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Disseminated tuberculosis complicated by intramuscular abscesses, meningoencephalitis, and hemophagocytic lymphohistiocytosis: a case report

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Abstract

Background As disseminated extrapulmonary tuberculosis infection can involve multiple systems and result in atypical clinical manifestations that mimic other diseases, the diagnosis may be difficult, especially in elderly patients. Delaying treatment can adversely affect the prognosis. And to achieve better prognosis, early detection and diagnosis are necessary, as well as early initiation of comprehensive treatment.

Case presentation We present the case of a 78-year-old man with disseminated tuberculosis who developed the uncommon complication of urinary retention due to a psoas abscess, meningoencephalitis, and the rare secondary hemophagocytic lymphohistiocytosis syndrome. The patient achieved a favorable outcome following targeted therapy with antitubercular medications.

Conclusions This case highlights that disseminated extrapulmonary tuberculosis infection can present with a variety of manifestations, and may exhibit many rare and complex clinical presentations. Prompt and accurate diagnosis and treatment play a crucial role in improving prognosis for the patients with persistent fever.

Keywords Disseminated tuberculosis infection, Tuberculous meningitis, Hemophagocytic lymphohistiocytosis, Urinary retention, Tuberculosis

Background

Although tuberculosis (TB) is usually quite common in clinical practice, disseminated extrapulmonary TB can involve multiple systems and produce atypical clinical manifestations that mimic other diseases, making diagnosis and treatment difficult [1]. This is particularly true for elderly patients with TB, as the lack of specific clinical manifestations and frequent comorbidities can mean that diagnosis and treatment are delayed, leading to a poor prognosis [2]. TB infection cannot be forgotten in patients presenting with diagnostic difficulties.

Here we present a case of disseminated TB initially presenting with fever, altered consciousness, urinary

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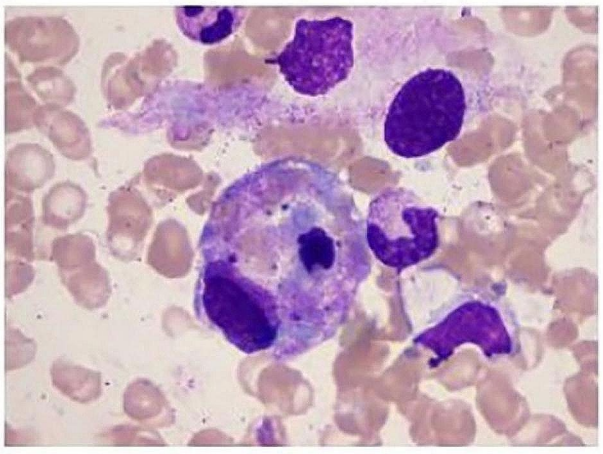

Fig. 1 The smear of bone marrow aspiration showed the features of HLH.

retention, and pancytopenia. The patient achieved a favorable outcome following targeted therapy with antitubercular medications. This complex and rare case emphasizes the need for prompt and accurate diagnosis and treatment, moreover, infection should be adequately excluded from the management of patients with persistent fever, as this may lead to serious consequences.

Case presentation

A 78-year-old man presented to Peking Union Medical Collage Hospital in June 2021 with a five-month history of persistent high-grade fever of up to 39.5 °C, which typically occurred at night and was accompanied by chills, fatigue, and appetite loss. There was no history of cough, sputum, dyspnea, headache, nausea, or vomiting. His complete blood count revealed pancytopenia, with a hemoglobin (HGB) of 90 g/L (normal range 120–160 g/L), total white blood cell count (WBC) of 2.26×10^9/L (normal range $3.5–9.5\times10^9$/L), with the absolute neutrophil count of 1.64×10^9/L (normal range $2.0\text{-}7.5\times10^9$/L), and a manual platelet count of 69×10^9/L (normal range $100–350\times10^9$/L). Blood biochemistry was unremarkable except for an elevated glutathione transaminase of 169 U/L (normal range 9–50 U/L). Bone marrow aspiration was performed to investigate the cause of pancytopenia, which showed active bone marrow hyperplasia with increased histiocytosis (4.8%) and phagocytic lymphohistiocytosis (1.4%) (Fig. 1). Further examination revealed elevated levels of soluble CD25 (>44,000 pg/ml), decreased natural killer cell activity (12.76%, normal range 15.11–26.91%), and fibrinogen (1.6 g/L, normal range 1.8–3.5 g/L), as well as increased ferritin (861.8 ng/ml, normal range 24–336 ng/ml) levels, which prompted a diagnosis of hemophagocytic lymphohistiocytosis (HLH). Additional tests including blood cultures, immunoglobulin G testing, *Borrelia burgdorferi* agglutination testing, cytomegalovirus DNA, and Epstein-Barr DNA testing were all negative. Chest computed tomography (CT) revealed only a few faint cord-like shadows in the right upper lung, a few small nodules in the left upper lobe, and several small lymph nodes in the mediastinum, which were non-specific and cannot be used to definitively diagnose a specific disease (Fig. 2). Positron emission computed tomography showed increased metabolic activity in some segments of central bone marrow, which appeared to be reactive hyperplasia.

Due to the risk of infection, the patient had been started on empirical prophylactic antimicrobials including amoxicillin, piperacillin tazobactam sodium, meropenem, and ganciclovir while being managed by the local hospital, but there was little improvement. Methylprednisolone was prescribed to alleviate the inflammatory response, with an initial dose of 80 mg daily, gradually tapering off thereafter, the total duration of glucocorticoid therapy lasted for 2 months. The peak temperature decreased slightly to 38–39 °C, but the ferritin level increased to 2666 ng/ml.

In May 2021, the patient developed new bilateral lower extremity pain, which was described as a sharp, "electric shock"-like sensation, with a visual analog score of 7–8 points. As the disease progressed, the patient developed mobility disorders and could not stand up after squatting. Lumbar spine MRI shows disc protrusion at L3-4 and L4-5 levels, as well as spinal canal stenosis at the L3-S1 level, no space-occupying lesions were seen within the spinal canal and no abnormal lesions were observed

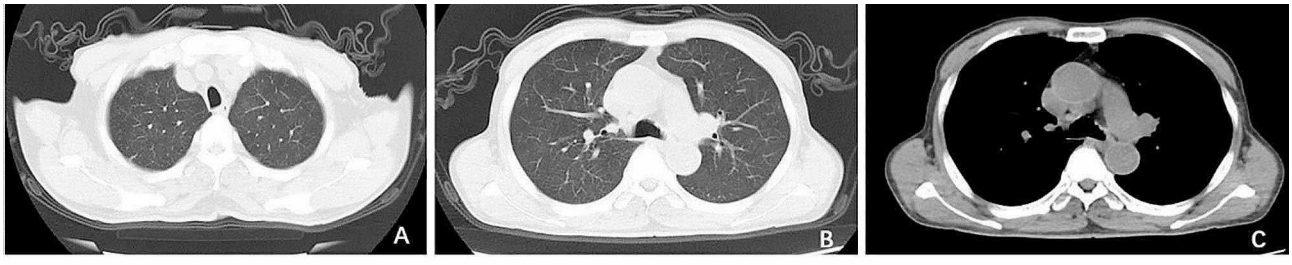

Fig. 2 Chest CT revealed little faint cord-like shadows in the right upper lung (figure **A**), a few small nodules in the left upper lobe (figure **B**), and several small lymph nodes in the mediastinum (figure **C**)

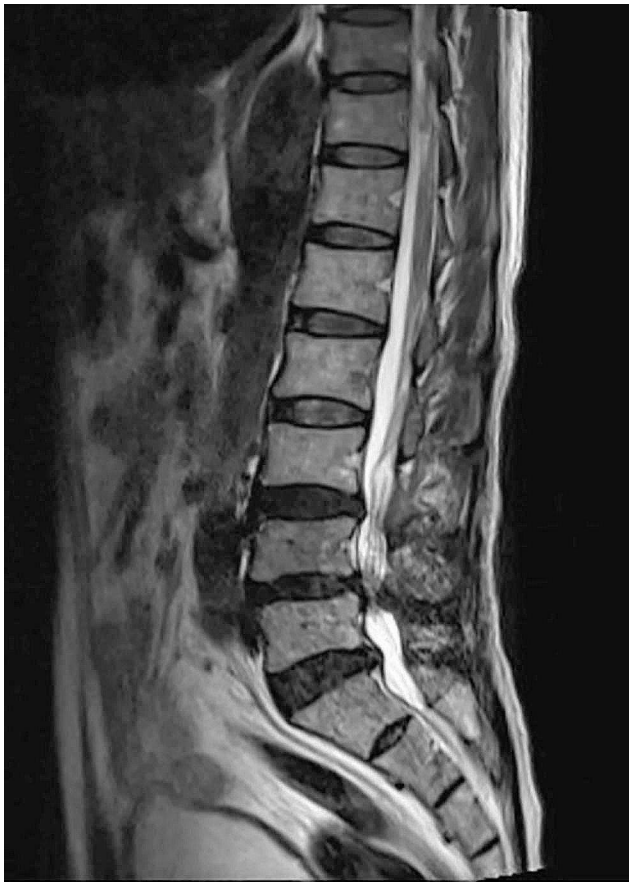

Fig. 3 Lumbar spine MRI shows disc protrusion at L3-4 and L4-5 levels, as well as spinal canal stenosis at the L3-S1 level, no space-occupying lesions were seen within the spinal canal and no abnormal lesions were observed in the vertebral bodies as well as in spinal cord

in the vertebral bodies as well as in spinal cord (Fig. 3). The fever persisted and indeed spiked to 40 °C, with the pain worsening during febrile episodes. Furthermore, the patient experienced a weight loss of 5 kg.

The patient was transferred to our hospital for further evaluation in June 2021. Re-enquiry of his past medical history revealed minimally invasive surgery for lumbar disc herniation and spinal stenosis in 2011. On admission, the patient was alert and had stable vital signs except for a blood pressure of 102/48 mmHg. Breath sounds at the base of both lungs were slightly decreased, but the remaining respiratory and abdominal examinations were unremarkable. Neurological examination revealed that the patient had symmetrical and bilateral lower limb hypoesthesia, muscle atrophy, and hypotonia, with muscle strength graded IV-, but no edema. The bilateral tendon reflexes were symmetrical, and there were no meningeal stimulation or pathological signs.

Laboratory data after admission showed that the hemoglobin had decreased to 72 g/L, creatinine had increased to 122 μmol/L (normal range 59–104 μmol/L), and other

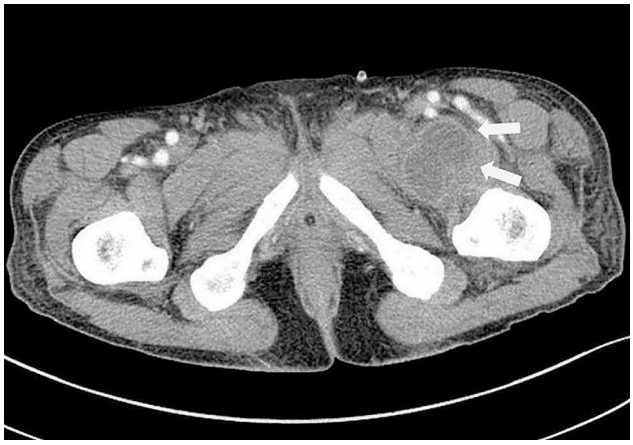

Fig. 4 Abdominal and pelvic CT scan showing multiple irregular low-density lesions in the left iliopsoas and proximal thigh muscles (marked by arrows), suggestive of intermuscular abscesses

routine laboratory tests showed no significant changes to prior results. The purified protein derivative skin test was positive. Based on the clinical features, infections and autoimmune diseases were highly suspected. Another set of aerobic and anaerobic blood cultures were sent, but these were again negative. To exclude polymyalgia rheumatica and other autoimmune diseases, fundus and hearing examinations were performed, which showed no obvious abnormalities, and similarly there were no autoantibody, temporal artery, nor renal artery ultrasound abnormalities.

On the third day of hospitalization, the patient developed drowsiness, slurred speech, and tangentiality in his responses. At the same time, his urine output markedly decreased with a post-voiding residual urine volume of ~900 ml on ultrasound examination. Abdominal and pelvic CT scans showed multiple small calcifications in the liver and peritoneal lymph nodes. Additionally, multiple irregular low-density lesions were observed in the left iliopsoas and proximal thigh muscles (Fig. 4), which potentially indicated intramuscular abscesses.

Since the patient's new clinical manifestations could have been related to central nervous system (CNS) lesions, lumbar puncture was performed within the first week of hospitalization and the cerebrospinal fluid (CSF) pressure was 120 mmH_2O. The cerebrospinal fluid (CSF) was colorless and transparent, with a total cell count of 2810×10^6/L and a WBC of 28×10^6/L (normal range $0–8\times10^6$/L), the majority mononuclear cells (27×10^6/L). The CSF protein concentration was 0.74 g/L, and glucose concentration was 4.3 mmol/L. Both acid-fast stain, Xpert MTB/RIF and culture for mycobacteria of CSF revealed negative. A head MRI revealed multiple enhancing nodules in the brain stem, cerebellar vermis, and cerebral hemispheres bilaterally (Fig. 5). CNS infection was highly suspected based on both the clinical

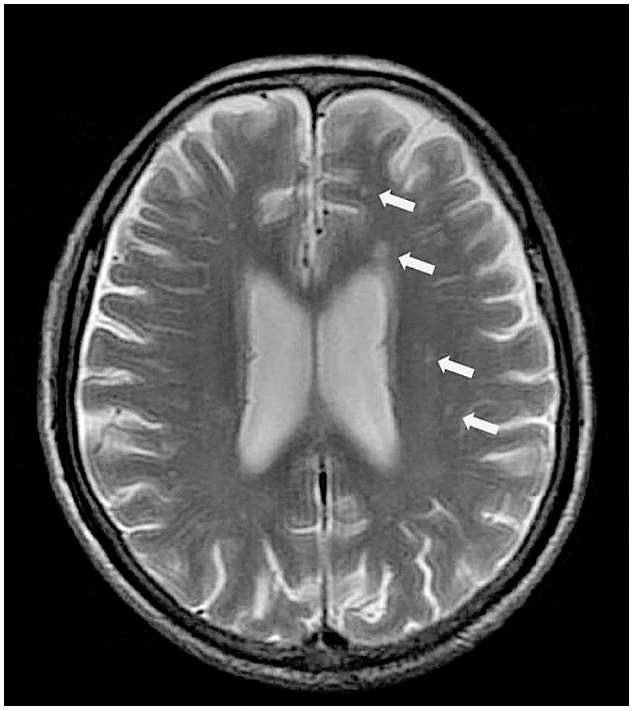

Fig. 5 Head magnetic resonance image revealing multiple enhancing nodules in the brain stem, cerebellar vermis, and cerebral hemispheres bilaterally (marked by arrows). Central nervous system infection was highly suspected based on both the clinical symptoms and imaging findings

symptoms and imaging findings. CT-guided needle biopsy and catheter drainage were performed on the tenth day of hospitalization for the left thigh intramuscular abscesses identified as low-density lesions. Although bacterial and fungal cultures of the fluid were negative, acid-fast staining was positive. Nested polymerase chain reaction (PCR) testing for *Mycobacterium tuberculosis (M. tuberculosis)* complex in the sputum was positive. Interestingly, two days after the drainage of intramuscular abscess, symptoms of urinary retention improved significantly, spontaneous urination resumed after removal of the urinary catheter.

Based on the patient's medical history, imaging, and cultures, disseminated TB with intramuscular abscesses, meningoencephalitis, and secondary HLH were suspected. Meanwhile, we reexamined the bone marrow aspiration and biopsy, the result of smear was consistent with previous sample, while the biopsy showed granuloma-like structures composed of epithelioid tissue cells in hematopoietic tissue were found, which suggested that the bone marrow may also be affected by tuberculosis infection. Consequently, the patient was administered anti-tuberculosis therapy with oral isoniazid 0.3 g per day, rifampin 0.45 g per day, ethambutol 0.75 g per day, and pyrazinamide 0.5 g three times per day on the second week of hospitalization, at same time, oral methylprednisolone was again prescribed to alleviate the inflammatory response, with an initial dose of 24 mg daily, and began to tapering off 2 weeks later, with a total duration of 2 months. The patient's peak temperature gradually subsided, and the lower extremity pain improved significantly. After two weeks, an ultrasound examination of the left iliopsoas muscle and lower limb revealed no abnormalities. The drainage tube was removed, and the patient was discharged on day 32 in stable condition, afebrile, and with complete relief from discomfort of both lower limbs.

During a follow-up visit four months later, the patient's overall clinical status had improved and his blood counts had normalized, including a WBC count of 3.11×10^9/L, hemoglobin of 104 g/L, and platelet of 188×10^9/L. C-reactive protein levels remained normal. At the same time, enhanced pelvic CT scans showed that the pre-existing iliopsoas and proximal thigh muscle abscesses had completely disappeared, and head-enhanced MRI showed that the multiple enhancing nodules scattered in the brain were significantly reduced compared to the previous one. Anti-tuberculosis medication was continued thereafter and discontinued at the end of 18 months of total therapy.

Discussion and conclusions

Tuberculosis is a chronic communicable infectious disease caused by *M. tuberculosis* [3]. Although the incidence of TB is relatively high in China, the diagnosis of disseminated tuberculosis can be challenging due to a lack of specific clinical manifestations, multiple system involvement, low sensitivity of acid-fast staining, and the time-consuming nature of culture, especially in severe cases [4].

Despite the patient being an elderly male and belonging to the high-risk population for tuberculosis infection, typical clinical manifestations were not present during the early stages of the disease. Furthermore, there were no radiological features of active tuberculosis infection in the lungs. Consequently, the initial diagnostic process did not prioritize screening for tuberculosis infection, hampering early diagnosis. As the patient's condition advanced rapidly in the later stages, the diagnosis of TB was confirmed through classical radiological features and subsequent isolation and identification of the organism. Therefore, it is essential to consider tuberculosis in patients presenting with atypical features, particularly in cases associated with HIV, the elderly, or the immunocompromised, who may neither exhibit classical tuberculosis features such as malaise, night sweats, localized pain, nor chronic or active lung lesions.

Hemophagocytic lymphohistiocytosis (HLH) is a rare but life-threatening immune overactivation syndrome. Clinical manifestations may include fever, cytopenia, splenomegaly, and CNS symptoms. This immune

overactivation state is often triggered by genetic factors, immune system diseases, hematologic malignancies, or infections [5]. Early detection and timely initiation of treatment are crucial to ensure survival. In this case, the patient initially presented with fever and cytopenia with elevated serum ferritin and soluble CD25 levels, decreased fibrinogen and natural killer cell activity, and phagocytosis of blood cells observed in bone marrow smears, confirming a diagnosis of HLH. HLH is an uncommon but fatal complication of disseminated TB that may induce systemic inflammatory response syndrome [6]. Clinical and imaging manifestations of tuberculosis-induced HLH are often atypical in these patients, and, when encountered, HLH is more commonly observed in patients with CNS tuberculosis [7]. For HLH secondary to infection, it is extremely important to treat the underlying cause and eliminate the source of immune activation. For stable patients with non-life-threatening conditions, correcting the underlying cause without specific HLH treatment can also achieve good results. However, conversely, if the triggering factor is not found in time, treatment solely targeting HLH is often unsatisfactory. In our case, the patient was treated with an adequate dose of steroids early on in the disease course, but this had little effect, moreover, the dissemination of tuberculosis infection discovered later might be related to the abuse of glucocorticoid. This is consistent with previous studies showing that tuberculosis-associated HLH cannot be treated with steroids or immunosuppressive agents alone. Without effective treatment for tuberculosis infection, patients with tuberculosis-induced HLH may experience rapid disease progression, with mortality rates as high as 100% in some reports [8]. Fortunately, in our case, targeted anti-tuberculosis treatment led to a rapid improvement in the patient's multi-system symptoms.

In this case, the patient presented with two distinctive clinical features. Firstly, urinary retention was observed upon admission. Considering the presence of lower limb pain, weakness, and muscle atrophy in the patient, it was first necessary to alert the patient that the urinary retention was due to spinal cord involvement. However, although lumbar spine MRI revealed disc protrusion and spinal stenosis of the spinal canal, the above lesions were not newly developed in this episode, and no intracanal mass lesions or spinal cord abnormalities were observed on imaging studies. Therefore, while it is difficult to completely rule out urinary retention caused by spinal cord inflammatory changes, the likelihood is low. Whereas previous literature has reported that pelvic infectious lesions such as iliac psoas abscess [9] may cause edema in surrounding tissues, leading to the development of urinary retention [10]. In this case, the symptoms of urinary retention significantly improved shortly after local abscess drainage, suggesting a stronger association with pelvic abscess. Additionally, the formation of abscesses in the iliac psoas and anterior aspect of the thigh in this case differs from the cold abscesses commonly seen in other patients with tuberculous infections. Typically, cold abscess formation occurs in patients with lumbar spine tuberculosis, in which the destruction of lumbar spine bone leads to localized inflammation and necrotic tissue drainage to the paravertebral region, resulting in the typical cold abscess. In this case, the abscess was not present in the paravertebral area, where cold abscesses are typically found, and there was no clear evidence of lumbar vertebral bone destruction on lumbar spine MRI. Therefore, it is considered that the formation of local abscesses may be due to hematogenous dissemination of mycobacterium tuberculosis.

TB-infected patients are frequently complicated by CNS TB, with a prevalence of approximately 1–5% [11]. CNS TB describes various manifestations of infection including meningitis, tuberculoma, spinal arachnoiditis, and transverse myelitis [12]. Tuberculous meningitis may present with concomitant tuberculoma, which is often clinically silent and can grow to a considerable size without meningeal inflammation [13]. Elderly patients generally exhibit more insidious clinical manifestations that sometimes lack specific symptoms compared with younger patients. In our case, at disease onset, the patient had tuberculous meningoencephalitis without typical clinical manifestations such as neck stiffness, vomiting, headache, or disordered consciousness. Neurological symptoms did not appear until over four months later, when the disease had already progressed, which further complicated the diagnosis.

This case report of a patient with disseminated tuberculosis, rare urinary retention due to a psoas abscess, and subsequent secondary hemophagocytic syndrome serves as a timely reminder of the importance of recognizing TB and its myriad complications. Timely administration of anti-tubercular treatment in combination with corticosteroids and/or immunoregulation, under careful monitoring, may lead to a favorable outcome. This case serves as a reminder that when encountering patients with high fever and multi-system involvement, utilizing of steroids without fully excluding infection, especially tuberculosis may lead to exacerbation or dissemination of the infection. While a single case report may not fully examine complex clinical scenarios resulting in fatal outcomes, ongoing data collection from such cases is imperative to prompt clinical suspicion.

Abbreviations

TB	Tuberculosis
WBC	White blood cell count
HLH	Hemophagocytic lymphohistiocytosis
CT	Computed tomography

CSF	Cerebrospinal fluid
M. tuberculosis	Mycobacterium tuberculosis
CNS	Central nervous system
PCR	Polymerase chain reaction

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Author contributions
YJ conceived this study. HL and XH contributed to data collection and wrote the initial draft of the manuscript; YJ revised the manuscript. All authors have read and approved the final manuscript.

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Data availability
All data generated or analyzed during this study are included in this published article.

Declarations

Ethics approval and consent to participate
We obtained ethics approval from the Peking Union Medical College Hospital review boards.

Consent for publication
Written informed consent was obtained from the patient and her son for publication of this case report and the images in it. A copy of the written consent is available by request.

Competing interests
The authors declare no competing interests.

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