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CASE REPORT

Death caused by strongyloides hyperinfection in a leprosy patient on treatment for a type II leprosy reaction

BUNSE LEANG*, LUT LYNEN**, RUTH TOOTILL*, STEPHEN GRIFFITHS+ & DIDIER MONCHY++

**Sihanouk Hospital Center of HOPE (SHCH), Street 134, Sangkat Veal Vong, Khan 7 Makara, PO Box 2318, Phnom Penh 3, Cambodia*

***Institute of Tropical Medicine (ITM) Antwerp, Belgium*

+Kean Khleang National Rehabilitation Center, Phnom Penh, Cambodia

++Institut Pasteur du Cambodge, Phnom Penh, Cambodia

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Summary *Strongyloides stercoralis* is present worldwide and can cause hyperinfection in patients on long-term immunosuppressive doses of steroids, as is sometimes the case for patients treated for leprosy reactions. Strongyloides hyperinfection can present with ileus, as is discussed in this case report. Physicians, including surgeons, should be aware of this entity in order to avoid an unnecessary laparotomy. Though patients may survive if diagnosed at an early stage, strongyloides hyperinfection syndrome has a mortality rate of 87% and prevention is therefore of utmost importance.

Introduction

Strongyloides stercoralis is a worldwide intestinal nematode. It infects 30 million people in 70 countries.[1] Prevalence of *S. stercoralis* in Argentina is 83%, Nigeria 25%, Brazil 13%, Guinea 6·4%, and for South-Esat Asia: Laos 19% and Thailand 11·2%, No reports are available from Cambodia.[1]

In immunocompetent patients, *S. stercoralis* infection usually results in asymptomatic chronic disease of the gut, which can remain undetected for decades (up to 50 years).[2] However, exacerbation of a chronic asymptomatic infection into Strongyloides hyperinfection (SH) syndrome is commonly reported in immunocompromised hosts resulting from corticosteroid treatment, chemotherapy for cancer, organ transplant recipients, autoimmune diseases, malnutrition, and rarely in HIV/AIDS. In a case-control study steroids users have 3·3 times more risk of developing strongyloidiasis.[3]

Correspondence to: B. Leang (Tel: +855 23 882 484 or +855 11 850 471; Fax: +855 23 882 485; e-mail: tmed1shch@online.com.kh)

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In immunocompromised states autoreinfection is greatly increased, resulting in a marked increase in the intestinal worm burden and in massive dissemination of autoinfective filariform larvae (FL) to the lungs and other tissues (skin, meninges, liver, biliary tract, spleen). This leads to the SH syndrome, with disseminated bacterial infection, resulting from leakage of gut flora on the surfaces of migrating larvae. SH results in a high mortality rate, up to 87%.[1]

We report a fatal case of SH resulting from long-term steroid use, presenting with ileus.

Case report

A 19-year-old male student presented to the emergency room of our hospital in May 2002 with abdominal distension and absence of stool and gas for 1 day. The history revealed that the patient had a type II leprosy reaction, for which he was put on prednisolone 50 mg PO daily with thalidomide in December 2001. After 4 weeks of therapy, the prednisolone was tapered slowly. In early February, the patient had been given benzyl benzoate for possible scabies. In March (prednisolone was at 20 mg daily), he developed a papular skin rash and prednisolone was increased again to 40 mg daily. One month later, widespread exfoliative skin lesions appeared. By mid-April, the patient had diarrhoea, for which pyrantel, metronidazole and cotrimoxazole were given. One week later, a peripheral blood count showed an eosinophilia of 12%.

On May 9, he again had diarrhoea and productive cough. Stool microscopy was requested but results are not available. One day later, the patient had abdominal distension, vomiting, no stool and gas. A diagnosis of ileus was made and he was referred to a public referral hospital in Phnom Penh. An upper endoscopy and laboratory tests showed non-specific findings, except for the presence of several polyps in the duodenum which were biopsied. After the procedure, his ileus improved and he was sent back to the health centre. Two days later, the ileus recurred. The patient's mother asked for him to go home, but the attending physician advised and assisted in bringing the patient to a private NGO-funded hospital (SHCH).

On arrival at this hospital, the patient was uncomfortable, agitated and tachypnoeic. His vital signs were: blood pressure 100/80 mmHg, heart rate 110 per minute, respiratory rate 28 per minute and temperature 38°C. He had cushingoid facies, mild pallor, but no jaundice or neck stiffness. Heart and lungs were normal. The skin overlying the distended abdomen showed striae, no rebound tenderness, no hepatosplenomegaly and no mass, but poor peristalsis and tympanic percussion were found. Second degree (40 × 50 mm) pressure bedsores were present on both hips. The lower limbs showed oedema 2+ up to the level of the knees. Rectal examination was mildly tender. Yellow muddy stool was present in the rectum, and a stool sample was sent to the laboratory.

Laboratory results showed a marked hypokalaemia of 1·9 meq/l (normal range: 3·5–5·0 meq/l) and the stool examination showed many *S. stercoralis* larvae. Gastric fluid and the exudates of skin lesions sent for direct smear and Gram stain did not show *S. stercoralis*. A supine abdominal X-ray showed distended bowels filled with air. A chest X-ray was unremarkable.

The reviewing surgeon diagnosed the boy as having ileus secondary to an abdominal infection, and no immediate surgical intervention was indicated. The patient was put on intravenous fluid with KCl, IV ceftriaxone, IV metronidazole and oral albendazole. Six hours after admission, the patient developed respiratory distress and hypotension. Ciprofloxacin IV was added and his septic shock was treated with IV fluids and dopamine infusion. Despite aggressive management, the patient died 24 h after admission.

The results of histopathology of the duodenal biopsies performed at the other hospital arrived after the patient's death, and showed massive amounts of *S. stercoralis* larvae in the mucosa (see Figure 1).

Discussion

The course of this patient's illness with diarrhoea, cough, peripheral eosinophilia, ileus, sepsis and the presence of many strongyloides stercoralis larvae in the stool and in the duodenal mucosa are strongly suggestive of strongyloides hyperinfection.

The patient died of presumed septic shock and acute respiratory distress syndrome. The patient was too sick to cough up sputum for *S. stercoralis* larvae detection. The micro-organisms responsible for his sepsis were probably of gut origin. No blood culture was done, but we gave broad-spectrum antibiotics to empirically cover Gram negatives and anaerobes. His hypokalaemia probably resulted from continuing gastric aspiration, poor intake and chronic diarrhoea.

The diagnosis of strongyloidiasis is often delayed and overlooked because of non-specific symptoms.[4] A study from southern Taiwan reported diarrhoea (74%), fever (70%), abdominal pain (59%), cough (37%), dyspnoea (33%), constipation (26%), leukocytosis (81%), anaemia (67%) and eosinophilia (44%).[4] Although non-specific and not a constant feature, peripheral blood eosinophilia $\geq 5\%$ is often associated with strongyloidiasis, especially in immunocompetent hosts.[5–8] Thus, physicians in endemic regions should include strongyloidiasis in the differential diagnosis when patients present with gastrointestinal and/or pulmonary symptoms with peripheral eosinophilia.[4]

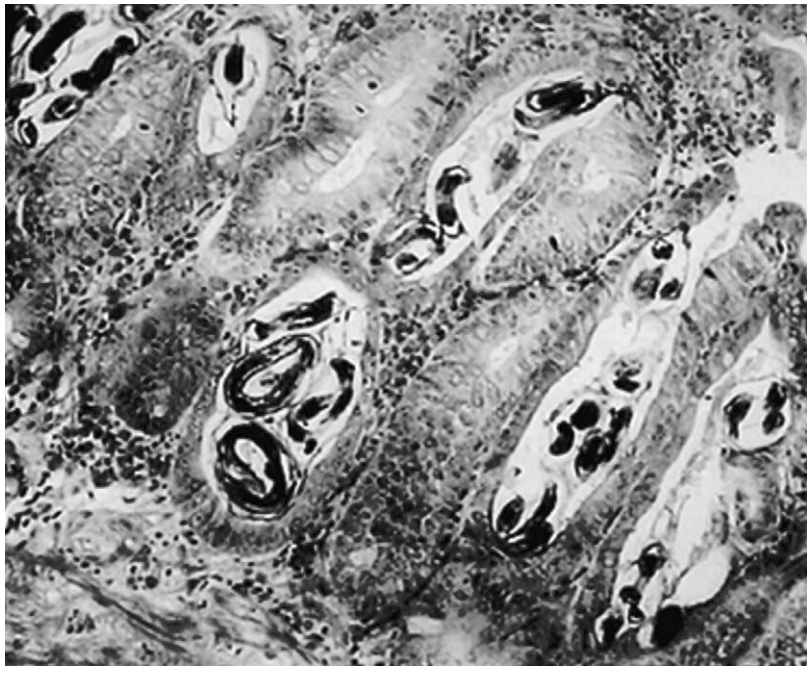

Figure 1. *Strongyloides stercoralis* filariform larvae in duodenal biopsy. Giemsa stain × 50.

Besides intestinal and pulmonary symptoms, larva currens skin lesions (rapidly progressing linear, serpiginous, urticarial streaks) are rare, but are the pathognomonic cutaneous manifestation of strongyloidiasis.[9] SH can present with ileus and may lead to an unnecessary laparotomy.[10,11]

Stool microscopy to identify *S. stercoralis* larvae or ova has variable sensitivity.[5] A direct stool microscopy has only a sensitivity of 30% and three specimens will increase the sensitivity to 60–70%.[5] Stool concentration increases the sensitivity of stool microscopy up to 80%.[5] *S. stercoralis* larvae or ova can also be detected in duodenal aspiration and embedded in the duodenal mucosa. *S. stercoralis* larvae can also be detected in sputum or bronchial washings. Other tests, available only at specialized centres, such as an ELISA test (IgE to *S. stercoralis* antigen) and agar plate culture have respectively 80–90%[5] and 96%[1] sensitivity.

Strongyloidiasis is a difficult infection to treat because of its autoinfective FL. Any truly effective anthelmintic must kill every autoinfective FL in order to remove the danger of potentially serious disease. This becomes even harder in cases with ileus due to poor absorption of the drug.

Albendazole is a well tolerated and safe treatment for strongyloidiasis. Pancytopenia and agranulocytosis are two very rare side effects. For strongyloidiasis, a dose of 400 mg orally twice daily for 5 days has a cure rate of 95%.[12] There is little data on how to use albendazole for SH. Ivermectin is registered as the drug of choice for the treatment of strongyloidiasis in the WHO's list of essential drugs.[1] The recommended dose is 200 mcg/kg/day taken as a single dose.[13] In SH, this single dose should be repeated on day 2, day 15 and day 16.[14] Because of its prohibitively high price, ivermectin is virtually unavailable in developing countries, except for veterinary use and in onchocercosis control programs.

The success of SH therapy is largely dependent on early recognition and prompt treatment. SH should be suspected when a patient on long-term immunosuppressive drugs (steroids) presents with severe gastrointestinal and respiratory tract symptoms, together with the presence of *S. stercoralis* larvae or ova in stool or duodenal fluid or sputum, with or without skin rash/ulcerations, sepsis, Gram-negative bactaeremia or central nervous system involvement.[15,16] SH should be treated aggressively with anti-parasitic drugs and antibiotics that target Gram negative bacteria (ceftazidime, ceftriaxone, ciprofloxacin, gentamycin). If peritonitis is suspected metronidazole should be added. Be aware of the possibility of fungal co-infection. If ivermectin is not available, start albendazole 400 mg PO twice daily and continue until at least three negative stool samples. An important therapeutic measure is to reduce the dose of steroids as low as possible.

In case of ileus due to SH where no response to an oral agent is apparent (due to poor absorption), there are reports of successful treatment by thiabendazole per rectum[11] and subcutaneous use of a veterinary preparation of ivermectin.[17]

Strongyloides hyperinfection is rarely reported in leprosy literature, but it may be under reported as the diagnosis could be missed like in this case report. A PubMed search using leprosy, strongyloides, strongyloidiasis, strongyloides hyperinfection as keywords found one fatal case report back in 1994.[18] Based on current epidemiological surveys of *S. stercoralis* prevalence in neighbouring countries (Thailand 11·2%, Laos 19%) and the burden of HIV/AIDS in Cambodia, strongylodiasis may be a problem. Because stool microscopy lacks sensitivity, it is probably more cost effective to treat than to screen all patients from high endemic countries.[19] In the Cambodian National Leprosy Elimination Program (NLEP), 3-month pre-packed tapered dose blister packs of steroids for the treatment of leprosy reactions in the field are available for use by leprosy control program supervisors. Often cases

of leprosy reaction in the field, particularly chronic type 2 reactions are not appropriately referred but are given two or more courses of these pre-packed blister packs of steroids. Following the fatal outcome in this case and the discovery of several other *S. stercoralis* positive stool samples in patients on treatment with steroids for leprosy reactions in the National Rehabilitation Unit, the NLEP has recommended to field staff that no more than one 3-month pack is issued to any patient in the field. On recurrence of the reaction, the patient should be referred to the hospital. In addition, the NLEP is considering adding albendazole to the pre-packed steroid blister packs. As these pre-packed steroids are available and used by paramedical staff in various developing countries, program managers may want to consider making similar recommendations for their own countries.

The case described here is an illustration of SH in a patient who received high dose steroids for a medical indication and prescribed by a physician. In developing countries, however, over-the-counter availability of steroids is the rule rather than the exception.[20] Moreover, steroids are frequently mixed with herbal medicines by traditional healers. Therefore, every physician working in a strongyloidiasis endemic region, or treating patients from endemic regions, needs to be aware of the SH syndrome and systematically enquire about potential steroid use or look for other signs of steroid abuse.

Conclusion

Leprosy patients living in strongyloidiasis endemic areas may develop a life threatening SH when their leprosy reactions are treated with steroids, without pre-treatment of an *S. stercoralis* infection. SH is an, often, fatal syndrome that can be prevented. It is more effective to treat all patients at risk before the start of immunosuppressive therapy, than to screen patients for a possible infection, especially when working in an endemic area. Early diagnosis and treatment is important in SH. Albendazole is well tolerated, but data are lacking for its use in SH. Ivermectin is more effective for the treatment of disseminated strongyloidiasis and is recommended for the treatment of *S. stercoralis* in SH. We strongly recommend the inclusion of albendazole and ivermectin in Cambodian referral hospitals' formulary. We also recommend a price reduction of ivermectin to make it accessible for developing countries.

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