Destructive Cryptococcal Osteomyelitis Mimicking Tuberculous Spondylitis

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Conflict of interest: None declared

Patient: Female, 56-year-old
Final Diagnosis: Cryptococcosis • disseminated cryptococcal osteomyelitis • osteomyelitis
Symptoms: Lower back pain
Clinical Procedure: —
Specialty: Infectious Diseases

Objective: Rare disease
Background: Cryptococcosis is an opportunistic fungal infection that typically occurs in patients with compromised immune systems, primarily affecting the respiratory and central nervous systems. However, cryptococcal osteomyelitis is a rare manifestation of cryptococcal infection, characterized by nonspecific clinical features. Here, we present a case of vertebral cryptococcal osteomyelitis in a middle-aged woman and discuss diagnostic approaches.

Case Report: A 56-year-old woman presented with lower back pain and limited mobility, without fever, and with a history of pulmonary tuberculosis. Physical examination revealed enlarged lymph nodes and tenderness in the thoracic vertebrae. A computed tomography-guided biopsy confirmed granulomatous inflammation caused by Cryptococcus, with abundant 10 μm spherical microbial spores. After 4 weeks of treatment with amphotericin B and fluconazole, symptoms and lesions improved. Upon discharge, the patient was prescribed oral fluconazole. Follow-up examinations showed a stable condition and a negative serum cryptococcal capsular polysaccharide antigen test.

Conclusions: Given the rarity and lack of specificity of clinical features of cryptococcal spondylitis, clinicians encountering similar presentations should consider tuberculous spondylitis and spinal tumors as differential diagnoses. Additionally, tissue biopsy of the affected vertebral bodies should be performed early to establish the type of vertebral infection, aiding in diagnosis, treatment, and prognosis.

Keywords: Cryptococcosis • Osteomyelitis • Thoracic Vertebrae • Opportunistic Infections

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Introduction

Cryptococciosis featuring 2 pathogenic species, Cryptococcus neoformans and Cryptococcus gattii, is an infection typically associated with immunocompromised individuals [1]. Cryptococcus neoformans has a propensity for disseminating to the lungs and central nervous system via the bloodstream or lymphatic system [2,3]. Pulmonary infections usually present with mild respiratory symptoms, such as coughing and dyspnea. Infections of the central nervous system usually present with significant clinical manifestations, including headaches, nausea, vomiting, and altered mental status. However, skeletal infection with Cryptococcus neoformans is rare, occurring in only 5% to 10% of disseminated cryptococcal infections [4]. Cryptococcal osteomyelitis commonly occurs in immunocompromised patients or those receiving immunosuppressive therapy, but can extremely rarely present in immunocompetent individuals [5]. Cryptococcal osteomyelitis most commonly affects the spine vertebrae, but there have been no reported cases of non-adjacent involvement in both the thoracic vertebrae and humerus in immunocompetent patients. This report presents the case of a 56-year-old woman with Cryptococcal vertebral osteomyelitis and the approach to diagnosis.

Case Report

A non-HIV-infected 56-year-old female patient was admitted to spinal surgery in our hospital due to 3 days of lower back pain and limited mobility. She had no chills, fever, cough, sputum, or other discomfort. The patient had a history of pulmonary tuberculosis 10 years ago, and had received standardized anti-tuberculosis treatment. She denied any history of contact with pets, surgery, trauma, blood transfusion, or allergies, as well as other systemic diseases. The physical examination revealed multifocal enlarged lymph nodes in the bilateral neck, clavicle, and armpit, which were firm but movable, with the largest one approximately 4 cm in diameter. The spine had its normal curvature, and there was slight tenderness and percussion pain in the thoracic vertebrae, particularly noticeable at the level of T10 spinous process. There was also tenderness in the bilateral paravertebral muscles and sacral spinous muscles, and significant tenderness in the lateral sides of the chest wall on both sides. Laboratory test results showed a white blood cell count of 4.50×10^9/L (reference range: 4.0-10.0×10^9/L), with neutrophil count of 3.86×10^9/L (reference: 1.8-6.3×10^9/L) and lymphocyte count of 0.26×10^9/L (reference: 1.1-3.2×10^9/L); hemoglobin level of 81 g/L (reference: 120-160 g/L), and platelet count of 72×10^9/L (reference: 100-300×10^9/L). Blood chemistry documented erythrocyte sedimentation rate of 72 mm/h (reference: <20 mm/h), C-reactive protein level of 85.7 mg/L (reference: <20 mg/L), and procalcitonin of <0.02 ng/mL (reference: <0.05 ng/mL). The T-SPOT test was positive, ESAT-6 for 38 spots and CFP-10 for 26 spots. HIV antibodies were negative. Other laboratory findings were all within the reference range. Computed tomography (CT) revealed fibrotic lesions in both lungs and obsolete pulmonary tuberculosis in the upper right lung (Figure 1A, 1B). It also revealed high-density dot shadows in the T5 vertebrae and irregular osteolytic lesions in the T10 vertebrae (Figure 2A). Further magnetic resonance imaging (MRI) showed marrow lesions in the C7-T2, T5, and T10 vertebral bodies, as well as a compressed fracture in the T10 vertebral body (Figure 2B, 2C). Single photon emission computed tomography (SPECT) indicated increased uptake of technetium-99m in the right humerus and the T10 vertebra (Figure 3). Lymph node ultrasound showed enlarged lymph nodes, with unclear structure in the bilateral neck, axillary, and right inguinal regions.

Figure 1. Chest computed tomography. (A, B) Old tuberculosis in the right upper lung, Bilateral lower lobe pulmonary infiltrates with a small amount of pleural effusion (on admission).
Figure 2. Posttherapy magnetic resonance imaging (MRI). Thoracic spine computed tomography (A) and MRI sagittal T1- and T2-weighted images (B, C) show T10 vertebral compression fracture (upon admission). (D) the sagittal T2-weighted of MRI after 1 month of antifungal treatment. (E) the sagittal T2-weighted of MRI after 3 months of antifungal treatment.

Figure 3. Single photon emission computed tomography (SPECT) shows increased uptake of technetium-99m in the area of T10 vertebra and the right humerus.
The patient was given a lymph node biopsy under interventional ultrasound guidance, and results showed that granulomatous inflammation of the lesion without caseous necrosis (Figure 4). However, the result of mycobacterium-specific non-radioactive DNA probes for the lesion was negative. To shed light on these confusing findings, a CT-guided needle biopsy for the lesion at T10 vertebrae was performed. Granulomatous inflammation and a considerable number of round microbial spores with 10 μm diameter were observed in the pathological examination. Further identification based on periodic acid-Schiff (PAS), acid-fast, and methenamine silver staining confirmed the microbial spores were Cryptococcus (Figure 5). The patient was then transferred to the Department of Infectious Disease and received follow-up excisional examination: the serum cryptococcal capsular polysaccharide antigen (Cr Ag) test was determined to be 1:160; the blood cultures were sterile; the cerebrospinal fluid routine test, culture, and Cr Ag test were negative.

Figure 4. Puncture biopsy-sample with hematoxylin and eosin staining of the right axillary lymph node tissue suggests granulomatous inflammation.

Figure 5. Computed tomography-guided needle biopsy for lesion at thoracic T10 vertebrae with staining method. (A) Hematoxylin and eosin stain reveals the granulomatous inflammation with histiocytes, multinucleated giant cells and leukomonocyte. (B) Acid-fast staining reveals acid-fast negative yeast cells. (C) Mucicarmine silver stain shows yeast-like organisms with a thick mucinous wall as highlighted (arrow). (D) Periodic acid-Schiff (PAS) stain reveals several 10 μm diameter PAS-positive spherules with prominent capsules. Magnification ×400.
were all negative. The craniocerebral MRI showed no abnormalities. The patient then received amphotericin B (0.6 mg/kg/day intravenously) plus flucytosine (100 mg/kg/day orally) for a 4-week induction, followed by fluconazole (400 mg/day orally) for 8 weeks of consolidation, and fluconazole (200 mg/day orally) for at least 6 months of maintenance. After 4 weeks of treatment initiation, the patient’s pain significantly improved, cryptococcal titers decreased (Table 1), and the lesion in T10 vertebrae was improved on MRI (Figure 2D, 2E). The patient was released from the hospital and instructed to continue the fluconazole treatment orally. A recent telephone follow-up revealed that the patient’s current condition was stable.

Table 1. Laboratory test results since the patient’s onset of illness.

<table>
<thead>
<tr>
<th></th>
<th>During admission</th>
<th>2 Weeks</th>
<th>3 Weeks</th>
<th>1 Month</th>
<th>3 Months</th>
<th>6 Months</th>
<th>16 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC (10⁹/L)</td>
<td>4.50</td>
<td>2.80</td>
<td>2.40</td>
<td>2.18</td>
<td>2.20</td>
<td>5.64</td>
<td>3.37</td>
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<tr>
<td>NEU (10⁹/L)</td>
<td>0.26</td>
<td>0.47</td>
<td>0.46</td>
<td>0.40</td>
<td>0.27</td>
<td>0.64</td>
<td>2.38</td>
</tr>
<tr>
<td>LY (10⁹/L)</td>
<td>0.26</td>
<td>0.47</td>
<td>0.46</td>
<td>0.40</td>
<td>0.27</td>
<td>0.64</td>
<td>0.66</td>
</tr>
<tr>
<td>ESR (mm/h)</td>
<td>72</td>
<td>–</td>
<td>49</td>
<td>34</td>
<td>65</td>
<td>88</td>
<td>57</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>85.70</td>
<td>8.67</td>
<td>9.27</td>
<td>–</td>
<td>17.31</td>
<td>13.06</td>
<td>–</td>
</tr>
<tr>
<td>PCT (ng/mL)</td>
<td>&lt;0.020</td>
<td>&lt;0.020</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>0.44</td>
<td>–</td>
</tr>
<tr>
<td>Cr Ag test</td>
<td>–</td>
<td>1: 160</td>
<td>–</td>
<td>–</td>
<td>1: 20</td>
<td>1: 50</td>
<td>Negative</td>
</tr>
</tbody>
</table>

*–’ signifies that the test was not performed. WBC – white blood count; NEU – neutrophil count; LY – lymphocyte count; ESR – erythrocyte sedimentation rate; CRP – C-reactive protein; PCT – procalcitonin; Cr Ag test – serum cryptococcal capsular polysaccharide antigen test.

Discussion

Cryptococcosis is usually an opportunistic infection and mainly occurs in patients with immunocompromised disorders or those receiving immunosuppressive therapy [6,7]. Vertebral cryptococcosis is clinically rare [8]. The most common symptoms of vertebral cryptococcosis are nonspecific clinical manifestations, such as soft tissue swelling or pain. Chills, fever, and fatigue are not the main clinical manifestations [9]. The patient in this case presented only with pain in the thoraco-lumbar region, without other discomfort, such as fever, making the clinical symptoms atypical. It is difficult to make a preliminary diagnosis through physical examination and routine laboratory tests alone, especially in an immunocompetent patient. Thus, a correct diagnosis would require the combination of hematomal examination, histopathological analysis, and microbiological culture results [10].

The vertebral bodies of the spine are commonly regarded as a frequent site for Cryptococcus infection, but its incidence is low [11]. There are 19 reports of spinal cryptococcal osteomyelitis [7-10,12-26]: 10 cases involved lumbar vertebrae, 7 involved thoracic vertebrae, 3 involved sacral vertebrae, and 1 involved cervical or coccygeal vertebrae. Among them 9 cases had isolated destructive bone lesions, and 10 cases were disseminated. Disseminated cryptococcal osteomyelitis refers to bone changes usually involving 2 or more bone sites. In 10 cases, 9 cases reported adjacent vertebral cryptococcal infection [7,12,13,18,19,21,23,25,26], and only 1 case was non-adjacent L1 and S1 vertebral cryptococcal infection [24]. To the best of our knowledge, the present report is the first documentation of multifocal cryptococcal osteomyelitis affecting the T10 vertebrae and the right humerus in an immunocompetent individual. Among cryptococcal lesions, only 5.4% affect the humerus as osteomyelitis [27]. In our patient, SPECT imaging revealed a lesion on the right humerus. However, due to the insignificant clinical features of the lesion’s location, further biopsy was not performed, and dynamic observation was conducted instead.

In this case, the imaging studies for the patient showed bone destruction and osteolytic changes around the T10 vertebrae, which exhibited similar radiological features to bone tuberculosis and tumor. Combined with the patient’s history of pulmonary tuberculosis, it was tended to be misdiagnosed as spinal tuberculosis. Among the 19 published cases of spinal cryptococcal osteomyelitis, 6 cases were misdiagnosed as skeletal tuberculosis [8-10,15,17,23], and 2 cases were diagnosed as malignant tumors [7,24]. Further evaluation through lesion site biopsy and pathological examination is necessary to establish a definitive diagnosis.

Histologically, Cryptococcus infection usually exhibits with non-necrotizing or necrotizing granulomas, especially for immunocompetent patients [28]. In our case, cervical lymph node...
biopsy and thoracic T10 vertebrae biopsy suggested non-necrotizing granulomatous inflammation. Due to this result, presumed to be similar to the quintessential granuloma, the tuberculosis in tuberculosis, further different staining methods can always be needed. In our case, the hematoxylin and eosin stains showed several spherules. These organisms were acid-fast negative yeast cells in acid-fast staining, varying in size (2-20 μm in diameter). Mucicarmine silver stain and PAS staining seemed to be helpful for the diagnosis of cryptococcal infection, as the organisms were highlighted as the mucin-rich capsule or PAS-positive spherules.

According to the latest literature, hematogenous dissemination or lymphatic spread through the lymphatic system has been defined as the main source of joint infections [29]. Most skeletal infections are caused by blood-borne microorganisms originating from pulmonary lesions, where they typically provoke a pronounced granulomatous reaction [26]. After Cryptococcus infection spreads, central nervous system involvement is the most common manifestation of cryptococcosis, causing meningoencephalitis [30]. Although the patient had no symptoms of central nervous system involvement, such as dizziness, headache, or neck stiffness, we performed a cerebrospinal fluid routine test, culture, Cr Ag test, and cranioencebral MRI to exclude the possibility of cryptococcal meningitis occurrence.

Although antifungal therapy is indispensable for the treatment of cryptococcal osteomyelitis, the preferred treatment approach remains controversial. The Infectious Diseases Society of America guidelines endorse the use of fluconazole and amphotericin B as initial therapy for cryptococcal meningitis, followed by fluconazole for maintenance treatment [31,32]. Among the 19 patients with spinal cryptococcal osteomyelitis, 7 were treated with a combination of amphotericin B and fluconazole, 8 were treated with fluconazole alone, and 4 received amphotericin B as a secondary treatment. Of those, 12 patients underwent surgical treatment. Ultimately, 5 (71.4%) patients in the combination antifungal therapy group achieved recovery, all 8 (100%) patients treated with fluconazole alone also achieved recovery, and 3 (75%) patients treated with amphotericin B achieved recovery. As we did not have a positive culture, the antifungal susceptibility testing could not be performed. Thus, our patient underwent combined antifungal therapy, and as of now, according to the follow-up results, the patient’s condition remains stable.

Conclusions

In this report, we present a rare case of multifocal destructive bone lesion and osteogranulomatous inflammation in the T10 vertebra and right humerus in an immunocompetent woman. The patient had no high-risk factors for fungal infection and had a strong tendency toward tuberculous infection, which could be easily overlooked. In cases of spinal cryptococcal osteomyelitis, reliance solely on clinical symptoms and imaging findings can be inadequate; therefore, prompt antigen testing, culture, and histopathological analysis are essential for accurate identification. Moreover, even in patients with disseminated cryptococcosis without signs of meningeal irritation, lumbar puncture should be performed to exclude central nervous system infection and prevent misdiagnosis. Antifungal therapy is indispensable for spinal cryptococcal osteomyelitis. However, in cases of severe spinal damage resulting in compression of the spinal cord and nerve injury, a combination of aggressive surgical treatment and antifungal therapy becomes paramount.

Department and Institution Where Work Was Done

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References:


