

CASE REPORT

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A case of apparent ART-associated immune reconstitution inflammatory syndrome in a patient with *Strongyloides stercoralis* infection

Dwayvania Miller, Yassine Kilani, Ebehiwele Ebhohon, Emnet Keftassa, Karen Hennessey, Addi Feinstein

ABSTRACT

Introduction: *Strongyloides* infection is most commonly caused by *Strongyloides stercoralis* (*S. stercoralis*). It often causes asymptomatic chronic infection but through the translocation of the parasite into the bloodstream, it can lead to disseminated strongyloidiasis (DS). We describe a case of a patient with human immunodeficiency virus (HIV) who developed Strongyloidiasis with the complication of vancomycin-resistant *Enterococcus* (VRE) meningitis. Notably, the clinical condition of the patient worsened after commencing anti-retroviral therapy (ART), raising concern for ART-associated immune reconstitution inflammatory syndrome (IRIS) to *S. stercoralis*.

Case Report: A 51-year-old African female with a past medical history of HIV presented with a 1-week history of abdominal pain and a 2-month history of generalized malaise, constipation, and weight loss. She improved with symptomatic management and commenced Biktaryv. She re-presented one month later with worsening gastrointestinal symptoms. Her hospital course was complicated by septicemia with worsening mentation.

Her repeat abdominal imaging showed ascending and transverse colitis and cerebrospinal fluid analysis was positive for vancomycin-resistant *Enterococcus faecium* (VRE). During her re-admission, the patient developed persistent watery diarrhea which was found to be positive for *S. stercoralis*. Despite medical therapy she demised on day 28 of admission.

Conclusion: Literature is very scarce concerning the progression of *S. stercoralis* infection to Strongyloides disseminated strongyloidiasis (DS) as a result of IRIS. As clinicians, we must have a high index of suspicion in our HIV population as DS can lead to fatal complications. It can also help guide management decisions concerning ART until complete eradication of *S. stercoralis* infection is obtained.

Keywords: Disseminated strongyloidiasis, IRIS, Strongyloidiasis, *Strongyloides stercoralis*

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INTRODUCTION

Strongyloides stercoralis is a soil-transmitted thread worm most prevalent in humid climates and resource-limited countries with poor sanitation. According to the

Centers for Disease Control (CDC), the global prevalence is estimated to be between 30 and 100 million people [1], with countries in Southeast Asia, Africa, and the Western Pacific region accounting for more than 75% of the cases [2]. In the United States, infections have been reported among individuals who have resided in endemic areas and among residents of southeastern states [3].

Infected individuals may remain asymptomatic with subclinical infection, for decades, with subsequent unmasking ensuing in individuals who become immunosuppressed. Manifestations of Strongyloides infection include acute infection with Loeffler's syndrome, chronic intestinal infection, asymptomatic autoinfection, symptomatic autoinfection, and hyperinfection with disseminated disease [3]. Initially, disseminated strongyloidiasis was considered an acquired immunodeficiency syndrome (AIDS)-defining illness in *S. stercoralis* endemic areas. Over the years, necropsy studies in endemic regions of Brazil and Africa showed no cases of disseminated strongyloidiasis in HIV-infected patients. The scarcity of reported cases led to the CDC and World Health Organization (WHO) removing strongyloidiasis as an AIDS-defining illness in 1987 [4]. Though it has been reported that there is an increased incidence of intestinal *S. stercoralis* in HIV patients, HIV infection does not increase the risk for Strongyloides hypersensitivity syndrome (HS) and disseminated strongyloidiasis (DS) [4]. Additionally, very few cases have been reported on the association between highly active anti-retroviral therapy (HAART) initiation and development of HS and DS due to immune reconstitution inflammatory syndrome (IRIS) [5].

Herein we present a case of a 51-year-old female patient, known to have human immunodeficiency virus (HIV), who developed DS complicated by *Escherichia coli* (*E. coli*) bacteremia and vancomycin-resistant *Enterococcus* (VRE) meningitis. Progression of her symptoms was noted after initiating HAART, causing concern for ART-associated IRIS to *S. stercoralis* in this patient.

CASE REPORT

A 51-year-old African female with a past medical history of human immunodeficiency virus (HIV) for 20 years, not on HAART, presented with a 1-week history of abdominal pain. The pain was intermittent but severe, located in the periumbilical and epigastric region, associated with nausea and multiple episodes of bilious vomiting. A review of systems was positive for two months of generalized malaise, body aches, chronic constipation, and weight loss. The patient denied diarrhea, fever, sick contacts, and recent travel outside the United States. Her laboratory investigations were significant for elevated white blood count (WBC) of 11.01 ($4.80\text{--}10.80 \times 10^3/\text{uL}$) with increased absolute lymphocyte count of 6.54 ($1.00\text{--}4.90 \times 10^3/\text{uL}$) and eosinophil count 0.65 ($0.10\text{--}0.40 \times$

$10^3/\text{uL}$). Her absolute CD4 count was 319 ($489\text{--}1457/\text{uL}$), CD4% was 7% (30–62%) and HIV viral load was 697,984 copies/mL. Computed tomography (CT) imaging of her abdomen without contrast showed mild wall thickening of the gastric antrum with possible enteritis. The patient was admitted, hydrated with intravenous fluids, and given symptomatic and antibiotic therapy for her enteritis. The patient was also started on Biktarvy and discharged home once symptoms resolved.

One month later, this patient re-presented to the emergency department with a history of abdominal pain with increasing intensity post-meals, additional unintentional weight loss (recorded 6.4 kg weight loss since previous discharge), decreased appetite/oral intake, and constipation requiring laxatives for bowel movements. All other reviews of systems were negative.

The abdominal exam was significant for epigastric tenderness. Neurologically, she was alert and oriented to person, place, and time. Her vital signs showed tachycardia to 109 beats per minute, blood pressure 109/77 mmHg, and temperature of 98 °F. Her labs on this admission showed WBC: $8.99 \times 10^3/\text{uL}$ (Differential: neutrophil $3.84 \times 10^3/\text{uL}$, lymphocytes $4.37 \times 10^3/\text{uL}$, and eosinophils $0.20 \times 10^3/\text{uL}$); hyponatremia of 128 mmol/L; hypochloremia of 89 mmol/L; metabolic alkalosis of 33 mmol/L; albumin 3.0 g/dL; viral load: <30 copies detected; CD4 count of 341/uL; and CD4% 10%). The patient's urinalysis was positive for a urinary tract infection (UTI). There was also an incidental finding of COVID-19 on this admission. Repeat CT abdominal imaging showed possible duodenal compression by the superior mesenteric artery with fecal material found throughout the colon. Our surgical team was consulted and recommended enemas to relieve constipation with a liquid diet for nutrition. The patient was admitted and treated for her UTI and dehydration. She was also restarted on her home medication.

Day 3 of our patient's hospital admission was complicated by a spontaneous right-sided pneumothorax resulting in a pigtail catheter being placed for management. On day 7 of admission she had her first temperature spike. Subsequent fever workup showed blood cultures positive for pan-sensitive *E. coli*. On day 10 of admission, our patient was noted to have altered mental status with bilious vomitus and was in respiratory distress. Repeat abdominal imaging showed ascending and transverse colitis with hyperemia of the small bowel wall in the left lower quadrant. Repeat chest X-ray showed the development of bilateral airspace and ground-glass consolidation with features suggestive of COVID pneumonia. The patient was intubated and transferred to the medical intensive care unit (ICU) for acute respiratory failure. A lumbar puncture was performed because of fever and altered mental status. Cerebrospinal fluid (CSF) showed: WBC 20 ($0\text{--}5/\text{uL}$) with a differential count of polymorphonuclear cells 46%; bands 1%; lymphocytes 53%; red blood cell (RBC) 37 ($0\text{--}1/\text{uL}$); CSF protein: 44.9 (15–45 mg/dL); CSF glucose: 115 (40–70 mg/dL).

The Biofire Meningitis and Encephalopathy Panels were negative. Cerebrospinal fluid and serum cryptococcal antigen were negative. However, CSF JC virus DNA by PCR was positive with 500 copies/mL (Ref Range and Units: Not detected) and her final CSF culture grew vancomycin-resistant *Enterococcus faecium* (VRE). The patient was started on Linezolid 600 mg twice daily, and intravenous (IV) corticosteroids were added during her ICU stay as her pressor requirements increased due to her worsening septic shock.

During her medical ICU (MICU) course, the patient developed loose bowel movements that persisted despite the discontinuation of laxative therapy. Stool studies were obtained and found to be positive for *S. stercoralis*. The patient was started on Ivermectin 12 mg daily via nasogastric tube.

Despite ongoing vasopressor support and antibiotic therapy, her clinical condition continued to deteriorate during her MICU stay. The patient developed acute renal failure and could not tolerate renal replacement therapy because of hemodynamic instability. The patient also developed status epilepticus requiring Keppra and benzodiazepine infusion. Family conferences were held throughout her hospital course with MICU and Palliative care. The family opted for our patient to have comfort care measures as her course worsened. The patient demised on day 28 of hospital admission.

DISCUSSION

Strongyloides stercoralis is the most common agent of Strongyloidiasis globally [1]. Strongyloidiasis can present with a wide range of clinical manifestations, the most common being the incidental discovery of peripheral eosinophilia in an otherwise asymptomatic patient [6–8]. In this case, the patient's initial presentation to the hospital was positive for peripheral eosinophilia with other non-specific gastrointestinal symptoms.

In summary, the life cycle of *S. stercoralis* occurs in the following manner. In the free-living cycle, *Strongyloides rhabditiform* larvae develop into infective filariform larvae and penetrates the host's skin. The parasite is transported to the lungs, and eventually migrates into the gastrointestinal (GI) tract. In the GI tract, the filariform larvae mature into adults and burrow themselves in the GI mucosa of the small intestine. They eventually produce eggs which develop into rhabditiform larvae and are excreted back into the soil to begin a new life cycle. Alternatively, autoinfection can occur in which rhabditiform larvae within the GI tract become infective filariform and penetrate the intestinal mucosa to migrate via the bloodstream and lymphatics to the lungs and the intestines to continue their life cycle. This increased host parasitic burden can cause Strongyloides hypersensitivity syndrome (HS) in immunocompromised patients. This infective larva can penetrate the intestinal mucosa and migrate to other organs outside the larva

life cycle's regular sites, resulting in disseminated strongyloidiasis [9]. Autoinfection occurs primarily in the immunocompromised hosts with impaired cell-mediated immunity such as HTLV1, patients receiving steroids or immunosuppressants, and transplant patients [10]. The resultant HS causes severe symptoms of intestinal obstruction, peritonitis, gastrointestinal bleeding, pneumonitis, alveolar hemorrhage, respiratory failure, or sepsis [9]. Disseminated strongyloidiasis is characterized by bloodborne infections, meningitis, encephalitis, or syndrome of inappropriate secretion of antidiuretic hormone (SIADH) [9]. Hyperinfection syndrome and disseminated disease have a mortality rate of up to 80–90% [9].

The CDC endorses that HIV/AIDS is not a risk factor for strongyloidiasis [1]. However, studies have shown a higher prevalence of *S. stercoralis* infection in HIV patients than in those without HIV [11]. The lack of progression of *S. stercoralis* infection to DS is hypothesized to be a result of the type of immunosuppressive effect observed in HIV patients compared to other immunocompromising states. Specifically, there is a more significant decline in the function of type 1 T helper (Th1) cells over type 2 T helper (Th2) cells in HIV [4]. Th1 helper cells promote interferon-gamma (IFN- γ), interleukin 2 (IL-2), and tumor necrosis factor-alpha (TNF- α) activity [4]. Th2 helper cell boosts humoral immunity and produces cytokines IL-4, IL-5, IL-10, and IL-13 [4]. Th2 helper cells are the dominant immune response in helminthic infections [4].

Additionally, IL-5 acts as an eosinophil colony-stimulating factor [4] and eosinophils play a defense role in helminthic infections. In contrast, persons living with HTLV-1 shift toward a greater Th1 cell immune response with less Th2 immune activity leaving them more susceptible to Strongyloidiasis [4]. Studies have also shown that low CD4 count due to HIV infection prevents larval maturation of Strongyloides in the host gut. Decreased larval maturation would result in reduced autoinfection and thus reduced incidence of Strongyloides hyperinfection syndrome and disseminated disease [12, 13].

On days 7 and 10 of this patient's admission, she was noted to have a significant decline in her clinical status with the findings of sepsis secondary to *E. coli* bacteremia and VRE meningitis. It is hypothesized that these complications were secondary to the translocation of gut bacteria attached to the infected *S. stercoralis* larvae into the bloodstream and crossing through the blood-brain barrier. As mentioned before, disseminated strongyloidiasis (DS) is not a common complication of Strongyloides infection in HIV patients. This led the medical team to question the inciting factor of this patient's disease progression. While our patient did have IV corticosteroids during her hospital course this was noted to be after her clinical decline and was added post intubation and vasopressor therapy to provide hemodynamic support. A literature review revealed a

plausible explanation of ART-associated IRIS causing the progression of *S. stercoralis* infection to HS and subsequent DS. Two distinct patterns of IRIS have been established in the literature, paradoxical and unmasking IRIS [14, 15]. Paradoxical IRIS occurs when signs and symptoms of opportunistic infections (OI) recur or acutely worsen while treatment is ongoing despite an initial positive response to treatment [15]. Unmasking IRIS occurs when a new OI occurs with a pronounced inflammatory reaction after HAART initiation [15]. The onset of IRIS varies from a few days to six months after HAART initiation [15]. It was difficult to use one of these definitions to characterize our patient as we do believe that her initial presentation was secondary to Strongyloides infection which was not diagnosed nor treated at that time. However, the patient's progression to DS was suggestive of unmasking IRIS as her second presentation to hospital after the initiation of Biktarvy showed rapid clinical deterioration with the complications of *E. coli* bacteremia and VRE meningitis. The presence

of immune reconstitution in this patient is evidenced by viral suppression and an increase in CD4 levels on follow-up testing during her second hospital admission.

ART-associated IRIS in *S. stercoralis* may also be different from the conventional pattern known in literature [11]. Aru et al. found that the IRIS reaction to Strongyloides in their HIV patient may not have been as a result of a significant host inflammatory response but that the immune reconstitution possibly caused a phenotypic shift in the organism to the invasive Strongyloides filariform leading to their patient's DS [11]. Though minimal research has been published on this mechanism of IRIS, it presents an alternative explanation to the mechanism of IRIS in our patient. Table 1 shows that our case would be the ninth reported case of apparent immune reconstitution leading to progression of *S. stercoralis* infection. It deserves further study as it could change management decisions concerning initiation or disruption of HAART therapy until complete eradication of *S. stercoralis* is obtained.

Table 1: Reporting of diagnostic and therapeutic data of apparent cases of immune reconstitution inflammatory syndrome to *S. Stercoralis* in HIV-infected patients

Authors	<i>S. stercoralis</i> diagnosis prior to ART	Days between ART and diagnosis	Prednisone prior to <i>S. stercoralis</i> diagnosis	CD4 ⁺ counts (cells/ μ L) before after ART initiation	RNA viral load (copies/mL) before after ART initiation	Histopathological evidence of inflammation?	Anti-helminthic therapy
Kim et al. (2004) [16]	No	23	Yes	32 ND	>750,000 900	ND	Ivermectin
Lanzafame et al. (2005) [17]	No	30–50	No	135 368	342,978 1208	ND	Thiabendazole daily for 10 days
Brown et al. (2006) [18]	Yes	100	No	30 60	>500,000 <50	ND	Ivermectin 5 times in 2 weeks
Taylor et al. (2007) [19]	No	42	Yes	96 78	75,000 891	ND	Ivermectin for 5 doses
Haddow et al. (2009) [14]	No	90	No	48 181	NR	No	None
Aru et al. (2017) [11]	Yes	19	No	3 7	138,572 75	No	Thiabendazole and Ivermectin: 7 and 14 days
Bar-Yoseph et al. (2017) [20]	Yes	~67	No	40 170	>2,000,000 100	Yes	Ivermectin for 7 days
Natrajan et al. (2018) [5]	No	30	No	68 140	867,000 9500	Yes	Albendazole and Ivermectin
Miller et al. (2022) [This Work]	No	57	No	319 341	697,984 <30	ND	Ivermectin for 2 days (course discontinued because of demise)

CONCLUSION

With the removal of strongyloidiasis as an AIDS-defining illness, the clinician's awareness of testing for *Strongyloides* infection in this population has decreased. In our institution, this case highlighted the importance of testing for *Strongyloides* in our HIV patients, especially in the setting of peripheral eosinophilia and migration from disease endemic areas. In addition, there is minimal information on ART-associated IRIS in *S. stercoralis* infection. As a result, the authors would conclude that clinicians should consider delaying initiation and disrupting HAART in the setting of *S. stercoralis* infection until complete eradication via anti-helminthic therapy is assured because of the possible disease progression to HS and DS with fatal outcomes. In conclusion, the authors support that further studies are needed on the complication of ART-induced IRIS in *Strongyloides* infection to help guide the management of our HIV patients with *S. stercoralis* in the future.

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Author Contributions

Dwayvania Miller – Conception of the work, Design of the work, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

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Written informed consent was obtained from the verbal consent obtained from patient's next of kin for publication of this article.

Conflict of Interest

Authors declare no conflict of interest.

Data Availability

All relevant data are within the paper and its Supporting Information files.

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