Fatal Outcome of a Hyperinfection Syndrome despite Successful Eradication of *Strongyloides* with Subcutaneous Ivermectin

H.P. Hauber, J. Galle, P.L. Chiodini, J. Rupp, R. Birke, E. Vollmer, P. Zabel, C. Lange

Abstract

We report the case of a 77-year-old man who developed a *Strongyloides* hyperinfection syndrome following immunosuppressive therapy more than 60 years after he moved away from an area endemic for *Strongyloides stercoralis*. Successful eradication of the nematode was achieved with an off label subcutaneous formulation of ivermectin. However, the patient subsequently died from acute respiratory distress syndrome (ARDS). Despite a high wormload in the stool and sputum of the patient and delayed infection control measures in the hospital, testing of the medical staff revealed a very low risk of *Strongyloides* transmission among healthcare workers.

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Case Report

A 77-year-old man was admitted to a tertiary hospital in July 2004 because of weight loss, vomiting, bloody diarrhea and fever. The patient grew up in Paraguay and had lived there until the age of 13 when he relocated to Germany. In April 2004 he had developed pANCA-positive microscopic polyangiitis with rapid progressive glomerulonephritis (serum creatinine 221 µmol/l). He had been treated with two pulse courses of cyclophosphamide (0.66 g/m^2) in April and June as well as daily prednisolone (60 mg).

On admission, laboratory examinations showed mild normochromic anemia (hemoglobin 9.4 g/dl), leukopenia (3,700/nl) and an elevated C-reactive protein (4.9 mg/dl). There was no eosinophilia in the peripheral blood. Moderate hyponatremia (124 mmol/l) and hypochloremia (90 mmol/l) were present. On the skin of the abdomen, back, and thighs a creeping urticarial eruption was noted (Figure 1 a). Esophago-gastro-duodenoscopy and colonoscopy showed extensive diffuse inflammation of the intestinal mucosa with profound petechia. In biopsy specimens from the esophagus, stomach, duodenum, and colon larvae of *Strongyloides stercoralis* were identified (Figure 1 b and c). Larvae of *S. stercoralis* were also found abundantly in bronchial washings and in the stool (Figure 2). No coinfection with other pathogens was observed in routine blood cultures and tracheal aspirate cultures. Chest X-rays showed patchy alveolar opacities (Figure 1 d).

The diagnosis of a *S. stercoralis* hyperinfection syndrome was made and combined therapy with broad-spectrum antibiotics (metronidazole, ciprofloxacin, vancomycin) and oral ivermectin (stromectol, 12 mg/d) was started. Stool microscopy was performed every 3 days.

The patient rapidly developed diffuse pneumonitis, and mechanical ventilation became necessary. After 3 days of ivermectin administration via a nasogastric tube, therapy was switched to a subcutaneous preparation of ivermectin, licensed for veterinary use, as an attempt of a life-saving measure (Ivomec, Merial GmbH, Germany; 0.6 ml of 10 mg/ml in each arm for 7 days (170 µg/kg/d) – total s.c. dose of 84 mg) following informed consent by the relatives. After 5 days of mechanical ventilation, respiration stabilized and the chest X-rays showed decreasing infiltrates. Extubation was performed on day 6 and intermittent noninvasive mechanical ventilation was continued. Because of a rapid increase in γGT levels on day 5 (6-fold) antibiotics were discontinued for 2 days but γGT levels only decreased after discontinuation of ivermectin treatment. During the course of treatment, liver transaminases and alkaline phosphatase were only slightly elevated (with a maximum of less than three times of the upper normal). There was ongoing thrombocytopenia (90,000–50,000/µl), mild anemia (10 mg/dl) and no lymphocytosis or leukocytosis. The C-reactive protein varied between 2.8 mg/dl and 11.6 mg/dl. Although inflammatory parameters decreased further on day 10 after initiation of the therapy, the patient suddenly developed severe hypoxemia within a few hours and died from acute respiratory distress syndrome (ARDS).

H. P. Hauber, R. Birke, P. Zabel, C. Lange *(corresponding author)*
Medical Clinic, Research Center Borstel, Parkallee 35, 23845 Borstel, Germany; Phone: (+49/4537) 188-332, Fax: -313, e-mail: clange@fz-borstel.de
J. Galle, E. Vollmer
Clinical and Experimental Pathology, Research Center Borstel, Borstel, Germany
P. L. Chiodini
Hospital for Tropical Diseases and London School of Hygiene and Tropical Medicine, London, UK
J. Rupp
Dept. of Microbiology, University Hospital Luebeck, Germany

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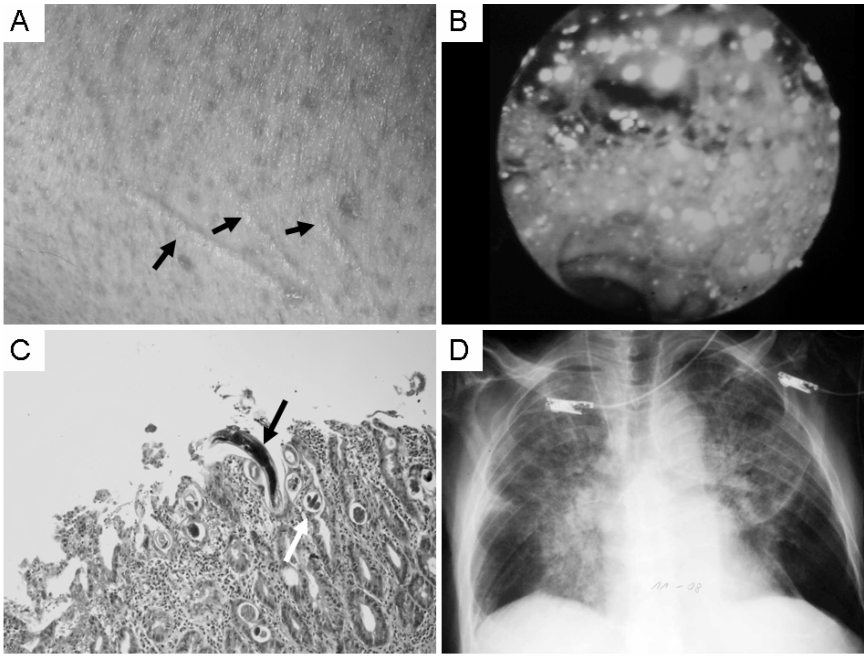

Figure 1. *Strongyloides* hyperinfection syndrome affects different organ systems. Pruri-tic linear wheal-like tracks (larva currens, indicated by arrows) are typical dermatologic manifestations **(A)**. Endoscopy shows hem-orrhagic inflammation of the duodenum **(B)**. Histology of duodenal biopsy specimens shows diffuse mucosal inflammation with ulceration, necrosis, and blood. An adult female worm (black arrow) and larvae (white arrow) of *S. stercoralis* can also be observed **(C)**. Bilateral interstitial infiltrates can be observed on chest X-rays **(D)**.

No larvae or adult worms were found in stool specimens or bronchial washings and no other infection was identified at the time of death. Autopsy was performed and confirmed the diagnosis of ARDS as the cause of death. Acute pulmonary embolization was ruled out as the cause of death. On autopsy the gastrointestinal tract (GIT), lungs, the skin and all other organs observed showed no signs of ongoing *Strongyloides* infection.

Discussion

S. stercoralis is an intestinal nematode that is widely endemic in Africa, Asia, Southeast Asia, and in Central and South America [1, 3–4]. It affects up to 100 million people [1, 2]. Infections are rare in the western European population. Humans become infected via penetration of the skin by filariform larvae present in damp soil. These larvae undergo migration after penetrating the human skin and enter the venous bloodstream. When they reach the lungs, they penetrate the alveoli, migrate through the bronchi to the pharynx where they are swallowed and travel down the esophagus and stomach to the small intestine. In the upper small bowel, larvae develop into adult female worms which produce rhabditiform larvae by parthenogenesis. Some of these larvae transform into filariform larvae, while still in the gut and penetrate the intestinal mucosa to reenter the intestinal-pulmonary-intestinal phase of the life cycle. As a result of this reinfection and in contrast to all other helminth infections, persistence of *S. stercoralis* infection in the human host can be lifelong. The worm seldom causes disease in healthy individuals [5], but in immunocompromised patients a hyperinfection syndrome can develop with a large number of filariform larvae entering the intestinal-pulmonary-intestinal cycle. Clinically the hyperinfection syndrome presents with diarrhea or ileus, gastrointestinal hemorrhage, bacteremia, pneumonia and/or meningitis [6, 7]. Mortality is up to 80% [8]. The most prominent risk factors for the development of the hyperinfection syndrome are glucocorticoid therapy, malnutrition, alcoholism [6] and underlying human T-cell lymphotrophic virus type 1 (HTLV1) infection.

Ivermectin or thiabendazole are the drugs of choice to treat *S. stercoralis* hyperinfection syndrome [6]. Ivermectin is much better tolerated and has been used successfully in cases that did not respond adequately to thiabendazole [9,10]. Parasitological cure was obtained in 24 of 29 patients (83%) treated with ivermectin in uncomplicated strongyloidiasis and was also achieved in seven out of seven patients with HIV-1 infection and a *S. stercoralis* hyperinfection syndrome [11, 12]. Both drugs are given orally but diffuse hemorrhagic inflammation of the intestinal tract can complicate intestinal absorption of these drugs.

At present no parenteral application of ivermectin is licensed for use in humans. However, subcutaneous application of a veterinary application of parenteral ivermectin was shown to be effective in a previous case [13]. In the present case, stool examinations and bronchial washings, as well as post-mortem findings, showed that off label use of a subcutaneous formulation of ivermectin given over 7 days was effective in clearing the infection.

Adverse effects of ivermectin have rarely been reported. Most often neurologic or unspecific symptoms like headache, nausea, dizziness, and rash are observed [14]. In our case we found a strong increase in γGT levels (6-fold) after 7 days of treatment with subcutaneous ivermectin that normalized after discontinuation of the therapy. In a previous study that was performed to investigate the safety and pharmacokinetics of escalating high doses of ivermectin, only one subject out of 51 (1.96%) developed

increased γGT levels (4-fold) which remained mildly elevated after discontinuation of therapy [14]. However, in that study ivermectin was given to healthy volunteers [14]. Pharmacokinetic studies with oral ivermectin showed that it was substantially better absorbed with a high fat meal [14]. In the previous report of subcutaneous application of ivermectin, no adverse effects were reported in a patient who received a total of fifteen 12 mg doses subcutaneously over a 22 day period ([13] and *P.L. Chiodini* personal communication 2005). In a study of ivermectin for spasticity in spinal-cord injury, *Costa* and *Diazgranados* [15] gave subcutaneous ivermectin at weekly or biweekly intervals, with doses up to 1.6 mg/kg. Ivermectin has also been given in daily doses of 200 µg/kg/d over 7 days in a rectal formulation. No clinical adverse effects were noted in any of the patients [16]. Nevertheless, although the doses of s.c. ivermectin used in this case did not exceed the dosages that have been used without complications previously, ivermectin-related toxicity can not be ruled out in this case and more data are needed on the pharmacokinetics of parenteral dosing with ivermectin.

Infection with *S. stercoralis* is endemic in the Americas but not in northern Europe. Infection rates of 1 to 7% in southern Poland and of 7.1% in Romania have been documented [17, 18]. Other surveys have shown prevalences ranging from 0.5% to 27.5% in British, Australian, American, and Canadian veterans who were prisoners of war in endemic areas in World War Two [19–23]. A seroprevalence between 11.8% and 76.6% was reported for Southeast Asian refugees arriving in Canada [24]. These data demonstrate that infection with *S. stercoralis* and hyperinfection syndrome can occur in regions that are traditionally low prevalence areas because of immigration or travel.

It is noteworthy that the patient in this report had moved away from Paraguay, an area endemic for *S. stercoralis*, 64 years prior to the development of the hyperinfection syndrome. He had not traveled to areas endemic for *S. stercoralis* since. Providing that the patient had been infected in his youth, this is the longest documented period of human *Strongyloides* infection to our knowledge.

In the *S. stercoralis* hyperinfection syndrome, pulmonary symptoms include cough, dyspnea, and wheezing. Filariform or rhabditiform larvae can be found in sputum, bronchoalveolar lavage fluid, and in lung biopsies [25–27]. Chest X-rays most frequently show bilateral or focal interstitial infiltrates [28, 29]. Lung abscesses, pleural effusion, nodular patterns mimicking miliary tuberculosis as well as normal chest radiographs have been described [30–32]. Alveolar hemorrhage [33, 34] or petechial hemorrhages with hyperemia of the bronchial, tracheal, and laryngeal mucosa have been reported [26, 33]. The lung can be affected directly by the parasite or secondarily by enteric bacteria (particularly gram-negative bacilli) that are translocated on the surface of the migrating worms [35–37]. Bacterial causes of meningitis, sepsis, and respiratory insufficiency are thus not uncommon. Therefore broad-spectrum antibiotic therapy in addition to antiparasitic treatment should be initiated as soon as possible once a *S. stercoralis* hyperinfection syndrome is suspected. *S. stercoralis* hyperinfection syndrome can lead to extensive damage of the lung parenchyma. ARDS is frequently observed in *S. stercoralis* hyperinfection syndrome and has also been described following the eradication of the parasite, as in the case presented here [38]. The underlying mechanisms are not well understood and need to be studied more carefully.

Several healthcare workers in our hospital had close contact with the patient without special infection control measures before the diagnosis of a *Strongyloides* hyperinfection syndrome was made. Because filariform larvae of *S. stercoralis* can penetrate the skin, all healthcare personnel who had had close contact with the patient were tested for *S. stercoralis* using ELISA (EIT, Fa DRG, Marburg, Germany). ELISA detects serum IgG against a crude extract of the filariform larvae of *S. stercoralis* [36]. Sensitivity and specificity of the test have been reported to be 88% to 95% and 29% to 99%, respectively. Positive and negative predictive values were calculated to be 30% to 97% and 95%, respectively [38–40]. Out of 48 tested persons in our institution only one had a reactive test (2.08%) 2 months following contact with the patient. This subject had a history of frequent travel to South America and Southeast Asia, so the source of infection in his case is unclear. The person was treated with ivermectin for 2 days (15 mg/d). Our findings agree with previously published data [41] showing that the risk of percutaneous infection with *S. stercoralis* from direct contact with human secretions is low.

In conclusion, we report the successful eradication of *S. stercoralis* in a patient with a hyperinfection syndrome by treatment with parenteral ivermectin. However, the patient subsequently died of ARDS. Despite close contact of healthcare workers with body secretions from the patient and a delay in the implementation of infection control measures, no nosocomial infection with *S. stercoralis* could be confirmed.

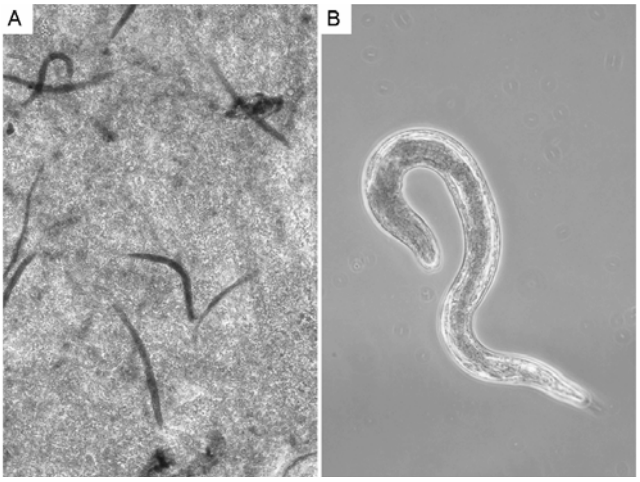

Figure 2. *S. stercoralis* larvae were found in stool specimens (A) and in bronchial washings (B) of the patient.

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