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Case report

Donor-derived fatal hyperinfection strongyloidiasis in renal transplant recipient

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ABSTRACT

Strongyloides stercoralis is a nematode, endemic in tropical and subtropical areas. Strongyloidiasis has been reported in recipients of hematopoietic stem cells, kidney, liver, heart, intestine, and pancreas, eventually presenting as disseminated strongyloidiasis and hyperinfection syndrome (SHS) which is associated with high mortality. We report one case of a recent renal transplant recipient, who presented with gastrointestinal and respiratory symptoms, evolving into shock. The identification of *Strongyloides stercoralis* in the bronchoalveolar lavage (BAL) lead us to the diagnosis of SHS. Treatment with subcutaneous ivermectin was started, however the patient did not survive. Retrospective serum donor analysis allowed us to identify the donor as the source of infection.

Introduction

Strongyloidiasis is a parasitic infection caused by Strongyloides stercoralis. A nematode endemic in tropical and subtropical areas, it is associated with inadequate sanitary conditions, although sporadic cases have been reported worldwide, including in southern Europe [1,2]. Strongyloides infection occurs through skin contact with contaminated soil. Filariform larvae penetrate the skin and migrate in the bloodstream to the alveolar spaces of the lungs, then are expectorated and swallowed, which results in small intestine infection. In the intestine, adult worms reproduce, and their eggs produce rhabditiform larvae that can be found in the stool or remain in the host and cause autoinfection. This autoinfection phenomenon enables the development of a dormant but persistent infection [3]. Half of the infected patients have symptoms, mainly sporadic nonspecific gastrointestinal or respiratory complaints. A serpiginous itchy rash ("larva currens") along the thighs and buttocks, may be present and is suggestive of infection. Laboratory findings are also nonspecific, although intermittent peripheral eosinophilia or high IgE levels might be present [4].

Healthy infected individuals are usually asymptomatic. Impaired host immune system, especially concerning cell-mediated immunity (long-term chronic steroid use, transplant recipients including bone marrow and solid organs, Human immunodeficiency virus infection and Human T-lymphotropic virus infection [HTLV] seems to be the main determinant in the development of disseminated Strongyloidiasis and hyperinfection syndrome (SHS) [1,5]. SHS consists of an accelerated cycle of autoinfection, with uncontrolled proliferation of larvae in its habitual reproductive organs (skin, lungs, gut), with dissemination to any organ outside of the gut and lungs (usually liver, brain, heart, and urinary tract) [6]. In the transplanted population, Strongyloidiasis has been reported in recipients of hematopoietic stem cells, kidney, liver, heart, intestine, and pancreas [7,8]. A review of *S. stercoralis* infection in renal transplant recipients reported a mortality rate of 49 %. *S. stercoralis* transmission by renal transplantation is uncommon and difficult to prove [9]. We report one case of fatal Strongylodiasis hyperinfection syndrome in a renal transplant recipient who received a kidney from a seropositive deceased donor diagnosed postmortem.

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Case report

A 68-year-old Caucasian Portuguese male presented to a tertiary hospital with a three-day history of emesis, diarrhea without blood or mucus and progressive shortness of breath. Two months before, he had received a renal transplant from a died donor for his end-stage renal pre-dialytic disease; the initial immunosuppressant therapy included basiliximab, mycophenolate mofetil (MMF), tacrolimus and methylprednisolone, and currently he was on MMF (750 mg twice daily), tacrolimus (6.5 mg twice daily) and prednisolone (12.5 mg daily). The donor had deceased from hemorrhagic stroke and the histology of the kidneys showed no fibrosis or significant changes on the glomerular and vascular levels. The patient was also receiving prophylaxis with valganciclovir (450 mg daily) because both had positive serology for cytomegalovirus, and trimethoprim/sulfamethoxazole (TMP/SMX) (160/800 mg three times a week). The recipient's epidemiological history was unremarkable. The patient serology for HTLV-I/II were negative.

At admission at the emergency department, he was apyretic, with O2 peripheral saturation of 100 % in room air, blood pressure (BP) of 108/68 mmHg and a heart rate (HR) of 115 bpm. Pulmonary auscultation showed a reduction of breath sounds at both bases, with no other alterations in the physical exam.

Complete blood cell count revealed a hemoglobin of 10.1 g/dL, white blood cell count of 7800/μL with 720 lymphocytes, and 1190 monocytes, without eosinophilia and 196000 platelets. He had a creatinine level of 2.19 mg/dL (creatinine clearance =35 mL/min) (in the previous month serum creatinine was 1.43 mg/dL), urea was 86 mg/dL, hepatic enzymes were within the normal range, albumin was 3.08 g/dL and C reactive protein was 127 mg/dL. Tacrolimus levels were 3.9 mg/dL. Urine analysis showed only mild proteinuria and hematuria, without evidence of nitrites nor leucocytes. Abdominal ultrasound showed no relevant alterations (atrophied native kidneys and transplanted kidney with normal morphology, without pyelocaliceal dilation and well-placed double J stent since the transplant). The patient was admitted to the Nephrology department, with the initial diagnosis of pyelonephritis and started on ciprofloxacin (400 mg every 24 h), alongside with ganciclovir (2.5 mg/kg iv every 12 h) and immunoglobulin at prophylaxis dose (100 mg/kg/dose).

He evolved with shock, worsening of respiratory failure with PaO2/FIO2 ratio of 100 and bilateral interstitial infiltrate in chest X-ray (Fig. 1A and B). He was intubated and noradrenalin was started. An emergency bronchoscopy was performed showing purulent secretion. Septic shock due to pneumonia was assumed and empirical piperacillin/tazobactam (2.275 g every 6 h) and vancomycin (loading dose 25 mg/kg IV) was started. Because of the immunosuppressed status TMP/SMX (20 mg/kg/day, IV every 8 h) was added, considering the hypotheses of *Pneumocystis* pneumonia (PJP). The acute physiological scores at 24 h in ICU were SAPS II of 48 and SOFA of 10 points.

The patient continued to worsen, with respiratory failure and needing maneuvers of alveolar recruitment (prone position) and failure of the transplanted kidney having started SLEDD (Sustained Low-Efficiency Daily Diafiltration). The next day *Strongyloides Stercoralis* was identified in the bronchoalveolar lavage (BAL) (Fig. 2) and had an identification of positive urinary antigens for *Streptococcus pneumoniae.* PJP was excluded. Subcutaneous ivermectin (200 μg/kg/day: 19 mg, every 24 h) was started, because there was no oral route available due to the severity of shock with associated paralytic ileus; before the beginning of ivermectin he had peripheral eosinophilia with 2200 cells/μL. The patient evolved into additional multiorgan dysfunction with liver and hematologic failure, with no response to antimicrobial treatment and increased dose of vasopressors and he died eight days after admission. All other microbiological samples were negative, including blood cultures.

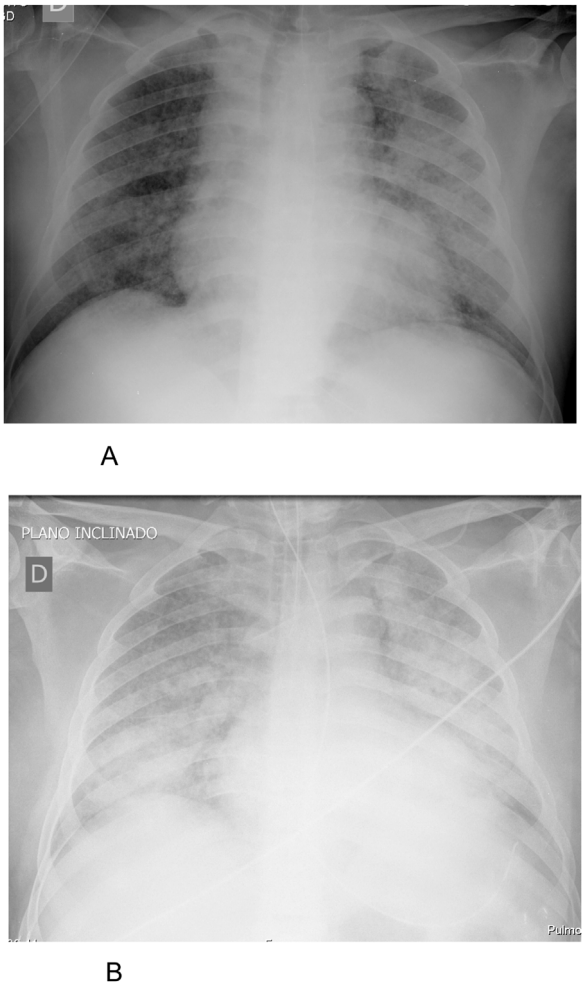

Fig. 1. A: X-ray at admission in ICU. B: X-ray 24 h after admission in ICU.

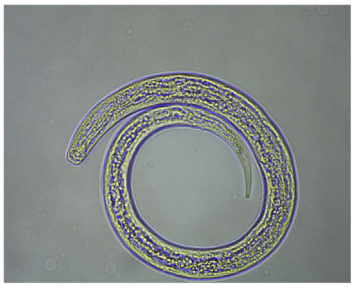

Fig. 2. Filariform larvae found Broncho alveolar lavage fluid.

The national institute of transplantation (Instituto Português do Sangue e da Transplantação (IPST)) was contacted and serology was performed on the other kidney recipient and the donor's stored blood. Both serologies were positive. The other recipient received prophylactic treatment. The serology was also performed in a blood sample of our patient, obtained before the transplant, and the result was negative.

Discussion

Infections are a major cause of morbidity and mortality in solid organ transplant recipients. They may be a challenge because those

patients may not manifest the typical signs and symptoms of infection, and their treatment may be complicated by drug interactions with the immunosuppressive therapy.

The non-specific nature of disease manifestations in transplant recipients often requires an early treatment initiation with broad-spectrum therapy before a specific etiologic diagnosis can be made. The gastrointestinal and respiratory symptoms presented by our patient, forced us to investigate some differential diagnosis - *Clostridium difficile*, CMV disease, other infectious causes of colitis and even to side effects from immunosuppressive treatment, especially related to mycophenolate mofetil. With respect to CMV infection, although basiliximab does not seem to increase the incidence, our patient was also on prophylactic therapy with valganciclovir, because, endogenous reactivation leading to CMV disease occurs in 10–15 % of seropositive recipients (D+/R+). In this case, the patient was under prophylaxis, which diminished the probability of CMV disease, despite this, high prevalence of CMV in the first year post-transplantation makes this clinical suspicion important [10,11].

Although *Strongyloides* hyperinfection after renal transplantation is uncommon, the real incidence is not known. Most patients that developed *Strongyloides* hyperinfection syndrome appear to have previous undetected chronic intestinal Strongyloidiasis, although primary *Strongyloides* infection in areas of endemicity, or donor-derived transmission can also occur [12,13]. Reactivation and donor-derived infection usually occurs during the first three months after the transplant, when immunosuppression is most intense [12–14].

Portugal is not currently an endemic country of strongyloidiasis, however there is data in describing the existence of some endemic focus and isolated cases of Strongyloidiasis in Portugal until 1967 [15]. Thus, considering our epidemiological setting, the characteristics of the parasite resulting in decades-long infection, the age and immunosuppression status of our patient, this infection had to be considered. In our case, a retrospectively screening for *S. stercoralis* was negative, and a posthumously donor's IgG was positive, leading us to assume that the helminthic infection was transmitted by the donor. The other kidney recipient, transplanted in a different institution, received prophylactic treatment.

The diagnosis of strongyloidiasis is usually made by serological methods or by detecting larvae in stools, though in the setting of hyperinfection syndrome larvae can be found as well in respiratory secretions, gastric aspirates, or in biopsy samples (from the stomach, jejunum, skin, or lungs). In this case, *S. stercoralis* was identified in BAL.

Regarding the treatment, oral ivermectin is recommended for uncomplicated strongyloidiasis and is usually well-tolerated with a higher cure rate than with albendazole. In patients with hyperinfection, and no available oral route, therapeutic options are limited. No parenteral anti-helminthic drugs are licensed for use in humans, but parenteral ivermectin is used in veterinary medicine. Although drug-related toxicity, parenteral ivermectin has been used in humans as rescue therapy, appearing to be effective and safe. [16,17]. Our patient was treated with subcutaneous formulation, 200 mg/kg/day, without local or systemic adverse reactions identified. Serum ivermectin concentrations were not evaluated.

Even though more studies are warranted to understand the role of parenteral ivermectin in SHS in humans, mainly for the critical ill patient without oral route available, if needed, this therapeutic option should be considered early. Furthermore, once the enteral route is available, oral dosing in addition to the subcutaneous route might increase efficacy because of enterohepatic circulation [18].

In immunocompromised patients, there is no established duration of treatment. At least, two weeks of daily therapy are recommended for chronic intestinal strongyloidiasis. Treatment of hyperinfection syndrome is difficult and longer, at least until documentation of microscopic clearance. In our patient that follow up was not possible. Other aspects of treatment to consider are: (1) reduction of immunosuppression in transplant recipients and (2) empirical addition of a broad-spectrum antibiotic, once bacterial complications as meningitis, sepsis, and respiratory insufficiency are common [8,19].

Attending to high mortality and difficulty to manage this infection, the authors emphasize the importance of pretransplant screening and primary prevention of SHS, not only recipients and donors from endemic areas or with eosinophilia, as preconized from The American Society of Transplantation [18,20], but also in epidemiological contexts as ours, when recipients and donors born when there's still existed strongyloidiasis in the country [15]. Another important aspect is the necessity of an invasive investigational approach in this recently transplanted patient, to a rapid diagnostic.

The authors also highlight the necessity of further investigation using subcutaneous ivermectin in humans, particularly in critical settings.

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Author statement

All authors have contributed to the manuscript.

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All authors have contributed to the manuscript.

Ana Cipriano: conceptualization, methodology, writing - original draft, review & editing.

Rita Dias, Ricardo Marinho, Sofia Correia: writing - original draft, review & editing.

Virginia Lopes, Teresa Cardoso, Irene Aragão: supervision, visualization, review & editing.

All authors read and approved the final version of the manuscript.

Declaration of Competing Interest

The authors declare that they have no conflict of interest.

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