Strongyloides Hyperinfection in Ethiopian Immigrants in Israel

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ABSTRACT: We report four cases of Strongyloides hyperinfection among Ethiopian immigrants, of which three were fatal. Many immigrants from countries in which Strongyloides is endemic settle in developed countries. A high index of suspicion will lead to earlier diagnosis and treatment of this disease. Testing for Strongyloides infestation in this susceptible population by enzyme-linked immunosorbent assay serology, stool testing or duodenal aspiration may prevent the fatal complications of hyperinfection.

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Strongyloides is an intestinal nematode infecting millions of people worldwide [1]. Infection is usually asymptomatic but immunosuppression may produce a fulminant illness often designated hyperinfection [1]. Due to increasing immigration from countries endemic for Strongyloides, physicians in developed countries may encounter this condition [2,3], although they are not well informed regarding Strongyloides infection in immigrant populations [4] and this may result in delayed diagnosis. We recently treated four cases of Strongyloides hyperinfection in Ethiopian immigrants in Israel within a one year period in a single medical center.

PATIENT DESCRIPTIONS [Table 1]

PATIENT 1

A 33 year old woman of Ethiopian origin complained of vomiting. She had been diagnosed with human immunodeficiency virus infection in 2005 but was non-compliant with antiretroviral therapy and was intermittently taking cotrimoxazole, lamivudine, tenofovir and efavirenz. Physical examination revealed that she was cachetic. The rest of the physical examination was unremarkable.

Laboratory examination showed hemoglobin 13.1 g/dl, leukocyte count 4.68 x10^3/μl with no eosinophilia, and a platelet count of 629 x 10^3/μl. Serum glucose was 126 mg/dl, renal function and electrolytes were normal. Alanine and aspartate aminotransferase, and gamma-glutamyltransferase were elevated to nearly twice the upper limit of normal and serum alkaline phosphatase was 182 U/dl.

A computed tomography scan of the abdomen revealed dilatation of the distal ileum and colonic wall thickening. Brain CT was normal. Colonoscopy (limited by poor bowel preparation) showed normal mucosa endoscopically and histologically to 25 cm. Esophagogastroduodenoscopy showed a normal esophagus and stomach but the post-bulbar portion of the duodenum was thickened and covered with a white exudate. The patient died from suspected sepsis after 5 days. The biopsy result was subsequently received, which showed

Table 1. Main features of four cases with a diagnosis of Strongyloides hyperinfection

Patient	Age, gender, immune dysfunction	Presentation	Eosinophilia	Time from presentation to diagnosis	Diagnostic method	Therapy	Outcome (at 30 days)
1	33 yrs, F, AIDS	General deterioration	None	10 days (postmortem)	Duodenal biopsy	None	Death
2	79 yrs, F, age	Bronchial spasm	None	5 days	Duodenal aspirate	Ivermectin for 10 days	Death
3	80 yrs, M, age, corticosteroids	COPD, recurrent enterococcal meningitis.	Intermittent	60 days (postmortem)	Duodenal biopsy	None	Death
4	35 yrs, F, AIDS	*E. coli* sepsis of unknown origin	None	2 days	Duodenal aspirate	Albendazole for 10 days	Recovery

Strongyloides stercoralis (larvae, worms and eggs) in the gastric mucosa and in the duodenum.

PATIENT 2

A 79 year old woman of Ethiopian origin was admitted with progressive dyspnea of several hours. Her medical history was unremarkable. On examination she was apyrexial, tachypneic to 40 per minute, with marked expiratory wheezing. Laboratory tests were notable only for a serum immunoglobulin E of 2000 mg/ml without eosinophilia. Mechanical ventilation was administered and she was treated with 1 g methylprednisolone. Three days later, the airway spasm subsided, but she had a fever of 40°C and leukocytosis of 40,000/μ with a marked shift to the left. There was no change in sputum production and the chest X-ray was unremarkable. She was treated with cetriaxone 2 g/day intravenously. Blood and sputum cultures were sterile.

A duodenal aspirate contained filariform larva of *S. stercoralis*. Ivermectin at a dose of 200 μg/kg was administered via nasogastric tube. A transient fall in both body temperature and white blood cell count followed. Subsequently *Pseudomonas aeruginosa* was detected in sputum and she received piperacillin and ciprofloxacin intravenously. However, during the course of the next 10 days the patient became febrile and developed hypotension. Blood cultures remained sterile. The patient died following a period of hypothermia and protracted hypotension.

PATIENT 3

An 80 year old man of Ethiopian origin was admitted following 2 days of fever, headache and nuchal rigidity. He had been treated with corticosteroids and cefuroxime for exacerbation of his chronic obstructive pulmonary disease. Cerebrospinal fluid examination revealed polymorphonuclear leukocytes 1800/ml, protein 580 mg/dl and glucose 35 mg/dl, and was sterile. Ceftriaxone, vancomycin and dexamethasone were given. Three days later, the CSF protein decreased to 80 mg/dl, with no change in glucose or polymorphs, but *Enterococcus faecium* was cultured and was regarded as a contaminant. Cryptococcus antigen, polymerase chain reaction for herpes simplex and *Mycobacterium tuberculosis*, HIV ELISA and VDRL serology were all negative, as was culture for *M. tuberculosis*. Empiric anti-tuberculosis therapy and dexamethasone were administered and the patient's condition improved but he stopped all treatment after 3 weeks. Two months later he was readmitted with acute sterile polymorphic leukocytosis meningitis, which responded to 3 weeks of empiric therapy with ceftriaxone, vancomycin and ampicillin. There was another relapse after 9 days and again no evidence for herpes, *M tuberculosis* or Cryptococcus. *Escherichia coli* bacteremia was detected. The previous antibiotic regimen, with dexamethasone, was restarted.

CT and magnetic resonance imaging of the abdomen and chest and spinal column were unremarkable. Following tapering off of the corticosteroids the patient developed headache, fever, nausea and odynophagia with recurrent diarrhea and intermittent eosinophilia to 3000/μl. Direct smear of stool was negative for ova or parasites. The stool was negative for *Clostridium difficile* toxin. Esophagogastroduodenoscopy revealed an ulcer in the second part of the duodenum. Repeat CSF examination showed elevated protein and leukocytes, low glucose (15 mg/dl) and *E. faecium*. The patient received anti-tuberculous medication and ampicillin but his condition deteriorated and he died 3 days later. The biopsy result from the duodenum was subsequently received, showing *S. stercoralis* in the duodenal crypts.

PATIENT 4

A 35 year old woman of Ethiopian origin was admitted with weakness, nausea and fever. She had been diagnosed with HIV 5 years previously and developed AIDS with recurrent cryptoccocal meningitis and *Pneumocystis jiroveci pneumonia*. She declined retroviral therapy. Physical examination revealed an apprehensive patient, with a temperature of 38°C, 30 breaths/minute respiratory rate and 110/minute pulse rate. Laboratory examination showed hemoglobin 5.6 g/dl, leukocyte count 0.34 x10³/μl and platelet count 86 x 10³/μl. Serum glucose was 79 mg/dl, serum sodium 130 mEq/L and serum albumin 2.3 g/L. Renal function, creatine phosphokinase and serum transaminases were all within normal limits. Urine analysis was normal. The patient received a packed red blood cell transfusion and was treated with intravenous ceftriaxone 2 g daily. *E. coli* grew from the admission blood cultures. Abdominal sonography was normal. In view of our experience with the previous three cases, a duodenal aspirate was taken and filariform larvae of *Strongyloides stercoralis* were detected. The patient was treated with albendazole 400 mg twice a day and her condition rapidly improved. Albendazole therapy was continued for 10 days. She was afebrile after 4 days and her neutropenia resolved.

DISCUSSION

We report four cases of Strongyloides hyperinfection in Ethiopian immigrants. These cases presented with diverse manifestations that underline the diagnostic challenge of this grave illness. The diagnosis of strongyloidiasis was specifically sought in cases 2 and 4 only, and in both of them duodenal aspirate allowed immediate diagnosis once the suspicion was raised. In the other cases, the diagnosis was

CSF = cerebrospinal fluid
HIV = human immunodeficiency virus
ELISA = enzyme-linked immunosorbent assay

made posthumously after receiving the results of gastric and duodenal biopsies.

Strongyloides, an intestinal nematode found in humans, is endemic in tropical and subtropical areas. Low socioeconomic status [3], alcoholism [5], white race [6], and male gender [3] have been associated with a higher prevalence of *S. stercoralis* stool positivity. Strongyloides infestation may result in accelerated autoinfection (hyperinfection) once alteration in immune status has developed, but it occasionally may arise in immunocompetent hosts [1,7]. In hyperinfection, larvae are increased in number but confined to the organs normally involved in the pulmonary autoinfective cycle (gastrointestinal peritoneum and lungs). Enteric bacteria can be carried by the filariform larvae or gain systemic access through intestinal ulcers and may affect any organ system, as documented in patient 3 with *E. faecium* in the CSF and patient 4 with *E. coli* bacteremia.

It is important to note that the eosinophilia characteristic of parasitic infestation is usually absent in hyperinfection [1,7]. Dissemination of Strongyloides beyond the pulmonary autoinfective cycle is termed dissemination and likely explains the clinical course in patient 3, who presented with relapsing meningitis caused by *E. faecium* [8]. Our patients were immune compromised due to age, steroids (patients 2 and 3) and HIV infection (patients 1 and 4). *S. stercoralis* hyperinfection has been reported in association with corticosteroid use even at low doses [9,10], with locally injected steroids [11] and adrenocorticotropin administration [12,13]. In addition, immunity wanes with age, and symptomatic strongyloidiasis has been described among survivors of Japanese prison camps from the Second World War [14].

Strongyloidiasis in developed countries is often a disease of immigrants from endemic areas [2,3]. Ethiopian immigrants in Israel have been shown to have Strongyloides; an examination of 5412 stool samples from Ethiopians in immigrant centers found that 219 (4.5%) were infected with *S. stercoralis* [15]. This is probably an underestimation since 25% of infected patients were shown to have negative stool samples [1].

Patients 1 and 4 had HIV infection and AIDS. Despite the high prevalence of HIV and *Strongyloides* co-infection among HIV carriers, there are relatively few reports of hyperinfection of *Strongyloides* in AIDS patients, and an inverse relationship between CD4 counts and the proportion of free-living larvae has been shown [16].

The wide and non-specific clinical presentation of Srongyloides hyperinfection and the common absence of elevated eosinophil count pose an inherent diagnostic challenge [1]. Recently, it was shown that physicians in training in the United States have limited knowledge regarding Strongyloides among immigrant populations [4] and that diagnostic consideration of Strongyloides is necessary when poorly explained manifestations of either wheezing or sepsis are encountered. Earlier diagnosis through widespread screening of at-risk patients from endemic areas may reduce fatalities [3]. Patients with chronic strongyloidiasis can present with intermittent vomiting, diarrhea, constipation, recurrent asthma, and the nephritic syndrome often with eosinophilia (common in chronic strongyloidiasis but rare in hyperinfection). In a review of 51 consecutive patients with *S. stercoralis* infection as a sole infection in Toronto over a 10 year period, eosinophilia was present in 42 (82.4%), with a mean eosinophil count of 890/μl [17]. The eosinophil count declined within 3 to 6 months after successful treatment. However, eosinophilia is not a specific finding and is often absent in hyperinfection [1,17].

A definitive diagnosis of strongyloidosis is usually based on the detection of larvae in the stool, although the sensitivity of a single stool examination using direct smear is 30% [1]. The sensitivity of stool examination is increased by repeated examination [18] and through various techniques that either concentrate the stool to increase the yield or capitalize on the ability of *S. stercoralis* to enter a free-living cycle of development and migrate into the liquid or agar, which enables easier detection and identification [19]. The agar plate is the most sensitive method for stool detection of S. *stercoralis* larvae. Serpiginous tracks formed by bacterial colonies carried by the spreading larvae over the agar are visible [20]. The detection of *S. stercoralis* is easier during hyperinfection as the number of worms is increased, and the larvae can be identified in wet mounts of a variety of samples from the involved sites [19].

The detection of larvae in duodenal aspirate is considered a very sensitive procedure. In a study of 33 patients with Strongyloides infection, duodenal aspiration enabled rapid identification of 76% of the cases; the parasite was present in the duodenal fluid alone and not in the stool in 67% [21]. The more invasive method of duodenal fluid sampling should be considered when there is a high index of suspicion for this grave complication, as in patients 2 and 4.

An enzyme immunosorbent assay EIA serologic test for *S. stercoralis* is now available. In 76 patients with confirmed *S. stercoralis* in stools the EIA had a sensitivity of 94.6%. In addition, a decrease in titer monitors the response to therapy [17]. A specific ELISA test is now available in Israel at Soroka University Medical Center, Beer Sheva (personal communication).

Asthma is common among Ethiopian immigrants to Israel [22]. It is possible that some cases of asthma in this population could be attributed to undiagnosed Strongyloides infection. When these patients are of a similar age as our patients 2 and 3 and treated with high doses of steroids systemically as in patient 3, hyperinfection may follow.

The treatment of strongyloidiasis consists of ivermectin or albendazole [1,3]. Ivermectin is considered the drug of choice

for both uncomplicated and complicated strongyloidiasis [23]. Ivermectin is more expensive but is more cost-effective [24]. The recommendation of ivermectin as first-line agent for complicated strongyloidiasis is deduced from the data on therapy for chronic infection. The recommended regimen for both agents in the case of hyperinfection is longer and is based on clearance of the larvae [1].

An increased index of suspicion for Strongyloides infection in immigrants from endemic areas may permit earlier diagnosis and treatment of this fatal complication of strongyloidiasis. Earlier screening for infestation with these worms in asymptomatic but vulnerable patients – either by repeated stool examinations or serology – may allow earlier diagnosis, which will lead to a higher rate of successful therapy and may significantly reduce the occurrence of hyperinfection [1,3].

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