

Laboratory Findings on a Patient with *Strongyloides Stercoralis* Pulmonary Infection after Long Term Steroid Hormone and Immunosuppressive Treatment

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Case report

Keywords: Strongyloides Stercoralis, Pulmonary Infection, Steroid Hormone, Immunosuppressive Agents, Hyperinfection

Posted Date: February 4th, 2020

DOI: <https://doi.org/10.21203/rs.2.22574/v1>

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Abstract

Background: *Strongyloides stercoralis* infection is common in tropical and humid areas worldwide. However, strongyloidiasis caused by *Strongyloides stercoralis* infection is often neglected in clinic. We report a misdiagnosed case of *Strongyloides stercoralis* infected female patient who had been admitted to four different hospitals for treatment, she eventually died upon *Strongyloides stercoralis* hyperinfection with pulmonary infection involved.

Case presentation: A *Strongyloides stercoralis* infected woman was misdiagnosed as community acquired pneumonia, connective tissue disease and Sjogren's syndrome, and treated by mistake.

She eventually died upon *Strongyloides stercoralis* hyperinfection with pulmonary infection involved. The patient's clinical presentations, imaging results of the lungs, numerous *Strongyloides Stercoralis* larvae and eggs found in the stool, increased eosinophil count in peripheral blood, and elevated serological IgE level were evidences of *Strongyloides stercoralis* hyperinfection.

Conclusion: The patient was infected with *Strongyloides Stercoralis* and died from the hyperinfection after long term use of immunosuppressive agents.

Background

Strongyloides stercoralis belongs to intestinal nematode endemic parasitic infection to most tropical regions, especially in developing countries, and it can remain asymptomatic for years, but an accelerated infection, called "hyperinfection" can cause death in immunosuppressed individuals [1, 2]. Individuals who have impaired immunity such as HIV (human immunodeficiency virus) infection, steroids use, organ transplantation, chemotherapy, diabetes, immunosuppression, tuberculosis, human T cell lymphotropic virus type I (HTLV-1) infection, hematologic malignancies, antidiuretic hormone use, and alcoholism are susceptible in *Strongyloides stercoralis* hyperinfection resulting in disseminated strongyloidiasis leading to mortality rates approaching 80% [3]. Strongyloidiasis is usually neglected in diagnosis because the infection is asymptomatic. Until now, due to the unspecific clinical symptom in infected individuals and the low sensitivity in strongyloidiasis diagnosis, many patients were misdiagnosed every year [4]. Herein, we report a misdiagnosed case of *Strongyloides stercoralis* infected female patient who had been admitted to four different hospitals for treatment, she eventually died upon *Strongyloides stercoralis* hyperinfection with pulmonary infection involved.

Case Presentation

A hospitalized 60-year-old woman, who was a native farmer from a rural area in Guangxi Zhuang Autonomous Region of Southern China who had never traveled to other places except for her living area, presented with high fever (42°C), headache, abdominal pain and distension. She had bowel movements twice a day with approximately 50 gram of black stool each time. She also presented with nausea and vomiting with brown gastric contents. She had a small amount of pink foamy phlegm with difficult

expectoration. She had a pale appearance. The respiratory sound was rough; rhonchi could be heard in both lungs; she had tenderness of the left upper abdomen. Pulmonary X-ray digital radiograph (DR) showed that both lung tips, the lower tongue segment of the left upper lung, and the middle lobe of the right lung had patch-like nodular shadows with a small pleural effusion in both thoracic cavities.

The patient had been admitted to four different hospitals (a tier 2 hospital of her county, three tier 3 hospitals in the City of Nanning of Guangxi Zhuang Autonomous Region) for treatment and had been diagnosed as “community acquired pneumonia, connective tissue disease, Sjogren's syndrome, systemic vasculitis of kidney with hematopoietic involvement”. She was given different types of antibiotics for infection treatment, she was also administered the steroid hormones Methylprednisolone, Prednisone and Dexamethasone, and the immunosuppressive compound Cyclophosphamide during the hospitalization in those four hospitals, however, she did not show a significant response. The above medications had been used intermittently for a period of one year. Her condition was sometimes aggravated. The patient's last admission for treatment was in May 2018 in the Respiratory Department and then was transferred to the Hematology Department of our hospital. She died eventually in the last hospitalization.

It is worthwhile to mention that the patient's first visit to her local county hospital and was diagnosed as community acquired pneumonia because of coughing, low fever, and other mild malaise. She did not show significant response from antibiotics treatment. She was then transferred to a tier 3 hospital in the City of Nanning for further treatment in which she was diagnosed as connective tissue disease and was treated with steroids and immunosuppressive compounds mentioned above, this therapeutic recipe was administered along with other treatment for a month without significant improvement. She then left the hospital returning home continuing the steroids and immunosuppressive compounds administration orally according to medical advice. She was admitted to the second tier 3 hospital which is a large medical university hospital for treatment because her condition was worsening. In this hospital, she was diagnosed as Sjogren's syndrome and was treated continually with steroid hormones and immunosuppressive compounds for a period of time (unknown) and backed home continuing the steroids and immunosuppressive compounds administration. She was then admitted to our hospital (tier 3 large) and for the last try of treatment where she was diagnosed as Sjogren's syndrome, systemic vasculitis of kidney with hematopoietic involvement. The duration of her treatment was one year with intermittent oral administration of steroid hormones and immunosuppressive compounds from the second hospital to the fourth hospital. It was unfortunate that none of the hospitals realized that she had strongyloidiasis.

The patient's laboratory values are shown in Table 1 and Fig. 1. More laboratory findings can be viewed in the Supplementary Data. In brief, the patient had an elevated white blood cell (WBC), neutrophils, and eosinophils counts, while displayed reduced red blood cell (RBC) counts, platelet counts, and hemoglobin concentration. She had also elevated serum cytokeratin 19 fragment (CYFRA21-1), urea, creatinine, C-reactive protein (CRP), and proclctinin (PCT) concentrations. Bone marrow morphology examination results showed an active marrow myeloid proliferation with elevated neutrophilic metamyelocyte and infection index (poisoning granules of leukocytes), the myeloid: erythroid ratio was 21.9 (normal is 1.5–

3.3:1) with low erythroid proliferation and low platelet count. Numerous *Strongyloides stercoralis* worms and eggs were found in stool with microscopic examination (Fig. 1A and B). All laboratory tests for autoimmune diseases and HIV were negative.

Table 1
Patient's Laboratory Test Results

Laboratory Test	Patient's Value	Reference Range
WBC (10E9/L)	20.05	3.6–10
Neutrophils (10E9/L)	15.78	1.7-7
Eosinophils (10E9/L)	1.96	0-0.8
RBC (10E12/L)	2.15	3.5–5.8
Hemoglobin (HGB, g/L)	69	105–160
Platelet (PLT, 10E9/L)	23	100–400
Cytokeratin 19 fragment (CYFRA21-1, µg/L)	140.87	0–5
Neuron-specific enolase (NSE, µg/L)	7.41	0–25
Cancer antigen 24 - 2 (CA242, U/ml)	5.52	0–20
Carcinoembryonic Antigen (CEA, µg/ml)	1.09	0–5
Cancer antigen 125 (CA125, U/ml)	6.67	0–35
Cancer antigen 19 - 9 (CA199, U/ml)	18.89	0–37
Alpha fetoprotein (AFP, µg/L)	2.09	0–20
Immunoglobulin E (IgE, IU/ml)	1040	0-165
γ-glutamyl-transpeptidase (γ-GT, U/L)	68	0–45

Laboratory Test	Patient's Value	Reference Range
Urea (mmol/L)	11.10	3.1–8.8
Creatinine (μmol/L)	106	45–84
Sputum bacteria examination	Gram stain positive Coccidia	Negative
Sputum culture	Candida glabrata growth (A few)	Negative
Vomitus Occult Blood Test	Positive	Negative
Fecal Occult Blood Test	Positive	Negative
Stool Analysis	Numerous Strongyloides Stercoralis eggs and nematodes found	Negative
Tuberculosis IgM and IgG	Negative	Negative
Interferon-gamma release assay T-SPOT	Negative	Negative
HIV antibody (S/CO)	0.07	0–1
C-reactive protein (CRP)	67.5	0–5
Procalcitonin (PCT, μg/L)	0.35	0-0.1
Bone marrow aspirate morphology	The morphologic examination of bone marrow indicated an active marrow myeloid proliferation with elevated neutrophilic metamyelocyte and infection index (poisoning granules of leukocytes), the myeloid:erythroid ratio was 21.9 (normal is 1.5–3.3:1) with low erythroid proliferation and low platelet count.	

The computerized tomography scan (CT) and digital radiography (DR) results displayed that the lungs had multiple patchy infiltration, nodule, or cord shadowing and a small amount of pleural effusion (Fig. 1C and D).

Discussion And Conclusions

Geohelminthic parasite can lead to a disseminated and fulminant hyperinfection syndrome in severely immunocompromised patients, or patients with HIV or HTLV-1 retroviral infections, especially those treated with high doses of corticosteroid therapy. Clinical features of strongyloidiasis are nonspecific, and it is necessary to pay highly suspicion for early diagnosis and improve the poor prognosis of patients

with hyperinfection syndrome [5]. The patient was living in a rural area in a damp and humid climate in Southern China which is an epidemic area of *Strongyloides Stercoralis*. *Strongyloides Stercoralis* pulmonary infection is a severe complication result from hyperinfection with the incidence as high as 87% of the *Strongyloides Stercoralis* infection and could result in death upon acute respiratory failure [6]. The diagnosis of *Strongyloides Stercoralis* pulmonary infection relies on chest X-ray, CT scan, and DR imaging findings such as diffuse, nodule, or cord shadowing, and patchy filtration.

Sputum pathogen examination is a common test in clinical practice. *Strongyloides Stercoralis* larvae in sputum is confirmatory evidence of *Strongyloides Stercoralis* pulmonary infection. The key to achieve a positive result is that the sputum must be from the lower part of the bronchial tree, and the test may be repeated several times if necessary [7]. Bronchoalveolar lavage (BAL) is an invasive procedure performed by a physician to collect the fluid from deep bronchi. The lavage fluid contains normal saline and the pathogens in the fluid will be diagnosed upon sending it to the laboratory. However, the pathogens are easily degraded in this fluid. Therefore, the sample must be processed immediately upon arrival in the laboratory and examined carefully. *Strongyloides Stercoralis* larvae existing in BAL fluid are also direct evidence of *Strongyloides Stercoralis* pulmonary infection. In this case, the patient was misdiagnosed for other disease rather than being considered as *Strongyloides Stercoralis* pulmonary infection, thus neglecting the BAL fluid examination. The existence of *Strongyloides Stercoralis* larvae and eggs in stool, together with the patient's clinical manifestations, radiologic features of the lungs, eosinophil count in hematology analysis, and serological IgE level are also important pieces of evidence of diagnosis of *Strongyloides Stercoralis* pulmonary infection. Numerous *Strongyloides Stercoralis* larvae and eggs found in stool is indirect but important evidence in this case (Table 1 and Fig. 1).

Strongyloides Stercoralis infection is a chronic disease process. The larvae usually invade the human body through skin and mucosal surfaces [8]. After intrusion, the adult worms migrate to the small intestine. Occasionally, the adult worms also migrate to the lungs, genitourinary system, kidney, liver or brain. Infection of the intestine and the lungs are more frequent, and thus digestive and respiratory symptoms are more common [1, 9, 10]. The manifestations of digestive system infection include abdominal pain and distension, diarrhea, nausea and vomiting. Endoscopy may reveal mucosal congestion, oozing, erosion, and ulceration of the stomach and intestine, and the infection can lead to intestinal obstruction or perforation. CT scan or X-ray Barium meal imaging of the upper digestive tract may display small intestinal obstruction, thickening of stomach and intestinal walls, giant duodenum, etc. The worm can also be found in the shunt fluid of stomach and duodenum [11]. In this case, the patient did not undergo gastroscopy examination because the physician did not realize her suffering from *Strongyloides Stercoralis* infection at the beginning. When the physicians had this in their mind, she was too weak to endure the procedure. There are reports mentioning that immunocompromise (HIV infection), diabetes, and long term steroid administration may cause *Strongyloides Stercoralis* opportunistic infection or exacerbate the severity of an original infection [12].

Respiratory infection caused by *Strongyloides Stercoralis* usually lack of unique clinical manifestations. The invasion of the lung by the worms may cause *Strongyloides* pneumonia or secondary bacterial

pneumonia. Patients usually present with hyperpnea, gasp, dyspnea, and respiratory failure. Pulmonary imaging displays either both lungs or single lung patchy infiltration shadowing and possibly a pleural effusion. The lung infection caused by *Strongyloides Stercoralis* is usually misdiagnosed. Larvae found in sputum or BAL fluid are a confirmatory diagnostic criterion [9].

The patient had high blood leukocytes, neutrophils, and eosinophils counts, elevated immunoglobulin E, C-reactive protein, and procalcitonin, indicating a pulmonary infection (parasitic and bacterial) (Table 1). Pulmonary imaging results showed patchy and nodule-like shadows and pleural effusion (Fig. 1). Although she had high serum CYFRA 21 - 1 level (140.87 α g/L) (Table 1), studies found that epithelial cells injured by inflammation, e.g. pneumonia or diabetic nephropathy caused serum CYFRA 21 - 1 elevation [13–15]. The chest imaging results did not support a malignancy of the lung. However, numerous *Strongyloides Stercoralis* eggs and larvae were found in the patient's stool. In addition, the patient had long term history of oral steroids and immunosuppressant drugs. For patients with *Strongyloides Stercoralis* infection, long term immunosuppressants may cause serious autoinfection [16], which is also the main reason of the patient's small intestine ulceration and digestive tract hemorrhage. The larvae (worms) invade brain, lungs, liver, kidneys, and other organs leading to visceral injuries and serious complications, such as respiratory failure and sepsis. The manifestations and history of this patient suggest that the *Strongyloides Stercoralis* larvae most likely had invaded her lungs resulting in pneumonia. Finding larvae in sputum or BAL fluid is direct confirmatory evidence.

An enzyme-linked immunosorbent assay (ELISA) used to detect the antibody against *Strongyloides Stercoralis* in the patient's sputum or cerebro-spinal fluid could be an indirect diagnostic method. Surveying eosinophils in the peripheral blood and serum IgE levels are useful in evaluating the severity of the infection and in predicting a patient's outcome. Higashiarakawa et al speculated that serum IgE levels are dependent on eosinophil counts. Study found that eosinophil counts were decreased in patients co-infected with *Strongyloides Stercoralis* and HTLV-1. However, the use of Steroids and immunosuppressant drugs can influence eosinophil counts and serum IgE levels [17–19]. This suggests that decreasing of eosinophil counts indicates an unfavorable outcome of *Strongyloides Stercoralis* infection.

The patient was too ill (with low immunity and abnormal renal and liver function) to be treated with Albendazole, which may induce the larvae (worms) to migrate and invade multiple organs in the body. The migration of worms could lead to a disseminated super infection or the release of degraded allogeneic protein from dead larvae (worms) worsening the patient's condition and clinical exacerbation [12]. She also had digestive tract hemorrhage, which is a contraindication of Albendazole. The patient was not treated with any anti *Strongyloides Stercoralis* medicine including the ivermectin because the physician did not realize she had the infection during the course of hospitalization. When the laboratory results were reported, the patient's relatives asked for discharge to return home due to the patient's condition was too serious. Indeed, the patient was very weak at the time of laboratory diagnostic findings to be treated with anti *Strongyloides Stercoralis*. Thus, she died on the way returning home shortly after the diagnosis of *Strongyloides Stercoralis* pulmonary infection after numerous larvae and eggs of *Strongyloides Stercoralis* were found in the stool.

Secondary pulmonary infection may occur when a patient has chronic *Strongyloides Stercoralis* infection as an underlying disease while receiving long term steroids and immunosuppressant drug treatment. Since *Strongyloides Stercoralis* infection is not common in clinical practice, clinicians lack diagnostic knowledge of this infection. Consequently, this patient was misdiagnosed and had been treated for community acquired pneumonia, autoimmune diseases, and hematologic system disorders.

Strongyloides Stercoralis eggs found in stool indicate that the patient had chronic *Strongyloides Stercoralis* infection based on her living condition as a farmer in an endemic area (Southern China). When the body's immune system is reduced, i.e. from the effects of immune suppression of steroids and immunosuppressants, the larvae (worms) may disseminate throughout the whole body and invade vital organs such as the lungs and brain. Symptoms of pulmonary infection, such as fever, coughing with little sputum, shortness of breath, abnormal pulmonary imaging studies, and elevated WBC and eosinophil counts and IgE levels are important manifestations and laboratory indicators. Patients who have a history of living in rural environments, especially from endemic areas, are at increased risk of parasitic infection and should prompt special diagnostic approaches.

The patient's immune system was compromised due to the long-term administration of oral steroids and immunosuppressants, thus leading to the disseminated infection in the end. Intestinal hemorrhage (black stool) was due to damage caused by either steroids and immunosuppressants or larval infestation. The cause of the abnormal kidney and liver function can be interpreted for the same reason as well. The anemia was most likely due to loss of appetite and suppression of the hematopoietic function of the bone marrow by steroids and immunosuppressants based on bone marrow examination.

All the tests for autoimmune diseases were negative (refer to the Supplementary Data), thus, the diagnosis of autoimmune diseases was not warranted.

Abbreviations

HIV: human immunodeficiency virus; HTLV-1: human T cell lymphotropic virus type I; DR: digital radiograph; WBC: white blood cell; RBC: red blood cell; CYFRA21-1: cytokeratin 19 fragment; CRP: C-reactive protein; PCT: proclitonin; CT: computerized tomography scan; BAL: bronchoalveolar lavage; ELISA: enzyme-linked immunosorbent assay.

Declarations

Acknowledgments

Not applicable.

Author contributions

Huayi Huang and Hongying Zhao designed the research project; Shuang Deng, Zhiqing Qin, Yuanzi Liang provided medical information and collecting evidences; Hongying Zhao and Li Liang performed the laboratory examination and interpretation; Hongying Zhao and Shuang Deng analyzed the data. Joseph Geradts carried out the English editing. Huayi Huang supervised the research as well as writing. All authors had contributed to this work.

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Funding

This study was supported by a grant from The Health and Family Planning Commission of Guangxi Zhuang Autonomous Region, Z2015353 (PI: Huayi Huang).

Availability of data and materials

All relevant data have been made available in the article. Raw data can be requested from the corresponding author.

Ethics approval and consent to participate

The study was approved by the Institute Review Board of the People's Hospital of Guangxi Zhuang Autonomous Region for the use of human materials. In addition, a consent agreement was obtained from the patient's relatives which was showed in the supplemental material.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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Figures

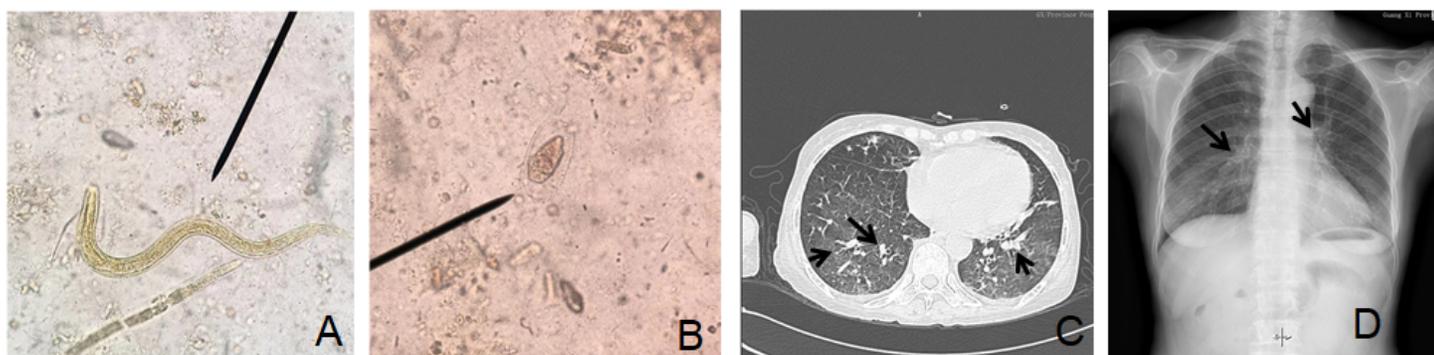


Figure 1

Microscopy results of stool examination and Imaging findings of the lungs from computerized tomography scan (CT) and digital radiography (DR). A: *Strongyloides Stercoralis* nematodes in stool under microscope; B: *Strongyloides Stercoralis* eggs in stool under microscope. x400; C: Computerized tomography displays high density, patchy, and cord shadows in the lungs (arrow pointed); D: Digital radiography displays a similar patchy results to CT scan in the lungs (anterioposterior and lateral position, arrow pointed).