Case Report

A case of lepromatous leprosy complicated by hemophagocytosis misdiagnosed as hemophagocytic lymphohistiocytosis

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SUMMARY

Leprosy is an infectious chronic granulomatous disease caused by Mycobacterium leprae. The disease mainly affects the skin, peripheral nerves, mucosa, and viscera. The World Health Organization has reported that most countries with high endemicity have reached the goal of eliminating leprosy (defined as reaching a prevalence of <1 leprosy case per 10 000 population) at the national level, after years of proactive control campaigns. The incidence of leprosy has been decreasing across the globe year by year. However, misdiagnosis happens occasionally due to the complexity of clinical manifestations and lack of physician awareness of this disease. We report a case of lepromatous leprosy complicated by hemophagocytosis misdiagnosed as hemophagocytic lymphohistiocytosis.

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1. Introduction

Leprosy is an infectious chronic granulomatous disease caused by Mycobacterium leprae (M. leprae). The disease mainly affects the skin, peripheral nerves, mucosa, and viscera. Incidence of leprosy has been decreasing across the globe year by year. However, misdiagnosis happens occasionally due to the complexity of clinical manifestations and physicians’ lack of awareness to this disease. Herein, we report a case of lepromatous leprosy (LL) complicated by hemophagocytosis misdiagnosed as hemophagocytic lymphohistiocytosis (HLH).

2. Case report

A 25-year-old male from Shandong, China was admitted to our hospital with the complaints of intermittent fever for 5 months and a painful swelling of the upper limbs for 10 days. The intermittent fever had started in February 2012, with no identifiable cause; the highest temperature was 40.5 °C. In May 2012, the patient visited a local hospital because of recurrence of the fever. Routine blood tests showed a white blood cell count (WBC) of 3.42 × 10^9/L, hemoglobin (Hb) of 115 g/L, and platelets (PLT) of 103 × 10^9/L. Biochemical tests showed alanine aminotransferase (ALT) of 45.8 U/L and lactate dehydrogenase (LDH) of 233.5 IU/L. A bone marrow biopsy showed one hemophagocytosis (HPC) per 100 nucleated cells and abdominal sonography revealed splenomegaly.

Levofloxacin was prescribed but the patient did not respond well. A dose of 10 mg dexamethasone was administered on June 5 and June 15. His temperature returned to the normal level and his general condition improved. Shortly after, his temperature increased to 39.2 °C again. Meanwhile the patient began to present hair loss on the right eyebrow, erythema, and subcutaneous nodes. Taking into consideration the intermittent fever, compromised liver function, splenomegaly, and hemophagocytosis in the bone marrow, hemophagocytic lymphohistiocytosis (HLH) was suspected and the patient was referred to our hospital.

A physical examination at the time of admission showed hair loss on the right eyebrow (Figure 1), multiple asymmetric nonscale macules, and 0.5–5.0 cm erythema nodosum on the limbs, with no tenderness or pruritus (Figure 2). The spleen was palpated at about 3 cm below the subcostal margin. Both forearms were mildly swollen and painful. Both hands were claw-shaped. The sensation of acupuncture was partially lost on the ulnar side of both hands. The bilateral ring fingers and little fingers showed limited movement and adduction of the little fingers was particularly poor (Figure 3).
Further tests on HLH-related parameters showed triglyceride 1.17 mmol/l, fibrinogen 4.41 g/l, serum ferritin 341.1 μg/l, natural killer (NK) cell activity 1.27%, and soluble CD25 3405.7 ng/l. No abnormality was observed on acknowledged primary HLH-related genes. It was not possible to diagnose the patient with HLH in accordance with the HLH-2004 diagnostic criteria.1 In order to diagnose the disease, ultrasonography was performed on both upper limbs, showing segmental enlargement and echo weakening in the bilateral ulnar nerves. Positron emission tomography and computed tomography (PET-CT) indicated hepatomegaly with asymmetric hypermetabolism in the distribution of radioactivity; the maximum standardized uptake value was 5.1. No obvious abnormality was detected in the bone marrow cytology and bone marrow biopsy.

Multiple granulomatous nodules were found in hepatic lobules. There was no caseous necrosis and no lymphoma lesion. Many bacilli were seen on acid-fast staining, suggesting a bacillary
infection of *Mycobacterium tuberculosis* or *Mycobacterium leprae*. A skin biopsy from the lateral aspect of the right thigh showed perineural and peridnexal granulomas containing foamy macrophages in the dermis. Acid-fast staining of a skin biopsy specimen showed acid-fast bacilli inside foamy macrophages. The bacterial index was 5+ (Figures 4–6).

Specific primers were designed according to the *M. leprae* conserved sequence (fragment design size 120 bp). After completing PCR amplification, sequencing was done. Comparison was made with the reference sequence (Br4923), and the gene sequence of *M. leprae* was found in the patient’s skin biopsy specimens. Taking into consideration the biopsy, PCR, and sequencing results and the clinical manifestations of madarosis, enlarged ulcer nerves, and lesions, a diagnosis of lepromatous leprosy (LL) was established. The patient was consequently administered oral prednisone 40 mg/day, dapsone 50 mg/day, clofazimine 100 mg/day, and rifampin 300 mg/month as antileprosy treatment. The patient’s symptoms improved greatly after 1 week and he was referred to a local hospital for continuing treatment. The patient left our hospital with a normal temperature and no erosion of new lesions (although the old ones had not improved noticeably), and the swollen and painful symptoms were alleviated in both upper limbs. Tests showed a WBC of 4.80 × 10^9//l and normal ALT/LDH. The anti-leprosy treatment was continued after discharge with a positive response. The patient resumed normal life and work during the 1-year follow-up.

3. Discussion

HLH is a syndrome characterized by fever, splenomegaly, hepatomegaly, pancytopenia, and hemophagocytosis in the bone marrow, liver, spleen, and lymphatic tissue. HLH may be primary or in a secondary form associated with infections, malignant lymphoma, and autoimmune disorders, etc. In this case, the patient was a young man with a clinical presentation of chronic disease, featuring repeated fever without an apparent reason, splenomegaly, leukopenia, reduced NK activity, and hemophagocytosis in the bone marrow; this led to a high suspicion of HLH. However, this diagnosis was not established due to insufficient compliance with the HLH-2004 diagnostic criteria. Therefore, the case should be considered as a suspected case rather than an established HLH case. The pathophysiological process of HLH is decreased cytotoxic T lymphocytes along with NK cytotoxic dysfunction. In patients with lepromatous leprosy, NK activity can be significantly depressed. This means that lepromatous leprosy patients have the pathophysiological basis to develop HLH. HLH is indisputably a disease that can be caused by *M. tuberculosis* infection. *M. leprae* and *M. tuberculosis* share some common features – both are acid-fast mycobacteria. So it is possible for patients with lepromatous leprosy to develop HLH. However, once it happens, it is not enough to simply treat the leprosy. Treatment to control the HLH should be given in a timely manner, because if left untreated, this disease has a high mortality.

Hemophagocytosis is not pathognomonic for HLH. It can also be found in different types of severe infection or inflammation. Goel et al. found that the sensitivity of hemophagocytosis was 83%, with a specificity of only 60%, suggesting that hemophagocytosis is not specific enough to be a screening test for HLH.2 HLH is characterized by complicated clinical manifestations and a poor prognosis. Therefore, more attention should be paid to suspected cases. However, it should also be noted that the diagnosis of HLH must be in compliance with the HLH-2004 diagnostic criteria to avoid any potential misdiagnosis and inappropriate treatment.

The patient in our case had visited various hospitals before he was finally diagnosed with leprosy at 5 months after disease onset. Besides the complexity of the clinical manifestations, the low incidence of leprosy is one of the important reasons for this situation. In China, a total of 1597 new cases were detected in 2009, with a case detection rate of 0.12 per 100 000 population. The leprosy situation in China is considered to be ‘low endemic’ with an unequal distribution in the southwest area including Yunnan, Sichuan, and Guizhou.1 In our case, the patient’s place of birth and residence is Shandong (East China) and he had not travelled to a highly endemic region; this led to the physicians’ under-awareness of leprosy. It was reported that among the 1462 new leprosy patients in China in 2007, nearly half were detected by passive test at the skin clinic. Case finding in low endemic areas of China remains a major challenge to leprosy control.3 Although leprosy is characterized by a low prevalence and high proportion of disability,2 as many as 50% of newly detected cases in Shandong in 2009 were reported with a grade 2 disability,2 suggesting that a large fraction of cases experienced a delayed diagnosis in the past few years. The misdiagnosis of the present case also resulted from a lack of leprosy knowledge, since the presence of hair loss on the right eyebrow, the characteristic lesions, the swollen and painful upper limbs, and enlarged ulcer nerves are typical of leprosy. As a result, campaigns to improve anti-leprosy knowledge should be held to train physicians in the diagnostic essentials and enhance their vigilance against suspected leprosy cases in non-endemic regions.

In conclusion, the incidence of leprosy is decreasing, but physicians should maintain an index of suspicion for cases in non-endemic regions. Hemophagocytosis is as an essential indicator of most secondary HLH, but it is not absolutely associated with HLH. Therefore, the diagnosis of HLH must be established in accordance with the HLH-2004 diagnostic criteria to avoid misdiagnosis and missed diagnosis.

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