Case Report

Post-Renal Transplant Miliary Mottling: Not Always Tuberculosis

Abstract

A 28-year-old male, 3 years post renal transplant with stable graft function, presented with vomiting for 2 days. He had graft dysfunction and graft biopsy done revealed acute cell - mediated rejection BANFF-IA. After receiving glucocorticoids for rejection, he developed severe enterocolitis and impending respiratory failure. Chest X-ray and computed tomography of the chest revealed miliary mottling. Evaluation showed presence of filariform larvae of *Strongyloides stercoralis* in the stool and sputum. A diagnosis of *Strongyloides* Hyperinfection Syndrome (SHS) was made. After a prolonged course of treatment with noninvasive ventilation, broad-spectrum antimicrobials, parenteral ivermectin and oral albendazole therapy, he eventually recovered. This case report is to highlight that *Strongyloides* Hyperinfection Syndrome should also be considered in the differential in any immunocompromised patient presenting with miliary mottling in imaging.

Keywords: *Ivermectin, miliary mottling, Strongyloides hyperinfection*

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Introduction

Strongyloidiasis is an elusive disease caused by the nematode parasite *Strongyloides stercoralis*. *Strongyloides* Hyperinfection Syndrome (SHS) is a rare, fatal disease, mostly seen in immunocompromised patients, occurring as a result of the peculiar feature of exaggerated autoinfection, involving the pulmonary and gastrointestinal systems. The Th2 subset of T cells and humoral immunity are specifically protective against parasitic infections. Any factor that suppresses these mechanisms (immunosuppressants or glucocorticoid therapy) can potentially trigger hyperinfection, which could be life-threatening.

Case Report

A 28-year-old male, who had undergone one haplomatch type live related renal transplant 3 years ago, with his mother as donor, presented with complaints of four episodes of vomiting and loss of appetite for 2 days. He had been doing quite well since his transplant, with a nadir creatinine of 1.6 mg/dL. He was on triple immunosuppressive therapy comprising prednisolone 7.5 mg/day, mycophenolate mofetil (MMF) 1 g/day and tacrolimus 4.5 mg/day.

General and systemic examinations were unremarkable. Urinalysis demonstrated presence of microscopic hematuria 2 + and albuminuria 2+. Hemoglobin was 11.9 g/dL, total leucocyte count 10,600 cells/mm^3, and platelets 2.1 lakhs. The serum creatinine was 3.5 mg/dL suggesting significant graft dysfunction. There were no previous episodes of allograft rejections. Tacrolimus level done 4 months prior to the current admission was 4.9 ng/mL.

Ultrasonogram of the abdomen and graft kidney was normal. Graft biopsy showed interstitial inflammation (i2), tubulitis (t2), and 10% interstitial fibrosis and tubular atrophy consistent with acute cell-mediated rejection BANFF IA. The patient did not have any clinical features of active infection and his chest X-ray was normal. He was treated with pulse intravenous methylprednisolone 500 mg, 250 mg, and 250 mg on 3 consecutive days following which his graft function improved gradually.

Two days later, he started complaining of vague abdominal discomfort, which progressed to intolerable abdominal pain with profuse vomiting. He experienced small-volume diarrhea associated with tenesmus. Stool microbiological analysis was sent. X-ray and computed tomography (CT) of abdomen showed ileus and bowel wall edema [Figure 1a].

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He was started on empirical antibiotics, oral nitazoxanide, and a single dose of oral ivermectin in view of suspicion of enterocolitis secondary to bacterial and parasitic etiology. Cytomegalovirus DNA quantification by polymerase chain reaction in blood revealed 1330 viral copies. Hence, he was initiated on oral valganciclovir.

He started having high-grade fever spikes with new-onset tachypnea. Worsening sepsis was considered likely. Hence, blood and urine cultures were done. Antibiotics were escalated with reduction in immunosuppression. Despite the above measures, respiratory distress worsened, and in view of impending respiratory failure, he was started on noninvasive ventilation. A repeat chest X-ray revealed miliary pattern of pulmonary infiltrates [Figure 1b].

CT chest was reported as miliary tuberculosis [Figure 1c], and the possibility of a fungal pneumonia was also considered which prompted initiation of anti-tubercular therapy (ATT) and amphotericin B empirically. Tacrolimus and MMF were withheld.

After 3 days of ATT and antifungal therapy, he further deteriorated. Meanwhile, the modified acid-fast bacilli staining of his stool specimen came out to be positive for *Cryptosporidium parvum* oocyst [Figure 2b], and a wet mount analysis of the same revealed hookworm eggs and numerous larvae of *Strongyloides stercoralis*.

The possibility of SHS was entertained, considering his deterioration after glucocorticoid therapy with predominant involvement of gastrointestinal and respiratory systems. An absolute eosinophil count of 660 cells/mm^3 was also noted. Hence, ATT and antifungals were stopped and he was initiated on tablet ivermectin 200 μg/kg/day and tablet albendazole 400 mg twice daily via nasogastric tube. He continued to have high-grade fever spikes with no improvement in his respiratory distress. He also developed petechial rash all over the abdomen.

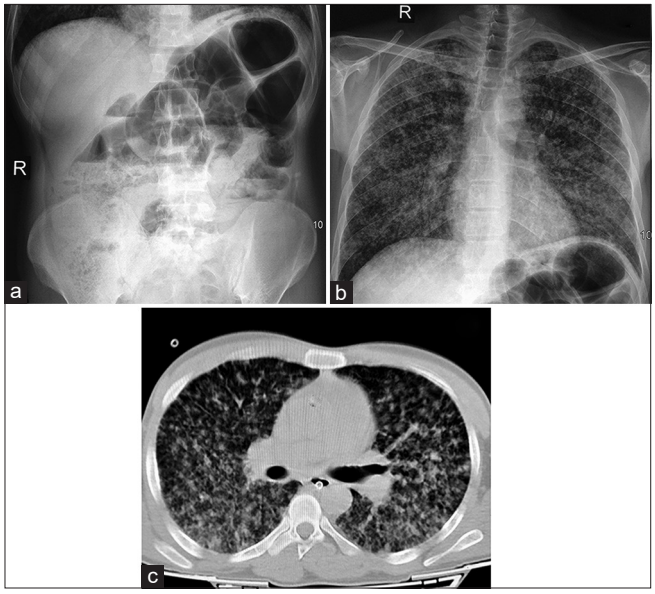

Figure 1: (a) X-ray abdomen revealing distended transverse and descending colon due to subacute intestinal obstruction. (b) Chest X-ray showing miliary mottling in bilateral lung fields. (c) Computed tomography of chest exhibiting multiple miliary nodules with interlobular septal thickening

Blood and urine cultures failed to isolate any organism. As he continued to deteriorate and secondary sepsis has been well-documented in SHS, antibiotics were further escalated. Furthermore, he had hemoptysis and concurrently, his hemoglobin dropped to 5.7 g/dL. A wet mount of the sputum revealed numerous live filariform larvae of *Strongyloides* entangled amidst red blood cells [Figure 2a]. Since there was little clinical improvement despite having initiated appropriate therapy, poor absorption of enteral ivermectin secondary to ileus was presumed. Extensive review of literature suggested the use of veterinary formulation of ivermectin in humans for severe disease with poor enteral absorption.[1,2]

After obtaining informed consent from the patient's family and approval from Institutional Ethics Committee, veterinary formulation of parenteral ivermectin was procured. It was administered at a dose of 200 μg/kg/day divided into two equal aliquots at two separate sites via subcutaneous route. The patient tolerated the therapy well.

After three doses of ivermectin, tachypnea, abdominal pain, fever, and rash started subsiding gradually. Immunosuppressants were gradually reintroduced. After seven doses of subcutaneous ivermectin, he was switched over to oral ivermectin therapy, which was continued for 2 weeks after three consecutive stool specimens were negative for *Strongyloides* larvae. Repeat X-ray of the chest and abdomen were normal. The patient is doing well and is currently being monitored on outpatient basis. He is on 4.5 mg/day of tacrolimus, 500 mg/day of MMF, and 7.5 mg/day of prednisolone. His graft function remains stable with a creatinine of 2.0 mg/dL.

Discussion

The life cycle of *Strongyloides* comprises a free-living form, the rhabditiform larvae, and a parasitic form, the filariform larvae. Humans acquire the infection when filariform larvae penetrate the skin or the oral mucosa. The larvae migrate through the venous circulation to enter the heart and then the lungs. During the maturation process,

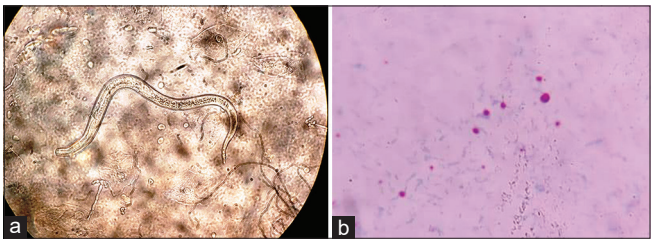

Figure 2: (a) Wet mount of the sputum showing filariform larvae of *Strongyloides stercoralis* ×40. (b) Modified acid-fast bacilli staining of the stool specimen showing oocyst of *Cryptosporidium parvum* ×100

they induce alveolar capillary bleeding and eosinophilic inflammation. From the alveoli, they enter the airway and are swallowed to eventually reach the small intestine where they mature into adult females capable of laying eggs.[3]

The eggs embryonate and hatch to release rhabditiform larvae, which molt into infective filariform larvae in the intestine. These larvae enter the circulation by piercing the colonic wall or perianal skin and complete an internal cycle. This process is called autoinfection.[4]

In hyperinfection syndrome, this classic life cycle is exaggerated; as a result, the parasite burden increases and turnaround accelerates.[5] It is estimated to happen in 1.5%–2.5% of the patients with strongyloidiasis. Hyperinfection syndrome and disseminated strongyloidiasis are not synonymous. Disseminated disease is defined by the presence of parasites in organs outside of the traditional life cycle.[6] Corticosteroids induce SHS by virtue of increasing apoptosis of Th2 cells, reducing the eosinophil count and inhibiting mast cell response.[7] They also increase ecdysteroid-like substances (sterols with non-hormonal anabolic effects) in the body mainly in the intestinal wall, which act as molting signals and lead to increased production of autoinfective filariform larvae culminating in hyperinfection.[8]

Clinical manifestations commonly involve the respiratory and gastrointestinal tract. The intestinal manifestations include severe cramping abdominal pain, watery diarrhea, weight loss, nausea, vomiting, and gastrointestinal bleeding. Occasionally, subacute intestinal obstruction and eosinophilic granulomatous enterocolitis can develop. The pulmonary manifestations include cough, dyspnea, wheezing, and hemoptysis due to alveolar hemorrhage.[9]

CT chest usually reveals areas of ground glass opacity with interlobular septal thickening and consolidation.[10] But in our case, extensive miliary pattern of infiltrates mimicking tuberculosis were seen, which to the best of our knowledge has never been reported in hyperinfection syndrome. In the setting of hemoptysis, hemoglobin drop, and respiratory distress, diffuse lung involvement was probably contributed by alveolar hemorrhage.

Gram-negative bacteremia can occur in SHS due to translocation of the gut pathogens, as the intestinal larvae penetrate into blood stream. The commonly cultured organisms include *Streptococcus bovis*, *Escherichia coli*, *Streptococcus fecalis*, *Klebsiella pneumonia*, and *Enterobacter* species.[11] This probably contributed to worsening sepsis in our patient; however, we could not demonstrate any organism in culture.

Diagnosis of SHS can be difficult to establish and entails a high level of suspicion. Eosinophilia is shown to be 93.5% sensitive and 93.1% specific in high-risk populations. But it is not sufficiently sensitive in patients with chronic infection and in those receiving corticosteroid therapy. However, peripheral eosinophilia in SHS is considered a good prognostic factor. Serological tests especially ELISA have a positive predictive value of 91% and a negative predictive value of 98%. But interpretation of positive results has to be done with caution as cross-reactivity exists with *Ascaris lumbricoides*.[12] Standard stool analysis is insensitive for detecting *Strongyloides* and it has a yield that does not exceed 46% even after three stool examinations. This is because of the fluctuation in the rate of excretion of larvae. But due to the large parasitic burden present in SHS, the yield in lung, bronchial, or small bowel biopsies can be quite high.[13]

Hyperinfection syndrome is associated with high morbidity and mortality. If left untreated, mortality rate approaches 100% which is partly related to delay in the diagnosis and initiation of treatment, as well as due to the accompanying Gram-negative sepsis.[5] Ivermectin, albendazole, and mebendazole have all shown to be effective against *Strongyloides*, but ivermectin is still considered to be the drug of choice. Oral ivermectin is preferred for intestinal strongyloidiasis, but many patients with SHS experience paralytic ileus, profuse vomiting, and diarrhea. This limits the delivery and absorption of oral medications, causing therapeutic challenge.[1,2]

Parenteral ivermectin is available only for veterinary use. But it has been occasionally used in humans with severe strongyloidiasis, refractory to oral agents.[1,2] Our patient was not an ideal candidate for oral ivermectin because of ileus and profuse vomiting. The Centre for Disease Control recommends ivermectin 200 μg/kg/day until stool and sputum examinations are negative for 2 weeks, and if possible to reduce or stop the immunosuppressive therapy. Oral albendazole 400 mg twice a day can be used as an adjunct for ivermectin.

Kidney Disease: Improving Global Outcome (KDIGO) recommends pretransplant screening using serology for strongyloidiasis in patients from endemic areas and to treat the same prior to transplantation if infection is identified. Due to the asymptomatic nature of intestinal strongyloidiasis and the risk for hyperinfection, the importance of screening before escalating immunosuppressive therapy has to be stressed upon.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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