

Case Report

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Disseminated Cryptococcosis with Pulmonary and Marrow Involvement Mimicking Radiological Features of Malignancy

The most commonly involved sites of cryptococcosis are the lungs and the central nervous system. Cryptococcal osteomyelitis is a rare complication of disseminated cryptococcosis, and the vertebrae are the most common site of this infection. The most common underlying disease is sarcoidosis, followed by tuberculosis and previous steroid therapy. Conservative treatment alone or treatment with a combination of the medical and surgical curettage is successful in most cases. We report a case of cryptococcal osteomyelitis in a 63-year-old immunocompetent male who presented with lower back pain over the sacral region for several years. Radiologic studies showed a pulmonary mass and a radiolytic lesion involving the left ischial bone, which mimicked pulmonary malignancy with bone metastasis. Biopsy of the lung mass and the bone lesion revealed abundant cryptococcal organisms, and cryptococcal osteomyelitis was diagnosed.

Cryptococcosis is a disseminated infection of man and animals caused by *Cryptococcus neoformans*. The most common sites are the lung and the central nervous system. Osseous involvement occurs in 5-10% of patients with disseminated cryptococcus.^{1,2} The typical radiological features are purely lytic, with discrete margins and usually without periosteal reaction.² These findings often contribute to the initial misdiagnosis of bone metastasis. We report a case of cryptococcosis in a 63-year-old male with a pulmonary mass and a lytic destruction lesion in the left ischium.

CASE REPORT

A 63-year-old male presented with lower back pain over the sacral area for several years. No accompanying chills or fever were noted. He denied a history of intravenous drug use, homosexual activity, or transfusion of blood products. He had no known history of any systemic disease. Pelvic radiography (Fig. 1) showed osteolytic

destruction involving the left ischial tuberosity. Chest radiograph showed a mass shadow in the left lung (Fig. 2A). Computed tomography (CT) of the chest (Figs. 2B & C) revealed a small round lesion at the superior segment of the left lower lobe. CT of the pelvis (Fig. 3) showed an osteolytic lesion at the left ischial bone with adjacent soft tissue infiltration. Whole-body Tc-99m



Fig. 1. Radiography of the pelvis showed a lytic bone destructive lesion involving the left ischial tuberosity (arrow).

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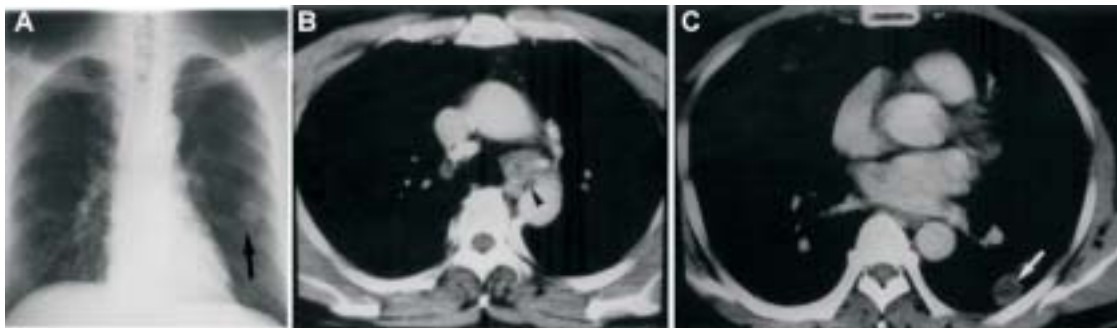


Fig. 2. Posteroanterior chest radiography and chest CT. (A) A round mass (2 × 2 cm) was visible in the middle zone of the left lung (black arrow). (B and C) Chest CT showed a mediastinal node (arrowhead) and a relatively well-defined small hypodense round mass at the superior segment of the left lower lobe in the subpleural distribution (white arrow).

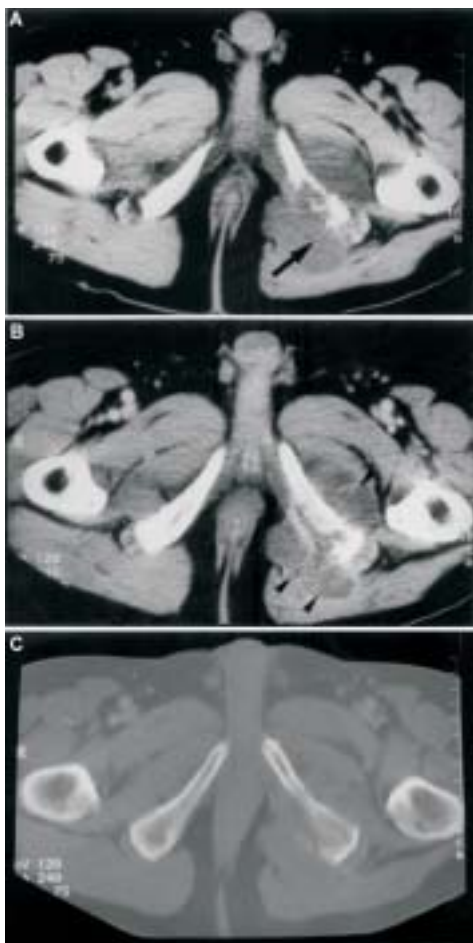


Fig. 3. Finding of CT scans of the pelvis. (A) Intramedullary bone destruction at the left ischial bone breaking through the cortex into the adjacent prominent soft tissue mass (arrow) but without calcification or tumor matrix present in the intramedullary cavity. (B) After contrast injection, the soft tissue component is slightly more hypodense than the muscle, with peripheral enhancement and central area of low density representing necrosis or fluid collection (arrowheads). (C) No definite periosteal reaction is apparent in the bone window scans.



Fig. 4. Whole-body and brain FDG-PET (2-[¹⁸F]-fluoro-2-deoxyglucose-positron emission tomography) scan. There are 2 round areas of intense FDG (2-[¹⁸F]-fluoro-2-deoxyglucose) uptake in the chest. One is the FDG uptake of the left pulmonary lesion (thin arrow) and the other is a mediastinal lesion (arrowhead). (maximal/average SUV for the 2 lesions were 4.4/2.5 and 5.4/3.4, respectively). Intense uptake is also seen in the medial part and surrounding the ischial tuberosity (maximal/average SUV =10.6/7.5) (thick arrows). (SUV = standard uptake value).

MDP (Technetium-99m methylene diphosphonate) bone scan showed increased tracer uptake in the left ischium (not shown). FDG (2-[¹⁸F]-fluoro-2-deoxyglucose)-positron emission tomography (PET) scan of the whole body and brain showed 2 round areas of intense uptake in the chest, and 1 large area in the left buttock (Fig. 4). Open biopsy of the left ischium and transthoracic needle biopsy of the left pulmonary mass showed many cryptococcus-like round capsulated fungi with budding appearance. Cerebrospinal fluid (CSF) and serum were positive for cryptococcal antigen by latex agglutination test. Indian ink stain of serum and CSF were negative. The patient was treated with 2030 mg of amphotericin B, and the pain over the sacral region subsided gradually. He was lost to follow-up after 1 month of treatment in our hospital.

DISCUSSION

Cryptococcus neoformans is a ubiquitous organism that can cause acute, subacute, or chronic systemic disease in humans. Clinical infection in humans usually involves the pulmonary and central venous systems. Osseous involvement occurs in 5-10% of patients with disseminated cryptococcosis.¹ Extrapulmonary cryptococcosis is typically chronic, with alternating periods of remission and exacerbation for as long as 16-20 years.² Hematogenous spread from pulmonary infection is the most likely route. Spread from a site of latent infection in a lymph node or direct spread from the skin is another possibility.¹ Isolated cryptococcal osteomyelitis without involvement of organic systems other than osseous structures can occur but is rare. However, most cases show pathological involvement of the other systemic organisms.³ Most cases of cryptococcal osteomyelitis occur in immunocompromised patients. Cryptococcal osteomyelitis with or without other sites of infection in immunocompetent patients is less frequent.^{1,4}

The most common osseous site in cryptococcal osteomyelitis is the spine, followed by pelvis and ribs.⁴ Radiological features of cryptococcal osteomyelitis are nonspecific. The typical radiological features are purely lytic, with discrete margins, mild surrounding sclerosis, and little or no periosteal reaction.^{1,3-5} Other infectious

agents and malignant neoplasms may yield lytic osseous lesions with imaging characteristics similar to cryptococcal osteomyelitis. The differential diagnosis includes other fungi, mycobacterium tuberculosis, atypical mycobacteria and *brucella*, while actinomycotic osteomyelitis generally is associated with disease in the adjacent soft tissue and is accompanied by marked periosteal reaction. The limited nature of the periostitis is more typical of cryptococcosis than of other fungal disorders.⁶ Primary osseous malignancy presents with periosteal reaction more often than metastatic neoplasms. Lung cancer commonly produces lytic metastasis to bone. Tumors metastatic to bone which produce predominately lytic lesions are neoplasms originating in the breast, kidney, prostate, thyroid, gastrointestinal tract, and melanoma. Although very uncommon, most cases of cryptococcal osteomyelitis with periosteal reaction have been observed in children or adolescents.^{7,8} In these cases, extensive periosteal reaction often contributes to an initial misdiagnosis of primary osseous sarcoma, such as Ewing sarcoma and osteogenic sarcoma.

Our patient had many of the radiographic and clinical features of cryptococcal osteomyelitis. However, lung cancer with bone metastasis was misdiagnosed due to the findings of a pulmonary mass with a mediastinal node, and a huge osteolytic bone destructive lesion in the right ischium. Three forms of pulmonary cryptococcal disease are recognized.¹¹ Pulmonary *cryptococcus* with a mediastinal node is common when there is a pathologically granulomatous reaction, producing an ill-defined mass, segmental consolidation, or an infiltrative mass on radiography. It is less associated with mediastinal or hilar node when air-space collections of fungus with minimal or no inflammatory reaction cause a well-defined mass to present radiographically. It is unusual in cases such as our patient with a well-defined pulmonary mass and a mediastinal node.

Tc-99m diphosphonates are presently the agents of choice for imaging of bone and joint. Blood flow is a necessary component for active bone tracer uptake. However, bone tracer uptake is nonspecific. All metastatic disease, benign bone tumor, fracture, metabolic disease, or infectious disease will show hot spots on the bone scan. The addition of Gallium-67 (Ga-67) or Indium-111 (In-111) WBCs may be necessary to increase

the specificity to differentiate bone infection from other skeletal lesions. Focally increased In-111 WBC or Ga-67 bone uptake, which is incongruent with the Tc-99m diphosphonate scan, should raise the suspicion of osteomyelitis.⁹ FDG PET is useful not only for diagnosing infection, but also for assessment of lesion activity. In our patient, the uptake of FDG in the left ischium was 10.6/7.5 (maximal/average standard uptake value), the FDG uptake of the 2 lesions in chest were 4.4/2.5 and 5.4/3.4 (maximal/average standard uptake value), respectively. It may be difficult to differentiate infectious or inflammatory lesions from malignant tumors solely by intensity of FDG uptake, because intense FDG uptake is often observed in some infectious or inflammatory lesions. Although not always possible, assessment of the time-activity course of FDG uptake postinjection may be helpful in differentiating inflammatory lesions from malignant lesions.¹⁰

The diagnosis of cryptococcal osteomyelitis is often made on morphologic identification of the organism in surgical study. Optimal therapy appears to involve a combination of amphotericin B, flucytosine, and surgical debridement.^{1,4}

Since the clinical and radiographic signs of cryptococcal osteomyelitis are not specific, diagnosis can be made only on culture or histological examination of tissue.¹ It is clear that determination of cryptococcal antigen in serum may prevent unnecessary invasive diagnostic procedures, providing that clinicians included cryptococcus in the differential diagnosis of a bone lesion.¹²

In conclusion, cryptococcal osteomyelitis can progress to fatal complications in an unpredictable manner. With an aggressive approach to both diagnosis and therapy, cryptococcal osteomyelitis, although rare, is a treatable disease that should be included in the differential di-

agnosis of lytic osseous lesions.

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