Cryptococcal osteomyelitis of the skull

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An otherwise healthy 65-year-old male from a rural area presented with a 1-month old non-tender scalp mass. He had a history of being stuck with a stone in the parietal region a year earlier but hadn’t developed any complications. Needle aspiration of the mass revealed numerous yeast cells, which were confirmed to be Cryptoccus neoformans. This case describes a rare presentation of C. neoformans infection in a human immunodeficiency virus (HIV)-negative patient. Moreover, while osteomyelitis due to Cryptoccus is generally preceded by fungemia, in the present case it was caused by direct inoculation of the etiologic agent. We review 11 similar cases published since 1983 in which most of the patients developed an insidious mass in their scalps with osteolytic lesions as seen on X-ray and all were HIV-negative. Nine of the eleven patients in these cases had good recovery after surgical debridement and treatment with amphotericin B, fluycytoci and/or fluconazole. The remaining two patients died during hospitalization. Cryptococcal osteomyelitis should be part of a differential diagnosis when confronted with an insidious growing mass or abscess of unclear origin in the scalp.

Keywords Cryptococcus neoformans, osteomyelitis, skull, cryptococcoma

Introduction

Cryptococcosis, formerly known as torulosis, is an opportunistic mycosis caused by members of the Cryptococcus neoformans complex. Although it has been known from the beginning of the 20th century when it occasionally affected immunocompetent humans, it has recently become more important due to its association with the human immunodeficiency virus (HIV) epidemic. In addition, C. neoformans infections typically involve the lungs and the central nervous system (CNS), but can also affect other organs, e.g., the skin, eye, prostate and rarely, the skeletal system [1].

Although first documented in a Mexican immigrant in 1935, the literature on cryptococcal osteomyelitis is limited [2]. Since the initial presentation, approximately 90 additional cases of cryptococcal infection with bone involvement have been reported, representing 5% of all such infections [3]. We believe that this percentage is decreasing due to the increased number of cases of cryptococcosis in HIV-positive patients who rarely present with bone involvement.

Cryptococcal osteomyelitis is often preceded by dissemination of the etiologic agent from the portal of entry and bone involvement is found in 10% of patients with disseminated disease. Osteomyelitis without fungemia is uncommon with a little more than 50 reported cases. In addition to systemic infection, cryptococcal osteomyelitis has been typically associated with sarcoidosis, tuberculosis, steroid therapy and diabetes [4].

When bone infections do occur, Cryptoccus most commonly is associated with the vertebrae, pelvis, ribs, femur and tibia, with one quarter of the patients having involvement of more than one bone [4,5]. The skull is a less frequent target, with only 18 previously reported cases [3,6–10]. We present here a case of cryptococcal osteomyelitis of the skull and review the literature relative to this previously known yet uncommon infection.

Case report

A 65-year-old Guatemalan agricultural worker with a 1-month-old scalp mass was seen at our Hospital. The
The patient had a history of being struck with a stone on the same region of the skull a year earlier. A few weeks after the accident, he developed a swelling over the area involved in the accident and presented to a clinic where he was diagnosed with soft tissue infection and abscess formation. Purulent material was drained from the lesion but no cultures were prepared from this material. He received treatment with an unknown antibiotic for 7 days and the lesion apparently healed. However, 10 months later he noted a slow-growing, painless soft mass on his scalp and had one episode of fever. He was then referred to the neurosurgery department for further evaluation.

There was no known history of systemic disease and the patient denied intravenous drug use, homosexual activities, or transfusion of blood products. During physical examination, a painless, soft, well-defined 10 cm mass was noted in the right parietal scalp. Overlying skin appeared normal with no swelling, warmth or tenderness. (Fig. 1A) Vital signs were normal and the rest of the physical examination, including neurological studies, was unremarkable.

X-rays of the skull revealed a 5-cm irregular osteolytic lesion over the right parietal bone. The chest X-rays failed to demonstrate any parenchymal lesions. Blood count and basic metabolic panel were unremarkable. Serology for HIV was reported as negative. Computed tomography with contrast enhancement revealed an abscess in the scalp with an underlying mass that eroded into the parietal bone and produced mild local compression (Fig. 1B).

A needle aspiration of the mass was performed from which 30 cc of hemorrhagic-like fluid was collected. Gram smear of the fluid showed fibrin, scarce neutrophils but no significant numbers of bacteria. However, examination of a Giemsa-stained portion of the fluid revealed occasional yeast cells (Fig. 2A). Gomori Grocott’s methenamine silver stain showed numerous round-to-oval, budding, non-encapsulated yeast cells (Fig. 2B) Portions of the sample were then inoculated onto Saboraud dextrose and Mycosel agar (BDL).

On the next day, serum cryptococcal antigen was reported positive by latex agglutination with a titer of 1:16. Lumbar puncture was not performed because it was considered a risky procedure that would not yield any other diagnostic information.

Two days after drainage, the abscess collected again with hemorrhagic fluid. The patient was prepared for craniotomy and surgical curettage. Surgery showed an abscess with a soft mass at its base, approximately 2 cm in diameter that eroded through the parietal bone and compromised the dura mater. The patient had an uneventful recovery after surgery.

Studies of a hematoxylin and eosin-stained decalcified bone specimen revealed an inflammatory infiltrate and formation of granulomas compatible with a cryptococcoma. A Periodic acid Schiff (PAS)-stained bone sample showed the same granulomatous reaction with spherical PAS-positive fungi within the cytoplasm of large macrophages (Fig. 3).

After 4 days, numerous colonies were recovered from Sabouraud agar. They were analyzed with the yeast assimilation test system API-ID32C (bioMérieux) and identified as C. neoformans isolates.

The patient received intravenous amphotericin B for 14 days and was discharged from our hospital with oral fluconazole. He has remained asymptomatic during a 2-month follow-up period.

The occurrence of a Cryptococcus infection in an immunocompetent patient living in an endemic area raised suspicion that the isolate might be Cryptococcus gattii and consequently subcultures were sent to the Mycotic Diseases Branch of the Centers for Disease Control and Prevention in Atlanta, Georgia for confirmation. The isolate was cultured...
Cryptococcal osteomyelitis of the skull develops as an insidious infection, patients having symptoms from 3 weeks to 1 year prior to diagnosis. All but three patients presented a soft exophytic mass. At presentation, half of them showed skin tenderness. In three cases, including the present report, skin lesions seemed to be the portal for direct inoculation of \textit{C. neoformans} from the environment [8,13]. Cryptococcal osteomyelitis shares many characteristics with cutaneous cryptococcosis. Direct inoculation after trauma is a common cause, although hematogenous dissemination and spread from adjacent infection areas are also responsible for many cases of osteomyelitis. Predisposing risk factors are very similar for both entities, i.e., corticosteroid use, solid organ transplantation, diabetes mellitus and T-cell deficiency. Treatment for both includes different combinations of surgical debridement and systemic antifungals. However, cutaneous infections have a more favorable course and immunocompetent patients with limited disease can be cured with surgical excision alone [18].

All cases presented a similar pattern on plain skull films, that is, an irregular, well defined, lytic lesion ranging from 2–5 cm in diameter, sometimes showing bone sequestrum. Tomographic findings correlated well with radiographs and half of them showed dura mater involvement. The only signs of CNS involvement were cortical...
enhancement and images of mild brain compression. All these features are not specific for Cryptococcus and other infectious etiologies (bacteria, mycobacteria and other fungi) should be considered in the differential diagnosis.

Diagnosis was accomplished in all cases through excision biopsy. In the present report, diagnosis was established after aspiration and the culture of the resulting pus or hemorrhagic fluid. This approach is safe, simple and can be useful for diagnosing coexisting cutaneous cryptococcosis [19]. The most common lesion shared characteristics of an abscess and in four cases it was accompanied by a granuloma or ‘cryptococcoma’.

The identification of the fungi recovered from the present patient was accomplished by conventional methods and culture of the isolate on DOPA agar and GCB media. Any infection with Cryptococcus spp. in an immunocompetent patient in an endemic region should always raise the suspicion that C. gattii is the etiologic agent. The differentiation between C. neoformans and C. gattii can be done reliably and at low cost using the CGB media [20]. However, the molecular characterization by DNA sequencing, even if technically challenging and expensive, is more specific and should be pursued.

One patient with an isolated lytic extradural lesion was treated only with surgical curettage and oral fluconazole but lumbar puncture was not reported [9]. If cerebrospinal fluid was sterile, this could offer a rationale for treating similar cases with fluconazole alone and not with amphotericin B as for meningitis. This regimen is appropriate for immunocompetent patients without cryptococcal meningitis or disseminated cryptococcosis [1].

In this review, two of the 12 patients died during hospitalization. The first patient had chronic cryptococcal meningitis and presented with advanced disease (seizures, loss of consciousness, fixed pupils, depressed reflexes). He

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### Table 1 Details of reported cases of cryptococcal osteomyelitis of the skull.

<table>
<thead>
<tr>
<th>Ref</th>
<th>Age/Sex</th>
<th>Risk Factors</th>
<th>Sites of involvement</th>
<th>Duration of cutaneous symptoms</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td>59/M</td>
<td>Chronic meningitis</td>
<td>Bilateral middle and inner ear</td>
<td>No relevant cutaneous findings 3 months</td>
<td>AmB (IV and Intraventricular) + 5FC Qx + AmB + 5FC</td>
<td>Died on 13th day of therapy</td>
</tr>
<tr>
<td>12</td>
<td>10/F</td>
<td>Systemic lupus erythematosus on steroids</td>
<td>Left parietal</td>
<td>N/A</td>
<td>Qx + AmB + 5FC</td>
<td>Died on 10th day postop.</td>
</tr>
<tr>
<td>13</td>
<td>55/F</td>
<td>Contaminated wound</td>
<td>Skull, patella and thigh</td>
<td>N/A</td>
<td>Qx + AmB + 5FC</td>
<td>7 years without relapse</td>
</tr>
<tr>
<td>14</td>
<td>68/F</td>
<td>T-lymphocytes deficiency, previous cryptococcal lung infection</td>
<td>Skull, upper lobe right lung</td>
<td>4 months</td>
<td>AmB + 5FC</td>
<td>Asymptomatic</td>
</tr>
<tr>
<td>3</td>
<td>39/M</td>
<td>No</td>
<td>Temporoparietal, neck nodule</td>
<td>6 weeks</td>
<td>Qx + AmB + 5FC</td>
<td>9 months without relapse</td>
</tr>
<tr>
<td>15</td>
<td>57/M</td>
<td>Cellular and humoral immunity impairment secondary to paracoccidioidomycosis</td>
<td>Frontal, mandible</td>
<td>2 months</td>
<td>AmB + 5FC</td>
<td>2 years without relapse</td>
</tr>
<tr>
<td>6</td>
<td>48/F</td>
<td>Chronic sinusitis</td>
<td>Sphenoid sinus, skull base</td>
<td>N/A</td>
<td>Qx + AmB + Fluconazole</td>
<td>N/A</td>
</tr>
<tr>
<td>7</td>
<td>17/F</td>
<td>Acute lymphoblastic leukemia in maintenance phase</td>
<td>Parietal</td>
<td>1 month</td>
<td>Qx + AmB + Fluconazole</td>
<td>N/A</td>
</tr>
<tr>
<td>8</td>
<td>51/M</td>
<td>Kidney transplant recipient</td>
<td>Parietooccipital</td>
<td>4 weeks</td>
<td>Qx + AmB (incomplete due to renal failure) + Fluconazole</td>
<td>12 months without relapse</td>
</tr>
<tr>
<td>9</td>
<td>38/F</td>
<td>Idiopathic lymphopenia</td>
<td>Frontoparietal</td>
<td>“Few weeks”</td>
<td>Qx + Fluconazole AmB + Fluconazole</td>
<td>N/A</td>
</tr>
<tr>
<td>10</td>
<td>42/M</td>
<td>Diabetes mellitus, tuberculous arthritis on treatment, renal clear cell carcinoma, transient low CD4 count</td>
<td>Frontal</td>
<td>N/A</td>
<td>Qx + AmB + Fluconazole</td>
<td>10 weeks without relapse</td>
</tr>
<tr>
<td>PR</td>
<td>65/M</td>
<td>No</td>
<td>Parietal</td>
<td>1 month</td>
<td>Qx + AmB + Fluconazole</td>
<td>2 months without relapse</td>
</tr>
</tbody>
</table>

Abbreviations: AmB, amphotericin B; IV, intravenous; 5FC, flucytocine; Qx, surgical debridement; PR, present report.
progressed to shock despite aggressive treatment with surgery, intravenous and intraventricular amphotericin B. The second individual had good postoperative recovery but developed nosocomial pneumonia and died 10 days later [11,12]. Cryptococcal osteomyelitis of the skull probably has a worse outcome, with a mortality of 16% (2/12) compared to 5% (2/40) for non-skull osteomyelitis as reported by Liu in 1998 [4].

This case report is significant because it is the third of osteomyelitis of the skull due to C. neoformans in an immunocompetent subject. It is also interesting because infection was not secondary to hematogenous dissemination but appeared after direct inoculation in a contaminated wound.

In conclusion, we suggest that cryptococcal osteomyelitis should be part of a differential diagnosis to be considered in an insidious growing soft mass or abscess in scalp of unclear origin, a skull mass with osteolytic lesions on imaging or a mass with histologic findings compatible with granuloma. Special stains and fungal culture should be performed in all lesions that fulfill these criteria.

Finally future studies are suggested to assess the risk factors for C. neoformans infection in tissues other than the lungs or the CNS, and to evaluate the risk of infection in immunocompetent patients and the best treatment approach of this type of infection.

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References


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