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Strongyloides stercoralis infection in transplanted patients

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Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Patient: Male, 36
Final Diagnosis: Strongyloidiasis
Symptoms: Abdominal pain • anorexia • eosinophilia • fever • letargy • weight loss
Medication: —
Clinical Procedure: —
Specialty: Infectious diseases

Objective: Challenging differential diagnosis, rare disease

Background: Strongyloidiasis is a worldwide infection, infecting approximately 100 million people in more than 70 countries. It is common in Southeast Asia, Latin America, Papua New Guinea and some parts of the United States. Malnutrition, cancer, organ transplantation, hemodialysis and prolonged use of corticosteroids increase the risk of this opportunistic infection. Undiagnosed and untreated, its mortality rate can be high.

Case Report: We present a 36 year old Black man with history of malignant hypertension and glomerulonephritis who had chronic eosinophilia and vague, poorly localized abdominal pain and tenderness. He received three deceased donor kidney transplants, two of them failed and the third one succeeded. However, after transplantation, his abdominal pain and discomfort increased, became anorexic, lost weight and developed fever and lethargy. Duodenal aspirate examination was positive for strongyloides stercoralis. Immunosuppressant medications were discontinued and he was treated with thiabendazole. In spite of treatment, his condition deteriorated and he expired.

Conclusions: Due to low sensitivity of stool and serological examinations, diagnosis of strongyloidiasis often is delayed. A high index of suspicion and prompt diagnosis and treatment are essential in decreasing the morbidity and mortality of this infection. Before organ transplantation, every attempt should be made to find the cause of peripheral blood eosinophilia and in endemic areas and among patients coming from countries where the infection is known to exist, organ recipients and donors should be screened for parasitic infections including strongyloidiasis

Key words: transplant • strongyloides • hyperifection

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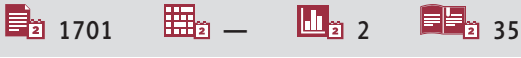

Background

Strongyloides stercoralis is a soil nematode [1] that is endemic in tropical and subtropical areas of the world, infecting approximately 100 million people in Southeast Asia, Latin America, Puerto Rico, southeastern and occasionally northern areas of the United States [2]. Overcrowded conditions and a high degree of migration from tropical areas of the world are responsible for the prevalence of this nematode in some metropolitan areas. Once the parasite has gained access to the host, it may reside there for decades. Hyperinfection with this opportunistic infection might occur in a variety of circumstances in which cell mediated immunity is depressed, like malnutrition, malignancy, human immunodeficiency virus infection(HIV), and patients who have received organ transplantation [3,4].

Case Report

The patient was a 36 year old Black man with history of arterial hypertension who was first hospitalized with several months history of abdominal pain and distention. He was noted to be hypertensive with cardiomegaly and retinal hemorrhages. Laboratory studies showed BUN 110 mg/dL, serum creatinine 16 mg/dL, C3 75 mg/dL, hematocrit 34% and erythrocyte sedimentation rate 47 mm/hr. Urinalysis showed 3 to 4 red blood cells per high power field and 2 to 3+ protein. Peripheral blood examination showed 31% eosinophils. Abdominal films showed small kidneys and multiple examinations of the stool for ova and parasites were negative. He was diagnosed to have malignant hypertension and membranoproliferative glomerulonephritis and his eosinophilia was thought to be related to hemodialysis. Because he was uremic, an arteriovenous fistula was established and he was placed on maintenance hemodialysis. Over the next four years, he was hospitalized twice, once with a urinary tract and a second time with a respiratory tract infection. Later on he received two deceased donor kidney transplants that failed and so a third transplant was attempted. Post-transplant, he was treated with immunosuppressants that included azathioprine, prednisone and cyclophosphamide. The kidney transplant functioned well and prednisone dose was gradually tapered down.

Following kidney transplantation, he continued to have mild abdominal pain that was diffuse, transient, not localizable and associated with anorexia, weight loss and vomiting coffee ground material. Eight months later, the pain became more intense and he was hospitalized. His abdomen was distended, bowel sounds were decreased and his stool was positive for occult blood. Laboratory examination showed, white blood cell count(WBC) 10800, with 8% eosinophils, BUN 97 mg/dL, creatinine 2.2 mg/dL and glucose 420 mg/dL. Plain x-rays of the abdomen showed distended bowels but no evidence of bowel perforation. Initially, he was treated conservatively and he showed signs of improvement but later he developed fever and progressive lethargy. Cerebrospinal fluid (CSF) fluid examination showed, cloudy fluid, with 191 WBCs/cmm, 95% neutrophils and 5% lymphocytes. He was treated for meningitis but all cultures came back negative. Chest x-ray was suggestive of pneumonia and a radiogram of the upper gastrointestinal tract was suggestive of diffuse thick infiltrative folds in the stomach and small intestine. These changes were thought to be parasitic in origin and therefore an upper gastrointestinal endoscopy (EGD) was done. Gastric and duodenal aspirates were obtained and they were positive for Strongyloides stercoralis larvae. Immunosuppressive medications were stopped and he was treated with thiabendazole but he continued to deteriorate and he expired a few weeks later. Permission for post-mortem examination was not granted.

Discussion

Strongyloides is a genus containing around 50 species that are obligate GI parasites of vertebrates. It infects mammals, reptiles, birds and amphibians. Two species of strongyloides infect humans, S Stercoralis and S fulleborni [5]. The latter is primarily seen in African primates but it can also infect humans. Strongyloides stercoralis is a soil parasitic infection that afflicts millions of people around the world. It was first described in French soldiers in Vietnam who had chronic diarrhea and it took 50 years to describe its life cycle (Figure 1). Strongyloides stercoralis usually resides in the duodenum and proximal jejunum. The female parasite produces eggs that are embedded in the intestinal mucosa and are capable of reproducing parthogenetically (Asexually) and produce first stage rhabditiform larvae that are 180 to 380 micrometer long, with a short rhabditoid esophagus and a prominent genital premodrium (Figure 2) [6]. These larvae pass through the stool, change into second, third and sometimes fourth stage filariform larvae, that may develop into free living adult males and females. The larvae penetrate the unbroken skin, enter the blood stream, travel to the lungs, ascend the trachea, enter the GI tract, penetrate the mucosa and live in-between the enterocytes. Sometimes, larvae, that have reached the third stage, directly penetrate the intestinal mucosa, enter the blood stream and reach other organs (Autoinfection). In doing so they carry intestinal bacteria on their surfaces and cause septicemia and meningitis (Hyperinfection). This repeated endogenous cycle leads to chronic infection that can last for decades [7]. This condition usually manifests itself by anorexia, nausea, poorly localizable abdominal pain and distention, diarrhea and sometimes bowel obstruction. Skin involvement is not uncommon and may be in the form of a serpiginous, migratory, urticarial rash, termed larva currens. Skin of buttocks, groin and trunk is more commonly affected than the skin covering the head and

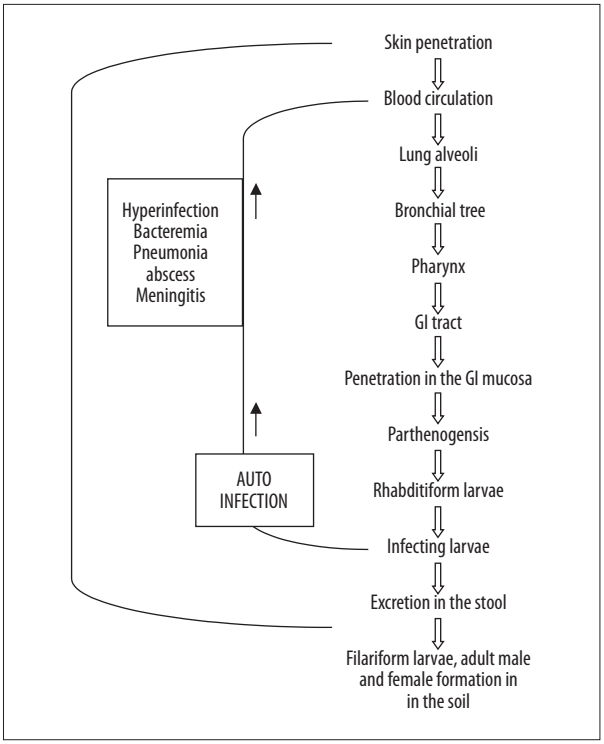

Figure 1. Life cycle of strongyloides stercoralis.

extremities. Lung involvement is usually asymptomatic but it may cause cough,dyspnea, pulmonary infiltrates, hemorrhage and bacterial abscess formation [8]. With hyperinfection and disruption of intestinal mucosal integrity, paralytic ileus, peritonitis, septicemia [9] and occasionally massive GI bleeding may ensue [10]. Immunocompromised states, like HIV, malnutrition, malignancy [11], severe nephrotic syndrome, organ transplantation, corticosteroid use and residence or travel to endemic areas should heighten level of suspicion for the presence of this infection [12].

Kidney disease, including nephrotic syndrome due to minimal change disease [13,14] and acute interstitial nephritis have been reported in association with strongyloidiasis. In one case, minimal change disease was proven by kidney biopsy and the disease remitted once the infection was treated with Ivermectin [15].

Strongyloidiasis should be suspected if there are suggestive clinical signs or symptoms, eosinophilia or suggestive serological findings. Eosinophilia, though a frequent marker of parasitic infection, may not be present in severely immunocomporomised patients and therefore its absence does not exclude the possibility of Strongyloides. Definitive diagnosis is based on the microscopic detection of larvae in the stool. However, in uncomplicated infections the worm load is low and the stool examination may be negative. Repeated stool examinations increase the chance of finding infecting larvae. Direct smear

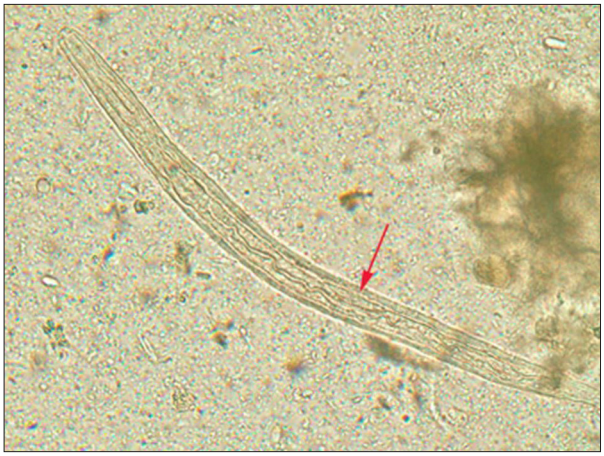

Figure 2. Rhabditoid larva of s stercoralis in an unstained wet mount of stool. The arrow points to the short buccal canal and the genital primordium.

of feces in saline-Lugol iodine solution, Baermann concentration, formalin-ethyl acetate concentration, Harada-Mori filter paper culture and agar nutrient plate culture are some of the techniques used to enhance discovery of the parasite [16]. Examination of the duodenal fluid for larvae has more sensitivity than stool examination. The parasite may also be found in the pleural and peritoneal fluid, mucinous cysts, lymph nodes, sputum and urine. Serological studies, including ELISA have a high sensitivity but a low specificity for strongyloides stercoralis infection [17]. Recently a novel real time PCR for the universal detection of strongyloides species was described [18] that is highly specific (100%) and may be helpful in some clinical settings.

Treating strongyloidiasis, like other worm infections, is a difficult issue partly because of the unreliability of stool examination results, low specificity of serologic testing and partly due to unfamiliarity of physicians, particularly in non-endemic areas [19]. Treatment with Ivermectin 200 mcg/kg, two daily doses, is considered to be the treatment of choice, with a cure rate as high as 100% [20]. It can be given orally, rectally, intravenously or subcutaneously [21]. Other drugs like thiabendazole and albendazole have been used as well. A randomized trial of a single dose of Ivermectin (200 mcg/kg) *vs.* albendazole (400 mg daily ×3) among 301 children infected with strongyloides stercoralis in Zanzibar showed a cure rate of 83 *vs.* 45% [22]. In another study involving cancer patients, thiabendazole was effective in 74% of patients infected with strongyloidiasis [23]. Ivermectin is a semi synthetic derivative of the avermectin B1, it is metabolized by the liver through cytochrome P450-3A4, but it does not significantly affect the activity of CYP 450-3A4 and CYP2D6 or CYP2C9 [24,25]. It is highly protein bound and therefore it is not dialyzable. Thiabendazole, albendazole and mebendazole are metabolized by the liver and excreted by the kidney. Due to this,

they should be used with caution in patients with kidney and liver disease. Regardless of which regimen is used to treat the patient, close follow up of the patient is mandatory to ensure that the infection is eradicated.

Strongyloidiasis has been described with all organ transplants, including heart, lung, liver, intestine, pancreas, bone marrow, but mostly it has been reported in kidney transplant patients. It can infect both donors and recipients. Every effort should be made before harvesting or transplanting organs in endemic areas or in suspicious circumstances to rule out parasitosis and particularly strongyloidiasis [26,27]. Prolonged corticosteroid use, either in the early post-transplant period or during treatment of rejection episodes, may reactivate dormant strongyloidiasis and promote its proliferation in infected hosts [28]. Cyclosporine may have protective effect [29,30] while tacrolimus increases the risk of infection. In a study in sprague-Dawley rats infected with strongyloides ratti, cyclosporine, given orally or subcutaneously, decreased the stool concentration of strongyloides by almost 50% and It neither synergized nor antagonized the effect of thiabendazole [31].

Our patient most likely had the infection at the time he was transplanted. Following transplantation, his condition deteriorated and although strongyloidiasis was diagnosed and treated promptly and his immunosuppressant medications were discontinued, he did not improve and he expired.

Unexplained peripheral blood eosinophilia, immunocompromised state, prolonged use of steroids, travel to endemic areas and especially organ transplantation should increase physician suspicion for this infection [32,33]. Close collaboration with infectious disease specialists is mandatory and very helpful. Failure to treat this infection promptly and adequately can be associated with a mortality rate that could reach as high as 40 to 70% [34]. In suspicious circumstances, empiric therapy can be justified [35].

Conclusions

Strongyloidiasis is a serious problem for immunocompromised and transplanted patients. Every attempt should be made to identify the cause of eosinophilia in transplant donors and recipients. This is particularly important in endemic areas and also in non-endemic areas where there is a large immigrant population. Once the infection is identified, immunosuppression should be reduced until the infection is treated.

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