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CASE BASED REVIEW

Strongyloides stercoralis infection in a patient with rheumatoid arthritis and type 2 diabetes mellitus: a case-based review

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Abstract

Strongyloides stercoralis (*S. stercoralis*), a human intestinal nematode, can lead to hyper/disseminated (HD) infection in patients treated with corticosteroids. Here, we report a case of strongyloidiasis in a 58-year-old female with a history of rheumatoid arthritis (RA) and type 2 diabetes mellitus (T2DM). The patient presented with abdominal pain and gastrointestinal (GI) bleeding. Stool was negative for parasitic agents in the first direct smear examination, and the patient with the probable diagnosis of *Helicobacter pylori* (*H. pylori*) infection or Crohn's disease received antibiotics and corticosteroids. Parasitic agents were not detected in further direct stool examinations, and the patient with the diagnosis of pneumonia, chronic kidney disease (CKD), ulcerative colitis, sepsis, and candidiasis received fungal, antibiotic, and corticosteroids medications. Low sensitivity of direct smear and the lack of using two methods in diagnosing intestinal parasitic infections led to delayed detection. In the fourth direct stool examination, rhabditiform larva of *S. stercoralis* was reported. The treatment of corticosteroids was discontinued and albendazole was started. A literature review was conducted by searching Medline, Embase, Scopus, and Web of Science with the keywords *S. stercoralis*, strongyloidiasis, RA, and T2DM. Our case indicates that screening *S. stercoralis* infection in high-risk groups, especially those who are candidates for corticosteroids medications, must be implemented using at least two diagnostic techniques.

Keywords Iran · Rheumatoid arthritis · *Strongyloides stercoralis* · Type 2 diabetes mellitus

Introduction

Soil-transmitted helminth (STH) infections, as the most common neglected tropical diseases (NTD) worldwide, affect more than 2 billion people or 24% of the world's subtype inhabitants [1, 2]. *Strongyloides stercoralis* (*S. stercoralis*), as one of the STH, has infected approximately 370 million people all over the world. The most affected regions are tropical and subtropical regions with a prevalence rate ranging from 10 to 60% [3]. Recent studies reveal the possible association between helminth infections, such as *S. stercoralis*, Lymphatic filariasis, and Schistosomiasis, and chronic inflammatory diseases, including rheumatoid arthritis (RA) and type 2 diabetes mellitus (T2DM) [4].

The early diagnosis of *S. stercoralis* infection plays an important role in saving the lives of strongyloidiasis cases, particularly patients treated with corticosteroids. Here, we report a case of strongyloidiasis in a patient who had suffered RA and T2DM. We also conducted a literature review on published strongyloidiasis cases treated with steroids.

Search strategy

The current study presents a case report and the relevant literature regarding a potential correlation between strongyloidiasis and chronic inflammatory diseases, which are treated with steroids. We searched PubMed, Web of Science, and Scopus using the terms "*S. stercoralis*" AND "Rheumatoid Arthritis," "strongyloidiasis" AND "Rheumatoid Arthritis,"

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"*S. stercoralis*" AND "diabetes," and "strongyloidiasis" AND "diabetes" from 1980 to 2019. We included case reports covering RA, DM, and clinical diseases treated with steroids published in English. The 22 identified case reports are shown in Table 1.

Case

A 58-year-old housewife, who lived in a rural area with history of RA and T2DM, presented clinical symptoms such as cough, abdominal pain getting worse after eating, blood in the stool, and melena. She also suffered from joint deformities at metacarpophalangeal joints, joints pain, and diabetic foot ulcers. Her outpatient medications included insulin and prednisolone. Her body temperature (BT) and respiratory rate (RR) were normal, and her blood pressure (BP) and heart rate (HR) were equal to 100/60 mmHg and 84 beats/min, respectively. She was admitted with the diagnosis of gastrointestinal (GI) bleeding to the internal medicine ward for further care. Her complete blood count (CBC) test revealed 9.3 × 1000/μl of white blood cells ((WBCs); (eosinophils, 4%)), 3 mil/μl of red blood cells (RBCs), 5.9 mg/dl of hemoglobin (Hb), 22.5% of hematocrit (Hct), and 569 × 1000/μl of platelets. Biochemistry analysis showed a blood sugar of 224 mg/dl, but urine analysis was normal. The stool examination of a loose and black fecal sample was negative for parasite and blood, and stool cultures were also negative. Her chest X-ray and abdominal ultrasound were normal, but due to eating food, the GI endoscopy was failed. While she was receiving hydroxychloroquine and methotrexate for RA, and metoclopramide for T2DM, due to the probable diagnosis of bacterial infections, such as *Helicobacter pylori* (*H. pylori*), pantoprazole, clindamycin, and ciprofloxacin were added to her treatment for 7 days, and the transfusion of red blood cells was performed for treating her anemia. The second stool examination of brown and loose feces was negative for parasite.

Table 1 Reported cases of strongyloidiasis in rheumatoid arthritis and diabetes mellitus and clinical diseases treated with steroids

First author	Year	No. of patients	Sex	Age (years)	Underlying disease	Treatment	Therapy prior to *S. stercoralis* diagnosis	Outcome	References
Coulter	1992	1	F	44	RA	Thiabendazole Mebendazole	Prednisolone	I	[27]
Mariotta	1996	1	M	64	IPF; CT	Mebendazole	Corticosteroids	D	[28]
Ting	2000	2	–	Above 65	COPD; CT	Mebendazole	Corticosteroids	1 (D), 1(I)	[19]
Kim	2003	1	M	69	RA	Albendazole	Corticosteroids, antacid	I	[29]
Koh	2004	1	F	69	RA	Ivermectin Albendazole	Prednisolone, methotrexate	D	[30]
Kim	2005	1	M	71	RA; DM	No treatment	Corticosteroids	D	[31]
Boatright	2005	1	M	56	RA	Ivermectin	Prednisone, etanercept	I	[32]
Krishnamurthy	2007	1	M	63	RA; DM	Ivermectin Thiabendazole	Prednisolone, methotrexate	I	[33]
Das	2007	1	M	50	RA	Ivermectin	Corticosteroids	I	[34]
Ben-Horin	2008	1	–	54	UC; CT	Ivermectin	Dexamethasone, mesalazine	I	[35]
Azira	2010	1	M	75	DM; CT	Albendazole	Azathioprine, prednisolone	D	[36]
Shafaghi	2010	1	F	65	DM; CT	Ivermectin	Prednisolone	I	[37]
Altintop	2010	1	F	68	RA; BA	Ivermectin	Prednisolone, methotrexate	I	[38]
Islam	2011	1	M	33	RA	Ivermectin Albendazole	Prednisolone methotrexate NSAIDs	I	[39]
Won	2015	1	F	72	DM, CT	Albendazole	Corticosteroids	I	[40]
Najjari	2016	1	M	54	DM; PV	Albendazole	Corticosteroids	D	[41]
Poveda	2017	1	F	64	RA; DM	Ivermectin	–	D	[42]
Dahal	2017	1	F	59	RA; DM	Ivermectin Albendazole	Methotrexate, abatacept Prednisone	D	[43]
Hadidi	2018	1	F	74	RA; BC	Ivermectin	Methotrexate	I	[44]
Cohen	2018	1	M	78	DM; CT	Ivermectin	Apixaban, corticosteroids	I	[45]
Khaliq	2018	1	M	75	RA; DM	Ivermectin	Infliximab Hydroxychloroquine sulfate Prednisone	D	[16]
Sharifdini	2018	1	F	60	DM; CT	Ivermectin	Methotrexate, prednisolone	I	[46]

M male, *F* female, *RA* rheumatoid arthritis, *I* Improvement, *IPF* idiopathic pulmonary fibrosis, *CT* corticosteroids therapy, *D* Death, *COPD* chronic obstructive pulmonary disease, *DM* diabetes mellitus, *UC* ulcerative colitis, *BA* bronchial asthma, *PV* pemphigus vulgaris, *BC* breast cancer, *NSAIDs* nonsteroidal anti-inflammatory drugs

Despite antibiotic therapy, improvement was not observed and she was discharged from the hospital with abdominal pain. The patient was requested to repeat the GI endoscopy several days later. After 10 days, the patient with an altered level of consciousness (ALOC) along with pulmonary and GI symptoms, such as diarrhea, vomit bile, dyspnea, and hemoptysis, was transferred to the hospital again. Because of her mouth ulcers, she was unable to eat anything or take any medicine. The patient had sacral pressure ulcers and had to wear diapers due to loss of bowel control. Her vital signs revealed tachypnea (RR of 32 breaths/min), tachycardia (HR of 170 beats/min), BT of 102.2 °F, and BP of 70/50 mmHg. Stool examination with a few WBCs and RBCs was reported negative for parasite the third time, and CBC test indicated a decrease in WBCs (1.3 × 1000/μl) and platelets count (172 × 1000/μl). A CT scan of her chest showed pneumonia in the right lung (Fig. 1), and the kidney ultrasonography indicated thickening of the parenchymal. The urine analysis showed hematuria (3+), proteinuria (3+), positive nitrite, high number of RBCs, and 20–25 WBCs per HPF (high-power field). In the urine culture, *Candida* was reported. The patient was diagnosed with the pneumonia, chronic kidney disease (CKD), ulcerative colitis, sepsis, and candidiasis and received medications such as sulfasalazine, hydrocortisone, metronidazole, fluconazole, nystatin, ranitidine, ceftazidime, and floxin. Stool examination was performed for the fourth time, but this time, rhabditiform larva was reported (Fig. 2). *Strongyloides stercoralis* filariform larva and adult forms were detected 48 and 72 h later using agar plate culture (Fig. 3). Following the report of *S. stercoralis* larva, a 10-day course of albendazole (400 mg/day) was started, and the corticosteroid medications was discontinued simultaneously. On the third day of the treatment with albendazole (July 4, 2018), the patient was discharged from the hospital in stable condition.

Discussion

Strongyloides stercoralis, as one of the human-infecting nematodes, has a complex life cycle which includes an autoinfective cycle; therefore, it may persist for many years in asymptomatic patients and, as a result, their treatment might be neglected [5]. In patients treated with corticosteroids, chronic infection can lead to HD strongyloidiasis [6]. Risk factors, such as infection with the human T-lymphotropic virus type I (HTLV-1), solid organ transplants, hematopoietic stem cell transplants (HSCT), multiple myeloma, and nephrotic syndrome, have been associated to hyperinfection syndrome or disseminated strongyloidiasis [7]. This condition can put the patient at risk of death because of infection with the gram-negative bacteremia and sepsis [8]. Different diagnostic techniques such as direct smear, Baermann, Harada Mori, and Agar plate culture are used for the detection of

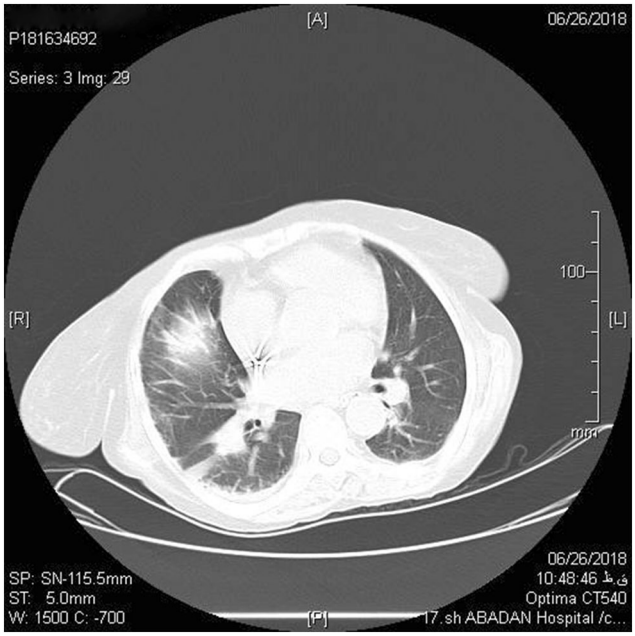

Fig. 1 Computed tomography (CT) scan of the chest showing pneumonia in the right lung

Strongyloides larva, but molecular techniques show higher sensitivity. Therefore, the necessity of using two diagnostic methods, especially in high-risk individuals who are treated with steroids, arises [9, 10].

In our patient, *S. stercoralis* was diagnosed in the fourth stool examination. It seems that one of the most important

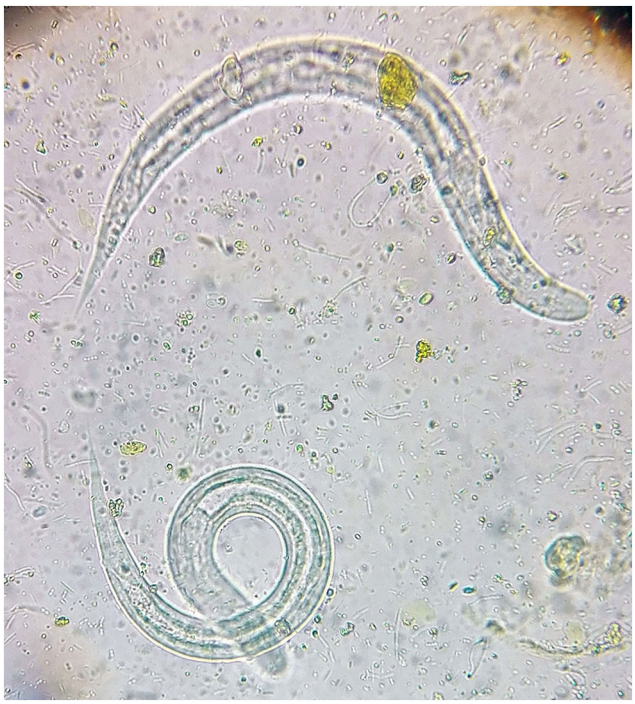

Fig. 2 Rhabditiform larva of *Strongyloides stercoralis* in unstained wet mount of stool (magnification × 400)

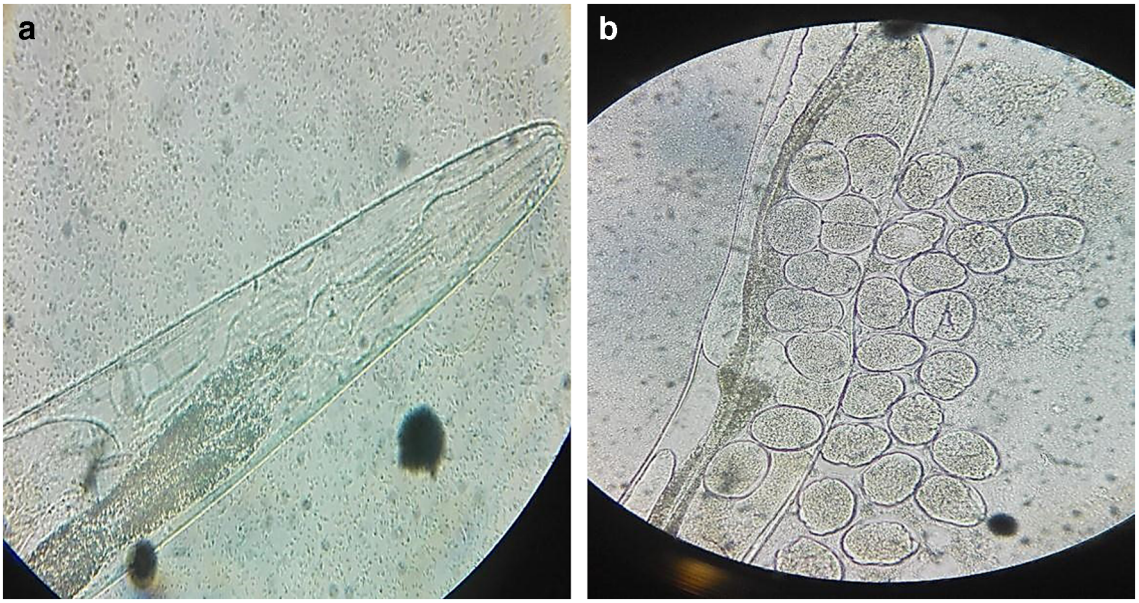

Fig. 3 Adult form of *Strongyloides stercoralis* in smears prepared from the agar plate culture. Short buccal cavity. **a** Rhabditiform esophagus of adult form. **b** Embryonated ova within uterus (magnification × 400)

causes of delayed detection is using a diagnostic method with a low sensitivity. In up to 70% of strongyloidiasis cases, the detection of larva might be failed by a single stool examination. Moreover, since in corticosteroid-treated patients severe strongyloidiasis has no pathognomonic clinical symptoms, it is difficult to be diagnosed [11]. In the present case, due to lack of timely detection of larva, the patient was admitted to the internal medicine ward with the probable diagnosis of other diseases such as ulcerative colitis and candidiasis. Therefore, while she was suffering from the two immunosuppressive diseases including RA and T2DM, the treatment with the corticosteroids and antibiotics made her condition worse. In all 22 case report studies, summarized in Table 1, corticosteroids were a part of their treatment regimen. Unfortunately, there are no adequate data on the prevalence of strongyloidiasis in different systemic rheumatic diseases [12]; however, several studies have reported that corticosteroids in patients with systemic lupus erythematosus (SLE), gout, and ankylosing spondylitis, making these patients susceptible to disseminated strongyloidiasis [13–16]. In immunocompetent patients, the strong and specific association of corticosteroids with HD infection should not be ignored [7]. Due to the lack of cooperation to obtain the patient's sputum specimen, the presence of larva in the sputum was not investigated. However, the development of GI and the occurrence of pulmonary symptoms, including dyspnea and hemoptysis, are most probable results of HD infection [17]. In addition to corticosteroids therapy, most probably, the place of residence and more contact with soil, particularly walking with naked feet, had put her at risk of *S. stercoralis* infection. Furthermore, the moisture and friction caused by her sacral pressure ulcers and wearing diapers could provide a suitable condition to enhance the entrance of larva through the patient's perianal skin (external autoinfection). Antibiotics therapy had also been a part of her treatment regimen; however, septic shock was another possible outcome of the infection and evidence for the disseminated strongyloidiasis (DS). It is estimated that approximately 70% of DS will lead to death [18]. Multiple organ involvement is the main cause of high mortality rate in DS [17]. Collected data in Table 1 shows that among 22 case report studies, 14 cases were treated by reducing the dose of steroids and starting the treatment with anti-parasitic drugs. Nevertheless, in nine cases, the treatment was not successful and the patients died. In one study, two strongyloidiasis cases were reported, of which one died and the other was improved [19]. Nonspecific clinical symptoms including abdominal pain, fever, diarrhea, melena, anemia, cough, and hemoptysis make it difficult to diagnose HD strongyloidiasis. Reactive arthritis also has been associated with strongyloidiasis, which usually involves the lower extremity large joints [20]. Several studies have described an association between parasitic diseases and rheumatic syndromes, such as poly arthritis, reactive arthritis, and oligoarthritis [21, 22]. Furthermore, low sensitivity of routine techniques such as direct smear leads to a delay in detection [17]. Although in most hyperinfection patients the treatment fails [23], delays in diagnosis can also reduce the chance of survival. According to the Centers for Disease Control and Prevention (CDC) guidelines, ivermectin is the first-line therapy in strongyloidiasis patients, particularly in hyperinfection cases [23]. Ivermectin, one of the best known antiparasitic drugs, is chemically derived from avermectin B1 and is widely used in human and veterinary medicine. It is active against a wide spectrum of parasitic nematodes but is not active against trematodes or tapeworms [24]. In our cases,

ivermectin was not available; thus, the patient was treated with albendazole. As shown in Table 1, the therapeutic pattern was not the same. Ivermectin was prescribed in 10 cases, albendazole in four cases, mebendazole in two cases, ivermectin + albendazole in three cases, ivermectin + thiabendazole in one case, thiabendazole + mebendazole in one case, and one case died before the treatment started. Generally, in 14 treated cases with ivermectin, 10 cases were improved and four cases died. In a study by Henriquez-Camacho et al., the effects of ivermectin versus albendazole and thiabendazole were assessed for treating chronic strongyloidiasis. The results revealed that ivermectin has better cure effects and is equally or better tolerated than albendazole. However, although compared to thiabendazole, ivermectin showed similar cure results, it was better tolerated [25]. Despite nephrotic syndrome has been described in chronic infections, due to history of RA and T2DM, it is difficult to correlate the presence of hematuria (3+), proteinuria (3+), and positive nitrite in the patient's specimen with nephrotic syndrome.

This study had an important limitation that should be considered in further studies. The patient had pulmonary symptoms, such as dyspnea and hemoptysis; however, tuberculosis was not investigated. Helminth infections and tuberculosis are co-endemic and share a major global burden. Recent studies have shown that intestinal helminths modulate or alter the host immune response against tuberculosis infection and disease [26]. Therefore, possibility of tuberculosis and helminths co-infections should be considered.

Conclusion

The early diagnosis plays a crucial role in saving the lives of strongyloidiasis cases, particularly immunocompromised patients. In the case of HD strongyloidiasis, nonspecific clinical symptoms may lead to a delay in the diagnosis and treatment of *S. stercoralis*. Therefore, screening *S. stercoralis* infection in high-risk groups, especially those who are candidates for corticosteroids medications, must be implemented using at least two diagnostic techniques.

Author contributions AA is an M. Sc. student of medical parasitology who made the diagnosis of strongyloidiasis. AKH is an internist who treated the patient. MB, who holds a Ph. D. in medical parasitology, analyzed the data and wrote the paper.

Compliance with ethical standards

Disclosures None.

Informed consent Information concerning the manuscript was provided to the patient. Then, the written informed consent was obtained from the patient for publication of this case report and any accompanying images.

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