

Short Communication

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Strongyloidiasis – diagnostic and therapeutic dilemmas in hyperinfection patients: a case series

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Abstract

The helminth infection caused by *Strongyloides stercoralis* is widespread in tropical regions, but rare in European countries. Unfamiliarity with the disease and diagnostic obstacles could contribute to its lethal outcome. Frequent use of corticosteroids during the COVID-19 pandemic could increase its significance. The aim of this retrospective descriptive study was to explore disease patterns and discuss clinical dilemmas in patients with *S. stercoralis* hyperinfection treated at the University Hospital for Infectious Diseases ‘Dr. Fran Mihaljević’ in Zagreb, Croatia, between 2010 and 2021. Five out of 22 (22.7%) immunosuppressed patients treated due to strongyloidiasis developed hyperinfection. All patients were male, median 64 years; four were immunosuppressed by corticosteroids (although ileum resection could have been the trigger in one) and one by rituximab. The diagnosis was established after a median of 1.5 months of symptom duration, accidentally in all patients, by visualizing the parasite in the gastric/duodenal mucosa in four cases, and bronchial aspirate in one. All patients were cachectic, four out of five had severe hypoalbuminemia and all suffered secondary bacterial/fungal infection. Despite combined antibiotic, antifungal and antihelminthic therapy, three out of five of the patients died, after failing to clear living parasites from stool samples. We can conclude that significant delays in diagnosis and lack of clinical suspicion were observed among our patients with the most severe clinical presentations of strongyloidiasis. Although being beyond diagnostic recommendations for strongyloidiasis, an early upper gastrointestinal endoscopy with mucosal sample analysis could expedite diagnosis in severe, immunosuppressed patients. The persistence of viable parasites in the stool despite antihelminthic therapy should be further investigated.

Introduction

Helminth infection caused by *Strongyloides stercoralis* is common in tropical regions but rare in European countries. The European countries with the most reported autochthonous cases of human strongyloidiasis in a 42-year period ending in 2019 are Spain (565 cases), Italy (264 cases) and France (33 cases). Croatia can be added to this group, with 79 cases in an 11-year period ending in 2021 (Ottino *et al.*, 2020; Balen Topić *et al.*, 2021).

The unique ability of perpetuated autoinfection can lead to a lifelong, often asymptomatic or mildly symptomatic, *S. stercoralis* infection in immunocompetent individuals. In the state of immunosuppression, usually caused by corticosteroids, the process of autoinfection can massively escalate leading to *Strongyloides* hyperinfection syndrome (SHS) and/or disseminated strongyloidiasis (DS), with a mortality rate of 60–87% in treated individuals (Vasquez-Rios *et al.*, 2019). During massive penetration, filariform larvae carry bacterial and/or fungal members of the intestinal flora on their cuticula towards the lungs, circulation and in some cases to other organs; most patients with SHS/DS actually succumb to secondary bacterial infection. As clinical symptoms and routine laboratory results can be nonspecific, severe forms of SHS/DS can be easily overlooked. The low sensitivity of microscopic stool sample examination and decreased sensitivity of serology in immunocompromised patients can further compromise the diagnostic process (Requena-Méndez *et al.*, 2013).

Recently, due to increased immigration from endemic regions with pooled seroprevalence of strongyloidiasis of 12.2% among the immigrants to developed countries (Asundi *et al.*, 2019), as well as the frequent use of corticosteroids during the COVID-19 pandemic, the clinical significance of strongyloidiasis seems to be rising even in countries with basically very low disease prevalence.

As unfamiliarity with the disease and diagnostic obstacles could delay diagnosis and contribute to lethal outcomes, we describe a case series of five patients with SHS to explore disease clinical patterns and to discuss diagnostic and therapeutic dilemmas.

Materials and methods

The work is based on a retrospective descriptive study of patients with SHS/DS treated at the University Hospital for Infectious Diseases 'Dr. Fran Mihaljević' in Zagreb, Croatia, from 2010 to 2021. The diagnosis was obtained by visualizing the larval stage of parasites using light microscopy – initially in all patients from extraintestinal samples: Pathohistological diagnostics (PHD) of gastric mucosa (three patients), duodenal mucosa (two patients) and microscopy of bronchial aspirate (one patient). Subsequently, three stool samples in all patients were analysed for cysts and ova using merthiolate-iodine-formaldehyde concentrations (MIFC) and native examination of wet-mount preparations. The last three patients were serologically tested (patients 3 and 4: ELISA test #9450 *Strongyloides ratti*, Bordier, Switzerland; manufacturer's declared sensitivity: 90%, specificity: 96%; and patient 5: quantitative ELISA Σ96 Bioactiva Diagnostica, Germany; manufacturer's declared sensitivity: 89.47%, specificity: 94.12%).

Results and discussion

Among 22 immunocompromised patients treated due to strongyloidiasis, five (22.7%) developed SHS. All were autochthonous males at a median age of 64 years (37–81), residing in central continental Croatia, including four from rural areas, with no travel history. The basic demographic features and history of the patients are shown in [table 1](#).

The median symptom duration before diagnosis was 1.5 (0.5–3) months. Chronic haematologic patients predominated. All patients were anti-HIV and the latest SARS CoV-2 negative. Patients were not tested for HTLV-1. Clinical features of patients are shown in [table 2](#).

All patients were described as cachectic, had anorexia and nausea, and recorded a recent weight loss ranging from 5 to 30 kg. However, four out of five patients were severely hypoalbuminemic (serum albumin range: 13.3–27.7 g/l). Nonspecific gastrointestinal symptoms were present in four out of five of the patients, which progressed to ileus in two of them. All patients had secondary infections caused by faecal microbiota. All bacterial isolates were susceptible to routinely tested antibiotics, and all patients were treated with adequate antimicrobial therapy. Patients 3 and 5 were treated in the intensive care unit, and patient 5 was mechanically ventilated and dialysed. *E. coli* was isolated from his blood and cerebrospinal fluid (CSF), and CSF examination was consistent with bacterial meningitis. Although no eosinophils or parasite larvae were found in the CSF, disseminated strongyloidiasis in the central nervous system (CNS) was suspected. This patient with severe consciousness impairment (GCS 7) died of a massive bilateral ischaemic cerebrovascular accident after 20 days of antimicrobial and 14 days of combined antiparasitic treatment without clinical improvement.

In all patients, strongyloidiasis was diagnosed accidentally, by analysing the upper gastrointestinal biopsy sample or bronchial aspirate. The concentration method subsequently used for the detection of cysts and ova in three stool samples proved positive in four out of five patients. In three deceased patients, motile rhabditiform larvae were seen in the native wet-mount stool samples, even during antiparasitic treatment, which was not the case in the surviving patients. Their abundant presence was recorded during antihelminthic therapy in a stool sample from patient 5 (see supplementary video 1). Patients 3 and 5 were serologically positive for *S. stercoralis*. Peripheral blood eosinophilia was absent in two out of five patients,

both of whom died. Despite combined antibiotic, antifungal and antihelminthic therapy, three out of five (60%) patients died.

All of our patients confirmed contact with soil in their medical history – four older patients lived in rural areas where they engaged in gardening and the youngest urban patient was probably exposed to soil during playtime with his pet dog on the ground in suburban surroundings. Changes in agricultural activities and improvement in environmental and personal sanitary conditions have contributed to human strongyloidiasis becoming a very rare disease in the region. However, recently diagnosed primo-infections confirm current endemicity of this parasite in the soil in central continental Croatia (Balen Topić *et al.*, 2021). Therefore, immunosuppressed residents and foreign travellers to this region should be advised to take contact precaution measures while patients undergoing planned immunosuppression and organ donors from Croatia should be screened for strongyloidiasis.

The long symptom duration before diagnosis and the accidental finding of the parasite without previous clinical suspicion in our immunosuppressed patients suggest that clinicians are unfamiliar with the SHS/DS and that severe disease forms may be underdiagnosed. But could clinical suspicion even be raised early in a region with a very low incidence of symptomatic strongyloidiasis?

According to our results, although aggravating gastrointestinal symptoms predominated, they were not specific enough to raise an early clinical suspicion. It seems that recent significant inappetence, weight loss and consecutive hypoalbuminemia are the most common clinical signs in gradually accelerating strongyloidiasis, progressing to SHS and secondary infections caused by gut flora.

A significant diagnostic obstacle, especially important in most severe cases, could be the absence of the peripheral blood eosinophilia, recorded in two out of three of our deceased patients. Besides deflection of clinical suspicion from parasitosis, leading thereby indirectly to delay in diagnosis, many reports have shown that lack of eosinophilia presents an ominous sign in strongyloidiasis, as it reflects weak or deficient Th2 response. The pivotal role of eosinophil-mediated cytotoxicity against filariform larvae of *S. strongyloides* has been visualized *in vivo* in the sputum of patients with mantle cell lymphoma and SHS (Incanni *et al.*, 2010). The enzyme immunoassay detecting *S. stercoralis* serum antibodies with reported sensitivity of up to 95% in the general population should be used as a screening tool in immunosuppressed patients, too. However, the sensitivity of this diagnostic method in immunosuppressed patients with severe SHS/DS is unknown. As observed in one of the three of our tested patients, cases of most severe forms of strongyloidiasis in immunosuppressed patients with negative serology can be found in the literature (Rodriguez *et al.*, 2015; Lier *et al.*, 2020b). In immunosuppressed patients, the stool microscopic examination (including the Baermann test) can also reveal negative results (Rodriguez *et al.*, 2015). It seems that in immunosuppressed patients, even if there was an early suspicion, clinicians could be easily misguided by negative results of common laboratory results and screening tests.

In a setting of frequent corticosteroid use during the COVID-19 pandemic, the diagnostic circumstances may be further complicated, primarily by the SARS-CoV-2-mediated eosinopenia, which was found in 71.7% of COVID-19 patients with pneumonia (Xie *et al.*, 2021). A case of vanished chronic eosinophilia in a patient with chronic strongyloidiasis, during acute COVID-19, before introducing corticosteroid therapy has been reported (Stylemans *et al.*, 2021). A case of severe DS during acute COVID-19, with zero eosinophils at admission and negative initial serum antibodies and stool analyses for ova and parasites,

Table 1. Demographic characteristics and medical history of patients with *Strongyloides stercoralis* hyperinfection treated at the University Hospital for Infectious Diseases 'Dr. Fran Mihaljević' from January 2010 to June 2021.

Patients (all males)	Age (years)	Year of treatment	Chronic disease	Type and dose of immunosuppression	Duration of symptoms before diagnosis (months)
1	81	2014	Interstitial granulomatous dermatitis; alcoholism	Methylprednisolone 1 × 16 mg/day	1
2	60	2015	Non-Hodgkin lymphoma	Methylprednisolone 1 × 16 mg/day (preceding: R-CHOP) ^a	0.5
3	37	2015	Crohn's disease	Methylprednisolone ^b 1 × 12 mg	2
4	64	2016	Non-Hodgkin lymphoma	Rituximab ^c 4th weekly dose of 375 mg/m ² /day	3
5	65	2021	Idiopathic thrombocytopenic purpura	Methylprednisolone dose?	1.5

^aThe fifth R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) regimen – ten days before symptoms.

^bMethylprednisolone was discontinued four weeks before the onset of symptoms which started six days after resection of the small bowel due to stenotic and fistulizing Crohn's disease.

^cMaintenance therapy.

Table 2. Clinical characteristics of patients with *Strongyloides stercoralis* hyperinfection treated at the University Hospital for Infectious Diseases 'Dr. Fran Mihaljević' from January 2010 to June 2021.

Patients (all males)	Clinical presentation ^a	Coinfection causative pathogen; sample	Max. fever, (tympa-nic, in °C)	Peripheral blood eosinophilia (absolute/μL; differential %)	Initial diagnosis; larvae found in:	Therapy	Outcome
1	Epigastric pain Recurrent sepsis Rash	<i>E. coli</i> ; blood	39.4	no	Gastric mucosa	Antibiotic Antifungal Albendazole 3 × 400 mg/day/ 4 weeks ^b	Lethal
2	Pneumonia Abdominal pain Ileus, rash	Negative (previous antibiotic therapy)	39.9	1204; 14	Bronchial aspirate	Antibiotic Antifungal Albendazole 3 × 400 mg/day/ 3 weeks ^b	Lethal
3	Chronic gastro-enterocolitis Ileus Recurrent sepsis	<i>E. coli</i> , <i>E. faecalis</i> <i>C. albicans</i> ; blood	40.4	6480; 44.2	Gastric and duodenal mucosa	Antibiotic Antifungal Albendazole 3 × 200 mg/day/ 10 days	Survived
4	Chronic gastro-enterocolitis Pyelonephritis	<i>P. mirabilis</i> ; urine	38.3	1966; 33.9	Duodenal mucosa	Antibiotic Albendazole 2 × 400 mg/day/ 14 days	Survived
5	Chronic gastro-enterocolitis Sepsis Purulent meningitis	<i>E. coli</i> ; blood and CSF	40.1	no	Gastric mucosa	Antibiotic Albendazole 2 × 400 mg/day/ 14 days ^b + Ivermectin 1 × 15 mg/day/ 9 days ^b	Lethal

^aAll patients were anorexic.

^bUntil death.

has been described (Lier *et al.*, 2020a). A nationwide survey in Spain showed that only 18% of the 121 centres included screening for strongyloidiasis in SARS-CoV-2 patients. There were 227 strongyloidiasis cases identified, among which four developed SHS and one patient died (Rodríguez-Guardado *et al.*, 2021).

However, most of the reported SHS/DS developed during the COVID-19 reconvalescence phase – on average 22.8 days and up to two months after hospital discharge in patients previously treated with corticosteroids (Gautam *et al.*, 2021; Pereira *et al.*, 2021). To accelerate diagnosis, we agree with the authors who

emphasize the value of an early upper (and sometimes even lower) gastrointestinal endoscopy and microscopic examination of gastrointestinal and/or respiratory tract samples in diagnosing SHS (Al-Sajee & Al-Hamdani, 2010; Rodriguez *et al.*, 2015; Lier *et al.*, 2020b; Bdioui *et al.*, 2021).

Besides diagnostic issues, there are many therapeutic controversies. Peroral ivermectin, which is considered the first-choice drug, is often not immediately available, as was the case in the first four of our patients, which is crucial for critically ill patients. Furthermore, ivermectin is registered only for intestinal strongyloidiasis. According to a meta-analysis which included 1147 patients, peroral ivermectin showed a higher parasitological cure rate than albendazole and thiabendazole (74–84% versus 48% and 69%, respectively). However, these data refer to patients with chronic intestinal strongyloidiasis (Henriquez-Camacho *et al.*, 2016). Due to the lack of data, the efficacy of ivermectin and albendazole in SHS/DS is difficult to assess. Given the high mortality of critical SHS/DS, it seems prudent to administer a combination of both drugs pending clinical improvement and parasitological negativization. The report of a successful treatment of previously intractable disseminated strongyloidiasis with a combination of oral ivermectin, partially in double-than-recommended dosage of 400 µg/kg/day, and albendazole for 14 days can be found in the literature (Pornsuriyasak *et al.*, 2004). Certainly, albendazole must be added to ivermectin if disseminated CNS infection is suspected or proven, as albendazole (unlike ivermectin) crosses the blood–brain barrier. The optimal duration of antiparasitic therapy in severe cases has not been determined, nor has the duration of empirical antibiotic treatment preventing secondary bacterial infections after the introduction of antiparasitic therapy. According to the clinical course of disease, the duration of antiparasitic therapy should be individually tailored. The World Gastroenterology Organisation recommends, especially in critically ill patients, to continue antiparasitic therapy for two weeks after negativization of previously positive samples (stool, urine, respiratory samples) (Farthing *et al.*, 2018). Although controlled trials are lacking, the clinical experience articulates against early discontinuation of antibiotic therapy after introducing antiparasitic treatment (Kow & Hasan, 2020; Lier *et al.*, 2020a, b).

Even though there is no published evidence of *S. stercoralis* resistance to antiparasitic drugs, some patients fail to clear the parasite from the gut despite antiparasitic therapy. As observed in our cohort, it is strongly associated with a lethal outcome. Recent research suggests an association between pre-treatment microbiome community composition or enterotype and therapeutic outcomes in patients with soil-transmitted nematodes (*Trichuris trichiura* and hookworm) (Schneeberger *et al.*, 2022). Presumably, failure to clear the parasite could have multiple causes, which remain to be elucidated.

The triggering role of rituximab was so far suspected in one case of SHS in a patient with mantle cell lymphoma (Incani *et al.*, 2010). As rituximab maintenance therapy was the only immunosuppression in one of our patients, we can confirm this observation. However, besides the possible triggering role of a recent ileum resection in one patient, corticosteroids in our case series represent the leading risk factor for SHS/DS.

In conclusion, lack of clinical suspicion and significant delay in diagnosis have been observed in our case series of the most severe strongyloidiasis forms. Although being beyond diagnostic recommendations, an early upper gastrointestinal endoscopy with pathohistology could accelerate diagnosis in immunosuppressed patients with nonspecific gastrointestinal symptoms, weight loss

and systemic, potentially recurrent infections caused by gut flora of an unknown pathogenesis. The reasons for persistence of parasites in the gut despite antihelminthic therapy should be further investigated. The choice and duration of antiparasitic therapy should be tailored individually. Education of the clinicians, especially those dealing with immunosuppressed persons in the low incidence countries, should be conducted.

Supplementary material. To view supplementary material for this article, please visit <https://doi.org/10.1017/S0022149X22000633>

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References

- Al-Sajee DMA and Al-Hamdani A (2010) A case of gastric and duodenal strongyloidiasis. *Sultan Qaboos University Medical Journal* **10**, 262–265.
- Asundi A, Beliavsky A, Liu XJ, Akaberi A, Schwarzer G, Bisoffi Z, Requena-Méndez A, Shrier I and Greenaway C (2019) Prevalence of strongyloidiasis and schistosomiasis among migrants: a systematic review and meta-analysis. *The Lancet Global Health* **7**, e236–e248.
- Balen Topić M, Marjanović E, Tomasović D and Sviben M (2021) Is strongyloidiasis currently autochthonous in Croatia? A retrospective study. *Transactions of The Royal Society of Tropical Medicine and Hygiene* **115**, 1298–1303.
- Bdioui A, Bchir A, Missaoui N, Hmissa S and Mokni M (2021) Histopathological diagnosis of strongyloidiasis hyperinfection in Tunisian patient with hodgkin lymphoma: case report. *Annals of Medicine and Surgery (London)* **66**, 102367.
- Farthing M, Albonico M, Bisoffi Z, *et al.* (2018) Management of strongyloidiasis. In *World Gastroenterology Organisation Global Guidelines*, World Gastroenterology Organisation. Available at <https://www.worldgastroenterology.org/guidelines/management-of-strongyloidiasis> (accessed 28 April 2022).
- Gautam D, Gupta A, Meher A, Siddiqui F and Singhai A (2021) Corticosteroids in COVID-19 pandemic have the potential to unearth hidden burden of strongyloidiasis. *IDCases* **25**, e01192.
- Henriquez-Camacho C, Gotuzzo E, Echevarria J, White AC Jr., Terashima A, Samalvides F, Pérez-Molina JA and Plana MN (2016) Ivermectin versus albendazole or thiabendazole for *Strongyloides stercoralis* infection. *Cochrane Database Systematic Reviews* **2016**, 53.
- Incani RN, Hernández M and González ME (2010) Hyperinfection by *Strongyloides stercoralis* probably associated with rituximab in a patient with mantle cell lymphoma and hyper eosinophilia. *Revista do Instituto de Medicina Tropical de Sao Paulo* **52**, 221–224.
- Kow CS and Hasan SS (2020) Concurrent antibiotic therapy in disseminated strongyloidiasis. *The American Journal of Tropical Medicine and Hygiene* **103**, 2149.
- Lier AJ, Davis MW and Topal JE (2020a) Antimicrobial management of disseminated strongyloidiasis in a COVID-19 patient. *The American Journal of Tropical Medicine and Hygiene* **103**, 2150.
- Lier AJ, Tuan JJ, Davis MW, Paulson N, McManus D, Campbell S, Peaper DR and Topal JE (2020b) Case report: disseminated strongyloidiasis in a patient with COVID-19. *The American Journal of Tropical Medicine and Hygiene* **103**, 1590–1592.

- Ottino L, Buonfrate D, Paradies P, Bisoffi Z, Antonelli A, Rossolini GM, Gabrielli S, Bartoloni A and Zammarchi L** (2020) Autochthonous human and canine *Strongyloides stercoralis* infection in Europe: report of a human case in an Italian teen and systematic review of the literature. *Pathogens* **9**, 439.
- Pereira CVM, Mastandrea GRA, Medeiros A, Gryscek RCB, Paula FM and Corral MA** (2021) COVID-19 and strongyloidiasis: what to expect from this coinfection? *Clinics (Sao Paulo)* **76**, e3528.
- Pornsuriyasak P, Nitichaoenpong K and Sakapibunnan A** (2004) Disseminated strongyloidiasis successfully treated with extended duration ivermectin combined with albendazole: a case report of intractable strongyloidiasis. *The Southeast Asian Journal of Tropical Medicine and Public Health* **35**, 531–534.
- Requena-Méndez A, Chiodini P, Bisoffi Z, Buonfrate D, Gotuzzo E and Muñoz J** (2013) The laboratory diagnosis and follow up of strongyloidiasis: a systematic review. *PLOS Neglected Tropical Diseases* **7**, e2002.
- Rodríguez EA, Abraham T and Williams FK** (2015) Severe strongyloidiasis with negative serology after corticosteroid treatment. *The American Journal of Case Reports* **16**, 95–98.
- Rodríguez-Guardado A, Álvarez-Martínez MJ, Flores MD, Sulleiro E, Torrés-Tendero D, Velasco M and Membrillo FJ** (2021) Screening for strongyloidiasis in Spain in the context of the SARS-CoV-2 pandemic: results of a survey on diagnosis and treatment. *Enfermedades Infecciosas Y Microbiología Clínica*. doi:10.1016/j.eimc.2021.11.010.
- Schneeberger PHH, Gueuning M, Welsche S, Hürlimann E, Dommann J, Häberli C, Frey JE, Sayasone S and Keiser J** (2022) Different gut microbial communities correlate with efficacy of albendazole-ivermectin against soil-transmitted helminthiases. *Nature Communications* **13**, 1063.
- Stylemans D, Van Cauwelaert S, D’Haenens A and Slabbynck H** (2021) COVID-19-associated eosinopenia in a patient with chronic eosinophilia due to chronic strongyloidiasis. *Infectious Diseases in Clinical Practice* **29**, e305–e306.
- Vasquez-Rios G, Pineda-Reyes R, Pineda-Reyes J, Marin R, Ruiz EF and Terashima A** (2019) *Strongyloides stercoralis* hyperinfection syndrome: a deeper understanding of a neglected disease. *Journal of Parasitic Diseases: Official Organ of the Indian Society for Parasitology* **43**, 167–175.
- Xie G, Ding F, Han L, Yin D, Lu H and Zhang M** (2021) The role of peripheral blood eosinophil counts in COVID-19 patients. *Allergy* **76**, 471–482.