Case Report

Acta Haematol 2011;126:63–67
DOI: 10.1159/000324799

Received: September 14, 2010
Accepted after revision: January 26, 2011
Published online: April 7, 2011

Disseminated *Strongyloides stercoralis* Infection in HTLV-1-Associated Adult T-Cell Leukemia/Lymphoma

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Key Words
Adult T-cell leukemia · Alemtuzumab · Corticosteroid · Disseminated *Strongyloides* · HTLV-1 · Human T-cell lymphotropic virus type-1

Abstract
A 55-year-old woman with human T-cell lymphotropic virus type-1 (HTLV-1)-associated adult T-cell leukemia (ATL) and a history of previously treated *Strongyloides stercoralis* infection received anti-CD52 monoclonal antibody therapy with alemtuzumab on a clinical trial. After an initial response, she developed ocular involvement by ATL. Alemtuzumab was stopped and high-dose corticosteroid therapy was started to palliate her ocular symptoms. Ten days later, the patient developed diarrhea, vomiting, fever, cough, skin rash, and a deteriorating mental status. She was diagnosed with disseminated *S. stercoralis*. Corticosteroids were discontinued and the patient received anthelmintic therapy with ivermectin and albendazole with complete clinical recovery.

Introduction

Infection with human T-cell lymphotropic virus type-1 (HTLV-1) is associated with development of adult T-cell leukemia (ATL) [1]. HTLV-1 also predisposes patients to recurrent and severe infection with the nematode parasite *Strongyloides stercoralis* [2]. Patients with chronic *Strongyloides* infection are susceptible to the life-threatening complication of disseminated strongyloidiasis (DS) if treated with immunosuppressive therapy, in particular corticosteroids. We present here a case of this unusual but serious condition as a complication of therapy of ATL.

Case Report

A 55-year-old woman from Barbados diagnosed with HTLV-1-associated ATL was enrolled in a phase II trial of alemtuzumab (Campath™ anti-CD52) for ATL. Her past medical history was significant for *S. stercoralis* infection that had been diagnosed 6 years earlier by endoscopy after a 5-month history of vomiting and diarrhea. She had been treated with ivermectin. A serologic diagnosis of HTLV-1 infection was made at that time; however, there was no evidence of ATL. Four months later, she underwent a jejunal resection and a gastrojejunostomy for a partial small

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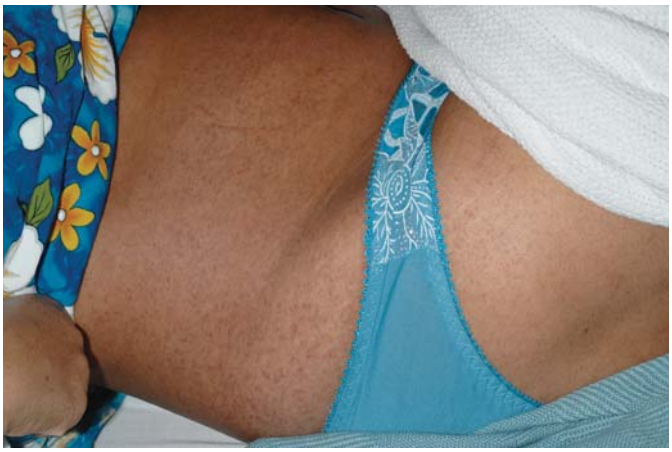

Fig. 1. Skin rash of disseminated *Strongyloides*.

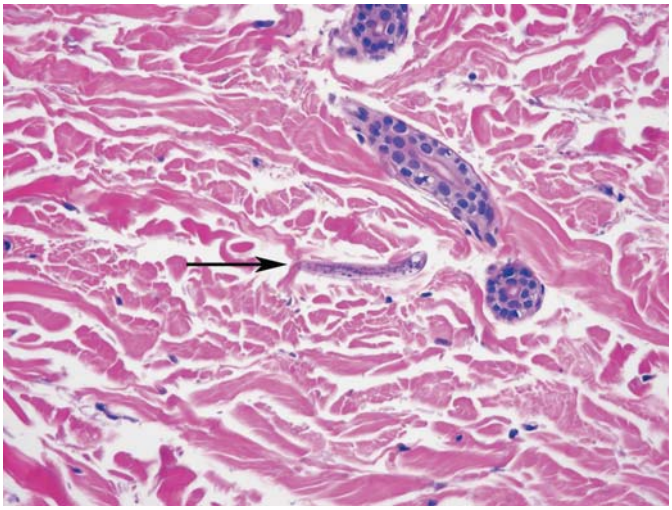

Fig. 2. *Strongyloides* larva in skin.

bowel obstruction. Six years later, she was empirically treated in Barbados with ivermectin for presumed strongyloidiasis after another bout of prolonged vomiting and diarrhea. No stool test was performed at that time. She responded clinically to the therapy. Later this same year, she was diagnosed with chronic ATL and enrolled in a clinical trial using daclizumab (humanized anti-CD25); however, her disease progressed.

She subsequently enrolled in another clinical trial and was treated with intravenous alemtuzumab. She received 30 mg three times weekly. Her circulating leukemic cell count promptly declined. However, after 10 weeks of treatment she developed decreased vision in her right eye. Ophthalmologic examination revealed a vitreous infiltrate. Vitreous biopsy and immunophenotyping of the vitreous infiltrate by flow cytometry revealed an aberrant T-cell population consistent with ATL. This was considered disease progression, and therefore the alemtuzumab was stopped and she was taken off the study. Daily oral dexamethasone 20 mg and prednisolone acetate 1% ophthalmic suspension were started as palliative treatment.

At a follow-up visit 10 days later, the patient complained of new onset watery diarrhea of up to 10 stools per day, and vomiting. She was found to have had a 2.7-kg weight loss and experienced an episode of near-syncope requiring hospital admission. She also complained of a pruritic rash on her abdomen and flank. On review of systems, the patient complained of a mild, dry cough, but no shortness of breath. She was afebrile, but tachycardic at 121 beats/min and had orthostatic hypotension. Pulse oximetry showed 96% saturation on room air. Pulmonary examination was notable for bibasilar rales. Her abdomen was soft and non-tender, without hepatosplenomegaly. An extensive petechial purpuric rash was noted on both flanks, extending to the mid-to-lower abdomen and thighs (fig. 1). Laboratory values showed a serum sodium of 125 mmol/l (reference range 135–145), potassium of 2.8 mmol/l (reference range 3.5–5.2), and a normal peripheral blood leukocyte count without eosinophilia. On direct smear of stool and sputum, numerous *S. stercoralis* larvae were seen. Computed tomographic (CT) scan of the chest showed patchy, 'ground-glass' infiltrates that had not been present 1 month previously. Blood cultures were negative for bacterial growth. A biopsy of the rash demonstrated *Strongyloides* larvae (fig. 2). Oral ivermectin 200 μg/kg once daily was initiated for DS.

One week later, the patient became acutely obtunded with a temperature of 39°C. She was hemodynamically stable with no focal neurological signs. Ivermectin was increased from 200 to 300 μg/kg/day and albendazole 400 mg twice daily via nasogastric tube was added, along with intravenous meropenem, vancomycin, ampicillin and acyclovir. CT scan of the brain was normal. Lumbar puncture and cerebrospinal fluid (CSF) analysis showed a total leukocyte count of 6,095 × 10^9/l cells with 98% neutrophils, with a protein concentration of 430 mg/dl (reference range 15–45) and glucose of 82 mg/dl (reference range 40–70) with a serum glucose of 236 mg/dl. Gram stain and bacterial culture, agar plate culture and a concentrated smear of CSF for *Strongyloides* larvae were all negative. CSF polymerase chain reaction for herpes simplex virus and human herpes virus-6, and a cryptococcal antigen test by EIA were negative. Repeat blood cultures showed no growth. Within 24 h, the patient became afebrile and her mental status improved. Repeat CSF analysis 2 days after the initial test showed the total leukocyte count decreased to 0.378 × 10^9/l cells with 93% neutrophils. Broad-spectrum antimicrobials were continued for 2 weeks and the patient's dexamethasone was tapered and discontinued. She remained on ivermectin and albendazole for 14 days after her stool examination was negative for *Strongyloides* for 5 consecutive days. This resulted in a total of 33 days of anthelmintic treatment.

At a follow-up visit 3 months later, the patient was well and without complaints, with normal stool and CSF studies. Ophthalmologic examination showed improvement in the vitreous infiltrate. Flow cytometry continued to demonstrate an aberrant T-cell population in the peripheral blood suspicious for ATL, but her total white count remained normal. Six months after discharge, the patient reported an episode of watery diarrhea, abdominal

discomfort and mild dizziness that resolved after she was treated with ivermectin (200 μg/kg/day) by her local physician in Barbados. No stool studies were done at the time of the acute illness. Stool studies at the time of her follow-up visit were negative for larvae and other infectious causes of diarrhea. One year later, the patient was well with no intercurrent symptoms and her stool examination for *Strongyloides* was negative.

Discussion

S. stercoralis is an intestinal nematode endemic to the tropics and subtopics with worldwide estimates of prevalence varying from 30 to 100 million people. In developed countries such as the United States, there is growing recognition of *Strongyloides* as a parasite of significance among immigrants, travelers and refugees [3, 4]. Chronic infection with *S. stercoralis* is frequently asymptomatic, although patients may complain of gastrointestinal symptoms such as diarrhea, abdominal pain, constipation and bloating, or have dermatologic findings, such as chronic urticaria or larva currens, a serpiginous rash located along the lower trunk, thighs or buttocks. Unusual manifestations include arthritis, nephrotic syndrome, chronic malabsorption, duodenal obstruction, focal hepatic lesions and asthma [5]. Hyperinfection syndrome (HIS) occurs when chronically infected individuals are administered corticosteroids, resulting in increased numbers of larvae and exacerbation of gastrointestinal and pulmonary symptoms [5]. DS occurs when large numbers of larvae migrate beyond from the gastrointestinal tract and lungs to ectopic sites such as the skin, as occurred in our patient [6]. The mortality associated with HIS or disseminated disease approaches 100% if untreated [5]. Death in patients with DS can result from Gram-negative or aseptic meningitis, bacteremia, or massive larval dissemination and hypovolemic shock [2].

Epidemiologic studies have shown that, in endemic areas, persons who are HTLV-1 seropositive have a significantly higher prevalence of *S. stercoralis* infection detected by stool examination compared to seronegative persons [2]. HTLV-1 coinfection plays a critical role in the development of HIS/DS by interfering with the immune response to *S. stercoralis*, most notably by decreasing the production of IL-4, IL-5, IL-13 and IgE in response to parasite antigens, resulting in an increase in autoinfection and decreased parasite killing [2]. Regulatory T-cell populations are also expanded in HTLV-1 and *S. stercoralis* coinfected individuals compared to persons infected with *S. stercoralis* alone suggesting another potential mechanism for decreased T-cell immunity to the parasite [7]. Consequently, HTLV-1 coinfected individuals are predisposed to more severe and recurrent strongyloidiasis. Decreased treatment efficacy is noted in these patients [2]. It is likely that our patient had persistent *Strongyloides* infection despite several treatments over a 6-year period, and that the episode of DS was a complication of this chronic infection.

Our patient was diagnosed with ATL many years after she developed the *Strongyloides* infection. Some studies have suggested that *S. stercoralis* infection promotes development of ATL in HTLV-1 infected individuals [8–10], but this hypothesis has been disputed on the grounds that ATL patients infected with *Strongyloides* have improved responses to chemotherapy [11], and HTVL-1 carriers coinfected with *Strongyloides* have a lower proviral loads than those with HTVL-1 alone [12].

Another major risk factor for the development of HIS/DS is the use of corticosteroids. Even a single dose of dexamethasone has been followed by the development of disseminated disease [13]. Other immunosuppressive drugs, including monoclonal antibodies such as alemtuzumab, have been implicated in the development of DS/HIS [14], although concurrent steroid use was associated with the majority of these cases, including our own.

The parasitological diagnosis of HIS/DS is usually straightforward because of the greatly increased parasite number, as larvae are easily found in stool or sputum, and have been incidentally found in blood smears, ascitic fluid, and bronchoalveolar lavage specimens [15]. Diagnosis of the chronically infected, asymptomatic individual, however, can be challenging, as adult parasites may produce only 10–15 eggs per day [16]. The sensitivity of a single, fresh stool specimen has been estimated to be as low as 30% [17]. Multiple stool specimens can increase the sensitivity [18]. Agar plate culture improves parasite detection considerably [19]. Aspiration of duodenal fluid for microscopic examination has been shown to be more sensitive (76%) than wet mount analysis of stool samples [20]. Serology by enzyme-linked immunosorbent assay (ELISA) based on crude larval antigen can be useful in excluding strongyloidiasis as part of the differential diagnosis. The sensitivity of this test has been determined to be ~95% [21], although this is reduced in patients with hematologic malignancies [22]. Serology utilizing a recombinant *Strongyloides* antigen has the advantage of eliminating cross-reactivity with filarial infections [23].

For chronic strongyloidiasis, oral ivermectin 200 μg/kg/day for 1–2 days is the drug of choice based on its efficacy and tolerability [24]. Groups in whom empiric ivermectin would be relatively contraindicated include:

pregnant or lactating women, children <1 year of age, or persons weighing <15 kg [5]. Alternatives include oral albendazole, 400 mg twice daily for 2–7 days, although albendazole has been associated with lower efficacy compared to ivermectin [25]. A few caveats for the presumptive treatment of *Strongyloides* exist. Ivermectin should not be used empirically in patients from Western and Central Africa at risk for *Loa loa* microfilaremia because of the potential for life-threatening encephalopathy in patients with blood microfilaria levels >5,000 microfilariae/ml [26]. The use of albendazole must similarly be weighed against the risk of exacerbating inflammatory reactions in patients with known neurocysticercosis, or in patients from neurocysticercosis-endemic regions with a seizure history of unknown etiology.

Regardless of treatment regimen, certain patients, such as those with HTLV-1 coinfection or hypogammaglobulinemia, have lower cure rates [2]. For this reason, these patients should be closely followed, as they remain at risk for the development of HIS/DS even after treatment. Currently, there is no test of cure for strongyloidiasis. Follow-up of patients after treatment with anthelmintics should routinely include multiple stool examinations to check for continued shedding of larvae. Resolution of peripheral eosinophilia has been observed in 90% of patients following treatment [24]. Although antibody levels typically persist after treatment, a decline in antibody levels has been noted in some patients 6 months after therapy [27, 28].

Once HIS/DS develops, it is generally advisable to continue therapy for at least 2 weeks after three or more negative stool studies, or longer if the patient remains immunosuppressed [5]. In critically ill patients with hypoalbuminemia or paralytic ileus, it can be difficult to achieve adequate serum levels of ivermectin. Parenteral ivermectin has been administered under an Investigational New Drug exemption with demonstrated improvement in serum ivermectin concentrations, although its use has not been systematically studied [29]. Off-label rectal administration has been useful in some patients with severe diarrhea [30]. Combination therapy with albendazole and ivermectin has not been well studied.

Several questions remain unanswered in the management of *Strongyloides* infection. A critical issue relevant to oncologists is whether secondary prophylaxis prior to the initiation of immunosuppressive therapy can prevent development of HIS/DS in chronically infected individuals. Cases of HIS/DS have occurred even after treatment and documented clearance of *Strongyloides* larvae in stools of chronically infected individuals undergoing solid organ transplantation [31]. For this reason, extended or intermittent courses of anthelmintics have been advocated by some, although a prophylactic regimen has yet to be defined [32, 33]. Screening of persons from endemic areas with serologic tests or repeated stool tests should occur prior to the initiation of immunosuppressive therapy. Infected individuals should be treated and monitored with serial stool examination and eosinophil counts post-treatment. HTLV-1 coinfected individuals should be considered at continued risk for HIS/DS despite anthelmintic treatment.

Conclusions

HTLV-1 infection, in addition to playing a causal role in the development of ATL, is a major risk factor for chronic *S. stercoralis* infection, and for the complications of hyperinfection and dissemination. Additional immunosuppressive therapy given to patients with HTLV-1 and *S. stercoralis* coinfection may trigger potentially fatal dissemination. Careful consideration should be given to these risks before administering steroids or other immunosuppressive therapy to such patients.

Acknowledgments

The authors gratefully acknowledge the assistance of Dr. Maria Turner, Dr. Rachel Bishop, and the clinical study staff (Melissa Law, Amara Pabon, Eunice Fox) at the National Institutes of Health for their help in caring for this patient. We additionally thank Dr. Thomas B. Nutman for his review of the manuscript.

This study was supported in part by the Intramural Research Program of the Center for Cancer Research, National Cancer Institute, and the National Institute of Allergy and Infectious Diseases, National Institutes of Health.

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