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CASE REPORT

PERIUMBILICAL PURPURIC RASH AS A CLUE TO THE DIAGNOSIS OF STRONGYLOIDIASIS AND HTLV-1 INFECTION

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ABSTRACT

Strongyloidiasis is a parasitic disease caused by the nematode *Strongyloides stercoralis,* widely distributed in Brazil. In general, it manifests with nonspecific gastrointestinal symptoms. However, in severe cases, pulmonary, neurological and systemic manifestations may occur, culminating in high mortality rates. Exceptionally, there may be a single-appearing periumbilical purpuric eruption. The prognosis is related to the rapid diagnosis and to beginning of the therapy. The case of an elderly man, former alcoholic, with chronic abdominal pain, fever and unexplained weight loss, in addition to periumbilical purpura is reported on this study. The manifestation motivated a specific investigation in which resulted in the diagnosis of strongyloidiasis and infection by human T-lymphotropic virus 1 (HTLV-1).

KEY WORDS: Strongyloidiasis; *Strongyloides stercoralis*; HTLV-1; Purpura

INTRODUCTION

Strongyloidiasis is considered a neglected tropical disease, it is caused by the parasite *Strongyloides stercoralis*, a helminth that can be found in the soil, and which it has humans as its main reservoir (Guerreiro et al., 2018; Krasnovska et al., 2022). Its distribution is global, but the nematode is known to impact, in particular, tropical and subtropical countries, including Brazil, Colombia and Sub-Saharan Africa, these geographical regions is known to be hyperendemic for *S. stercoralis* (Barreto et al., 2022; Krasnovska et al., 2022). The disease is often asymptomatic, but some individuals may have a severe clinical condition (Fernandez et al., 2016; Barreto et al., 2022). These severe forms generally affect immunocompromised patients, such as those infected

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with the human T-lymphotropic virus 1 (HTLV-1) (Fernandez et al., 2016; Guerreiro et al., 2018). The dermatological manifestations may be peculiar providing an important clue for the diagnosis even though rare (Fernandez et al., 2016).

A 70-year-old male patient case was reported. He underwent trough an abdominal pain and wasting syndrome investigation, he had a typical periumbilical purpuric eruption, which had allowed the diagnosis of strongyloidiasis and HTLV-1 infection.

CASE REPORT

A 70-year-old man living on the coast from the Espírito Santo State, in Brazil, was hospitalized by the general surgery team from the University Hospital, with reports of abdominal pain in the mesogastrium, in which was more intense after meals, and that had started nine months before his hospitalization, asthenia, adynamia, inappetence and 20 kilograms loss of weight in the last two months prior the hospital admission. He reported intermittent fever for 15 days. The patient denied use of any medication or having any comorbidities, except for previous alcoholism, with consumption of one liter of distillate per day, between 10 and 68 years of age. During the physical examination, there was pain on deep palpation in the epigastrium, mesogastrium and right hypochondrium, with no signs of peritoneal irritation, in addition to purpuric, asymptomatic skin lesions which were limited to the abdomen and proximal region of the thighs (Figure).

The laboratory results demonstrated normochromic/ normocytic anemia and eosinophilia. Computed tomography of the abdomen showed dilatation in the intrahepatic and in the common bile ducts, with an abrupt periampullary end, and the dimensions of the portal vein increased, as well as ectasia and tortuosity in some mesenteric venous branches, of undetermined origin. Under the hypotheses of Vater's ampullary or pancreas tumor, the assistant team opted to continue the investigation. Cholangioresonance revealed thickening in the distal common bile duct, close to the duodenal papilla. In the upper digestive endoscopy (UGE), there was erosive esophagitis, gastric stasis and an ulcero-infiltrative lesion with a macroscopic aspect suggestive of neoplasia in the second duodenal portion, where biopsy material was collected.

Due to the persistence of the fever, eosinophilia and anemia, evaluations were requested by the Infectiology and the Internal Medicine teams. Considering the peculiar aspect of skin lesions there was a clinical suspicion of strongyloidiasis. The examination for eggs and parasites (O&P) in the feces showed larvae of *S. stercoralis*, and histopathological analysis of duodenal ulcer revealed some fibrinonecrotic leukocyte material with abundant larvae suggestive of *S. stercoralis*, as well as foci of ulceration

and abundant intermingled eosinophils, without evidence of neoplasia. An incisional skin biopsy was also performed, whose anatomopathology showed perivascular and periadnexal dermatitis with eosinophilia, without vasculitis. During the screening for possible causes of immunosuppression, serology for HTLV-1 was positive, later confirmed by the Western Blot assay. The other serologies, laboratory tests, and chest tomography showed no abnormalities.

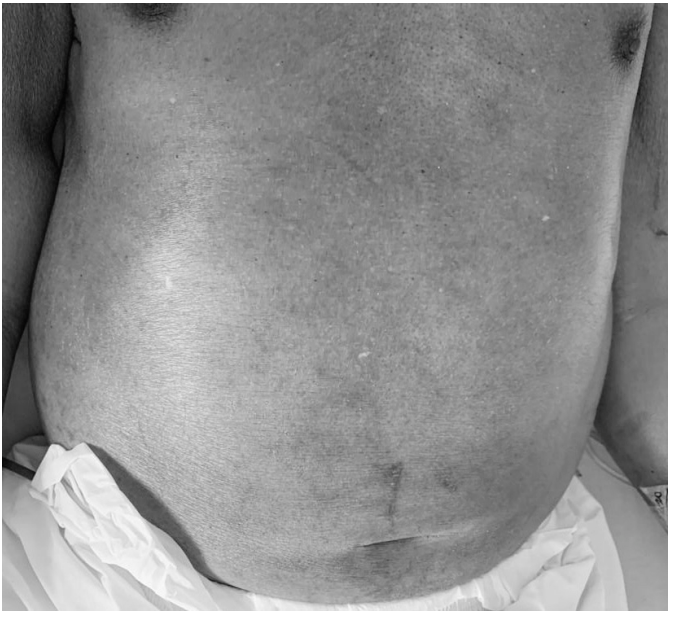

Figure. During physical examination, the patient had an asymptomatic purpuric rash on the abdomen and proximal region of the thighs.

The patient underwent treatment with ivermectin 200mcg/kg/day and progressed with gradual improvement of the clinical and dermatological conditions as well as laboratorial findings, including resolution of eosinophilia and negative control stool O&P's. His ex-wife underwent screening for HTLV-1, which was negative. The patient had no children.

Throughout the three years of follow-up, the patient was included in the outpatient programs for the prevention of alcoholism relapse and for quarterly or half-yearly appointments at the infectiology service. He remained without complaints and without notable changes in the following routine laboratory tests.

DISCUSSION

Strongyloidiasis affects about 370 million people worldwide (Barreto et al., 2022). Its etiological agent is the nematode *S. stercoralis*, found in the soil as filariform larvae (Krasnovska et al., 2022). That is how, after contact, the helminth penetrates the intact skin barrier and it migrates from the venous system to the lungs and intestine. In the intestinal tract, the parasite reproduces, and the eggs are either passed in the stool or hatch as rhabditoidea larvae (Fernandez et al., 2016; Guerreiro et al., 2018; Krasnovska et al., 2022). If these larvae mature into filariform inside the digestive tract, the host may be reinfected, determining a cycle of persistent autoinfection (Fernandez et al., 2016; Krasnovska et al., 2022). Patients are often asymptomatic, or have nonspecific gastrointestinal manifestations, sometimes accompanied by eosinophilia during routine examinations (Guerreiro et al., 2018; Krasnovska et al., 2022).

In some cases, however, *S. stercoralis* larvae are able to penetrate the intestinal mucosa and to reach the bloodstream, which results in the systemic spread of the nematode (Guerreiro et al., 2018). Severe cases are rare, and generally they may occur in immunocompromised patients, with high mortality rates (Fernandez et al., 2016; Guerreiro et al., 2018; Barreto et al., 2022; Krasnovska et al., 2022). The incidence is especially high in individuals undergoing immunosuppression with corticosteroids (Krasnovska et al., 2022; Talukder et al., 2022). There is a possibility that these drugs, in addition to affecting the immune response, have a direct action on *S. stercoralis* larvae, facilitating their development in the intestine. It has been demonstrated that the helminth has a nuclear receptor, DAF-12, which regulates its progression and it seems to have been stimulated by methylprednisolone in infected mice (Gordon et al., 2021).

Other causes of impaired immune response associated with worse conditions include other immunosuppressive medications, solid organ transplantation, HTLV-1 infection, cancers, leukemias, alcoholism and advanced age (Guerreiro et al., 2018; de Souza et al., 2020; Gordon et al., 2021; Barreto et al., 2022). In the reported case, the patient had a history of heavy drinking and he was later diagnosed as being infected by HTLV-1.

In 1984, the association between *S. stercoralis* and HTLV-1 was first described in the island of Okinawa, Japan (Nakada et al., 1984). Since then, studies have unequivocally demonstrated an increase in the rates of strongyloidiasis in those infected with the virus, with a prevalence at least 2.4 times higher in this population (Barreto et al., 2022). The distribution of HTLV-1, which is very prevalent in low- and middle-income countries, may be related to overlap, given the endemicity of *S. stercoralis* (Rosadas & Taylor, 2022). HTLV-1 belongs to the group of retroviruses and it is transmitted through breastfeeding, sexual intercourse, contaminated blood transfusion and

sharing contaminated needles. It infects approximately 5 to 10 million people worldwide, and it is considered endemic in Africa, Caribbean, Japan and South America (Springer et al., 2021). Brazil is the country with the highest absolute number of HTLV-1 cases, and co-infection rates vary between 12% and 14% (Barreto et al., 2022). Co-infection increases the risk of hyper-infection and dissemination of the nematode, as well as lethality (Gordon et al., 2021). The severity of the condition is markedly accentuated in HTLV-1 carriers in poverty, with precarious sanitary conditions (Barreto et al., 2022).

HTLV-1 infection also seems to increase the persistence of the parasite in the co-infected host (Rosadas & Taylor, 2022). Like patients undergoing corticosteroid therapy, individuals infected with HTLV-1 have a marked reduction in the production of interleukins (IL)-4 and IL-5, and an impaired T-helper type 2 (Th2) immune response, responsible for the control of several helminthiases, including strongyloidiasis (Martyn et al., 2019; Springer et al., 2021; Talukder et al., 2022). Co-infected patients also have reduced levels of eosinophils, total and parasite-specific immunoglobulin E (Martyn et al., 2019). HTLV-1 carriers have higher rates of therapeutic failure, described as the persistent excretion of the parasite despite treatment (Rosadas & Taylor, 2022). Thus, HTLV-1 appears to reduce the host's ability to activate an effective Th2 immune response, predisposing to *Strongyloides* hyper infection and relapsing after treatment (Martyn et al., 2019). On the other hand, strongyloidiasis has been shown to increase the likelihood of developing HTLV-1-related diseases such as adult T-cell leukemia/ lymphoma (ATL) (Barreto et al., 2022). Apparently, co-infection by *Strongyloides* induces polyclonal expansion of HTLV-1 infected cells through activation of the IL-2/ IL-2R system, which would increase this risk (Talukder et al., 2022). The reported patient has maintained his clinical follow-up, and for three years, he has remained without any evidence of disorders related to the viral infection. According to the Guide for Clinical Management of HTLV Infection (Brasil, 2021), diagnostic testing for HTLV-1/2 infection is imperative for HTLV-1/2 infected people´s family members and for their sexual partners. In the reported case, the patient's ex-wife was tested, with negative results.

Alcoholism is also related to increased susceptibility to severe infections by *S. stercoralis* (de Souza et al., 2020; Gordon et al., 2021). It is postulated that alterations in the hypothalamic-pituitary-adrenal axis of alcoholics increase the levels of endogenous steroids, facilitating parasite development and self-infection (de Souza et al., 2020). It is also possible that the reduction in gastrointestinal motility induced by alcohol, increases the permanence of the larvae in the intestine, thus being the period sufficient for them to undergo maturation (de Souza et al., 2020). In addition, factors such as malnutrition, loss of integrity of the intestinal mucosa and poor hygiene may be associated with an increased risk of severe disease in these patients (Gordon et al., 2021). Some studies also suggest that IgE downregulation

occurs in alcoholics, which could favor the spread of the nematode (de Souza et al., 2020). Although strongyloidiasis is more classically related to HTLV-1 infection rather than due to alcoholism, it was not possible to determine, in this reported case, which of the entities was more determinant for the condition. However, it is believed that the sum of these factors contributed to the parasitic disease.

Clinically, strongyloidiasis is usually asymptomatic or with nonspecific symptoms. Patients may experience intermittent diarrhea, constipation, nausea, and vomiting. In severe cases, pulmonary and neurological manifestations, ascites and bacteremia, among others, may occur (Fernandez et al., 2016; Guerreiro et al., 2018; Krolewiecki & Nutman, 2019; Krasnovska et al., 2022). In these cases, cutaneous involvement is rare and, when it occurs, it usually causes an indistinct rash, urticaria, or diffuse purpuric lesions (Fernandez et al., 2016; Guerreiro et al., 2018; Krasnovska et al., 2022). Larva currens, a serpiginous, migratory, and very itchy rash, has also been described, particularly in the perianal area (Fernandez et al., 2016; Reinehr et al., 2018). Exceptionally, as in the reported case, there may be a peculiar purpuric eruption on the abdomen. The lesions are non-palpable petechiae and purpura, with a "fingerprint" pattern, located in the periumbilical region and in the anterior portion of the thighs (Fernandez et al., 2016; Krasnovska et al., 2022). The manifestation is considered a sign of poor prognosis and it occurs due to the migration of *S. stercoralis* larvae from the vessel wall to the dermis, causing extravasation of red blood cells (Fernandez et al., 2016; Reinehr et al., 2018). Increased pressure in the portal vein determines retrograde flow of blood rich in parasites through the portosystemic shunt of the umbilical and periumbilical vessels (Fernandez et al., 2016). The possibility that chronic liver disease and positive pressure ventilation are associated with the onset of the condition has been described (Fernandez et al., 2016). Although rare, periumbilical purpuric eruption is a *sui generis* clinical presentation, and may represent a warning sign for the investigation of strongyloidiasis, as it was in this report.

Early diagnosis and prompt treatment are essential for a better prognosis (Guerreiro et al., 2018; Barreto et al., 2022). For the laboratory analysis, serology, parasitological examination of feces (stool O&P test), direct observation of the helminth and DNA research may be performed (Costa et al., 2021; Krasnovska et al., 2022). Faced with the clinical suspicion of a severe condition in immunosuppressed patients, negative serology is not considered as reliable, and the analyzes must be performed on two or more stool samples, in addition to molecular tests, when available (Costa et al., 2021). Finding eosinophilia is common, as in this report, and, in some cases, the histopathological examination of skin biopsy of periumbilical purpura may demonstrate parasites around the blood vessels, as well as signs absence of vasculitis (Krasnovska et al., 2022).

In this reported case, evolution of the disease it was allowed by the delay in diagnosis, considering that the patient remained, for about nine months, with a nonspecific, but worrisome, condition. The worsening of symptoms during the two months prior to his hospitalization, including the significant weight loss, may have led the team that admitted him, to the neoplasia suspected diagnosis. It is possible that an early clinical and infectious evaluation could facilitate a faster diagnosis. However, the low clinical suspicion of strongyloidiasis in a country with such a serious epidemiology is a valid concern.

The therapeutic scheme of choice is oral ivermectin, at a dose of 200mcg/kg/day (Fernandez et al., 2016; Guerreiro et al., 2018; Krasnovska et al., 2022). In cases where tolerability or absorption by the oral route is questionable, such as in patients with reduced level of consciousness, intestinal wall edema secondary to lymphatic vessel damage, or paralytic ileus, parenteral administration of the drug may be necessary (Guerreiro et al., 2018; Krasnovska et al., 2022). The use of veterinary preparation for this purpose has been reported (Guerreiro et al., 2018). Other treatment options include thiabendazole and albendazole (Fernandez et al., 2016; Guerreiro et al., 2018; Krasnovska et al., 2022). The mortality rate of severe strongyloidiasis ranges between 70% and 90% (Fernandez et al., 2016).

A case of strongyloidiasis in a former alcoholic patient who was later diagnosed as being infected by HTLV-1 was reported in this article, who´s his unique cutaneous manifestation motivated the investigation of the parasite. Considering the agent's endemicity in Brazil and the high lethality associated with severe cases of the disease, it is imperative that physicians are aware of the clinical presentation of the condition. It is also important to emphasize that patients diagnosed as having HTLV-1 infection must be clinically checked up regularly and their family members and sexual contacts must be tested, considering the transmission routes, in order to reduce the prevalence of viral infection.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest to disclose.

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