Case Report

Disseminated *Mycobacterium kansasii* infection associated with hemophagocytic syndrome

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1. Introduction

*Mycobacterium kansasii*, a non-tuberculous Mycobacterium (NTM), is ubiquitous in the environment and widespread in water and soil. In cities, tap water is the common reservoir for *M. kansasii*. The incidence of *M. kansasii* infection has increased over the past decades, especially in immunocompromised patients such as those with AIDS, organ transplantation, malignancy, chemotherapy, and dialysis. 

*M. kansasii* infections may also occur in healthy adult and pediatric patients. Pulmonary infections and lymphadenitis are most common, but, rarely, disseminated infection also occurs.

Hemophagocytic syndrome (hemophagocytic lymphohistiocytosis) represents a severe hyperinflammatory condition with hypercytokinemia due to a highly stimulated but ineffective immune response. Hemophagocytic syndrome may be primary, as observed in familial hemophagocytic lymphohistiocytosis, Chediak–Higashi syndrome, Griscelli syndrome, and X-linked lymphoproliferative syndrome, or secondary, occurring most commonly in infection. Leading trigger agents are viruses, especially the Epstein–Barr virus (EBV) and cytomegalovirus (CMV). Rare cases of *Mycobacterium* infections triggering hemophagocytosis have been reported. Here we report a rare case of a disseminated NTM infection with life-threatening hemophagocytic syndrome.

2. Case report

A 60-year-old woman with a 10-year history of hypertension, with regular control and follow-ups at a local clinic, presented to our hospital. Ten days before this admission she had suffered from intermittent fever with chills, anorexia, and right upper quadrant pain. There was no productive cough, sore throat, flank pain, or arthralgia. She denied night sweats or weight loss. No recent travel history or animal contact history was reported. She was a cook and was exposed to tap water as part of work-related cooking and cleaning-up. She had taken herbal pills intermittently for general soreness in the last year.

On arrival at the emergency room, her consciousness was clear and oriented; her body temperature was 39.2 °C, pulse rate 132/min, and blood pressure 117/56 mmHg. Tenderness in the right upper abdominal quadrant with hepatosplenomegaly was detected. There was no Murphy's sign or rebound pain.
tions were negative for heart murmur, lymphadenopathy, or any skin lesion. Abnormal laboratory data included hemoglobin 10.6 g/dl, white blood cell (WBC) count 2.13 × 10^9/l, aspartate transaminase 94 IU/l (normal upper limit, 31 IU/l), alanine transaminase 94 IU/l (normal upper limit, 41 IU/l), and γ-glutamyl-transpeptidase 77 IU/l (normal upper limit, 52 IU/l). A chest film was normal, however a 12-lead ECG showed sinus tachycardia. A computed tomography (CT) scan of the abdomen revealed hepatosplenomegaly. Intravenous cefmetazole was administered empirically due to a suspicion of biliary tract infection. However spiking fever was noted and intravenous cefmetazole was replaced with ceftriaxone and doxycycline. Nevertheless, her WBC and platelet counts gradually decreased, and elevated lactate dehydrogenase (1188 U/l; normal upper limit, 460 U/l), alkaline phosphatase (202 U/l; normal upper limit, 230 IU/l), and ferritin (up to 8317 ng/ml) were also noted. Hemophagocytic syndrome was suspected. Virus profiles including HIV, hepatitis B virus, hepatitis C virus, CMV, EBV, and Cryptococcus antigen, as well as autoimmune profiles were negative. A bone marrow biopsy showed interstitial lymphohistiocytosis with granulomatous inflammation, and acid-fast stain was negative (Figure 1).

Due to a suspicion of mycobacterial infection, anti-tuberculosis medications including isoniazid, rifampin, and ethambutol were prescribed. An enzyme-linked immunosorbent spot (ELISPOT) assay and TB PCR of bone marrow were all negative. A chest CT disclosed multiple mediastinal lymphadenopathy. Agranulocytosis with leukocytopenia (white cell count 0.51 × 10^9/l), anemia (hemoglobin, 8.1 g/dl), and thrombocytopenia (platelets 3 × 10^9/l) was noted, accompanied by fever. The bone marrow study was repeated and a smear showed a few engulfed histiocytes, compatible with hemophagocytosis (Figure 2). Therefore, intravenous immunoglobulin and methylprednisolone 40 mg every 12 hours were given. The fever peak decreased for a short period but increased later. Bone marrow and liver cultures all yielded Mycobacterium kansasii. Thus, disseminated M. kansasii infection was confirmed and azithromycin was added to the antibiotic regimen of isoniazid, rifampin, pyrazinamide, and ethambutol. Fever subsided and blood cell counts gradually increased.

A follow-up chest CT scan showed decreased size of the mediastinal lymphadenopathy. The patient was discharged three weeks after initiating anti-tuberculosis therapy. She was discharged with a prescription for anti-mycobacterial medication and with regular outpatient clinic follow-up. However, right lower thigh pain was noted five months following discharge, exacerbated by a fall from a bicycle. Magnetic resonance imaging (MRI) showed a bone tumor with pathological fracture at the right distal femoral shaft. A bone biopsy was carried out and granulocytic sarcoma was confirmed. A thallium-201 tumor scan revealed results compatible with the MRI and the absence of any other lesion. She received chemotherapy for granulocytic sarcoma at our oncology department.

3. Discussion

Hemophagocytic syndrome is an infrequent disorder that is typically associated with fever and worsening general status, spleen and liver enlargement with lymphadenopathy, and involvement of other organs including skin, brain, and lung. Most reported cases of hemophagocytic syndrome in patients with mycobacterial infections have been associated with Mycobacterium tuberculosis,9–15 and only three cases have been reported in patients with NTM infections.7,8,16 A search of the English language literature for the period 1960–2008 revealed ours to be the first report of disseminated M. kansasii infection with documented hemophagocytic syndrome.

M. kansasii is a slower growing group and the most virulent of the NTM. Tap water is thought to be the major reservoir of M. kansasii in cities. Person-to-person transmission has not been documented.5 Our patient, a cook with potentially excessive contact with tap water, might have acquired the infection during preparation and clean-up. Because the clinical picture and pathological and acid-fast stain findings may not be distinguishable from tuberculosis, an interferon-γ enzyme-linked immunospot assay or tuberculosis DNA PCR can be checked to screen for the likelihood of tuberculosis. High-performance liquid chromatography (HPLC) analysis of mycolic acid esters can be used if available to replace colony morphology and pigmentation studies for the early presumptive identification of M. kansasii.17 In our patient, the results of TB-PCR and ELISPOT were all negative, but she responded to isoniazid, rifampin, pyrazinamide, and ethambutol. This situation supports the diagnosis of M. kansasii infection.

Disseminated infection is rare and cultures from bone marrow, liver, and other sterile sites are usually necessary for a diagnosis. Most M. kansasii infections develop in patients who are immunocompromised or have an underlying disease. The risk factors for M.
kansasii infection include HIV infection, pre-existing lung disease, use of immunosuppressive agents, diabetes, alcoholism, and hematologic malignancy.1–3 Our patient was eventually found to have an occult malignancy during follow-up. Therefore, the need for close follow-up of the host status should be emphasized.

In conclusion, mycobacterial infections associated with hemophagocytic syndrome are rare but should be considered in those patients where there is associated fever of unknown origin. Early aggressive survey of the etiology and optimal treatment of the underlying disease improve the outcome of life-threatening hemophagocytic syndrome. Bone marrow and liver studies, including cultures for mycobacterium, are necessary for patients with fever of unknown origin. Close monitoring of immunocompromised conditions such as HIV infection or occult malignancies in patients with a disseminated NTM infection is emphasized.

Conflict of interest: No conflict of interest to declare.

References