Localized *Histoplasma* Osteomyelitis of the Fibula in a Immunocompetent Teenage Boy: A Case Report

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Running title : A case of localized HO.
Abstract

Background: Infection of the local bone with *Histoplasma capsulatum* is rare and difficult to diagnosis, particularly in immunocompetent subjects, expect exposing to a large inoculum of organisms.

Case Presentation: An 11-year-old boy presented with a localized histoplasma osteomyelitis in the left fibula without any evidence of abnormal immunological function or systemic disease. After surgical clearance of the lesion and homologous cancellous bone, the patient was treated orally with voriconazole for six months. The patient completely recovered with full function of his left leg during the five year follow-up.

Conclusions: Histoplasmosis osteomyelitis can occasionally occur in immunocompetent individuals and be complete cured by surgical clearance of the lesion and antibiotics treatment.

Keywords: *Histoplasma* osteomyelitis; *Histoplasma capsulatum*; immunocompetent.
BACKGROUND

*Histoplasma capsulatum*, a thermally dimorphic fungus, is endemic across North and Central America, particularly in the region of the Mississippi river. Exposure to the organism can cause fatal disseminated fungemia in immunocompromised patients, but only results in an asymptomatic infection in most immunocompetent subjects [1]. Although the organism is found worldwide, cases of histoplasmosis are rare in China. In the past several decades, only a few cases have been reported and infection with *H capsulatum* only in the bone is rather rare. In addition, infection with *H capsulatum* is often neglected by Chinese physicians when they differentially diagnose opportunistic infections in patients with abnormal immunological functions [2-10].

We diagnosed and treated one uncommon patient, who had no any sign of abnormal immune function or other chronic disease, with *Histoplasma* osteomyelitis only in the fibula. We followed the patient for 5 years, and he did not have any adverse consequences. We report this case to discuss our experience in the diagnosis and treatment of patients with histoplama osteomyelitis of the bone.

Case Presentation

An 11-year-old boy was admitted in our hospital on Feb 20, 2006. He complained of the swelling pain of lateral compartment of the lower leg for one week, accompanied by local erythema. He had no fever or chills at the time of admission. In general, he was healthy and had no systemic chronic disease or a history of injury in the lower extremity. He denied recent travel or drug use. He was a native resident.
The patient denied exposure to any infectious patients and the history of infusion.

Physical examination revealed that body temperature was 37\degree C, blood pressure was 118/78 mmHg, heart rate was 78 beats min\(^{-1}\), respiratory rate was 19 breaths min\(^{-1}\), and body weight was 46 kg. The patient appeared to be in good nutritional condition.

There were no notable lymphadenopathy and hepatomegaly as well as unremarkable findings in his heart and lungs. There was a 2×1 cm red skin nodule with mild tenderness in the lateral malleolus near the left ankle of the fibula. The movement of his ankle joint was satisfactory. His arterial pulse was detected on the dorsum of foot, and he was able to move his toe normally.

Laboratory testing indicated that his blood white cell count was 8.6×10\(^9\)/L: neutrophils accounting for 58.3% and lymphocytes for 31.6%. The hematocrit was 36.0%. He was negative for anti-HIV, anti-Syphilis, anti-HCV, anti-HAV IgM, and HBsAb. The concentrations of serum alkaline phosphatase (ALP) was 226 U/L, slightly higher than the cutoff value for abnormal patients: >140 U/L), and total bilirubin was 0.19 mg/dl, which was lower than the cutoff value of 0.30 mg/dl. The concentrations of plasma electrolytes, creatinine, urea nitrogen, and albumin were within normal ranges.

Radiological imaging revealed a cystic lesion with bone growth, absorption, and defused edges in his left ankle (**Fig. 1**). Computed tomography (CT) of the lower extremities displayed possible bone cysts or osteomyelitis in the distal left fibula, accompanied by discontinuous bone cortex and decreased cortical thickness, but
without surrounding soft tissue swelling (Fig. 2). Magnetic resonance imaging (MRI) of the lower extremities found a slightly increased size in the distal left fibula with a low signal of uneven T1WI and T2WI. MRI also showed extensive low T1W1 and high T2W1 in the surrounding soft tissues with unclear edges (Fig. 3). The patient was suspected for a bone tumor or infectious cyst. Two days after admission, the patient was subjected a surgery on the distal lesion in the left fibula. During the surgery, we observed that the lateral cortical bone was still intact and that the subcortex was filled with brown fish meat-like tissue with a size of 3×1×1 cm. Intraoperative examination of a frozen section suggested *nonossifying fibroma*. The lesion tissues with mild margin were scraped using a curette, and the tissue cavity was treated sequentially with carbolic acid, alcohol, and hydrogen peroxide. Finally, the cavity was filled with homologous cancellous bone and the wounds were sutured. Histological analysis revealed round and oval spores as well as granulomatous inflammatory cells in the lesion tissue sections, accompanied by positive periodic acid-schiff staining and periodic acid methenamine-silver staining, but negative smear acid-fast staining (Fig. 4). The patient was diagnosed with a localized histoplama osteomyelitis and was treated orally with voriconazole (400 mg, q.i.d) for six months. There was no significant discomfort or adverse effects during the anti-fungal treatment. The patient was in stable condition after the surgery without fever, and his wound was healing well. The patient was discharged with outpatient instructions to avoid weight-loading for one week after the surgery. The patient was followed up for five years (Fig. 5). He had normal function in his left leg without any adverse
complaints.

**Conclusions**

H. capsulatum infection causes histoplasmosis, which usually occurs in the lungs. The environmental reservoir of H. capsulatum is soil [11]. People acquire H. capsulatum infection usually through the inhalation of conidial forms of the organism present in the environment, such as soils inhabited by chickens. Our case had no obvious source for infection. He denied recent travel history and was retaining living in the countryside of Southeast China in Zhejiang Province where there are many breeding chicken and ducks in the farmer house. His father was a chicken farmer and there were chickens in his home. He reminded that he used to clean the chicken coop for helping his family’s poultry farming before he became ill. It is possible that he obtained H. capsulatum infection from the poultry. Indeed, the prevalence of potential H. capsulatum infection in Southeast China is higher than that in Northwest China [9].

Infection of immunocompetent subjects with H. capsulatum usually causes either asymptomatic or mild influenza like illnesses with fever, headache, malaise, cough, and chest pain, which spontaneously disappear within a few days. Infected individuals can carry H. capsulatum for many years. When the patient becomes immunosuppressed he can develop disseminated histoplasmosis that can affect the lungs, CNS, liver, spleen, and rheumatologic, ocular, and hematologic systems [12]. However, patients with histoplasmosis in the bone and muscle tissues are extremely
rare [12]. There are 25 reported cases of confirmed muscle-bone histoplasmosis. Among them, most patients were disseminated histoplasmosis and there were only 6 patients, who suffered from simple bone histoplasmosis with a lesion in the distal radius or carpal bones. [13-17]. There was only one reported case with lower limb histoplasmosis. A patient with Non-Hodgkin's lymphoma was accompanied with H. capsulatum infection in the tibia [14]. Therefore, to the best of our knowledge, this is the first report of a localized histoplasma osteomyelitis in the fibula in an immunocompetent young boy.

Different from filling the surgical lesion with bone cement or antibiotic beads in adult patients, the surgical cavity of the patient was filled with homologous cancellous bone to reconstruct a stable distal tibiofibular syndesmosis and ankle joint. Indeed, radiological images and physical examination have demonstrated that the function and structure of the surgical muscles and bone tissues completely recovered. The patient is capable of normal and strenuous exercise, even soccer. Itraconazole and amphotericin B were listed as the drugs for the treatment of histoplasmosis [18]. Amphotericin B has been accepted as a standard drug for the treatment of patients with severe illness, but it occasionally has severe side-effects. Amphotericin B has been recommended for induction therapy for disseminated histoplasmosis in patients with acquired immunodeficiency syndrome, and maintenance with either amphotericin B or an oral azole antifungal agent (itraconazole). Conazoles can be alternatively used for the treatment of disseminated histoplasmosis, and itraconazole may be used for both induction and maintenance treatment [19]. However, according to the medicine
instruction of itraconazole, there are not enough proofs for the children medication. Consequently, we treated the 11 year old boy with voriconazole, a conazole with clear statment of teenage medication guides in the medicine instruction. And the prognosis is quite satisfied as the follow-up results.

In summary, we report one unique case of localized histoplasmosis osteomyelitis without immunocompromised evidence. This disease was difficult to be diagnosed by common radiological examinations. We experienced that surgical removal of the lesion and local treatment with autologous bone transplantation, together with systemic treatment with antibiotics were effective for the control of infection and functional recovery.

Consent

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent (in Chinese) is available for review upon requested.

The authors declare that they have no competing interests.

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Figure Legends

Figure 1. X-ray imaging of the left ankle revealed a cystic transparent lesion and the absorption of the inner edge of bone at the distal of fibula.

Figure 2. CT of the distal left fibula showing a cystic and low density image with eccentric enlargement as well as discontinuous bone vortex and decreased cortical thickness.

Figure 3. MRI revealed (a) a slightly increased size of lower left fibula, low signal of T1WI with uneven inner signal. (b) MRI also showed medium or low T2WI signal of the lower fibula and the surrounding soft tissues with high signal and unclear edges.

Figure 4. (a) *Histoplasma capsulatum* can be observed in the plasma of histocytes and multinuclear giant cells and there were clear haloes around the bacteria. HE 400 × (b) *Histoplasma capsulatum* can be clearly demonstrated in red by Periodic acid-Schiff stain (arrows): the shape of the spores are round or oval, mostly identical appearance. There are empty halos around the bacteria. PAS 400 ×

Figure 5. X-ray imaging of the distal fibula. (a) three months after the surgery; (b) six
months after the surgery, and (c) five years after the surgery.