Rare disease

Hyperinfection with *Strongyloides stercoralis*

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Summary

Strongyloidiasis is caused by *Strongyloides stercoralis*, which commonly produces gastrointestinal problems. If immune systems are compromised, the nematode larvae may spread and produce *Strongyloides* hyperinfection. Diagnosis of strongyloidiasis is based on the observation of larvae in coproparasitological studies. We present a case of a 49-year-old man, VIH, who developed *Strongyloides* hyperinfection, diagnosed postmortem. Our patient reached the dissemination stage, which resulted in severe damage to the stomach and intestine, perforation of the intestinal wall, as well as sepsis due to the dissemination of bacteria. The diagnosis is difficult because of the low larvae excretion in stools. It is usually performed by the microscopic examination of fresh and fixed enriched stool samples. Serology was reported to be useful for screening and follow-up after treatment. This case reaffirms that HIV immunosuppression favours the dissemination of *S stercoralis* larvae. Thus, a search for intestinal parasites should be considered in similar cases.

BACKGROUND

Strongyloidiasis is caused by the nematode *S stercoralis*, which commonly produces gastrointestinal problems and occasionally pulmonary problems due to autoinfection. If immune systems are compromised, the nematode larvae may spread and produce *Strongyloides* hyperinfection, with potentially high mortality. After migration, female *S stercoralis* parasites penetrate the wall of the small intestine in human hosts and deposit their eggs in the submucosa. The eggs develop rapidly and release larvae into the intestinal mucosa.¹ Larval migration produces an intense pulmonary inflammatory response and the formation of granulomas, which can lead to petechial haemorrhages, diffuse pneumonitis, multiple areas of pneumonic consolidation, sputum, pleural effusion and other symptoms. In the intestine, inflammation occurs primarily due to infiltration by eosinophils and the mucosa becomes dysfunctional with mucosal secretion, haemorrhagic foci, congestion and the development of oedema in the intestinal walls. Diagnosis of strongyloidiasis is based on the observation of larvae in coproparasitological studies. However, the identification of nematodes in biological fluids and histological studies has increased in recent years because of an increasing number of patients with compromised immune systems who develop *Strongyloides* hyperinfection.²

CASE PRESENTATION

The patient was a 49-year-old man born in Mexico City, who initiated his sexual life at the age of 17 as a homosexual and had been diagnosed with HIV 5 years prior to this study, but had not received treatment, because he decided not to receive it.

His current symptoms started two days before he was hospitalised with intense epigastric pain accompanied by nausea and gastrobiliary vomiting, with asthenia and

adynamia, there were no respiratory symptoms. A few hours before hospitalisation, he experienced an incident of haematemesis. He was admitted as an emergency with a diagnosis of bleeding in the upper digestive tube, which was probably caused by a peptic ulcer. Upon admission, the patient had the following vital signs: blood pressure=110/70 mm Hg, heart rate=93 beats/min, respiration rate=18 breaths/min and temperature=36°C. A physical examination showed that the patient was alert, very pale, dehydrated, with loose white patches in the oral cavity and he experienced pain during medium palpation of the epigastrium, although no abnormal growths or visceromegaly were detected.

Intravenous fluids were administered and endoscopy was performed, which detected a haematic lake containing a giant clot, resulting in the procedure being stopped and resumed the next day. The results were as follows: normal pharynx, hypopharynx and oesophagus; stomach containing undigested food; normal body and antrum; central pylorus permanently open, permitting the passage of the endoscope; denuded and sphacelated mucosa in the duodenum from the bulb to the second part which was covered with fibrin; subepithelial haemorrhage and isolated erosions measuring >5 mm, predominantly in the distal region of the second duodenal part; and friable mucosa in the second and third parts, with areas of fibrin that covered the entire circumference. The endoscopic diagnosis was a giant intestinal ulcer, which was probably caused by cytomegalovirus (CMV) (figure 1).

The Infectology Service was consulted and treatment started with fluconazole, trimethoprim-sulfamethoxazole and ganciclovir. During the second consultation, 2 days after the previous consultation, with the Infectology Service, the patient was alert, cooperative and very pale, with severe dehydration, tachycardia and orthostatic

Figure 1 Endoscopic duodenal mucosa with oedematous and stiff bile plaque attached, pale and fine haemorrhagic points, with some superficial erosions.

hypotension. There were three episodes of haematemesis (750 ml in total) and meleena. The patient was moved to the intensive care unit (ICU) with a diagnosis of stage C3 AIDS (viral load 60 000 copies/ml, CD4 count 30 cells/ μ l), bleeding of the upper digestive tract, giant intestinal ulcer due to a probable CMV infection and hypovolemic shock. His vital signs at this time were as follows: blood pressure=80/40 mm Hg, heart rate=127 beats/min, respiration rate=26 breaths/min, temperature=35°C. Resuscitation was initiated with liquids and blood products, including transfusion of globular packages and platelets. There was a new haemorrhage of approximately 1200 ml and the application of aminocaproic acid was initiated, while an emergency endoscopy for sclerotherapy was also ordered. The patient continued to have bleeding incidents with high consumption of blood derivatives, a non-productive cough and rapid respiratory deterioration that required the use of a ventilator. Treatment for sepsis was initiated with imipenem/cilastatin. The laboratory results indicated a high HIV viral load but CMV was negative.

An exploratory laparotomy was performed because of continued haemodynamic deterioration, which detected

free intestinal contents in the abdominal cavity, multiple ulcers in the duodenum and necrosis of the second part of the duodenum reaching up to the first part of the ileum. Thus, 90 cm of the intestine was excised and a stoma was created, while the specimen was sent for histopathological analysis.

The patient's condition deteriorated in the ICU, with indications of a sepsis that was resistant to treatment and he died a few hours later.

The Pathology Service macroscopic examination of the excised specimen found the following: a portion of jejunum measuring 25 cm having a rough and frayed proximal edge with opaque serosa, which were rough with fibrinopurulent effusions; and red-coloured mucosa with multiple ulcers, raised borders and a haemorrhagic background (the largest measured 1×1 cm) near the border perforations of the wall (figures 2 and 3); a 19 cm portion of the duodenum having a red wine-coloured serous surface with a necrotic appearance and badly defined borders; and a portion of the pancreas measuring 2×2 cm (figure 4) lacking macroscopic alterations on its surface; mucosa which was hyperaemic when cut and multiple ulcers, some of which were confluent.

A microscopic study found eggs and larvae that corresponded morphologically to *S. stercoralis* at the back of the foveolae, which were surrounded by a dense inflammatory infiltration containing lymphocytes, plasma and histiocytes (figures 5–7). The bottom of the ulcer was haemorrhagic with an abundance of granular tissue, while the peritoneum showed inflammation with polymorphous nuclear leucocytes and bands of fibrin with haemorrhaging. A peripancreatic lymphatic ganglion lacked lymphoid follicles, while the marginal sinus and sinusoids contained leucocytes and histiocytes with emperipolesis and a few giant cells of the foreign body type. The pancreas was unaltered. The final diagnosis of the pathology was strongyloidiasis hyperinfection and lymphadenopathy associated with AIDS.

DISCUSSION

In cases like the one presented here, strongyloidiasis passes through five stages in the human host. In the first stage, an infection occurs when the infecting larvae

Figure 2 Portion of duodenum and jejunum with necrosis, perforation and multiple ulcers.

Figure 3 Ulcers in the jejunum.

penetrate the skin or mucosa. The second stage, migration, begins after the larvae enter the host and move from the site of penetration via the lymphatic or blood vessels to the lungs, before passing from the capillaries to the alveoli, ascending by the bronchial tree to the oesophagus and descending to the small intestine. During the third stage of maturation, they develop into female adults, which penetrate and lodge in the intestinal wall, where the parasite reproduces by parthenogenesis and releases eggs that hatch to produce larvae in an autoinfection cycle, which then migrate from the intestine to the liver, lungs and the intestine again. If the patient is immunodepressed, these cycles of autoinfection are intensified and the number of parasites increases greatly, which leads to hyperinfection. The larvae are disseminated to various systems, such as the nervous system, respiratory system and digestive system, during periods of migration in stage five, which leads to dissemination.^{4 5} Our patient had reached the dissemination stage, which resulted in severe damage to the stomach and intestine, bleeding ulcerous lesions and perforation of the intestinal wall, as well as sepsis due to the dissemination of bacteria from the intestine after larval migration.

In contrast to immunodeficient individuals with HIV, *Strongyloides* hyperinfection is rare in immunocompetent patients. According to the published data, mortality varies from 15% to 87%^{6 7} of which 27–89%⁸ of cases generally result from septicaemic infections caused by Gram-negative bacteria, as was the case with our patient.

Figure 4 Necrotic duodenum, there is a small portion of the pancreas.

Figure 5 Court of jejunum, we observe bleeding and acute inflammation around the parasite.

The normal immune response begins after the migration of filariform larvae, with the integration of antigens and antigen-presenting cells that communicate with T CD4 lymphocyte effector mechanisms to stimulate Th1 and Th2 cells. The latter release interleukins and activate mast cells, B lymphocytes and eosinophils, while immunoglobulin E is produced. The eosinophils migrate to tissues attacked by the parasites, particularly the intestinal wall. There are various immune system cells which are also stimulated, the stimulation results in a strong Th1 response and the intense production of IgG4, with reduced production of IgE.^{9 10} This immune response is severely diminished in patients with a compromised immune system, which is particularly evident in the minimal presence of eosinophils in the intestine and other tissues.⁹ In immunocompetent patients most chronic *Strongyloides* infections are asymptomatic and the only laboratory finding may be eosinophilia.¹⁰ In the patient described in this study, inflammatory response zones developed in the

Figure 6 Court of jejunum, inflammatory response with histocytes and polymorphonuclear leucocytes.

Figure 7 Court of jejunum shows dense infiltration of polymorphonuclear leucocytes surrounding the parasite.

walls of the small intestine, as indicated by the presence of histiocytes and polymorphonuclear leucocytes, whereas there were no eosinophils, which is a symptom when strongyloidiasis occurs in HIV patients (figures 5–7). It should be noted that the diagnosis was not made in the living patient, but instead it was based on a histopathological study of the resected intestine. The diagnosis based on the endoscopic study was a CMV infection (figure 1), which led to a deviation in the diagnostic pathway. This highlights the difficulties of diagnosing *Strongyloides* hyperinfections.^{11 12}

Other forms of compromised immune system that may favour the dissemination of *S. stercoralis* include multiple myeloma, allogeneic stem cell transplantation, Crohn's disease, myasthenia gravis, ANCA+ crescentic glomerulonephritis, HTLV-1, malnutrition, lymphoma, kidney transplants, chronic alcoholism and the use of steroids, rituximab and interferon.^{9 13–22}

The diagnosis was difficult because of the low larvae excretion in stools. It is usually performed by the microscopic examination of fresh and fixed enriched stool samples. The agar plate culture has been reported as more sensitive than the fresh stool observation and the Ritchie's methods. Studies reported the highest sensitivity for the agar plate culture method (96%). Serology was reported to be useful for screening and follow-up after treatment, because enzyme immunoassay was used in many laboratories, out of endemic areas. Loutfy and others had reported 94.6% enzyme immunoassay sensitivity, Van Doorn reported for enzyme immunoassay a specificity ranging from 95% to 97.7% and a sensitivity of 83–93% depending on the test used.^{10 12} Santos *et al*²³ reported that eosinophilia was not a common finding in their study, only one of eight patients with *S. stercoralis* infection had eosinophilia.

The most common endoscopic findings reported in few papers are mucosal oedema, erythema, friability, white villi, erosion and pseudopolyps. In *S. stercoralis* infection, presence of protein-losing enteropathy was also observed. The most common histopathological findings showed oedema and infiltration of the lamina propria by

lymphocytes and plasmocytes, shortened or absent villus, cryptitis and crypt hyperplasia, epithelial layer infiltration by numerous intraepithelial lymphocytes and antigen-presenting cells and the presence of lymphagectasia,²³ as reported in this case.

Some papers reported that endoscopic examination was not more effective than the stool parasitological detection of pathogens, except in cases of cytomegalovirus, which favours the idea of requesting a stool sample examination before performing an endoscopy in patients with abdominal complaints.²³

In the present case, the advanced damage and complications of necrosis, intestinal perforations and bacterial sepsis made it very difficult for the patient to respond to specific antiparasitic treatments, such as ivermectin, albendazole or tiabendazole. The patient was managed using antimicrobial treatments that were adequate for a bacterial infection, while abdominal surgery with intestinal resection was performed too late.

This case reconfirms that HIV immunosuppression favours the dissemination of *S. stercoralis* larvae. Thus, a search for intestinal protozoan and helminthic parasites should be considered in similar cases to ensure timely antiparasitic treatments and avoid the serious complications described here.

Learning points

- This case reconfirms that in HIV patients a search for intestinal protozoan and helminthic parasites should be considered.
- In any immunosuppressed patient with abdominal symptoms studies should be conducted to rule out parasitic infections.
- No need for invasive studies of first intention to make the diagnosis of strongyloidiasis.

Competing interests None.

Patient consent Obtained.

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