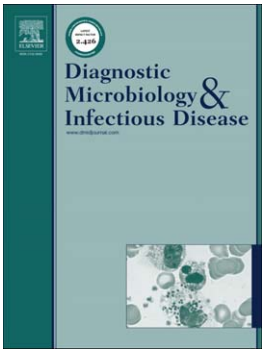

A Case of *Strongyloides* Hyperinfection Syndrome in the Setting of Persistent Eosinophilia but Negative Serology

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Title: A Case of *Strongyloides* Hyperinfection Syndrome in the Setting of Persistent Eosinophilia but Negative Serology

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Running Title: strongyloides hyperinfection syndrome

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Abstract

Strongyloides stercoralis is a unique intestinal nematode with the ability to replicate and complete its life cycle without leaving the host. We report a fatal case of *Strongyloides* hyperinfection syndrome in a patient who had persistent eosinophilia for several years but negative *Strongyloides* serology. Our case suggests that ELISA serologies cannot solely be relied upon to diagnose *Strongyloides stercoralis* infection; history and clinical judgment remain crucial to this diagnosis.

Key Words: strongyloidiasis; hyperinfection; eosinophilia; serology

Introduction

Severe complicated strongyloidiasis, including hyperinfection and disseminated disease, is a well-known entity with high mortality (**1**). It results from accelerated autoinfection by the *Strongyloides stercoralis* when the host immunity is impaired. In uncomplicated cases, several stool exams are needed for diagnosis since a single sample has 30% sensitivity (**2)**. Consequently, most clinicians use serology which is more sensitive to confirm the diagnosis. In complicated cases, however, the larvae are readily seen on stool, sputum and other tissue specimens (**3**).
We describe a case of a patient with persistent eosinophilia but negative S*trongyloides* serology who subsequently became immunocompromised and developed *Strongyloides* hyperinfection syndrome.

Case.

A 46 year-old male presented with persistent cough for 3 months. The cough was occasionally productive of white sputum and came in paroxysms, leading to vomiting. He also complained of severe fatigue and watery diarrhea for 7 days. He had lost 20 pounds due to oral intolerance.

His medical history included human immunodeficiency virus type 1 (HIV-1) and Burkitt's lymphoma. Prior to the onset of his cough, the patient had been receiving chemotherapy for several months. His outpatient medications included antiretrovirals and trimethoprim-sulfamethoxazole (TMP-SMX) for *Pneumocystis jirovecii* prophylaxis. The patient lived in New York City and denied recent travel. He was born in South America and had immigrated to the United States over 20 years prior.

Physical exam was remarkable for fever (with temperature to 101.7° F), tachypnea (respiratory rate of 32 breaths/minute) and tachycardia (heart rate of 115 beats/minute). He was severely cachectic with bitemporal muscle wasting and had bibasilar crackles on lung auscultation. Labs showed a leukocyte count of 2.2 K/μL (75% neutrophils, 16.2% lymphocytes and 0.2% eosinophils). CD4+ T-cell count was 14 cells/mL and HIV-1 viral load was 772,824 copies/mL.

A chest X-ray revealed patchy bilateral ground-glass opacities (**Fig.1**). CT scan of the chest showed innumerable nodular opacities diffusely throughout both lungs with areas of confluence (**Fig. 2**). The patient was started on empiric broad-spectrum antibiotics as well as TMP-SMX with prednisone for *Pneumocystis jirovecii*. Blood cultures grew multidrug-resistant (MDR) *Escherichia coli*. Three days later, he developed acute respiratory failure requiring intubation. Bronchoscopy done a week after admission showed parasitic organisms morphologically consistent with *Strongyloides* species (**Fig.3**). He was diagnosed with hyperinfection syndrome and started on rectal ivermectin and oral albendazole. Unfortunately, he expired shortly thereafter.

Our patient was first diagnosed with HIV-1 in 2012. At the time, he had a CD4+ T-cell count of 8 cells/mL, HIV-1 viral load of 597,172 copies/mL and a leukocyte count of 4.1 K/μL

(18% neutrophils, 15% lymphocytes and 39% eosinophils). *Stronglyoides* serology at that time was negative (IgG: 0.43 IV [normal <1.49 IV; equivocal 1.50 -2.10 IV; positive: >2.11]. His eosinophilia persisted until after the second cycle of chemotherapy, which coincided with the origin of his cough. A timeline of events is shown (**Fig. 4).**

Discussion:

Strongyloides stercoralis is an intestinal nematode, endemic in the tropical and subtropical regions of the world (**1**). It has an estimated global prevalence of between 3 million and 100 million people. In the United States, it has limited endemicity in the Southeast and the Appalachia, with high infection rates seen in immigrants from endemic countries (1, 4). It is acquired mainly by exposure to the filariform larvae in the soil, and rarely from person to person spread during close physical contact or via donor-derived infection in solid-organ transplant recipients. (**3, 5, 6**,).

A unique ability of *Strongyloides stercoralis* is autoinfection; it can replicate and complete its life cycle without leaving the host. This can result in an increase in numbers in the absence of exogenous reinfection and produce overwhelming infection in immunocompromised patients (**1**).

The infections produced by *S. stercoralis* may be acute, chronic or complicated, depending on the host's immunity (**1**). In chronic uncomplicated strongyloidiasis, there is harmony between the parasite and host. About 50% of patients are asymptomatic at this stage since autoinfection is well-regulated by the host's cell-mediated immunity and the numbers of adult worms are low. 75% of these patients will have eosinophilia, ranging from 10% and 15% (**2, 7**). Severe complicated strongyloidiasis includes hyperinfection and disseminated disease, and usually results from accelerated autoinfection when the host immunity is impaired. Eosinophilia is usually absent at this stage (**1, 8**)

The diagnosis of strongyloidiasis relies on epidemiologic history, microscopic exam of the stool and serology **(1**). In uncomplicated cases, repeat stool exams are often necessary because a single stool only has 30% sensitivity (**1, 2**). However, in hyperinfection and disseminated strongyloidiasis, the filariform larvae are readily seen on stool, sputum, bronchoalveolar lavage, and tissue specimens.

Of particular interest to us is *Stronglyoides* serology which is often used to diagnose strongyloidiasis. There are several *Stronglyoides* IgG assays and one has been reported to have a sensitivity and specificity approaching 100% (**8, 9**). In our case, despite the persistent eosinophilia and eventual diagnosis of strongyloidiasis, the IgG assay was negative. How reliable, then, are the *strongyloides* serologies? In patients from endemic regions with persistent eosinophilia but negative *strongyloides* serologies, should empiric treatment for strongyloidiasis be given?

The standard enzyme-linked immunosorbent (ELISA) assays measure IgG responses to *Strongyloides* somatic antigen extracts (of the infective stage larvae), which are prepared by isolating worms from the feces of infected patients or experimental animals. Although it has a

sensitivity of 85% to 95%, this assay cross-reacts with other helminths which makes it less specific (**2, 8**). Most commercially available ELISAs have now adopted a newer assay which uses recombinant NIE antigen derived from the infective L3 stage of the parasite (**10**). This technique has a sensitivity of 87.5% to 97% and a specificity of 94 to 94.5%. Our patient was tested using this assay.

The luciferase immunoprecipitation systems (LIPS) assay detects IgG antibodies to NIE antigen and *S. stercoralis* immunoreactive (SsIR) antigen (**9**). This technique has a sensitivity and specificity approaching 100%. It has no cross-reactivity with sera from filaria-infected patients and there is evidence of seroconversion to negative following treatment (**8, 9**). It is not commercially available at this time.

A recent study by Anderson *et al.* comparing the commercially-available *Strongyloides* ELISA assays with the LIPS assay found significant variability in the results (**11**). The authors concluded that the assays must be interpreted alongside the history and laboratory data before confirming or excluding strongyloidiasis.

Our case and the high mortality associated with disseminated strongyloidiasis (**1, 7**) suggest that the currently available commercial *Strongyloides* ELISA serology cannot solely be relied upon to diagnose *S. stercoralis* infection. Unless the LIPS assay becomes available, we suggest that patients with unexplained eosinophilia from endemic regions but negative *Strongyloides* serology be empirically treated with ivermectin for presumed strongyloidiasis.

Funding: None

Conflicts of Interest: None

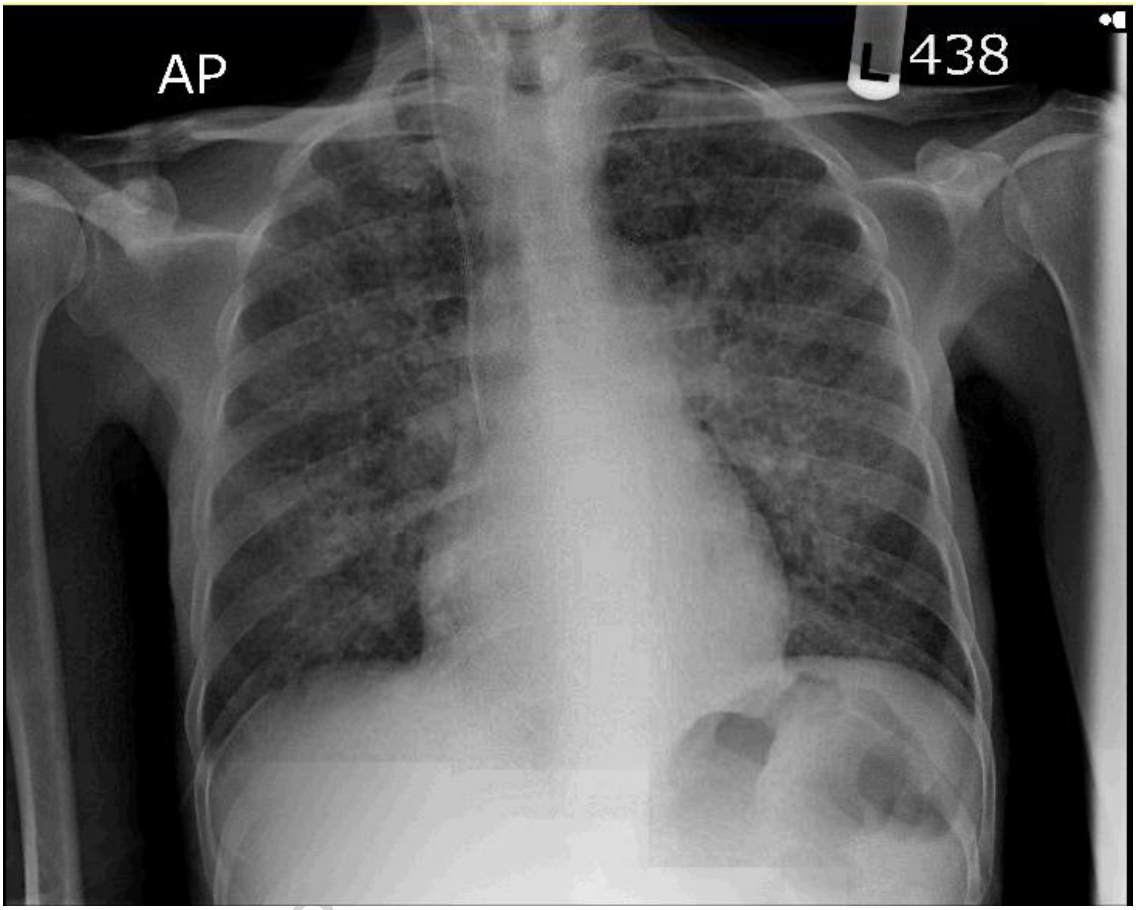

Figure 1. Chest X-ray showing widespread ill-defined opacities

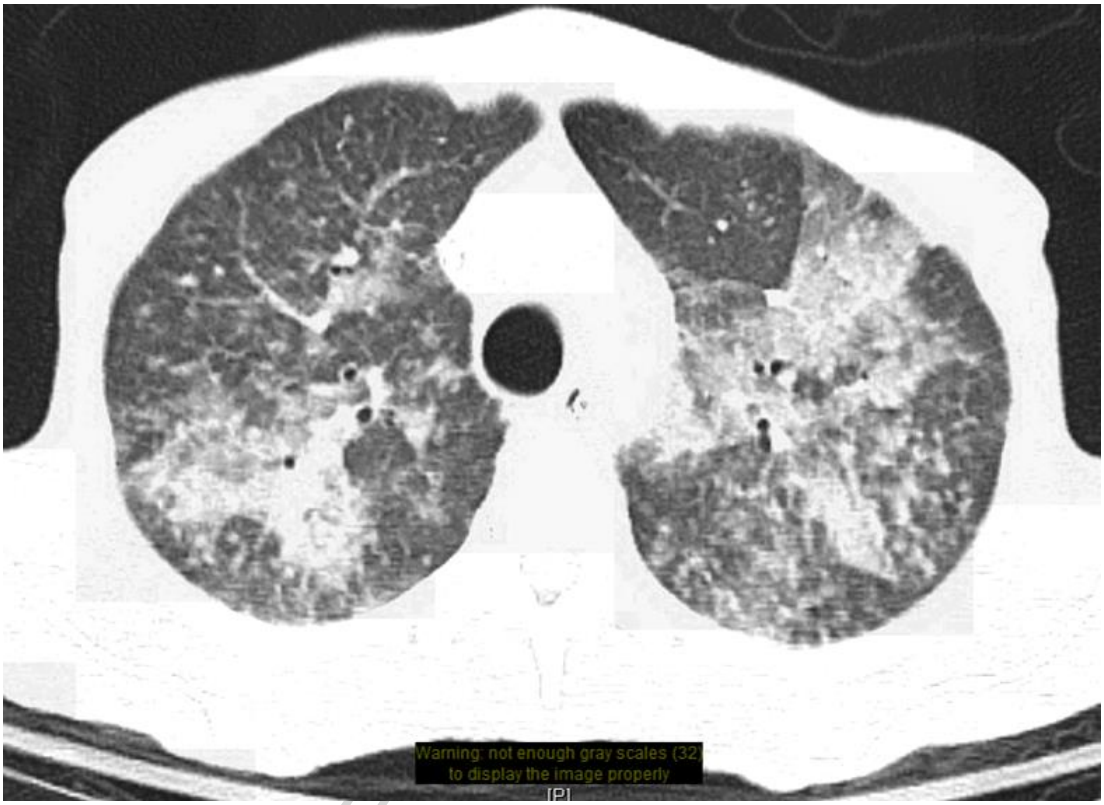

Figure 2. Computed tomography (CT) scan of the chest showing innumerable nodular opacities diffusely throughout both lungs with additional confluent regions of opacity.

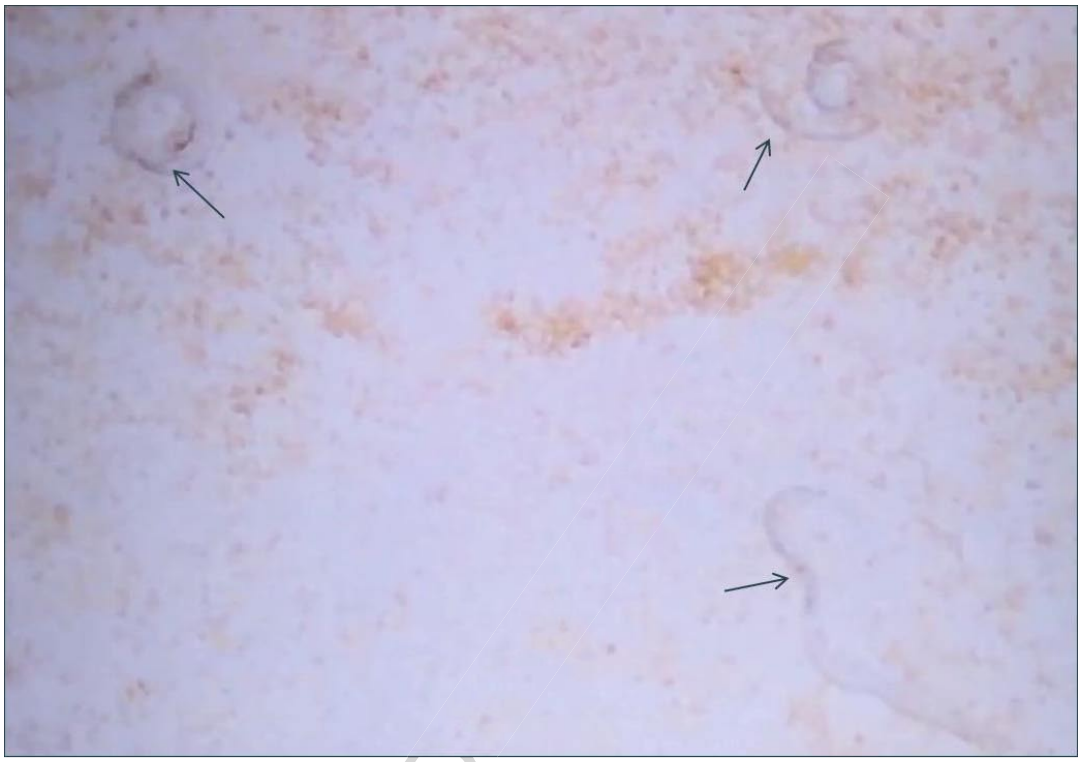

Figure 3. Bronchoalveolar lavage (BAL) iodine wet-mount (magnification 400X) specimen showing parasitic organisms morphologically consistent with *Strongyloides* species. Eggs containing larvae, larvae hatching from eggs and larvae at various life cycle stages with prominent genital primordium and short buccal cavity (arrows) were seen.

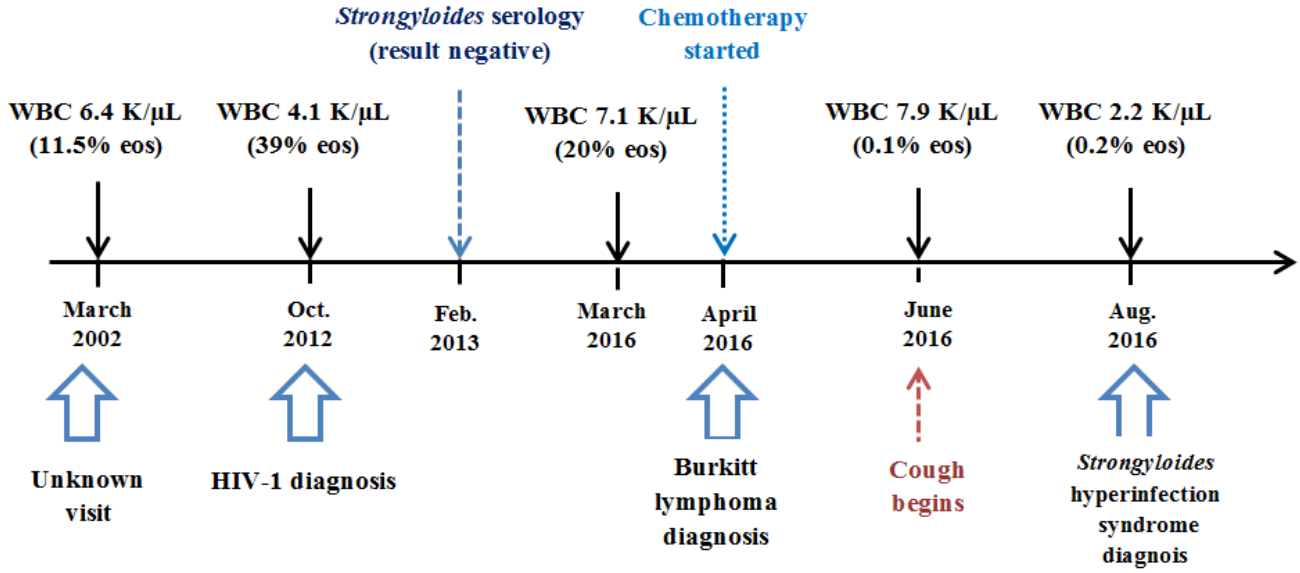

Figure 4. Timeline of our patient's clinic visits and hospitalizations. *WBC*, white blood cell count; ***eos,*** eosinophils, ***HIV*-1**, Human immunodeficiency virus type 1

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