Case Report: Coinfection with *Hymenolepis nana*, *Hymenolepis diminuta*, *Giardia intestinalis*, and Human Immunodeficiency Virus: A Case Report with Complex Immunologic Interactions

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Abstract. We describe the case of a 43-year-old human immunodeficiency virus–infected man receiving combined antiretroviral therapy and coinfecting with *Hymenolepis nana*, *Hymenolepis diminuta*, and *Giardia intestinalis*, presenting as chronic diarrhea and critical weight loss. Immunological aspects of these interactions are reviewed.

INTRODUCTION

The etiology of chronic diarrhea in human immunodeficiency virus (HIV)–infected patients receiving combined antiretroviral therapy (cART) has been associated with acquired immunodeficiency syndrome–defining events such as intestinal cryptosporidiosis or cystoisosporiasis lasting more than 1 month.^{1,2} In patients with advanced HIV infection, diarrhea is considered an independent marker of poor prognosis with severe gastroenteritis, the second most common cause of death.^{1,3} In underprivileged urban, tropical settings, intestinal infections due to neglected, non-opportunistic protozoa and helminth species could also become a life-threatening condition. We present a severe case of giardiasis and hymenolepiasis coinfection in a man of same-sex relationship with advanced HIV infection.

CASE REPORT

In March 2015, a 43-year-old HIV-infected man, a rescue team worker from Caracas, Venezuela, was referred to our outpatient clinic with a 2-month history of diarrhea with 12–15 watery, explosive stools per day, abdominal pain, dehydration, fetid flatulence, and weight loss of 10 kg (16% of body mass). In the previous year, he described episodes of self-limiting steatorrhea alternating with watery diarrhea lasting 3–4 days, self-medicated with trimethoprim–sulfamethoxazole. His HIV infection was diagnosed 15 years previously and he had been receiving treatment for the last 12 years with apparent adherence. He was receiving abacavir, lamivudine, and lopinavir–ritonavir. Physical examination revealed an emaciated man weighing 62 kg. Ova and parasite screening of three, sequential, fresh stool samples identified *Giardia intestinalis* cysts and trophozoites and *Hymenolepis nana* and *Hymenolepis diminuta* eggs. Kinyoun stain, Baermann test, and agar plate culture for *Strongyloides stercoralis* were negative. Blood tests showed normal albumin without eosinophilia or anemia. The most recent CD4⁺ and CD8⁺ T-cell counts and HIV viral load were 101 cells/mm³, 2,486 cells/mm³, and 104,000/copies respectively.

Praziquantel (25 mg/kg single dose) and secnidazole (2 g/day for 3 days with a second course 15 days later due to the likelihood of *G. intestinalis* reinfection) were given. A remarkable clinical improvement with weight gain and diminution of the stool output (two per day) with more consistency but still explosive was achieved. Three days after the last dose of secnidazole, repeated stool samples revealed *G. intestinalis* cysts again but no *Hymenolepis* sp. eggs. Nitazoxanide (500 mg/twice daily for 3 days) was chosen to treat giardiasis, having ruled out *Cryptosporidium* sp. with negative Kinyoun stain. The patient gained 8 kg with persisting steatorrhea and lactose intolerance without recovery of cysts in subsequent fecal smears.

DISCUSSION

Hymenolepiasis diagnosis is based on the demonstration of the cestode eggs by stool microscopy. *Hymenolepis nana* eggs differ from those of *H. diminuta*. The first measures 30–47 µm in diameter, and contain an oncosphere with six hooks surrounded by an inner membrane with polar thickenings from which four to eight polar filaments arise and extend to the space between the oncosphere and the outer shell (Figure 1).⁴ *Hymenolepis diminuta*, a rat tapeworm that accidentally infects humans through the ingestion of infected fleas, is phylogenetically close to *H. nana*; nevertheless, their eggs are yellowish and larger. They measure 60–80 µm in diameter and the oncosphere is unmistakably separated from the outer membrane by a clear space without polar filaments.⁴ The low *H. diminuta* burden in this patient hampered egg recovery, even in concentrated stool samples.

Since immune response against *H. nana* is considered to be thymus dependent, the fecundity and longevity of this cestode vary between normal and athymic mice due to an inadequate immune response (eosinophil infiltration) against the cysticercoids.⁵ In immunosuppressed hosts, the lifespan of the parasite is longer than expected and also the likelihood of reinfection through egg ingestion is enhanced; therefore, massive infections could occur from high inoculum of eggs or cysticercoids resulting in the development of multiple generations of adults of *H. nana*.^{5,6}

Giardia intestinalis is widely distributed in tropical and subtropical regions. In Venezuelan urban settings, a prevalence of 20% has been reported.⁷ Similarly, *G. intestinalis* has been described as the most prevalent parasitic fecal

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FIGURE 1. Unstained wet mount of concentrated stools (100 $\times$). (A) *Hymenolepis nana* egg. The arrows point to the polar filaments. (B) The arrows point to the cysts of *Giardia intestinalis*.

pathogen in HIV-infected patients from urban Ghana (19%) regardless of their immune or cART status.⁸ In other African series, giardiasis prevalence is higher in HIV versus non-HIV-infected individuals and is more common without cART and ≤ 200 CD4⁺ T cells/mm³.⁹ Poor water sanitation, lack of personal hygiene, the presence of other family members infected with *G. intestinalis*, and oro-anal sexual practices are recognized as risk factors for its acquisition.^{10,11} In tropical areas, with high prevalence of soil-transmitted helminths, coinfection with *G. intestinalis* is expected.

The role of CD4⁺ T lymphocytes and *G. intestinalis* in humans has recently been reviewed.¹² Less is known about the immune interactions between this protozoan and HIV, but there is a strong association with the causation of diarrhea.^{10,13} The absence of these cells could contribute to the failure to control acute giardiasis, leading to chronic infection.¹² Th17 cells, a subset of CD4⁺ T cells characterized by interleukin (IL)-17A, IL-17F, and IL-22 production are related to homeostasis of the mucosal intestinal barrier and are involved in the effector immune response against *Giardia* that is likely to induce the parasitological cure of the disease.^{12,14,15} In early nontreated HIV infection, CD4⁺ T cells of the gut are targeted and massively depleted.¹⁵ As a result, Th17 cells are also diminished in the intestinal lymphoid tissue and in peripheral blood, resulting in bacterial translocation, immune activation, and disease progression.^{16,17} We hypothesize that anti-*Giardia* immunity is expected to be hampered in advanced HIV infection in part due to functional/quantitative diminution of Th17 cells. A deficiency in the synthesis of anti-*Giardia* IgA due to lack of B-cell activation, with the theoretical failure to limit the trophozoite adhesion to the duodenum and subsequent extension to the entire small intestine might also explain the present patient's patent malabsorption syndrome. Antibody-independent control of *G. intestinalis* infection in mice has also been suggested, but the backbone of an anti-*Giardia* effective immune response is a functional T CD4⁺ cell, that cooperates with B lymphocytes for the specific antibody synthesis and that also provides help for other cellular control mechanisms.¹⁸

Different approaches to the interactions between the anti-*Giardia* and the antihelminth immune responses have already been proposed.^{19,20} *Giardia intestinalis* and *Trichinella spiralis* coinfection in an animal model demonstrated a polar-

ized Th2 immune response that failed to control trophozoite multiplication.¹⁹ *Ascaris lumbricoides* has also been recognized as an immune modulating factor in *Giardia*-infected patients.²⁰ Light loads of this nematode in children parasitized with *G. intestinalis* are correlated with higher concentrations of IL-13, IL-6, and interferon- γ stimulated by the protozoan, as well as higher levels of specific IgG and IgE against *G. intestinalis* antigens, when compared with *Giardia*-free patients.²⁰ Children infected with moderate *A. lumbricoides* worm burden have decreased levels of the above-mentioned immune markers due to higher IL-10 concentrations stimulated by the helminth.²⁰ Furthermore, the likelihood of *Giardia* reinfection after secnidazole treatment is directly correlated with the intensity of *A. lumbricoides* infection.²⁰ Immune response models in human and nonhuman hosts infected with *Hymenolepis* sp. and *Giardia* have not already been published, but taking into consideration the above data, moderate tapeworm burdens could also be implied in a remarkably polarized Th2 immune response in *G. intestinalis*-coinfected patients. We propose that the impairment of the absorptive functions of the small intestine, chronic diarrhea, dehydration, and weight loss in the present patient are secondary to an imbalance between the Th1, Th2, and Th17 immune response against *Hymenolepis* sp., *G. intestinalis*, and nonvirological suppressed advanced HIV infection. Unfortunately, besides CD4⁺ and CD8⁺ T-cell counts, other immunological data from this patient are not available. A single dose of praziquantel eradicated *Hymenolepis* spp. but two nonconventional courses of secnidazole treatment were not sufficient to attain *G. intestinalis* parasitological cure. Although reinfection cannot be excluded, *G. intestinalis* resistance to nitroimidazoles has also been proposed as a cause of refractory infection. Therefore, nitazoxanide was chosen as an anti-*Giardia* alternative. Post-giardiasis steatorrhea and lactose intolerance versus chronic giardiasis with serial negative stool examinations are still diagnostic and therapeutic issues in our country, where molecular biology is not currently used as a widespread tool for intestinal parasitic research. In our patient, empirical cART change and optimal adherence to tenofovir, emtricitabine, and efavirenz was encouraged. Anti-*Pneumocystis jirovecii* prophylaxis with trimethoprim-sulfamethoxazole, water sanitation, and better hygiene practices with a closer parasitological follow-up were recommended.

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