of studies showing that *G. duodenalis* infections are more prevalent and symptomatic in immunosuppressed patients than in immunocompetent hosts. Particularly in

patients with combined variable immunodeficiency (CVID) giardiasis is frequently observed [8,9].

Common variable immunodeficiency (CVID) is the most common symptomatic primary immunodeficiency and characterized by reduced levels of serum IgG, IgA, and/or IgM. Most of the patients suffer from infections with pathogens affecting mucous membranes of the respiratory and gastrointestinal tract. Gastrointestinal complications range from 20% to 60% of the patients with CVID. The main intestinal symptom is persistent or transient diarrhoea. *G. duodenalis* is the most common organism found in these patients [10,11].

In this case, the patient was diagnosed with CVID and using intravenous immunoglobulin monthly for nine years. His serum levels of IgG, IgA and IgM were decreased. He was suffering from chronic watery diarrhoea, abdominal cramps and weight loss. Microscopic examination of stool revealed a high number of *Giardia* trophozoites and cysts.

The nitroimidazoles including metronidazole, tinidazole, ornidazole, and secnidazole are the most commonly used agents to treat giardiasis. However, treatment failure with nitroimidazoles has become more prevalent in recent years. Nabarro *et al.* reported that treatment failure in a hospital in London increased from 15.1% in 2008 to 40.2% in 2013 [12].

Carter *et al.* presented a review of nitroimidazole-refractory *G. duodenalis* infection and treatment options. There are several agents such as albendazole, chloroquine, nitazoxanide, quinacrine and paromomycin whose efficacies have been demonstrated in patients with nitroimidazole-refractory giardiasis. Despite of appropriate courses of treatment some patients may develop persistent infection [13]. In our case, metronidazole, trimethoprim-sulfamethoxazole, ornidazole, albendazole, paromomycine and nitazoxanide treatments were administered but failed to cure giardiasis.

Mukku *et al.* presented a case of refractory giardiasis in a renal transplant patient. In the 2nd month of the post-transplant period the patient had diarrhoea and malabsorption and his duodenal biopsy revealed *G. duodenalis* trophozoites. After treatment with metronidazole for seven days his symptoms persisted. He was diagnosed as having refractory giardiasis and was successfully treated with combination of tinidazole and doxycycline for 21 days. In this case it is reported that a combination therapy for long duration is effective in the treatment of refractory giardiasis in renal transplant patients [14]. Requena-Méndez *et al.* reported a prospective study in patients with giardiasis treated with nitroimidazoles and 20% of the patients

presented persistent giardiasis after nitroimidazole treatment. In these refractory patients, short course of quinacrine therapy were found effective [15]. Muñoz Gutiérrez *et al.* also reported a 22% failure rate of nitroimidazole treatment in Spanish travellers. They found that quinacrine treatment was more effective than albendazole and paromomycin therapy in eradicating *G. duodenalis* [16]. In our case, because of treatment failure with metronidazole and trimethoprim-sulfamethoxazole, the patient received a second course of treatment with ornidazole. But his symptoms and trophozoite excretion in the stool persisted after a 14 day-treatment with ornidazole. A ten day-treatment with albendazole was also ineffective to eradicate the trophozoites. Prolonged treatment with ornidazole or metronidazole for three months failed to cure giardiasis as well. In this case, quinacrine could not be used because it is not available in Turkey.

Nitazoxanide, which is a thiazolide antiparasitic agent, has shown efficacy against several protozoan infections especially cryptosporidiosis and giardiasis in humans [17]. Coskun *et al.* presented a case of drug resistance *G. duodenalis* treated with nitazoxanide [18]. In our case in spite of using nitazoxanide for 15 days the patient's symptoms persisted, and stool samples demonstrated *Giardia* trophozoites and cysts again.

Combination therapies have been identified as useful alternatives to treatment failures in patients with giardiasis. Metronidazole with albendazole, paromomycine, quinacrine and nitazoxanide are the most common combinations found effective against refractory giardiasis [19,20]. In our case trimethoprim-sulfamethoxazole plus metronidazole and paromomycine plus nitazoxanide combination regimens implemented were found ineffective.

There are several alternative therapies for the treatment of patients with refractory giardiasis. Especially combination therapies have been shown to be safe and effective.

In our case, despite application of higher and longer courses of nitroimidazoles and combination therapies, our patient's symptoms and parasite excretion continued. Persistence of infection is presumably relevant to immunosuppression, especially immunoglobulin A (Ig A) deficiency.

Eventually, treatment failures are common in giardiasis. Further clinical trials are needed to establish the optimal therapy for the patients with drug-resistant giardiasis.

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