

CASE REPORT

Strongyloides hyperinfection syndrome and cytomegalovirus infection in a patient with type II diabetes mellitus

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SUMMARY

Strongyloidiasis is a gastrointestinal parasitic infection caused by percutaneous infection with *Strongyloides stercoralis*, which is mainly distributed in the tropics and subtropics worldwide. Digestive symptoms like diarrhea and abdominal pain are the main manifestation, but serious infections such as bacterial pneumonia, purulent meningitis and sepsis also occur in immunocompromised individuals. Herein, we present a rare case of a type II diabetes mellitus (T2DM) patient presented with gastrointestinal hemorrhage and sepsis caused by concomitant *Strongyloides stercoralis* and cytomegalovirus (CMV) infection. This 51-year-old male patient presented to the hospital with vomiting, diarrhea, dyspnea, palpitation and weakness. Examination revealed skin soft-tissue infection with T2DM, and upper endoscopy revealed gastric mucosal erosion and hemorrhage. Radiology revealed bilateral diffuse interstitial infiltrates and thickened walls of the colon. Importantly, stool and vomitus examination showed numerous larvae of *Strongyloides stercoralis*. Then the diagnosis of *Strongyloides* hyperinfection syndrome was made. But antibiotics and albendazole treatment did not improve the patient's symptoms of gastrointestinal bleeding and sepsis. Subsequently, other pathogens were screened by sequence and a positive CMV gene was found in the peripheral blood. Thus, antibiotics, albendazole and ganciclovir were all used which ultimately resolved the infection in this patient. Therefore, this case indicated CMV could also be co-infected with *Strongyloides stercoralis* in the immunocompromised patient, which remind us that an CMV test should also be performed when encountered in severe strongyloidiasis infection, which could improve the prognosis of the patient.

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INTRODUCTION

The soil-transmitted threadworm *Strongyloides stercoralis* is one of the most neglected among the so-called neglected tropical diseases. Since the first case of strongyloidiasis was reported in China in 1973, there were 330 confirmed cases as of 2011 (Wang *et al.*, 2013). It is an emerging disease in China, and can cause serious complications and mortality. Public and clinical awareness needs to be raised to improve prevention and control (Chen *et al.*, 2022). In clinics, *Strongyloides stercoralis* infection typically presents with nonspecific gastrointestinal symptoms with no definitive endoscopic findings. Moreover, immunocompromised hosts with strongyloidiasis may also

develop a tremendous disease burden and extraintestinal dissemination with multiorgan system failure, with risk of coinfection with other pathogenic organisms (Crowe *et al.*, 2019). Therefore, a high degree of suspicion should be maintained for *Strongyloides stercoralis* infection in immunocompromised patients from endemic areas who have disease risk factors such as malnutrition, infections like leprosy, tuberculosis, malignancies, and diabetes, which could lead to severe hyperinfection and dissemination. The early diagnosis of *Strongyloides stercoralis* infection plays a critical role in saving the lives of strongyloidiasis cases, particularly in immunocompromised patients. CMV is known as Human Herpesvirus type 5 (HHV-5), which is also an important opportunistic pathogen that causes morbidity and mortality in immunocompromised patients, leading to symptoms such as fever, interstitial pneumonia, enteritis, hepatitis, gastritis, and encephalitis (Ashida *et al.*, 2020). CMV infection tends to increase with the number of immunocompromised individuals (radiation injury and malignant tumor, etc.). Here, we report a

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case of *Strongyloides* hyperinfection syndrome in a T2DM patient who also suffered CMV. To our knowledge, we are the first to report a case of coinfection of *Strongyloides stercoralis* and CMV in China with case-based review.

CASE REPORT

A 51-year-old male from Hainan, South China, presented to the Hainan General Hospital due to aggravated palpitation. He had diarrhea and vomiting 5 days before admission and complained of intermittent whole abdominal pain. Past history including hypertension, coronary disease, T2DM, uric arthritis, chronic renal insufficiency and skin soft-tissue infection. He had received irregular oral medications

for T2DM in the previous 5 years, but did not receive steroids or immunosuppressive drugs.

Vital signs showed arterial blood pressure of 81/61 mmHg, pulse rate of 71 beats/min, body temperature of 36.5°C, and respiratory rate of 20/min. Coarse breath sound was found in both lung fields. Hematological results showed a leukocyte count of $19.88 \times 10^9/L$, $13.81 \times 10^9/L$ neutrophils, $2.87 \times 10^9/L$ lymphocytes, $1.43 \times 10^9/L$ eosinophils, hemoglobin level of 107 g/L, and platelet count of $452 \times 10^9/L$. Other laboratory tests showed aspartate aminotransferase, 70.9U/L (normal 15.0-40.0 U/L); blood urea nitrogen, 22.3 mmol/L (normal 3.1-8.0 mmol/L); creatinine, 269.0 $\mu\text{mol/L}$ (normal 57.0-97.0 $\mu\text{mol/L}$); total protein, 40.8 g/L (normal 65.0-85.0 g/L); and albumin, 13.8 g/L (normal 40.0-55.0 g/L). The levels of pro-B-

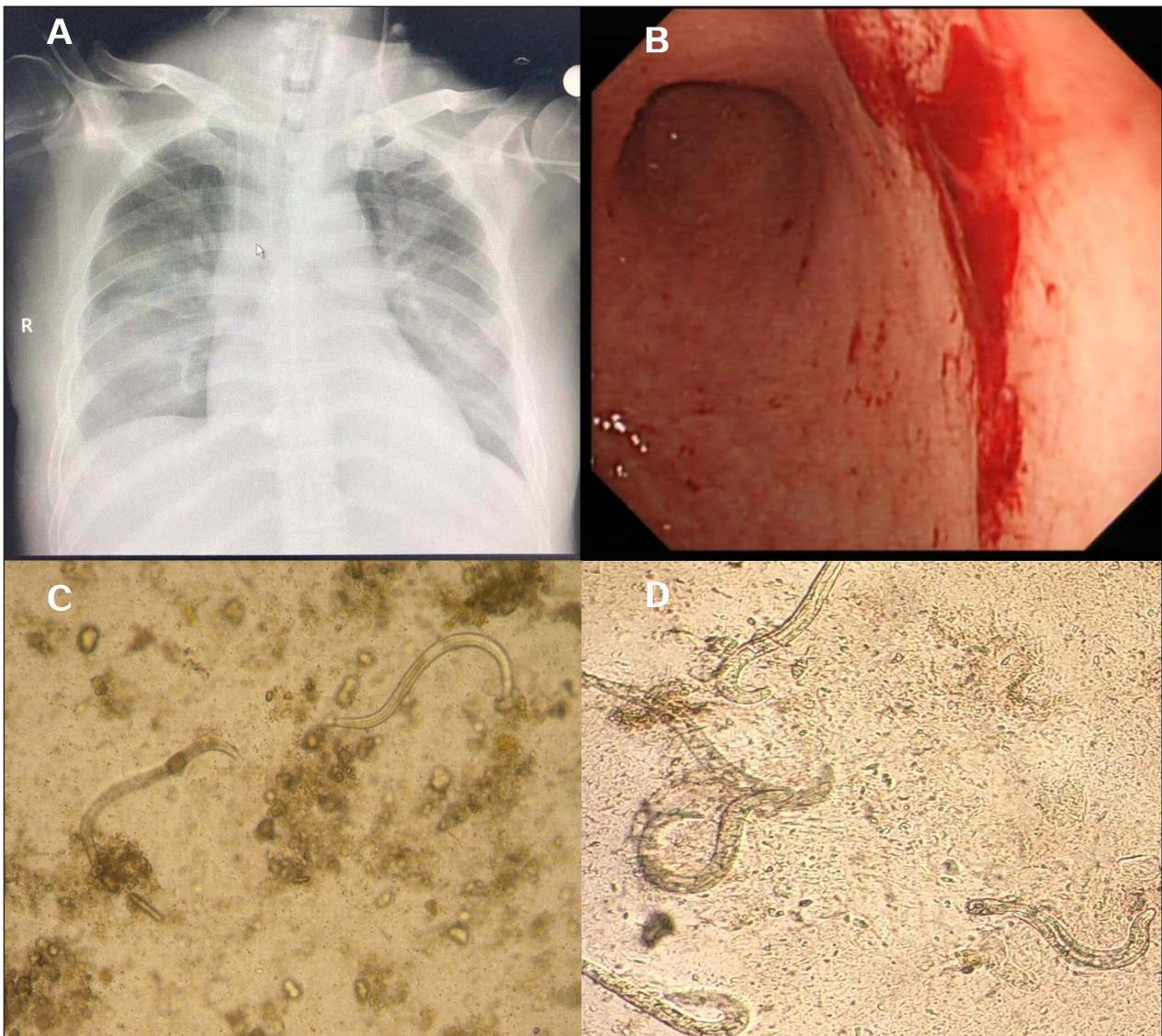


Figure 1 - *Strongyloides* hyperinfection syndrome and cytomegalovirus infection in a patient with type II diabetes mellitus. (A) Chest radiography revealed diffuse bilateral infiltration in both whole lung fields. (B) An upper endoscopy showed gastric mucosal erosion and hemorrhage. (C,D) Rhabditiform larva of *Strongyloides stercoralis* in unstained wet mount of stools(C) and vomitus (D) (magnification $\times 100$).

type natriuretic peptide and C-reactive protein were 35000 ng/L (normal, <125 ng/L) and 197.4 mg/L (normal, <8.2 mg/L). Mycobacterium tuberculosis and Human Immunodeficiency Virus (HIV) tests were negative. Chest radiography revealed diffuse bilateral infiltration in both whole lung fields (*Figure 1A*). An upper endoscopy revealed gastric mucosal erosion and hemorrhage (*Figure 1B*). Abdominal CT showed diffuse thickening of the walls of the colon. Furthermore, the result of stool occult blood testing was positive. Microscopic examination of stool was repeated with freshly collected stool samples on three separate occasions, which also demonstrated motile rhabditiform larvae of *Strongyloides stercoralis* (*Figure 1C*). Meanwhile, vomitus also showed rhabditiform larvae of *Strongyloides stercoralis* under microscopy (*Figure 1D*). Thus, a large number of *Strongyloides stercoralis* larvae from feces and vomitus provided diagnostic proof of the hyperinfection syndrome. We also sent the microscopy picture to a parasitologist, who confirmed Strongyloidiasis. As a result of the above findings, an initial diagnosis of *Strongyloides* hyperinfection syndrome was made. Thus, meropenem, linezolid, and albendazole were all added to his treatment for the following 7 days. However, despite these antibiotic and antiparasitic therapy, this patient did not significantly improve. Instead, this patient began to develop high fever, with significantly decreased hemoglobin, and significantly increased infection index. Subsequently, a next generation sequence of other pathogens was ordered and results revealed the CMV infection in peripheral blood. Thus, a diagnosis of *Strongyloides stercoralis* with concurrent CMV co-infection was established, and therapy was switched to a combination with antibiotics, ganciclovir and albendazole. After a 2-week course of treatment, his stool became semisolid and stool *Strongyloides stercoralis* could not be found under the microscope on consecutive days. The symptoms of this patient significantly improved and he was discharged from the hospital. He is still alive after 4 years, and *Strongyloides stercoralis* were not found in the stool samples of this patient when tested every year.

DISCUSSION

Strongyloides stercoralis, one of the human-infecting nematodes, has a complex life cycle that includes an autoinfective cycle. It can cause asymptomatic chronic infections that may persist for decades because of the ability of the parasite to sustain itself by low-level autoinfection (Ashiri *et al.*, 2019). Also, it is a gastrointestinal parasitic nematode that is widely distributed in tropical and subtropical regions of Asia and South America (Ashida *et al.*, 2020). Gastrointestinal and dermatologic complaints, when present, are usually mild and include abdominal

pain, diarrhea, constipation, vomiting, anorexia and urticaria (Rodríguez-Pérez *et al.*, 2020). Risk factors, such as infection with Human T-lymphotropic Virus type 1 (HTLV-1), solid organ transplants, hematopoietic stem cell transplants (HSCT), multiple myeloma, and nephrotic syndrome, have been associated with the hyperinfection syndrome or disseminated Strongyloidiasis (Ashiri *et al.*, 2019). Moreover, *Strongyloides* hyperinfection is the term often used for the phenomenon in which the number of *Strongyloides stercoralis* organisms increases dramatically and worms are found especially in extraintestinal regions (Kim 2018). Large numbers of intestinal bacteria may enter the blood with the worms, resulting in serious infections such as pulmonary mycoplasmosis, pyogenic meningitis, and bacterial pneumonia.

Cell-mediated immunosuppression can trigger the massive dissemination of *Strongyloides stercoralis* larvae. In patients treated with corticosteroids, chronic infection can lead to *Strongyloides* hyperinfection syndrome. The increased larval burden in *Strongyloides* hyperinfection syndrome explains the development or exacerbation of gastrointestinal and respiratory symptoms (Cohen *et al.*, 2018; Saeed *et al.*, 2019; Rodríguez-Pérez *et al.*, 2020). Patients with *Strongyloides* hyperinfection syndrome often have severe complications, such as paralytic ileus, bowel obstruction, bacteremia, meningitis, respiratory failure, and multiorgan dysfunction. Consequently, mortality is overwhelmingly high with proportions above 60% (Rehman *et al.*, 2007; Vini *et al.*, 2021). In this case, the patient could also develop *Strongyloides* hyperinfection syndrome despite not being on any immunosuppressive medication. Uncontrolled T2DM could have contributed to immunosuppressive cell-mediated immune response, then associated with the concurrent *Strongyloides* hyperinfection syndrome and cytomegalovirus infection. Due to lack of cooperation in obtaining the patient's sputum specimen, the presence of larva in the sputum was not investigated. However, the development of gastrointestinal bleeding, sepsis and dyspnea, as well as the discovery of numerous larvae in vomitus and stool, are the most probable and easily observed results of *Strongyloides* hyperinfection syndrome. Moreover, ivermectin is the first-line drug for the strongyloidiasis, with an estimated efficacy of about 86% and excellent tolerability. Unfortunately, ivermectin is not available in our hospital, so albendazole (400mg/d for two weeks) was used for this patient with good results, although albendazole has a lower efficacy, with usage advised when ivermectin is not available or not recommended (Buonfrate *et al.*, 2022).

In immunocompetent patients, CMV is usually asymptomatic or can present with flu-like symptoms and possibly enlarged lymph nodes and/or spleen. For these patients, it is usually self-limiting and

does not progress any further (Ahmad *et al.*, 2021). Immunocompromised patients, however, are afflicted with a more severe and disseminating infection. CMV infection can cause severe and potentially fatal infection involving interstitial pneumonia, enteritis, hepatitis, gastritis, and encephalitis in presence of immunosuppression (Baburao *et al.*, 2020). This case report revealed gastric mucosal erosion and hemorrhage by upper endoscopy, highlighting how devastating a common Herpesviridae virus can be to a host with a suppressed immune system, even co-infected *Strongyloides stercoralis*.

The patient we reported here is a poorly-controlled T2DM who could be regarded as an immunocompromised patient. He is at great risk of infection by opportunistic pathogens, which include *Strongyloides stercoralis* and CMV. At the very start, stool and vomitus under microscopy revealed numerous larvae of *Strongyloides stercoralis*, and an initial diagnosis of *Strongyloides hyperinfection syndrome* was made. Thus, albendazole and antibiotics was initiated. However, the symptoms and indicators of sepsis and gastrointestinal hemorrhage did not significantly improve. When screening for other pathogen genes, the CMV gene was positive. Then, a diagnosis of T2DM with *Strongyloides hyperinfection syndrome* and CMV infection was established, therapy was switched to a combination of antibiotics, albendazole, and ganciclovir, which ultimately resulted in rapid discharge from the intensive care unit. Therefore, this severe case points out that an opportunistic CMV could also be co-infected with *Strongyloides stercoralis* in the immunocompromised patient, reminding us that other microbiology tests should also be performed simultaneously when encountered in severe *Strongyloidiasis* infection, which could significantly improve the prognosis of these infected patients.

CONCLUSION

In conclusion, in the event of unexplained respiratory infections, gastrointestinal bleeding, and sepsis in immunocompromised patients from the tropics, *Strongyloides hyperinfection syndrome* could be a cause for a medical emergency. Also, in addition to screening for *Strongyloides stercoralis*, other microbiology tests like CMV genes or antigens should also be performed.

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Ethical Approval

This study was approved by the ethics committee of Hainan General Hospital, Hainan Affiliated Hospital of Hainan Medical College, China.

Patient consent statement

This study did not involve any personal information and reported only laboratory data. Therefore, patient consent was waived, and the waiver was approved by Hainan General Hospital, Hainan Affiliated Hospital of Hainan Medical College, China.

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