Rare disease

Coccidioidomycosis masquerading as malignancy

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Summary

Skeletal coccidioidomycosis is extremely rare and in the non-endemic areas, diagnosis is often delayed or missed resulting in extensive and unnecessary medical investigation for other diseases. The authors report a case of disseminated skeletal coccidioidomycosis in a previously healthy person living in a non-endemic area, who was initially thought to have a malignancy. Due to the presence of multiple expansile lytic bone lesions on x-rays and CT scan, an extensive investigation for malignancy was done. Diagnosis of coccidioidomycosis was made when H&E and Gomori's methenamine silver staining of a bone biopsy sample revealed multiple fungal spherules, which were confirmed to be *Coccidioides immitis* by culture and PCR. On questioning, the patient admitted to have spent 2 weeks in Arizona (an endemic area) few months ago. He was discharged home on long-term fluconazole. At 1 month clinical follow-up, a significant improvement in his lesions was noticed.

BACKGROUND

Skeletal coccidioidomycosis, a type of disseminated coccidioidomycosis, is extremely rare and in the non-endemic areas, diagnosis is often delayed or missed resulting in extensive and unnecessary medical investigation for other diseases. Disseminated coccidioidomycosis is more likely to occur in patients with immunosuppression from drugs, malignancy, HIV infection or other causes.^{1 2} We report a case of disseminated skeletal coccidioidomycosis in a previously healthy immunocompetent person living in Michigan (a non-endemic area), who was initially thought to have a malignancy. This case emphasises the importance of obtaining a good clinical history; including history of travel to areas endemic for certain diseases.

CASE PRESENTATION

A 44-year-old African-American male with no medical history was admitted with complaint of painful lumps over his left clavicle and scapula for 3 months. The lesion on

clavicle had burst open and was draining pus for last few days. He denied any history of fever, weight loss, change in appetite or bone pains. He was born and brought up in southeast Michigan. On examination, he was afebrile with stable vital signs. There was a 2×2 cm ulcerated lesion with purulent drainage on left mid-clavicular area (figure 1) and a 4×3 cm, hard, immobile, non-fluctuant lump at superior edge of left scapula. There were no palpable cervical, axillary or inguinal lymph-nodes.

Chest x-ray showed clear lungs and normal mediastinum. Radiographs and CT scan of upper extremities showed a pathological fracture of left clavicle and expansile lytic lesions in both clavicles, left scapula, scapular spine and C7, T1 and T7 vertebral bodies (figures 2 and 3).

Figure 1 Ulcerated lesion with purulent drainage on the left mid-clavicular area.

Figure 2 X-ray of left upper extremity showing an expansile swelling with cortical disruption and irregular margins in the region of mid-clavicle, suggestive of a pathological fracture of left clavicle and possible osteomyelitis.

Bone scan showed areas of focally increased uptake in left mid-clavicle, mid-thoracic spine and lateral aspect of left 11th rib (figure 4).

A non-traumatic fracture of clavicle in a healthy male was concerning for bone disease, malignancy or metastasis. Laboratory investigation revealed normal serum and urine protein electrophoresis, negative urine Bence-Jones proteins, normal prostate specific antigen, negative HIV 1/2 and negative fluorescent-stain for acid-fast bacilli. CT abdomen and pelvis showed multiple lytic lesions of iliac bones, left ischium, sacrum and L4 vertebrae (figure 5). Histopathology of the biopsy sample from clavicular lesion demonstrated multi-nucleated giant cells and necrotic zones with multiple fungal spherules and endospores (figures 6–8). Morphologically, the fungus had appearance of *Coccidioides immitis*, which was confirmed when culture grew *C immitis* (figure 9) and methicillin-resistant *Staphylococcus aureus* (MRSA). The identity of fungus was confirmed by PCR method as well. On questioning, the patient admitted to have spent 2 weeks in Arizona few months ago.

Figure 3 CT scan showing lytic lesions in both clavicles and body of C7 vertebra.

DIFFERENTIAL DIAGNOSIS

In an adult, major differential diagnosis of multiple lytic bone lesions include multiple myeloma, bone metastasis, disseminated tuberculosis and granulomatous diseases. Among infectious causes, in addition to disseminated tuberculosis, brucellosis and blastomycosis are also important differentials. Brucellosis is a worldwide zoonosis caused by small gram-negative non-encapsulated coccobacilli of the genus *Brucella*.³ It is characterised by a granulomatous reaction in the reticuloendothelial system and may affect several organs with varying clinical manifestations. Osteoarticular involvement is one of the common manifestation, particularly in *Brucella suis* infections, and may include spondylitis, sacroiliitis, osteomyelitis, peripheral arthritis, bursitis and tenosynovitis.³ *Brucella* osteomyelitis may produce lytic bone lesions resembling neoplasm.

Blastomycosis is a systemic pyogranulomatous infection caused by dimorphic fungus, *Blastomyces dermatitidis*. It is endemic in the south central and north central USA.

Osteomyelitis is a common extrapulmonary manifestation of blastomycosis, occurring in up to one quarter of patients with multiorgan disease.⁴ Vertebrae, pelvis and sacrum are the most commonly involved bones and a well-circumscribed, osteolytic lesion is the most common radiographic finding. Biopsy of the bone lesions may reveal granuloma formation, suppuration and/or necrosis.

As mentioned above, this patient had normal serum and urine protein electrophoresis, negative urine Bence-Jones proteins, normal prostate specific antigen, negative HIV 1/2 and negative fluorescent-stain for acid-fast bacilli. X-ray and CT scan of the chest showed normal lungs and mediastinum. Other than the presence of lytic bone lesions at multiple sites, CT abdomen and pelvis did not reveal any abnormal masses. First clue to the diagnosis of skeletal

Figure 4 Bone scan demonstrating areas of focally increased uptake in left mid-clavicle, mid-thoracic spine and lateral aspect of left 11th rib.

Figure 5 CT abdomen/pelvis showing lytic lesions in both iliac bones, ischium and L4 vertebral body.

Figure 6 H&E staining of the biopsy sample from clavicular lesion showing necrotic granulomatous tissue and a multinucleated giant cell with fungal spherule.

coccidioidomycosis was provided by findings of the bone biopsy sample. When a history was elicited at this point, the patient admitted to have spent 2 weeks in an endemic area few months ago. If this travel history was available at the initial encounter, investigations could have been directed accordingly to expedite the diagnosis.

TREATMENT

The patient was treated with daptomycin for MRSA infection (due to high minimum inhibitory concentration of vancomycin) and started on fluconazole for skeletal coccidioidomycosis. Once clinically stable, he was discharged home on long-term fluconazole therapy with the plan to follow-up in infectious diseases clinic.

OUTCOME AND FOLLOW-UP

At 1 month follow-up in infectious diseases clinic, left clavicular wound had healed and there was a decrease in the size of scapular mass.

Figure 7 H&E staining of the bone biopsy sample showing necrotic tissue with interspersed bony spicules.

Figure 8 Gomori's methenamine silver staining of the biopsy sample from clavicular lesion showing fungal spherules (circular structures).

DISCUSSION

Coccidioidomycosis, a systemic fungal infection caused by dimorphic soil fungi, *C immitis* or *C posadasii*, is endemic in northern Mexico, the southwestern USA, and parts of Central and South America.¹ The primary infection occurs in lungs and is asymptomatic in more than 60% of the cases.² Less than 1% of infections result in disseminated disease, which may involve any organ. Skeletal coccidioidomycosis is extremely rare and occurs in 10 to 50% of the patients with disseminated disease.¹

In skeletal coccidioidomycosis, vertebral osteomyelitis is commonly seen with occasional involvement of the sacrum and ileum. Lesions become evident in a subacute or chronic fashion and may easily be mistaken for malignancy, tuberculosis or other granulomatous diseases.⁵ Symptoms depend on the site of infection and may be difficult to differentiate from infection of these organs due to other pathogens. If the initial pulmonary infection goes unrecognised, the diagnosis of extrapulmonary coccidioidomycosis is frequently delayed by weeks or even months due to indolent nature of the infection and lack of specificity of symptoms.⁶

Figure 9 Morphology of the fungus grown on culture showing mycelial phase of *Coccidioides immitis* with coarse, septate, hyphae and anthroconidia.

Oral azole antifungal agents such as fluconazole and itraconazole are the initial drugs of choice for coccidioidomycosis. Amphotericin B alone or in combination with azoles is reserved for patients with rapidly worsening lesions or lesions located in vital sites such as spine. Surgical debridement or stabilisation may be used as an adjunctive treatment in selected cases.⁷

Because of the potential impact on the spinal cord and mobility, management of vertebral lesions may require surgical debridement and stabilisation to control the infection.¹ Immediate surgical decompression is recommended for lesions with evidence of cord compression. For patients with stable vertebrae with no evidence of cord compression, medical treatment may be initiated without immediate surgical intervention.¹ Due to substantial risk of relapse with discontinuation of antifungal drugs, extended treatment of >12 months duration may be required in patients with vertebral infection to avoid the adverse effect of recurrences at these vital sites.⁸

Our patient most likely had an asymptomatic pulmonary infection after his visit to the endemic area and later on, developed extensive osteomyelitis of multiple bones.

Although it is rare to see extensive extrapulmonary disease as the first manifestation in an immunocompetent patient, clinicians should increase their awareness and consideration of this disease in patients with history of travel to endemic areas.

Learning points

- ▶ Coccidioidomycosis is endemic in northern Mexico, the southwestern USA, and parts of Central and South America.
- ▶ Skeletal coccidioidomycosis may easily be mistaken for malignancy, tuberculosis or other granulomatous diseases.
- ▶ Diagnosis of coccidioidomycosis should be considered in patients living in non-endemic areas with suspicious symptoms and history of travel to endemic areas.

Competing interests None.

Patient consent Obtained.

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