

Steroid therapy in COVID-19 as a triggering factor for *Strongyloides stercoralis* hyperinfection



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ABSTRACT

Strongyloides stercoralis is a nematode with worldwide geographical distribution, most frequent in tropical areas, especially prevalent in areas with poor sanitary conditions. The disease caused by *S. stercoralis* is known as strongyloidiasis and parasitism is usually asymptomatic. Infection by this nematode may, however, present severe symptoms in hosts with immune system deficiencies. The aim of this research is to investigate, through a review of current scientific literature, the treatment of severe COVID-19 with immunosuppressants as a triggering factor for *Strongyloides stercoralis* hyperinfection. There are scarce records in the scientific literature on *Strongyloides stercoralis* hyperinfection consequent to treatment of COVID-19 with steroid drugs, mainly in endemic areas. We believe that this complication may be highly underestimated. The finding of eosinophilia in the blood count of patients after receiving immunosuppressive therapy during COVID-19 corticoid treatment is an important marker for the possibility of *Strongyloides stercoralis* hyperinfection and should prompt laboratory studies for nematode screening, mainly serology and PCR.

Keywords: *Strongyloides stercoralis*, Hyperinfection, COVID-19.

1 INTRODUCTION

Strongyloides stercoralis is a nematode with worldwide geographical distribution, more frequent in tropical zones, especially prevalent in areas with poor sanitary conditions. The disease caused by *Strongyloides stercoralis* is known as strongyloidiasis, and was first described by the French physician Louis Normand in the year 1876, when he observed the nematode in the fecal material of



soldiers returning from Cochinchina, a region where Vietnam is present, naming the discovered parasite as *Anguillula stercoralis* (STREIT, 2021; RIVERA et al., 2021).

The main form of acquisition of parasitosis by *Strongyloides stercoralis* is by skin contact with soil contaminated with the infective form of the nematode. The filarioid larvae actively penetrate the skin, migrating through the bloodstream and lymphatic streams to the lungs, where they enter the alveolar sacs. On this occasion, it can cause itching and skin rash at the site of penetration. The filarioid larvae move through the respiratory tract, ascend the tracheobronchial tree toward the glottis, and are swallowed by the host. These larvae mature and transform into the adult form, parasitizing the intestinal mucosa, mainly duodenum and jejunum. Adult females produce eggs by parthenogenesis and the eggs hatch in the intestine, releasing rhabditiform larvae, which develop in the intestinal lumen. The rhabditiform larval form is eliminated in the feces, contaminating the soil, where the sexual reproduction of the nematode occurs and the evolution to the filarioid form in the environment. The duration of the cycle lasts from three to four weeks. In the parasitized individual, self-contamination may occur when rhabditiform larvae evolve into infective filarioid larvae within the human gastrointestinal tract. These larvae can penetrate the intestinal mucosa or perianal mucosa, reaching the blood or lymphatic networks and following the infective course to the lungs and again to the intestine. This peculiarity allows *Strongyloides stercoralis* to complete its evolutionary cycle without leaving the organism of its host, unlike other parasitic nematodes (PAGE et al., 2018; LUVIRA et al., 2022; CZERESNIA & WEISS, 2022; PRASAD & SAHU, 2022).

Strongyloides stercoralis parasitism is usually asymptomatic. Infection by this nematode can, however, present severe conditions in hosts with deficiencies in the immune system, such as in individuals undergoing immunosuppressive therapies, patients with AIDS, HTLV-1 infection, organ recipients in need of drug maintenance, cancer (mainly hematological), tuberculosis and in states of severe malnutrition. In these cases, a high number of parasites completes the reinfection cycle, causing hyperinfection or disseminated strongyloidiasis. This clinical condition causes high mortality rates, presenting signs and symptoms such as abdominal pain, nausea, vomiting, diarrhea, intestinal involvement with edema, obstructions, ulcerations and hemorrhage with the possibility of peritonitis and secondary bacterial infection; cough, dyspnea, hoarseness, pneumonia, hemoptysis, and respiratory failure. Thus, hyperinfection by *Strongyloides stercoralis* should be analyzed as a systemic disease, not just as an intestinal parasitosis, because it more broadly compromises the patient's health (AHMADPOUR et al., 2019; AMIN et al., 2019; LUVIRA et al., 2022; CZERESNIA & WEISS, 2022; PRASAD & SAHU, 2022).

Strongyloidiasis is particularly prevalent in underserved populations, with poor sanitary conditions, which allow the continuity of the cycles of infection and reinfection, whose access to health services for diagnosis and treatment are insufficient. It is estimated that there are about 370 million



people with strongyloidiasis in the world, with estimated prevalences between 10% and 40% of the population of tropical and subtropical countries (KROLEWIECKI & NUTMAN, 2019; BUONFRATE et al., 2020; LUVIRA et al., 2022), but in some regions such as Peru, Kenya, Namibia and Papua New Guinea prevalence rates may exceed 70% (CZERESNIA & WEISS, 2022). Strongyloidiasis is a highly neglected disease, and there is currently little knowledge about its actual incidence in many of the endemic areas (BUONFRATE et al., 2020; LUVIRA et al., 2022).

The COVID-19 pandemic has given rise to a number of challenges not only because of the virus, but because of the circumstances in which co-infections and latent diseases can become risk factors for patients' lives. The objective of this research is to investigate, through the review of the current scientific literature, the treatment of severe COVID-19 with immunosuppressants as a triggering factor of hyperinfection by *Strongyloides stercoralis*.

2 METHOD

The methodological design chosen for the research was that of narrative review. The reference material was obtained from the PubMed, SciELO and Google Scholar databases. The following descriptors were used as a search strategy, in various combinations: "SARS-CoV-2", "COVID-19"; "*Strongyloides*", "strongyloidiasis". The initial selection consisted of the compilation of clinical cases of *Strongyloides* hyperinfection resulting from the treatment of COVID-19 with immunosuppressants, with a time frame of publication between the year 2019 and the month of November 2022. After reading each article and case report, the pre-selected material was evaluated. Articles with incomplete data or whose diagnostic interpretation did not prove the association between treatment with immunosuppressants in COVID-19 and the development of *S. stercoralis* hyperinfection were excluded. The selected case reports were summarized in their most important clinical aspects for analysis purposes.

3 RESULT

Researchers Feria et al. (2022) reported two cases of reactivation of *Strongyloides stercoralis* in patients with COVID-19. A 44-year-old man from Bolivia who has lived in Spain for 17 years has been hospitalized with severe pneumonia from SARS-CoV-2. The patient received oxygen therapy and treatment with Dexamethasone for seven days. On the seventh day, generalized pruritus and the appearance of a skin lesion in the abdomen began, and eosinophilia was observed. Serology for *S. stercoralis* was positive for IgG and the treatment was performed with Ivermectin for two days, which resolved the skin condition. A 74-year-old Honduran woman who has lived in Spain for seven years was hospitalized with COVID-19 pneumonia. After 10 days of treatment with Dexamethasone, the patient presented with severe pruritus, predominantly in the upper extremities, and an erythematous



lesion in the periumbilical region. Serology for *S. stercoralis* was positive for IgG and treatment with Ivermectin for 10 days resulted in complete resolution of the clinical picture. After three months, the patients remained asymptomatic, but with positive IgG for *Strongyloides*.

One case of strongyloidiasis subsequent to COVID-19 was reported by Pintos-Pascual et al. (2021). The 70-year-old patient was hospitalized in Madrid, Spain, with a dry cough, fever, dyspnea and chest pain. The test was positive for SARS-CoV-2 and due to the degradation of respiratory functions, there was a need for therapy with methylprednisolone, tocilizumab and anakinra. Corticosteroid treatment lasted 30 days. One month after medical discharge, the individual had epigastric abdominal pain. The blood count revealed leukocytosis with eosinophilia. As the patient was Ecuadorian and a rural worker until 2008, there was clinical suspicion of strongyloidiasis. *Strongyloides* infection was confirmed by serological tests and coproscopies. The patient was treated with Albendazole for three days. After a few weeks with the persistence of symptoms, another coproscopy was ordered and *Strongyloides* larvae were again observed. Treatment with Ivermectin was initiated, which definitively resolved the parasitism by *Strongyloides*.

A 45-year-old Ecuadorian who had been living in Spain for twenty years was admitted with COVID-19 in respiratory failure to an emergency hospital in Madrid. Nuñez-Gómez et al (2021) describe that the patient required oxygen therapy and received Dexamethasone. The clinical history indicated that the individual had an episode of skin rash in 2018, with suspected allergy, without there being a determination of the cause. Serology for *Strongyloides* was positive on the seventh day of hospitalization and Ivermectin therapy was started on the eighth day. A few hours after the administration of Ivermectin, the appearance of diffuse macropapular skin rash with pruritus was observed. That same day, the examination of the feces revealed the presence of larvae of *S. stercoralis*. The authors point out that hyperinfection by *Strongyloides stercoralis* occurred in the context of corticosteroid use a few days after therapy with this type of drug, but emphasize the efficacy of Ivermectin, which resolved the parasitosis in 48 hours of treatment, which was continued for a total of 14 days.

Styemans et al. (2021) reported the clinical case of a 59-year-old man, a native of Ecuador and resident in Belgium for seven years, taken to the emergency department of a hospital in the European country with signs of severe COVID-19, confirmed through PCR testing. The patient was intubated and received drug treatment with Anakinra and Methylprednisolone for one month, with progressive improvement of viral pneumonia. At forty-nine days of hospitalization, the blood count showed eosinophilia, and the review of the patient's clinical history in previous hospitalizations revealed chronic eosinophilia. The result of serological tests for *S. stercoralis* was positive and the infestation was confirmed for the nematode by PCR of fecal sample. A single dose of Ivermectin was sufficient



to overcome the parasitosis, with the regression of eosinophilia, and after one week the patient was discharged from the hospital.

Marchese et al. (2021) reported on a 57-year-old woman in southeastern Italy who was hospitalized with typical symptoms of COVID-19. SARS-CoV-2 infection was confirmed by PCR. The patient had previously used small doses of Prednisone for the treatment of Still's Disease, The patient was treated with Hydroxychloroquine, Lopinavir/Ritonavir, Enoxaparin and Dexamethasone. On the fifth day of hospitalization, the dose of Dexamethasone was increased to 20 mg/day for six days. The clinical conditions gradually improved when on the twenty-fifth day of hospitalization the patient presented eosinophilia and reported abdominal pain and pruritus. Coproscopy revealed the presence of rhabditiform larvae of *S. stercoralis*, and IgG serology showed a titre of 1:640. Treatment with Ivermectin was initiated for four days, which resulted in the rapid decline of eosinophilia and resolution of symptoms. The patient reported, after diagnosis, that she had diffuse pruritus for the last ten years, treated with topical steroids that only partially resolved the symptoms.

A case of strongyloidiasis disseminated during treatment for COVID-19 in the United States of America was reported by Patel et al. (2021). A 72-year-old man from Nicaragua was hospitalized with dyspnea and the PCR test was positive for SARS-CoV-2 infection. The worsening of hypoxia led to hospitalization in the Intensive Care Unit, where the patient was intubated and treated with Dexamethasone and anticoagulants. The clinical picture deteriorated and tracheostomy was required. Subsequently, multidrug-resistant *Escherichia coli* pneumonia was detected, with the patient progressing to shock, being treated with vasopressors and high rates of steroids. Marked eosinophilia was observed and coproscopies revealed the presence of parasite eggs. On microscopic examination, the presence of rhabditiform larvae indicated infection by *S. stercoralis*, and the observation of bronchoalveolar lavage showed the presence of *Strongyloides larvae*. The patient was diagnosed with disseminated strongyloidiasis and treated with Ivermectin.

Alkaabba et al. (2022) described a case of strongyloidiasis after treatment of COVID-19 infection in a 76-year-old male patient hospitalized complaining of abdominal pain in the United States of America. The patient had been treated for COVID-19 two weeks earlier with the use of nasal cannula oxygen, Dexamethasone and Remdesivir for five days, as well as convalescent plasma therapy. During COVID-19, leukocytosis with eosinophilia was observed. Intestinal biopsy was performed to determine the etiology, the result of which indicated duodenitis with acute infection and necrosis, suggestive of parasitic infection. Coproscopy revealed the presence of larvae and eggs of *S. stercoralis*. The patient was treated with the antiulcer Sucralfate and two doses of Ivermectin, reporting improvement of symptoms in a few days and receiving medical discharge. The patient reported that he did not inhabit or visit areas endemic for *Strongyloides*.



Kim & Sivasubramanian. (2022) reported the case of a 63-year-old Cambodian woman admitted to a hospital in California, United States of America, with classic signs of COVID-19 and PCR-confirmed SARS-CoV-2 infection. The patient was treated with Dexamethasone, Remdesivir and Baricitinib. With the improvement in her general condition on the sixth day, she was transferred to the primary care ward. On the twenty-eighth day of hospitalization, there was worsening of the respiratory status, with fever and eosinophilia. Microscopic examination of the bronchoalveolar lavage revealed the presence of *Strongyloides* spp. larvae . Stool samples were negative for the nematode, but serology for IgG was positive, and it was decided to undergo Ivermectin therapy for 14 days. The subsequent culture of bronchoalveolar lavage was positive for *Escherichia coli*, the patient presented encephalopathy and progressed to death.

A case of strongyloidiasis after COVID-19 in a 68-year-old patient in the United States of America was presented by Lier et al. (2020). The patient, an Ecuadorian, was a rural worker in his country of origin. The individual was hospitalized with COVID-19, with structural damage to the lungs resulting from the worsening of the acute viral illness. For the treatment of the cytokine cascade, doses of methylprednisolone and tocilizumab were administered. In the first week of hospitalization, bronchoalveolar lavage culture was positive only for commensal bacteria of the respiratory tract. On the twelfth day, the blood culture was positive for *Streptococcus constellatus* and *Citrobacter freundii*, and the bronchoalveolar lavage culture was positive for *Staphylococcus aureus* and *Pseudomonas aeruginosa*, which guided antibiotic therapy with Ciprofloxacin, Cefazolin and Metronidazole, and the administration of Methylprednisolone was discontinued. On the nineteenth day, serpentine trails were noticed in the chocolate agar culture medium where material obtained from bronchoalveolar lavage was sown. Microscopic observation showed the presence of larvae of *Strongyloides stercoralis*, and on the twenty-first day of hospitalization eosinophilia was observed. The treatment of parasitosis was performed with the use of Ivermectin and Albendazole. Serology for *S. stercoralis* remained positive until the twenty-eighth day of hospitalization.

A case of strongyloidiasis triggered by steroid use in the treatment of COVID-19 in Oman was described by Busaidi et al. (2022). The researchers report that a 55-year-old patient, hospitalized in April 2020 for acute SARS-CoV-2 pneumonia, received treatment with Dexamethasone for five days during hospitalization and follow-up of corticosteroid use for five weeks in the convalescence period. The following month, the patient experienced nausea, lack of appetite and weight loss of 10 kg. The first clinical suspicion was of *Enterobius vermicularis* infestation, which was treated with a single dose of Albendazole. The symptoms persisted and the examinations performed in the following week revealed eosinophilia and a picture of cholestasis. Coproscopy showed the presence of *Strongyloides stercoralis* larvae and the individual received two doses of Albendazole and two doses of Ivermectin.



After one month, the complete remission of strongyloidiasis and the extinction of symptoms were verified.

Gautam et al. (2021) described the clinical case of a 53-year-old patient in India, hospitalized due to COVID-19, who required treatment with methylprednisolone for 5 days, receiving medical discharge after two weeks. A month and a half after recovering from COVID-19, he returned to the hospital with fever, diarrhea, and abdominal discomfort. Endoscopy revealed a hiatal hernia with duodenal ulcer. Blood culture was negative, while fecal occult blood test was positive. On microscopic examination of fresh feces, rhabditiform larvae of *Strongyloides stercoralis* were observed. The ulcer was treated with Pantoprazole, while the drug plan for parasitosis was based on the use of Ivermectin and Albendazole for two weeks. After this period, no larvae of *S. stercoralis* were detected in the feces.

A case of *Strongyloides* hyperinfection consequent to corticosteroid therapy in a patient with COVID-19 in Iran was presented by Babazadeh et al. (2022), The 70-year-old patient was seen with signs of severe COVID-19, receiving high doses of Dexamethasone for ten days. Three weeks after treatment for COVID-19, he presented to the hospital unit with chest discomfort, nausea and anorexia. Endoscopy demonstrated the presence of lesions in the duodenum. Histopathological examination showed the presence of numerous *S. stercoralis* eggs and eosinophilic infiltration in the mucosa. The patient was treated with Ivermectin for seven days and Albendazole for ten days. After this period, the symptoms disappeared.

4 DISCUSSION

The scientific literature is scarce regarding cases of reactivation of latent *Strongyloides stercoralis* infection as a consequence of the treatment of COVID-19 with immunosuppressive drugs. The signs and symptoms of hyperinfection are the same as those presented in cases of immunosuppression not linked to the context of COVID-19 and its treatment. The use of antiparasitics was effective and resolved the clinical picture in all cases where there were no additional complications to COVID-19. A recurrent factor in all cases described, expected for hyperinfection by *S. stercoralis*, is eosinophilia in these patients, in contrast to the eosinopenia present in COVID-19, in which the degree of decrease in circulating eosinophils serves as a predictive factor of the severity of acute viral disease. The diagnosis of *S. stercoralis* hyperinfection occurred between seven days and two months after corticosteroid therapy.

The phenomenon of hyperinfection by *Strongyloides stercoralis* is attributed to the loss of immune containment capacity that favors the rapid multiplication of the nematode (LUVIRA et al., 2022; CZERESNIA & WEISS, 2022; PRASAD & SAHU, 2022), or that the metabolites of steroids used in treatment can mimic ecdysteroids, substances involved in *Strongyloides* multiplication processes (GENTA, 1992; HERBERT et al., 2022). Hyperinfection in patients undergoing



immunosuppression has been known since before the COVID-19 pandemic, but the multiplication of the number of individuals requiring steroid therapy to contain the cytokine cascade in severe forms of COVID-19 amplifies the possibility of incidence of disseminated strongyloidiasis. The scarcity of scientific literature on the subject may indicate that hyperinfections resulting from the treatment of COVID-19 are highly underestimated. It may contribute to the lack of diagnosis of hyperinfection the similarity of some signs and symptoms in the post-COVID-19 period and in the long COVID syndrome, especially in more moderate cases. Among the coincident and most pointed symptoms for the post-COVID-19 or long-term illness period are fatigue, dyspnea, cough, fever, nausea, and digestive disorders (BANDA et al., 2020; LOPEZ-LEON et al., 2021; DESAI et al., 2022; BOGARIU & DUMITRASCO, 2022), in addition to erythema, skin rash and pruritus (CONFORTI et al., 2020; Dudani et al., 2022; MASSOD et al., 2022).

Most of the cases of *Strongyloides hyperinfection* as a consequence of the use of corticosteroids in the treatment of COVID-19 reported in the current scientific literature refer to patients living outside endemic areas. Even so, we emphasize that the possibility that hyperinfection is not diagnosed among migrants outside endemic areas is high, due to the lack of medical repertoire for health professionals unaccustomed to this parasitosis, and the non-routine performance of tests for the detection of *Strongyloides*. Byard (2019) states that the incidence and geographical area of occurrence of strongyloidiasis is increasing, especially due to the large number of migrants and refugees, with an increasing number of undiagnosed cases. Jenks et al. (2022) conducted a retrospective study of the medical history of migrant patients at a hospital in New York state, United States of America. They reported 68 migrants who had COVID-19 who also had eosinophilia and 29 who had a confirmed diagnosis for strongyloidiasis. Although the proportion of patients with these conditions was small (1.0% and 0.5%, respectively), the authors point out that the infestation by this nematode and the possibility of hyperinfection in the context of the application of steroids in the treatment of COVID-19 is underestimated due to the few serology tests for *Strongyloides* among the medical records examined. According to Asundi et al. (2019), the seroprevalence of strongyloidiasis among migrants in the world is 9 to 15-9%. This key population had a high risk of COVID-19 infection and mortality. Norberg et al. (2021) also point out that migrants from countries with a lower human development index – many of these countries endemic for *S. stercoralis* – are part of the subgroup most at risk for SARS-CoV-2 infection. In addition, vulnerabilities inherent to individuals whose migration occurs unofficially or outside of cross-border movement regulations, such as difficulties or fear of detention in accessing health services, are of particular concern in cases of hyperinfection after treatment of COVID-19, which can constitute a serious health risk to these individuals.



5 CONCLUSION

There is a paucity of records in the scientific literature on *Strongyloides stercoralis* hyperinfection consequent to the treatment of COVID-19 with steroid medications, especially in endemic areas. We believe that this complication can be highly underestimated, since it is in the same context of depletion of the immune system observed in other pathogenesis and clinical conditions known to trigger hyperinfection, notably the use of steroids. Steroid medications like Dexamethasone and Methylprednisolone are widely used in cytokine cascade containment therapy in severe COVID-19. In the context of a pandemic, with a high number of patients undergoing steroid therapy, an increased incidence of hyperinfection cases is expected in the population of individuals with chronic or asymptomatic strongyloidiasis.

The finding of eosinophilia in the blood count of patients at a time after immunosuppressive drug therapy during the treatment of COVID-19 is an important marker for the possibility of hyperinfection by *Strongyloides stercoralis* and should give rise to laboratory studies for the detection of the nematode, especially serology and PCR. We believe that the adoption of antiparasitics in COVID-19 treatment protocols when steroid use is necessary is an important measure in areas endemic for *S. stercoralis*, as well as in patients from these regions, to avoid triggering hyperinfection.



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