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LETTER TO THE EDITOR

Strongyloides hyperinfection syndrome following simultaneous heart and kidney transplantation

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We report a case of Strongyloides hyperinfection syndrome (SHS) causing death in a patient approximately 1 month following simultaneous heart and kidney transplantation (HKTx).

The patient was a 61-year-old Caucasian male who had lived in Florida. He underwent four-vessel coronary artery bypass grafting for coronary artery disease in 1992 with myocardial infarctions and percutaneous coronary interventions. He also had insulin-dependent diabetes mellitus with retinopathy and nephropathy, requiring hemodialysis. His preoperative status was NYHA IV with an ejection fraction of 30–35% and pulmonary hypertension (85/30 mmHg). He underwent HKTx for ischemic cardiomyopathy and end-stage renal disease. His immunosuppressive protocol consisted of antithymocyte globulin, tacrolimus, mycophenolate mofetil, and steroids. Acyclovir and trimethoprim/sulfamethoxazole were given as prophylaxis per transplant protocol. Postoperatively the patient developed delayed kidney allograft function and required hemodialysis. His respiratory condition gradually deteriorated with worsening pulmonary edema despite adequate hemodialysis and right ventricular biopsy negative for rejection. Severe leukocytosis (WBC 12 100–45 300) persisted after the operation despite various therapies. On postoperative day (POD) 27 the patient developed dehiscence at the kidney transplant incision site because of a noninfectious wound seroma and underwent primary surgical repair. In addition, at that time, it was noted that a CMV DNA-PCR performed on the patient was positive for 3700 copies/ml. Acyclovir was discontinued and the patient was started on ganciclovir intravenously. Subsequently, CMV DNA-PCR was decreased to 1000 copies/ml on POD 32, and 375 copies/ml on POD 35.

On POD 28, a chest CT was obtained because of worsening oxygenation, which showed extensive infiltrates consistent with acute respiratory distress syndrome (ARDS). The patient was intubated and underwent bronchoscopy with bronchoalveolar lavage and transbronchial biopsies, which were nonrevealing. In addition, transthoracic echocardiogram was performed on POD 28, which demonstrated preserved left ventricular ejection fraction of 60–65%, moderate right ventricular systolic dysfunction, severe right atrial enlargement and severe tricuspid regurgitation. Three days later, on POD 31, the patient was noted to have hemoptysis and repeat bronchoscopy revealed diffuse hemorrhage. High dose corticosteroids were begun for worsening ARDS and the patient received CMV hyperimmune globulin because of concerns for possible CMV pneumonia. Despite high level mechanical ventilation, the patient's oxygenation worsened necessitating the addition of nitric oxide. The patient progressively deteriorated with hypotension refractory to pressor support and increasing difficulty with oxygenation. On POD 36, the patient died. Throughout the clinical course, he never developed acute rejection of the transplanted organs as evidenced by multiple biopsies (heart biopsies on POD 6, 13, 20, 28, renal biopsy on POD 8).

The postmortem examination revealed *Strongyloides stercoralis* larvae in the alveoli with accompanying severe bilateral lobar pneumonia and diffuse intra-alveolar hemorrhage (Fig. 1a). Autopsy specimens also revealed numerous *S. stercoralis* larvae in the transplanted heart and kidney, esophagus, stomach, and small and large bowel, many of them infiltrating through the mucosa and sub-mucosa and some reaching the lymphatic and blood vessels.

Strongyloides hyperinfection syndrome is an augmentation of the life cycle, which is medically important because it can lead to overwhelming and disseminated infection in immunocompromised patients including solid organ transplant recipients and carries the potential for high mortality rates (about 70%) [1,2]. In solid organ transplant patients increased corticosteroid dosages is the most frequent risk factor for development of SHS [3,4] and have been associated with the development of the hyperinfection syndrome and dissemination of the organism [5,6]. Meanwhile, not only the reactivation and dissemination of *S. stercoralis* in recipients but also transmissions of *S. stercoralis* from deceased donors may be serious problems [7]. There were some reports regarding SHS acquired from the donor in kidney- [8], intestinal [7], pancreatic transplantation [9]. Donors and recipients in endemic areas, a history of other helminthic infections,

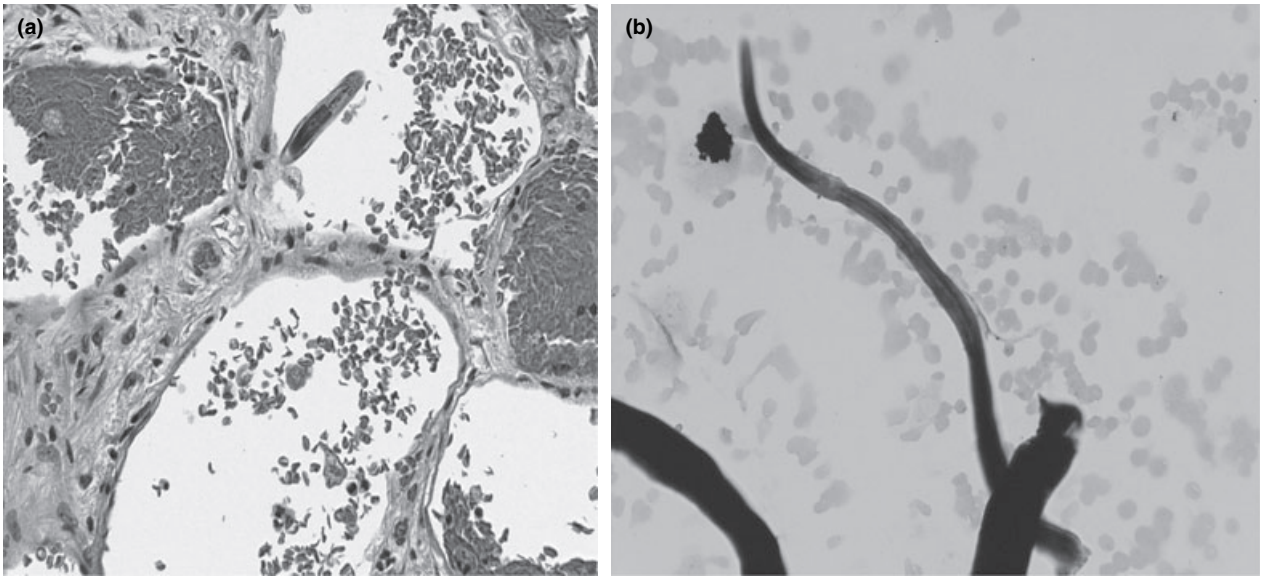

Figure 1 (a) Autopsy specimen of the lung. The lung showed diffuse intra-alveolar hemorrhage with patchy intra-alveolar fibrin and patchy widening of the septa. Numerous *Strongyloides stercoralis* filariform larvae were present within alveolar spaces, alveolar septa, and connective tissue. (b) Cytology specimen from bronchoalveolar lavage (BAL). Retrospective examination of cytology specimen of the BAL showed filariform larva of *S. stercoralis* noted among artifactual fibers of similar size and shape on Gomori methenamine silver stain.

Table 1. Strongyloides hyperinfection syndrome after heart transplantation.

Case	Age (years)	Gender	Residence	Ope	Eosinophil (%)	Immunosuppression	Onset (days)	Rejection	Symptom	Infected organ	Outcome
1	54	Male	OH (visit KN, TN)	HTx	21	Pre, TAC, MMF	74	Yes	Nausea, hematemesis	Lungs, colon, brain	Death
2	56	Female	KN	HTx	Normal	Pre, TAC, AZT	41	Yes	Dyspnea, petechial rash	Lungs, small intestine	Death
3	61	Male	FL	KHTx	32.3	Pre, TAC, MMF	22	No	Dyspnea	Lungs, gastrointestine	Death

OH, Ohio; KN, Kentucky; TN, Tennessee; FL, Florida; HTx, orthotopic heart transplantation; KHTx, simultaneous kidney and heart transplantation; Pre, prednisone; TAC, tacrolimus; MMF, mycophenolate mofetile; AZT, azathioprine.

unexplained eosinophilia, unexplained gastrointestinal complaints should be screened [3]. To our knowledge, this is the first reported case of SHS in a simultaneous HKTx recipient, and there are only two other cases of SHS reported in cardiac transplant patients [10,11] (Table 1).

Most immunocompetent individuals with acute infection with *S. stercoralis* may be associated with skin rashes or pruritus, peripheral blood eosinophilia, and gastrointestinal symptoms. Preoperatively, our patient had mild gastrointestinal symptoms (nausea, vomiting and diarrhea) with intermittent absolute eosinophilia (up to 32.3%) over the 4- to 5-year period prior to transplantation. He developed severe dyspnea with pulmonary infiltrates, but SHS was not diagnosed until autopsy.

Retrospectively, our patient's bronchoalveolar lavage cytology specimens were reviewed and one slide did show a single *S. stercoralis* worm. Because there were so few *S. stercoralis* worms and the fact that it mimics junk material usually seen in bronchoalveolar specimens, it was missed in the premortal biopsy specimen. The organism was obscured by the background of amorphous nonspecific material (Fig. 1b). The transbronchial biopsy showed subtle changes of acute alveolar damage but did not show the presence of *S. stercoralis*. Flow cytometry performed on the bronchoalveolar lavage fluid showed numerous alveolar macrophages and occasional neutrophils, eosinophils, and respiratory epithelial cells.

Eosinophilia has sensitivities of up to 80%, however this does not apply to immunocompromised hosts

including transplant patients, where the sensitivities are much reduced (eosinophilia < 20%) [12]. Unfortunately, eosinophilia is not a common finding after transplant because corticosteroids depress cell-mediated immunity [10,13]. Actually, the several reports including our case demonstrated that the recipients with SHS had no eosiophilia postoperatively [7,9].

Recommended diagnostic studies include: serology on peripheral blood using an enzyme-linked immunosorbent assay for *S. stercoralis* antigens, which is highly diagnostic with typical specificities of 95–97.7% and sensitivities of 83–95% [14]; stool examination using a single specimen for *S. stercoralis* larvae can have a high false negative rate with the sensitivity of around 30% [15].

Recently, endemic rates of *Strongyloides* infection in developed countries and the United States have increased, requiring greater clinician awareness. It's important to pay attention to the presence of preoperative eosiophilia in recipients for considering SHS infection, because it is almost universally fatal and difficult to diagnose SHS after transplantation.

Shugo Mizuno,[1] Taku Iida,[1] Ivan Zendejas,[1]
Tomas D. Martin,[2] Denise C. Schain,[3]
Bradley Turner[4] and Shiro Fujita[1]
1 Division of Transplantation and Hepatobiliary Surgery, Department of Surgery, University of Florida College of Medicine, Gainesville, FL, USA
2 Division of Thoracic and Cardiovascular Surgery, Department of Surgery, University of Florida College of Medicine, Gainesville, FL, USA
3 Division of Infectious Disease, Department of Internal Medicine, University of Florida College of Medicine, Gainesville, FL, USA
4 Department of Pathology, Immunology and Laboratory Medicine, University of Florida College of Medicine, Gainesville, FL, USA

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