Disseminated *Strongyloides Stercoralis* Hyperinfection in An Immunocompetent Patient First Diagnosed by Metagenomic Next-Generation Sequencing in Cerebrospinal Fluid: A Case Report

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Research Article

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Abstract

Background

Disseminated *Strongyloides stercoralis* hyperinfection is rarely described in immunocompetent individuals and can lead to fatal outcomes if not recognized and diagnosed early. Non-specific clinical manifestations, such as pneumonia and gastroenteritis, pose a diagnostic dilemma.

Case presentation:

We report a case of a 67-year-old Chinese male who presented with two months of abdominal pain, fever, headache, vomiting, constipation, and slight cough with sputum. He had been in good health and had no history of glucocorticoid use. He was diagnosed with enterococcal meningitis and intestinal obstruction at a local hospital and improved after treatment with vancomycin, but symptoms of headache and abdominal pain soon recurred. The metagenomic next-generation sequencing (mNGS) of the cerebrospinal fluid using Illumina X10 sequencer revealed 7 sequence reads matching *Strongyloides stercoralis*. Disseminated strongyloidiasis was suspected. Next, microscopic examination of gastric fluid revealed Larvae of *S. stercoralis*. DNA extracted of larvae, the presence of both *S. stercoralis* ribosomal DNA gene and mitochondrial cytochrome c oxidase subunit 1 gene was identified. Disseminated strongyloidiasis was diagnosed. Albendazole (400 mg, twice daily) was used and the patient recovered gradually.

Conclusions

S. stercoralis hyperinfection can occur in immunocompetent individuals, imposing challenges for diagnosis. mNGS may be a useful tool for detecting rare infectious disease. The case would help clinicians to raise awareness of strongyloidiasis in non-endemic areas and reduce fatality.

Background

Strongyloides stercoralis is a soil-transmitted helminth that can persist and replicate in humans and cause strongyloidiasis. It is endemic in tropical and subtropical areas and areas with limited resources[1]. Reports of cases in China have been largely concentrated in Guangxi and Yunnan provinces, southern China[2, 3]. Strongyloidiasis may be asymptomatic or mild gastrointestinal or pulmonary symptoms in immunocompetent hosts, while in immunocompromised hosts it may present as fatal disseminated disease and/or septic shock[4]. Disseminated *Strongyloides stercoralis* infection in immunocompetent hosts is rare. The lack of disease-specific manifestations makes the diagnosis of strongyloidiasis challenging, especially in non-endemic areas.

The common diagnostic methods of strongyloidiasis included faecal examination for strongyloides larvae and serological approaches[5]. However, the sensitivity of faecal examination is low[6], and faeces cannot be obtained in patients with intestinal obstruction. It is also difficult for physicians in non-endemic areas to think of using serological screening methods when they are not considering strongyloidiasis. With the development of metagenomic next-generation sequencing (mNGS) technology in recent years, it has gradually become an attractive and promising approach for pathogen detection[7]. mNGS of cerebrospinal fluid (CSF) can also improve the diagnosis of neurologic infections[8].

Here, we describe an immunocompetent case with disseminated *Strongyloides stercoralis* hyperinfection with intestinal obstruction in a non-endemic area. He was first diagnosed by mNGS of CSF and later confirmed by gastric fluid microscopy and polymerase chain reaction (PCR) gene sequencing.

Case Presentation

A 67-year-old Chinese male was admitted to our hospital for 2-month abdominal pain, fever, headache, vomiting, constipation, and slight cough with sputum but without shortness of breath. He had no underlying diseases and no history of glucocorticoid use, alcoholism or history of travel to *S. stercoralis* endemic areas. CSF analysis at a local hospital two months prior to the admission showed increased white blood cells (WBC, 3,534 cell/ μ l) and proteins (1.97 g/L) and a positive CSF culture with *Enterococcus avium*. He was diagnosed with bacterial meningitis and intestinal obstruction there. His conditions improved after receiving vancomycin but two days prior to the admission he had recurrent, severe vomiting and abdominal pain and therefore was transferred to our hospital for referral. The patient had a 10-kg weight loss in the previous two months. On examination, he was afebrile but had neck stiffness. Anaphylactoid purpura were present on both upper limbs (Fig. 1A) and facial skin. Signs of meningeal irritation were positive. Crackles were heard bilaterally in the lower lungs on auscultation. Right lower abdominal tenderness and scanty bowel sounds were noted. His routine blood work on admission revealed 7.2×10^9 /L WBC (normal range, $3.5-9.5 \times 10^9$ /L) with 86.8% neutrophils, 7.4% lymphocytes and 0% eosinophils, and moderate anemia with 80 g/L hemoglobin. Serum tests for human immunodeficiency virus (HIV), hepatitis B virus (HBV), hepatitis C virus (HCV) and syphilis were negative. PCR testing of a blood sample for human T lymphocyte virus 1 (HTLV-1) was also negative. Enhanced brain magnetic resonance imaging (MRI) showed a few patches near bilateral ventricles and partial thickening and strengthening of the endocranium (Fig. 1B). An enhanced abdominal computer tomography (CT) scan exhibited proximal small intestinal obstruction (Fig. 1C). A CT scan of the chest revealed bronchiectasis with secondary pulmonary infection (Fig. 1D). Lumbar puncture on admission revealed clear CSF with 20 red blood cells and 18 WBC per microliter. Meningitis was diagnosed and meropenem was given at 2 g every 8 h for empirical therapy.

Two days after admission, the patient developed palpitations and shortness of breath. The respiratory rate 32 breaths per minute, the blood pressure was 85/55 mmHg, ventricular rate 160 beats per minute, and the oxygen saturation 97% while he was breathing ambient air. His hemoglobin level was 64 g/L (reference range, 120 to 160 g/L). His brain natriuretic peptide and troponin-T levels increased to 6825

ng/L (normal range, 0-227 ng/L) and 34.0 ng/L (normal range, 0–14 ng/L) respectively. Electrocardiogram indicated atrial fibrillation, which improved after administration of cedilanid and amiodarone. Third sputum smear tests were negative for bacteria, fungi, acid-fast bacilli, ova or parasites. Sputum aerobic culture grew *Klebsiella pneumoniae*. Because the patient has a long course of disease, the etiology of intracranial infection is unknown, mNGS of the CSF was performed using an Illumina X10 sequencer with a unilateral read length of 75 bp. The results of mNGS were available on the third day after admission and among the 10,656,825 generated clean reads, there were 7 sequence reads matching *Strongyloides stercoralis* but no reads matched any other parasites and microorganisms. Larvae of *S. stercoralis* were identified in gastric fluid retrieved from the gastrointestinal tube on the third day after admission based on morphology (Fig. 2). DNA extracted of larvae using a DNeasy Blood & Tissue Kit (QIAGEN; Hilden, Germany) was subjected to PCR amplification for both *S. stercoralis* ribosomal DNA gene and mitochondrial cytochrome c oxidase subunit 1 (*cox1*) gene as described previously[9, 10]. Both PCR assays were positive and sequencing amplicons confirmed the presence of *S. stercoralis* with the ribosomal DNA sequence the *cox1* sequence being deposited in GenBank under accession no. MW604696 and MW578283, respectively. *S. stercoralis* hyperinfection was therefore diagnosed. As ivermectin and mebendazole were unavailable for human use in China, two weeks of albendazole (400 mg, twice daily) was used instead. The patient recovered gradually. Two months after discharge, he gained 4kg in outpatient follow-up, but he had new purpura on both upper limbs. He was given another course of albendazole for 2 weeks and gradually improved. Figure 2 showed the changes of purpura in his right forearm during the follow-up.

Discussion And Conclusions

Strongyloidiasis is mainly endemic in tropical and subtropical regions and sporadic in temperate regions. In particular, a high incidence of strongyloidiasis is present in South America and Southeast Asia [11]. Few cases have been reported from Sichuan provinces, southwest China. Our patient is a farmer living in Chengdu with a subtropical climate, which is not an epidemic area of strongyloidiasis as only sporadic cases have been reported locally [3] and a province-wide surveillance for 3- to 6-year-old children by stool sampling revealed a 0.05% (6 out of 11,403 children) prevalence of *S. stercoralis* [12]. In non-epidemic areas, *S. stercoralis* infection is often neglected and not included in differential diagnoses for patients with intestinal obstruction, rashes, pneumonia and meningitis. As coincident infections with enteric organisms including *Enterococcus* spp. are common [13, 14], in retrospect meningitis and intestinal obstruction diagnosed two months prior to the present admission may have marked the start of *S. stercoralis* hyperinfection. HIV or HTLV-1 infection, malignancy, current chemotherapy and alcoholism are common risk factors for disseminated *S. stercoralis* infection [15]. By contrast, this patient has no such conditions or any other known immunocompromised factors. A few previous studies have also found the uncommon occurrence of strongyloidiasis in immunocompetent individuals, which is typically accompanied by elevated eosinophils [16, 17]. However, eosinophils were not elevated in this case, which made the diagnosis of strongyloidiasis more challenging.

Stool examination for larvae, serology and molecular biologic techniques can all be used to diagnose *S. stercoralis* infection [5, 18]. As the patient had intestinal obstruction, no stools were available, and we

therefore used gastric fluid and CSF for examination. Although *S. stercoralis* larvae were detected in gastric fluid but not CSF in this patient, previous studies have demonstrated low sensitivity of gastric fluid and CSF for detecting *S. stercoralis* [3, 6]. Unfortunately, in non-endemic areas serological methods are usually not available as they are in our hospital. In recent years, mNGS is increasingly being used in clinical practice owing to rapid technological developments and substantially reduced costs in China, therefore, mNGS may be a useful tool for detecting *S. stercoralis* in non-endemic areas.

Therapeutic options for strongyloidiasis are limited and typically include ivermectin and benzimidazoles (albendazole and thiabendazole). Ivermectin is currently the most effective treatment for strongyloidiasis [14, 19], but human preparations of oral ivermectin are not available in some countries including China at present, and oral veterinary preparations have been attempted in some cases [20]. In addition, veterinary preparations involve some risk of overdosing, particularly when more concentrated formulations for large animal species, such as cattle, are not properly diluted. As ivermectin is not available, we administered oral albendazole, and the treatment was successful. Perhaps because of intracranial involvement, this patient was treated with albendazole for a longer duration than previously reported patients [3]. Albendazole may be an alternative option for strongyloidiasis as suggested before [21, 22] but the efficacy warrants further investigation.

In summary, we present the case of a patient from a non-endemic area with a delayed diagnosis of *S. stercoralis* hyperinfection. Owing to its increased use in some countries like China, mNGS may be a useful tool to detect *S. stercoralis* in patients. This case will help clinicians by raising awareness of strongyloidiasis in non-endemic areas.

Abbreviations

CSF

Cerebrospinal fluid; CT:computer tomography; HBV:hepatitis B virus; HCV:hepatitis C virus; HIV:human immunodeficiency virus; HTLV-1:human T lymphocyte virus 1; MRI:magnetic resonance imaging; mNGS:Metagenomic next-generation sequencing; WBC:white blood cell

Declarations

Ethics approval and consent to participate

All investigations and interventions were in accordance with ethical standards.

Consent for publication

The authors declare that the written informed consent for publication has been obtained from the patient.

Availability of data and materials

All data generated or analysed during this study are included in this published article.

Competing interests

The authors declare no conflict of interest.

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Authors' contribution

ZZ and JQ designed the study. JQ collected and interpreted the clinical data and drafted the manuscript. ZZ modified the manuscript and finally approved the version to be published.

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Figures

Figure 1

The presentation of this case and the detection of *S. stercoralis* larvae. Anaphylactoid purpura were present on left upper limb (A). Abdominal CT imaging showed that the ileocecum was swollen and thickened (white arrow) and the proximal small intestine was obstructed with air-fluid level (red arrow). (B). Brain MRI showed patches near bilateral ventricles (red arrow) and partial endocranium thickened (C). Chest CT revealed bronchiectasis with secondary pulmonary infection (D).

Figure 2

Larvae of *S. stercoralis* were identified in gastric fluid (unstained, × 400).

Figure 3

The changes of purpura in right forearm of the patient. Schonlein purpura in his right forearm at admission (A), after 10 days of treatment (B), two months after discharge (C), after the second course of treatment (D).