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Diagnostic challenge of *Strongyloides stercoralis* hyperinfection syndrome: a case report

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Abstract

Strongyloides stercoralis causes chronic, mostly asymptomatic infections but hyperinfection syndrome may occur in immunosuppressed patients, especially in those receiving corticosteroids. We report a case of *S. stercoralis* hyperinfection syndrome in a solid organ transplant recipient that occurred approximately 2.5 months after heart transplantation. The patient presented to the intensive care unit with acute respiratory distress, bacteremia, and petechial rash on abdomen and toe. Microbiology testing of respiratory samples excluded infection with *Pneumocystis jirovecii*, respiratory viruses, pathogenic bacteria and fungi. No eosinophilia was found. Histopathological examination of the skin biopsy of the petechial rash provided the first indication of the diagnosis, revealing the presence of isolated filariform *S. stercoralis* larvae in the dermis. Subsequent microbiology testing confirmed the diagnosis. This case highlights the role of histopathological examination of a skin rash in diagnosing patients with atypical clinical presentation of *Strongyloides* hyperinfection syndrome.

Keywords: *Strongyloides stercoralis*, transplant, hyperinfection syndrome, petechiae, skin

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Introduction

Strongyloides stercoralis is an intestinal nematode that causes chronic, mostly asymptomatic infections. However, fulminant fatal illness with parasite dissemination may occur in individuals with compromised immunity, especially those receiving corticosteroids (1). Although *S. stercoralis* is considered to be a disease of tropical and subtropical areas, its prevalence has also been increasing in temperate regions, including various European countries (2). Unfortunately, the signs and symptoms of hyperinfection syndrome vary widely and may be atypical in immunosuppressed patients (1). Patients with *Strongyloides* hyperinfection syndrome tend to present with acute respiratory distress and a Gram-negative sepsis/bacteremia (3). Rarely, dermatological manifestations such as periumbilical petechiae or purpura may be the first signs of hyperinfection syndrome (4).

Case report

A 62-year-old Caucasian female was admitted to the intensive care unit (ICU) with acute respiratory failure. Her medical history was significant for diabetes mellitus type 2, arterial hypertension, dyslipidaemia, hypothyroidism, past hepatitis B (HBV) infection and a heart transplantation 2.5 months prior. Approximately 1.5 months after transplantation, the patient was hospitalized due to increased troponin levels and segmental contraction abnormalities on echocardiogram. Transplant rejection was suspected and methylprednisolone dosage was increased. Follow-up echocardiogram showed no improvement, with serum troponin levels stagnating at around 800 ng/l; however, histopathological examination of the heart biopsy sample excluded organ rejection. The patient subsequently developed a macular rash, clinically suspected of urticarial exanthema, which resolved after antihistaminic treatment; however, abdominal petechiae quickly followed (Fig. 1).

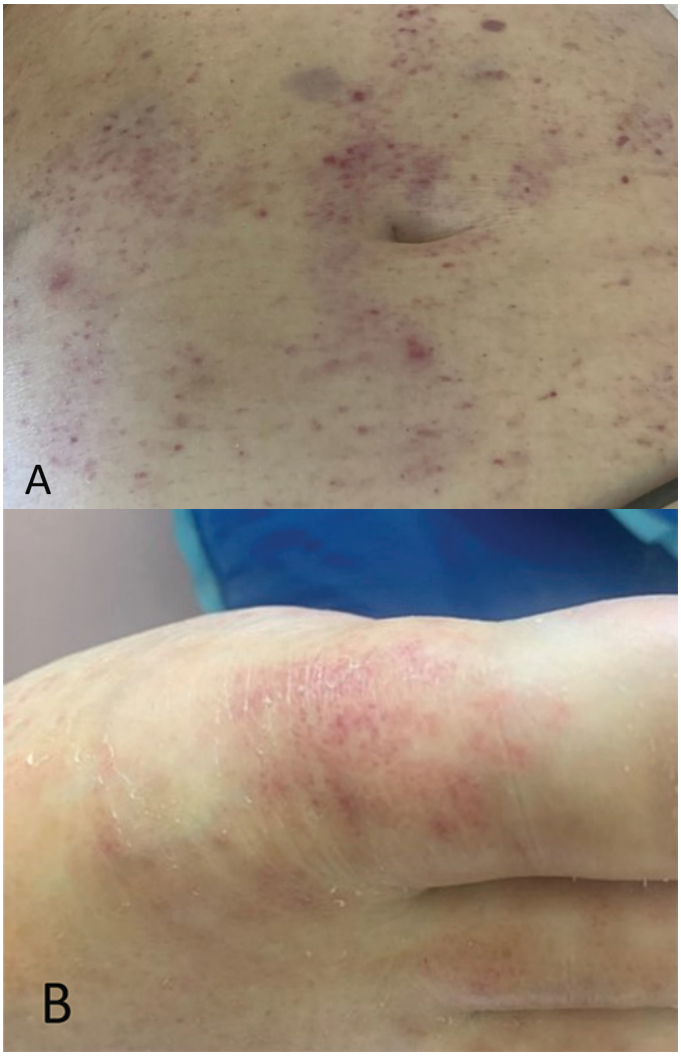

Figure 1 | Periumbilical petechiae (A) and petechial rash on toes (B).

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Three days prior to ICU admission, the patient's pulmonary function deteriorated, requiring supplemental oxygen therapy. Due to increased beta-D-glucan (83.4 pg/ml) and diffuse bilateral ground-glass opacities on chest CT scan, *Pneumocystis jirovecii* pneumonia (PCP) was initially suspected. Extensive microbiology testing excluded PCP and respiratory infection with atypical bacteria, fungi and respiratory viruses (including SARS-CoV-2). Extended spectrum β-lactamase (ESBL)-producing *Klebsiella pneumoniae* was isolated from blood cultures, urine and bronchoalveolar lavage samples, for which she received antibiotic treatment with meropenem. Nevertheless, the patient became hypotensive and her pulmonary function continued to deteriorate, necessitating transfer to ICU and intubation.

On admission to ICU, her leukocytes were 10^9/l and no eosinophilia was found. Despite continuously increased beta-D-glucan levels (highest value = 267.8 pg/ml), diagnosis of invasive aspergillosis was deemed unlikely due to negative results for galactomannan, PCR for *Aspergillus* spp. and lack of growth on culture. Hemorrhagic fever with renal syndrome was also suspected due to an ongoing hantaviral outbreak in Slovenia and the presence of petechial rash; however, hantavirus serology and PCR testing were negative. The diagnosis of strongyloidiasis was first suspected by the dermopathologist, who identified the presence of isolated scattered filariform *S. stercoralis* larvae within the dermis from the excisional skin biopsy of the petechial rash (Fig. 2).

On receiving the pathologist's report, serology testing for *S. stercoralis* was immediately performed using *S. ratti* ELISA (Bordier Affinity Products SA, Crissier, Switzerland), which confirmed the presence of anti-*Strongyloides* IgG. Additionally, real-time PCR and microscopic examination of various samples were performed (Table 1). The diagnosis of *Strongyloides* hyperinfection syndrome was thus established and ivermectin (200 µg/kg per day) was immediately administered; however, the patient's condition continued to deteriorate. She developed irreversible shock and died 2 days later. The transplant center was immediately contacted and it was confirmed that the donor was not infected with *S. stercoralis*.

Table 1 | **Microbiology testing results for *Strongyloides*.**

Days since ICU admission	Sample type	Microscopic examination	Real-time PCR
2	BAL*	Negative	Positive
6	Endotracheal aspirate	Positive	Positive
7	Stool	Negative	Positive

ICU = intensive care unit, BAL = bronchoalveolar lavage, PCR = polymerase chain reaction. * tested in retrograde, the sample was initially submitted for *P. jirovecii* PCR testing.

Discussion

Strongyloides stercoralis is a common human parasite with widespread global distribution. The infection is usually acquired by walking barefoot on contaminated soil in endemic countries in tropical and subtropical climates (2). Nevertheless, infection rates are also on the rise in many countries with a temperate climate, with several reports of the emergence of the disease in areas that are considered to be non-endemic for the disease (5). To date, the prevalence of *Strongyloides* infection in Slovenia has not been systematically investigated but some reports are available for neighboring countries. For example, in northern Italy, 8% (97/1,137) and 1% (13/1,178) of individuals with and without eosinophilia, respectively, had a positive serology test result for *Strongyloides*, while even higher rates were observed among immigrants (17% and 2%, respectively) (6). In addition, the Balkans, the region from which immigrants in Slovenia most commonly originate, is also considered to be an endemic region for strongyloidiasis, with an estimated seroprevalence of 7.3% among Bosnian farmers, schoolchildren and miners (7). A more recent study evaluating the prevalence of *Strongyloides* infection and hyperinfection syndrome among renal allograft recipients in Central Europe identified serologic evidence of infection in 3% of tested patients (8). Due to the exclusion of *Strongyloides* infection in the donor and positive serology for *Strongyloides* in our patient, it is highly likely that the infection occurred before the patient underwent organ transplantation. Unfortunately, determining the exact origin of infection may be challenging since chronic infection may asymptomatically persist for up to 50 years (9).

In addition to infection with human T-cell lymphotropic virus-1 (HTLV-1) and hematological malignancies, treatment with corticosteroids is the main trigger predisposing to the development of *S. stercoralis* hyperinfection syndrome (2, 10), which occurs due to an increase in the parasite load followed by increased penetration of the bowel mucosa by infective larvae. Whereas hyperinfection is defined as the presence of numerous migrating *Strongyloides* larvae in organs normally involved in the pulmonary autoinfection cycle (i.e., lungs and gastrointestinal tract), dissemination implies migration of larvae to organs that are not ordinarily involved in the classic pulmonary life cycle of the nematode, including the skin, mesenteric lymph nodes, gallbladder, liver, dia-

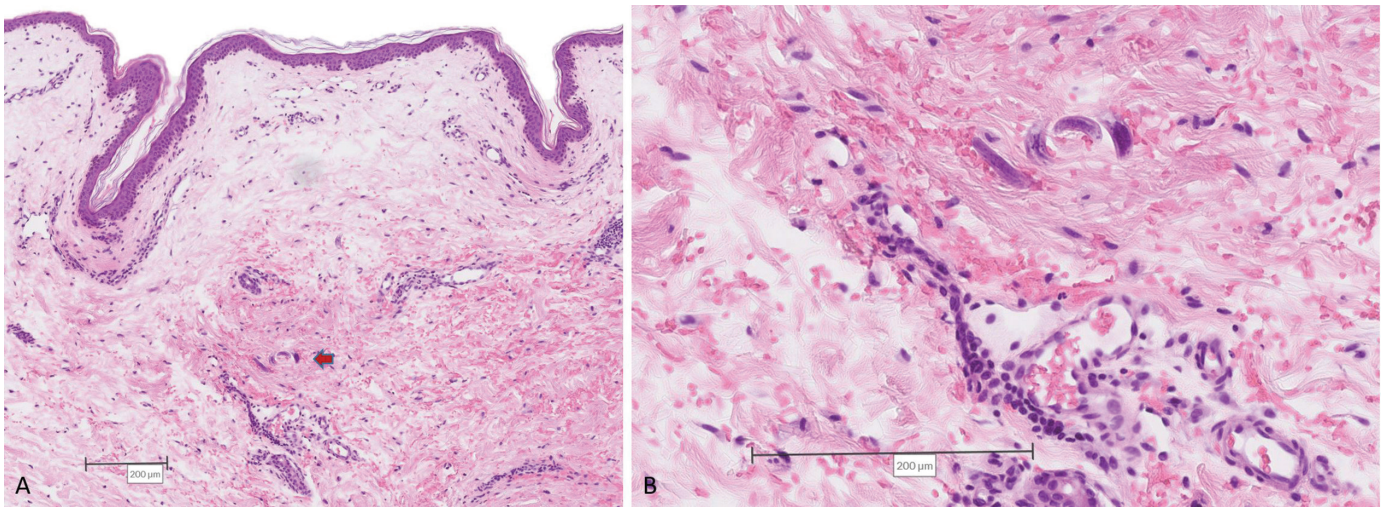

Figure 2 | Cutaneous strongyloidiasis. (A) A low power magnification reveals unremarkable epidermis, areas of erythrocyte extavasation in the dermis and scattered larvae in the reticular dermis (arrow). (B) Higher magnification depicting larvae. A mild perivascular lymphocytic infiltrate can also be appreciated.

phragm, heart, pancreas, skeletal muscle, kidneys, ovaries, and brain (3, 11). Interestingly, *Strongyloides* hyperinfection syndrome can develop in patients receiving high-dose, low-dose and even locally injected corticosteroids (10). Due to the high fatality rate (up to 80%), timely recognition of the infection is of utmost importance (12). Ideally, treatment with ivermectin or albendazole should be initiated before the induction of immunosuppressive treatment; however, prophylactic anthelmintic therapy is also possible for those who are immunocompromised at the time of strongyloidiasis diagnosis (1).

Dermatologic manifestations of *Strongyloides* hyperinfection syndrome include intensely itchy migratory serpiginous rash, petechiae and purpura that usually develop on the abdomen, proximal thighs and buttocks (1). Periumbilical purpura (the "thumb print sign") is considered to be a rare but pathognomonic feature of hyperinfection syndrome, caused by migration of larvae through vessels into the dermis (13). Unfortunately, the signs and symptoms of hyperinfection syndrome in our patient were somewhat atypical. Initially, a macular exanthema that resolved after antihistaminic treatment was observed, followed quickly by petechial rash without classical periumbilical purpura or linear streaks (Fig. 1), not raising the suspicion of strongyloidiasis. In addition, parasitic infestation was also not immediately suspected due to normal eosinophil counts. Strongyloidiasis is approximately nine-times more common in individuals with eosinophilia than in those with normal eosinophils (5); however, lack of eosinophilia on presentation, especially if the patient is immunosuppressed, should not be considered a reliable marker for excluding underlying chronic strongyloidiasis (14). In fact, eosinophilia may be present in only 16.4% of patients with parasite dissemination (5). The lack of familiarity with strongyloidiasis by health care providers (especially in non-endemic countries) is another concerning issue that delays appropriate management. As shown previously (5), in approximately 12% of severe strongyloidiasis cases the correct diagnosis was only made post mortem.

Lastly, this case report also raises the question of pre-transplant screening for *Strongyloides* of allograft recipients. A systematic review of case reports on severe strongyloidiasis showed that pre-transplant serological screening was mentioned in only 10% (3/29 cases of solid organ/bone marrow transplantations) (5). While pre-transplant screening for strongyloidiasis is recommended in some endemic countries and/or populations with particularly high potential for exposure to *Strongyloides* (15), such protocols have not yet been uniformly adopted in non-endemic areas. Rarely, infection can also be transmitted through cadaveric transplant allografts (1). Hence, in order to minimize post-transplant infectious complications, recipient and donor screening should be implemented in transplantation programs in Central Europe, especially because *Strongyloides* infection rates are increasing due to migration and travel to endemic regions (8).

To conclude, asymptomatic *S. stercoralis* infections should be considered even in individuals residing in non-endemic regions (especially if they are receiving corticosteroids) and regardless of their eosinophil count. Histopathological examination of periumbilical rash may aid in establishing a correct diagnosis, particularly in patients with atypical dermatological presentations. Because of the increasing prevalence of strongyloidiasis in Europe and the proportion of immunosuppressed patients, pre-transplant screening may be warranted in donors and organ recipients.

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