Skeletal cryptococcosis: Case report and review of the literature

LORI WOOD MD, LIL MIEDZINSKI MD FRCPC

L WOOD, L MIEDZINSKI. Skeletal cryptococcosis: Case report and review of the literature. Can J Infect Dis 1996;7(2):125-133. A case of isolated cryptococcal skull infection is presented in a patient with unexplained CD4 lymphopenia and chronic hepatitis B. All cases of this disease reported in the English literature from 1956 to the present are reviewed. The literature suggests that skeletal cryptococcosis is manifested in only 5% to 10% of recognized cases of disseminated cryptococcosis and that isolated skeletal disease without evidence of other tissue involvement is even less common. When isolated bony disease does occur it tends to occur in immunocompromised hosts, particularly those with defects of cell mediated immunity. Any bony site can be involved, most commonly the vertebrae, with the presentation often being a soft tissue swelling and pain in the affected area. Systemic constitutional symptoms occur in a minority of patients. Radiographic investigations are nonspecific and the gold standard of diagnosis remains culture isolation from bone tissue. The most commonly employed therapy for isolated bone disease is amphotericin alone or combined with surgical debridement. The new azoles may have a role in future therapy.

Key Words: Bone infection, Cryptococcus, Fluconazole, Osteomyelitis, Skeletal infection

Cryptococcose squelettique : rapport de cas et survol de la littérature

RÉSUMÉ : Un cas isolé d'infection crânienne cryptococcique est présenté chez un patient présentant une lymphopénie des CD4 et une hépatite chronique B inexplicables. Tous les cas de ce type de maladie signalés dans la littérature de langue anglaise de 1956 jusqu'à nos jours ont été passés en revue. Selon la littérature, la cryptococcose squelettique se manifeste chez 5 % à 8 % seulement des cas reconnus de cryptococcose disséminée et cette maladie squelettique isolée, sans autre atteinte tissulaire est encore moins fréquente. Lorsqu'une maladie osseuse isolée se manifeste, elle tend à survenir chez des hôtes immunodéprimés, particulièrement chez ceux qui présentent des anomalies de l'immunité à médiation cellulaire. Tout siège osseux peut être affecté, les plus fréquents étant les vertèbres et le tableau se compose souvent d'une enflure des tissus mous et d'une douleur au siège de l'infection. Les symptômes systémiques se manifestent chez une minorité de patients. Les examens radiologiques ne sont pas spécifiques et la norme diagnostique demeure la culture de tissu osseux. Le traitement le plus souvent employé dans les cas de maladies osseuses isolées est l'amphotéricine seule ou en association avec un débridement chirurgical. Les nouveaux médicaments de type azole pourraient exercer un rôle dans le traitement futur.

Division of Infectious Diseases, University of Alberta Hospitals, Edmonton, Alberta

Correspondence and reprints: Dr L Miedzinski, Division of Infectious Diseases, 2E4.11 Walter Mackenzie Health Sciences Center, University of Alberta Hospitals, Edmonton, Alberta T6G 2B7. Telephone 403-492-7313, fax 403-492-7137, e-mail lil@nshade.uah.ualberta.ca

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Cryptococcus neoformans is a ubiquitous fungus that most commonly causes infection involving the lungs and central nervous system. It rarely causes skeletal infection in humans, but when it does, it tends to affect immunocompromised hosts with obvious disease processes or laboratory detected immunological abnormalities. Given the substantial increase of immunocompromised hosts as a consequence of malignancies, transplantation and their respective therapies, the frequency of invasive fungal infections has risen and will likely continue to do so. We present a case of isolated cryptococcal skeletal infection, review the literature related to this topic and summarize the reported cases in the English literature of isolated skeletal cryptococcal disease from 1956, when amphotericin became available, to August 1995.

CASE PRESENTATION

A 49-year-old Chinese male cook presented in January 1994 with headache, initially localized to the superior aspect of his skull but later lateralized to the left. It was described as sharp, dull and throbbing at different times. By February 1994 the headache was waking him at night and requiring regular acetaminophen with only partial pain relief. Over a three-week period, he developed a tender, fluctuant, left temporal mass with no associated induration, erythema or discharge. No other neurological or constitutional symptoms such as fever, weight loss or night sweats were present. Of note, the patient had exposure to pigeons when visiting Hong Kong in the year before his diagnosis.

Significant past medical history included chronic hepatitis B most likely acquired by vertical transmission and first documented in 1988. He had been referred to the Hepatology Clinic at the University of Alberta Hospitals for enrolment in a trial of an investigational antiviral agent, 3TC, which was started November 16, 1993. The agent was discontinued February 24, 1994 to establish whether it might be contributing to the patient's symptomatology.

Out-patient investigations included plain x-ray of the skull, nuclear medicine bone scan and a nonaugmented computed tomography scan of the head. These identified a single bony lytic lesion in the left temporal area with corresponding soft tissue swelling, a focal area of increased uptake in the same area (Figure 1) and major destructive changes in the left temporal area (Figure 2).

The patient was admitted April 10, 1994 for elective excision of the bony lesion. The differential diagnosis was extensive and included malignancy, infection, and benign epidermoid or dermoid cyst. A white blood cell count was 9.2×10^6 cells/L with 84% neutrophils, 8% lymphocytes, 6% monocytes and 1% eosinophils. The patient had a normal chest x-ray. At surgery, a subgaleal and epidural collection of purulent material was found, incised and drained. The material was submitted for pathology examination, routine culture and sensitivity, as well as mycobacterial and fungal stains and culture.

Material from the lesion showed yeast-like organisms on direct mycological examination using periodic acid-Schiff stain, the typical appearance of *C. neoformans* on India ink

Figure 1) Technetium-99m methylene diphosphonate bone scan. An area of increased uptake in the left temporal bone corresponding to a lytic lesion on plain skull film is shown

Figure 2) Nonaugmented computed tomography of the head. Destructive changes in the left temporal bone with associated soft tissue swelling and a subgaleal collection are shown

stain, and was positive for cryptococcal antigen using a Wampole latex agglutination test (International Biological Labs, Inc, New Jersey). Subsequently *C neoformans* was isolated on phytone yeast extract agar culture media. Further investigations for evidence of disseminated cryptococcal disease included a lumbar puncture, which was negative on India ink stain and negative for cryptococcal antigen. Blood and cerebrospinal fluid (CSF) fungal cultures were also negative.

The patient was diagnosed with cryptococcal skeletal infection of the skull with no other evidence of disease. Because cryptococcosis does not usually occur in immunocompetent hosts, an underlying predisposing condition was investigated. Human immunodeficiency virus (HIV) serotesting was negative on four occasions including a search for p24 core antigen by enzyme immunoassay. Serum immunoglobulin levels were normal. Delayed hypersensitivity skin testing showed a positive reaction to five tuberculin units. However, bloodwork was significantly abnormal in showing a marked CD4 lymphopenia with an absolute count of 0.15×10^9 cells/L. Repeat estimates demonstrated counts less than 0.2×10^9 on four estimates over an 18-month period. An explanation for this remains obscure. Serotesting for human T cell leukemia virus (HTLV) -I and HTLV-II was also negative.

The patient was started on intravenous amphotericin B and received a total dose of 300 mg over eight days. Over this time his creatinine rose from a baseline of 107 μmol to 158 μmol , correlating with a measured 24 h creatinine clearance of 49 mL/min/1.7 m². Therapy was changed to oral fluconazole 200 mg/day, which he continued for six months with progressive clinical improvement. A nuclear medicine immunoglobulin scan on May 2, 1994 was interpreted as a normal postoperative scan, and a bone scan on July 19, 1995 revealed no active osteomyelitis and only changes consistent with postoperative status.

Unlike for other patients with CD4 lymphopenia due to AIDS who usually remain on lifelong antifungal therapy after documented cryptococcal disease, it was decided to discontinue fluconazole after six months and to observe the patient. He is receiving prophylaxis against *Pneumocystis carinii* pneumonia in the form of daily cotrimoxazole and remains clinically well 18 months after his diagnosis and treatment.

LITERATURE REVIEW

C neoformans is an encapsulated, spherical fungus that reproduces by budding and is recognized to have worldwide distribution. It can produce disease in both immunocompetent and immunocompromised hosts, most commonly affecting the pulmonary and central nervous systems where it can cause an acute, subacute, or chronic infection. The portal of entry is via inhalation of airborne particles, with bird droppings and associated soil being the major environmental source. The true incidence of pulmonary cryptococcal infections is not known because disease can be asymptomatic or associated with vague, nonspecific symptoms. It often resolves spontaneously and requires no treatment in immunocompetent hosts. Kerker et al (1) reviewed all cases of

cryptococcal infections evaluated at the Medical College of Virginia Hospitals over a 14-year period from 1966 to 1980. A total of 93 patients with cryptococcal infections were identified, with pulmonary involvement clinically present in 12.9% of patients, central nervous system (CNS) involvement in 55.9%, and combined pulmonary and CNS involvement in 31.2%. The phrase 'clinically involved' is relevant because Lewis and Rabinovich (2) reported 45% of patients with clinical CNS disease had lung involvement on autopsy that was not recognized ante-mortem. CNS infection most commonly involves the leptomeninges but may also include cerebral, intraventricular and spinal cord granulomas (1,3).

Skeletal cryptococcal infections are a very uncommon manifestation of disseminated cryptococcal disease occurring in only 5% to 10% of patients with disseminated disease (4,5), with isolated skeletal cryptococcal infections occurring even less commonly. It is felt that most skeletal cryptococcal infections arise secondary to hematogenous spread from a primary pulmonary infection. Other potential sources are bony trauma, embolic phenomenon, contiguous skin infection or contiguous neural infection (6). Any bony site may be involved, with the most commonly reported being vertebrae, pelvis and ribs. The disease may occur at a single site or multiple sites (7,8).

Isolated skeletal cryptococcal disease such as in the case presented is very uncommon. To gain a better understanding of this disease entity, the involved sites, treatment and outcome, a comprehensive search for all published case reports of isolated skeletal cryptococcal disease was undertaken. A MEDLINE search was done of the English-language literature published from 1966 through August 1995 using the terms 'cryptococcus', 'osteomyelitis', 'bone' and 'skeletal'. A manual search was then done for other contributions during this time as well as of the literature published from 1956 through 1966. Forty-five cases including the present case were found and are listed in Table 1. Cases were excluded if they reported positive culture, stain, or histology of other tissues or organs such as cutaneous lesions (6,9), CSF involvement (10,11), sputum (12,13), joint involvement (14-16) or chest x-ray abnormalities that improved with antifungal therapy (17,18). Patients with soft tissue collections or abscesses adjacent to the involved bone were included in this series. In cases that did not mention investigations for disseminated disease, it has been assumed that the patients had isolated disease, and they have been included in this review.

It can be seen from the 45 identified cases that isolated cryptococcal skeletal infection can occur in any age group, and can range from an incidental radiological finding to a systemic disease with local and constitutional signs and symptoms. Sixty-two per cent (28 of 45) of patients had one site involved, whereas 38% (17 of 45) had more than one site involved. In these 45 cases, 80 bony sites were involved, with the most frequent being the vertebrae in 29% (23 of 80), the ribs in 11% (nine of 80), tibia in 10% (eight of 80) and femur in 9% (seven of 80). The most commonly described clinical presentation was soft tissue swelling and pain of variable duration ranging from an acute presentation to 33 months. Fever was not a

TABLE 1
Summary of 45 cases of isolated skeletal cryptococcosis from 1956 to 1995

Case/Ref	Age/Sex	Bony site involved	Predisposing factor(s)	Treatment	Outcome
1/3	71M	Frontal bone	CLL Immunosuppressive drugs	Debridement Ampho	"did well"
2/4	23M	Rib 8	Sarcoidosis steroids	5FC x 6 weeks	Well at 40 months; no evidence of x-ray disease
3/7	40F	Ulna	Sarcoidosis; CMI abnormalities on lab tests	Curettage	Asymptomatic at 5 weeks
4/7	68M	Scapula	CMI abnormalities on lab tests	Ampho (1000 mg)	Acute renal failure 2 ampho; well at 4 years
5/7, 47	15M	Distal humerus	None noted	Ampho (395 mg)	Died at 2 years with TB, hepatitis and pneumonia; elbow normal at autopsy
6/18	9M	Proximal tibia	None noted	Ampho (1500 mg)	Well at 2 years; x-ray resolution
7/18	18M	Proximal tibia	None noted	Ampho (1500 mg)	Well at 2 years; x-ray resolution
8/19	84M	Rib, T10, T11, sacrum, femur	DM; lung cancer (at autopsy)	None	Diagnosed at autopsy
9/20	35F	Distal tibia	None noted	Curettage	No sign of infection at 2 years; disabled but working at previous job
10/21	50M	T9, T10, T11	None noted (chronic hepatitis)	Curettage x2 ampho (1105 mg) 5FC (2202 mg)	
11/22	33M	5th costosternal junction	None noted	Excision ampho (480 mg)	Well at 29 months
12/44	54M	Calcaneus; distal tibia; ulna – bilateral	Squamous cell cancer; CMI abnormalities on lab tests	Curettage calcaneus/tibia ampho – D/C 2 toxicity 5FC (2700 g)	x-rays improved; died 2 years later of cancer
13/45, 48	10M	Scapula	IL-2 deficiency HIV negative	Ampho/5FC x 3 months	No evidence of disease at 4 years
14/31	33M	Acromium scapula	Sarcoidosis steroids	None	Bone lesion culture positive in retrospect; presented 1 year later with CNS disease; died 32 months after onset of bone disease; died 4 months after onset of CNS disease
15/33	10F	Parietal bone	SLE steroids	Craniotomy; ampho; 5FC	Died day 10 postoperation of bilateral pneumonia/ respiratory failure; no autopsy
16/32	34F	T5, rib 5, paraspinal abscess	Sarcoidosis		Died at open biopsy from presumed PE
17/36		Orbit	No mention	Ampho x 2 weeks ketoconazole	Lost to follow-up
18/37	58M	Proximal tibia	None noted	Debridement; ampho/ gentamicin (intralesional) x 4 months; ketoconazole (48 g)	No evidence of disease at 2 years
19/49	5F	Femur	None noted	Curettage	x-rays improved; asymptomatic at 18 months
20/49	29F	Ileum – 2 lesions	None noted	Excision ampho/5FC x 2 days	Asymptomatic at 18 months
21/50	63F	Distal humerus; parietooccipital bone	DM; sarcoidosis; steroids	Ampho	Unknown
22/51	54F	Clavicle	DM; HIV-negative	Ampho; 5FC	x-ray improved at 10 months

TABLE 1 (cont'd)

23/52	43M	Mid tibia	?Sarcoidosis (on basis of CXR)	Curettage; potassium iodide x 2 months	x-rays improved at 1 year; died 2 years later of unknown cause
24/53	17M	L1, rib 12	Open trauma to back 8 year previously	Excision; amphi (510 mg)	Well at 27 months
25/54	11F	Femur	CMI abnormalities on lab tests	Curettage; amphi (93 mg) 5FC x 6 weeks	Well at 4 months; x-rays no change
26/55	24F	Ileum, sacrum, L4, L5, tibia, humeri, clavicle, ribs 6 and 7	CMI abnormalities on lab tests + pigeon exposure	Amphi (4 g)	Well at 30 months; x-ray resolution
27/56	19F	Calcaneus	Sarcoidosis	Amphi; 5FC	"good" response
28/57	1M	C2, C3	None noted	Curettage; amphi (134 mg); 5FC (73 g)	Well at 16 months; x-ray improvement
29/58	71M	Rib 4	Squamous cell cancer	Amphi; 5FC	Asymptomatic
30/59	80F	Rib 3; acromium	DM; CMI abnormalities on lab tests	Curettage; 5FC (284 g)	Bone scan – no change at 9 months; clinical resolution; died of CAD at 13 months
31/60	42F	Clavicle, humerus	None noted	Excision clavicle; curettage humerus; amphi (1500 mg)	x-ray improvement at 3 months
32/61	33M	Femur	None noted	Amphi	Improved at 3 years
33/62	56F	4th metatarsal; upper radius	None noted	Excision x 2; amphi (50-100 mg)	Normal x-ray at 3 years
34/63	73F	Femur – fractured	DM	ORIF; amphi (975 mg)	Well at 20 days, using walker; x-ray improvement
35/64	69F	Tibia	Sarcoidosis	Amphi	Died 3 months later of MI/PE while still on treatment
36/65	13F	Femur	None noted; normal CMI lab tests	Amphi (1321 mg); 5FC x 1 month	Asymptomatic at 2 years
37/66	10F	Ileum	CMI abnormalities on lab tests	Amphi (504 mg) 5FC (224 g)	"did well"
38/67	32F	Clavicle, T2, T3; paravertebral abscess	None noted	Vertebral decompression; amphi	Lower limb weakness at 4 months
39/68	24M	Femur	None noted	Curettage; amphi (1000 mg)	Well at 6 months; x-ray resolution at 2 months
40/69	26M	T5-8; paraspinal mass	None noted	Amphi x 10 weeks	Well at 1 year; x-rays improved
41/70	44F	T4; soft tissue mass between ribs 3 and 4	Sarcoidosis	Amphi (1060 mg)	Asymptomatic at 11 months; x-rays improved
42/71	35F	Humerus + abscess	Sarcoidosis	Amphi	x-ray improvement
43/72	27	L2, L3; paraspinal abscess	None noted; T cell function normal	Amphi x 7 weeks 5FC x 7 weeks	x-rays improved at 7 weeks
44/73	42F	T8-10; chest wall abscess; paravertebral, prevertebral, epidural space collections	?Sarcoidosis (on basis of CXR); HIV-negative	Amphi	
45/current case	49M	Temporal bone	CD4 lymphopenia	Debridement; amphi (300 mg); fluconazole (36,000 mg)	Asymptomatic at 18 months

Amphi amphotericin B; C Cervical; CAD Coronary artery disease; CLL Chronic lymphocytic leukemia; CMI Cell mediated immunity; CNS Central nervous system; CXR Chest x-ray; D/C Discontinued; DM Diabetes mellitus; 5FC Flucytosine; HIV Human immunodeficiency virus; IL-2 Interleukin-2; L Lumbar; MI Myocardial infarction; ORIF Open reduction and internal fixation; PE Pulmonary embolus; Ref Reference; SLE Systemic lupus erythematosus; T Thoracic; TB Tuberculosis

common feature and present in only 18% (eight of 45) of patients in this review, comparable with a previous series reporting 17.9% (8). The white blood cell count is often normal in patients with cryptococcal disease including osteomyelitis, and this is confirmed in this review. The erythrocyte sedimentation rate can be elevated and of variable range. Neither are specific for cryptococcal skeletal infections as opposed to infections in other locations or due to other organisms.

The radiological evidence is usually indicative of osteomyelitis but, again, is not specific for a fungal etiology. Common findings include a lytic lesion eroding the inner and outer tables but without surrounding sclerosis or periosteal changes and an overlying soft tissue mass (6). All of the patients in this series had a lytic bone lesion on plain film. Given the nonspecific radiological findings, as well as the nonspecific clinical and laboratory picture, the diagnosis of cryptococcosis is often delayed or not made ante-mortem (19). The differential diagnosis includes other mycotic infections as well as bacterial infections such as those due to *Staphylococcus aureus* and less common bacteria including brucella, actinomyces, mycobacterium tuberculosis and atypical mycobacteria. Neoplastic lesions ranging from primary osteogenic sarcoma and myeloma to metastatic carcinoma can also mimic the radiological picture. This type of osteolytic skull lesion can also be seen with parietal foramina, dermoid cysts, hemangiomas and meningoceles (3). Several of the patients in this series were treated for other diagnoses such as bacterial osteomyelitis (20), neoplasm (21) and tuberculosis (22) before the correct diagnosis was made.

Temporal bone involvement with cryptococcal disease has been documented in only four cases from 1956 until the present (23-26), with this case making the total five. Each of the previously described cases was associated with cryptococcal meningitis with involvement of the nerves in the internal auditory canal. The case presented, to our knowledge, is the first report of isolated temporal bone involvement with *C. neoformans*.

In our series, the diagnosis of skeletal cryptococcosis was made by a number of techniques but generally involved examination of lesion material whether from aspiration, incision and drainage, draining sinuses or open biopsy. The sample should be sent for smear, culture and histological examination. Disseminated disease should be sought in all patients with any form of cryptococcosis, whether the patient is immunocompetent or immunocompromised. The seemingly 'normal' immunocompetent host may not always be so, as is discussed below. A relevant examination for disseminated cryptococcal infection includes a chest x-ray; lumbar puncture for India ink staining, antigen testing and culture; urine cultures; blood culture; sputum stain and culture; and skin lesion cultures if applicable (27). Francisco et al (28) present a case of a febrile woman with lymphoma in whom an ante-mortem diagnosis of disseminated cryptococcal infection was made with direct examination and culture of a bone marrow aspiration and biopsy. They suggest that a bone marrow examination be performed in high risk patients with an obscure febrile illness. Detection of cryptococcal antigen in serum should also

be performed given its high sensitivity and specificity (18). However, because serum cryptococcal antibodies are present in only 30% to 40% of patients, this latter test is of limited value (27). Despite availability of the above-mentioned investigations, it is evident in some case reports that the burden of cryptococcus can be greater than suspected clinically (2,19).

Once cryptococcosis has been diagnosed, a decision regarding appropriate and effective therapy must be made. Because the distinction between disseminated and local disease is often quite difficult and since the majority of skeletal cryptococcal infections probably result from hematogenous spread from the lungs, it is generally felt that all patients with skeletal cryptococcosis warrant some form of systemic therapy, and that the role of surgery is to lessen the infectious burden and prevent leptomeningeal involvement (6,18). Some authors, however, suggest that surgical debridement alone may suffice in some cases of isolated skeletal cryptococcosis (7). Before the introduction of amphotericin in 1956, there were case reports of skeletal cryptococcosis with various clinical courses, ranging from spontaneous resolution to resolution with curettage to resolution with roentgen treatment and oral potassium iodide and to death (5). From the cases reviewed, it is obvious that a large variety of therapies have been used with success. The most common therapy for isolated skeletal disease has been amphotericin alone or combined with surgical debridement; however, in some cases surgery alone, 5FC (flucytosine) alone or a combination of systemic chemotherapy was used. Although there have been a few case reports of 5FC monotherapy (4,5,29) there have also been case reports of resistant organisms developing. Therefore, if used, this agent should be used only in combination with another antifungal (30).

In reviewing the outcome of these 45 cases, it appears that only four died as a result of their disease: one with eventual widespread dissemination occurring months after the presentation of isolated skeletal disease was unrecognized (31); one with significant comorbid diseases (19); and two with peri-operative complications related to debridement and biopsy (32,33). The other 41 had a variable follow-up, with the majority having radiological and clinical improvement.

An attractive alternative form of therapy for cryptococcosis may be the oral azoles, given their good oral bioavailability and reported success in treatment of other forms of cryptococcosis. The majority of studies of the azoles in cryptococcal disease have focused on management of cryptococcal meningitis in AIDS patients. A recent trial with this patient population using primary therapy with fluconazole or with amphotericin B showed that both were equally efficacious (34) although other reports have not reached similar conclusions (35), and further trials are required to answer this question. There have been no reported cases of isolated skeletal cryptococcosis occurring in association with AIDS or positive HIV serology. This review found two other case reports of azole use in cryptococcal skeletal infections (36,37). A note of caution needs to be made regarding the possibility of the development of azole resistance (38).

There remains significant uncertainty regarding the dose and duration of treatment as well as the means of assessing

treatment efficacy when the only disease is isolated skeletal infection. Efficacy of therapy is often judged radiologically because many patients do not have systemic symptoms or other laboratory abnormalities to follow. All patients with any form of cryptococcal infection must be followed given the propensity of this organism to relapse as well as to cause chronic infections, especially in immunocompromised hosts. Disseminated disease must be excluded in all patients, both immunocompromised and immunocompetent, and if present, must be treated.

The treatment decisions referred to above rely on the clinician being able to distinguish between immunocompetent and immunocompromised hosts. The classical immunocompromise described in association with skeletal cryptococcosis involves abnormalities of cellular immunity such as those seen with lymphoma, leukemia, sarcoidosis and long term steroid use. It has been suggested in previous reports that approximately half of patients with any form of cryptococcosis will have an underlying disease or are receiving a therapy that affects cell mediated immunity (27). Table 2 summarizes the predisposing conditions noted in the case reports reviewed. There has been only one other report of skeletal cryptococcosis being associated with chronic hepatitis (21), which represented our patient's only other medical abnormality aside from CD4 lymphopenia, which in itself probably represents his predisposing condition and is probably not related to the hepatitis B infection (39-41). There have been no reported cases of isolated skeletal cryptococcosis occurring in association with AIDS or positive HIV serology.

Seemingly immunocompetent patients may be subclinically immunocompromised as in the present case as well as others in this review. Schimpff and Bennett (42) examined abnormalities of cell mediated immunity in patients with cryptococcal infections. Seemingly 'immunocompetent' patients who had been cured of cryptococcal infections for at least a year had subtle but reproducible abnormalities in skin tests, lymphocyte migration inhibition and lymphocyte transformation compared with controls. Similar findings have been found by other investigators (43). However, specific studies of immunological function are not commonly recorded in patients with cryptococcal infection. In this review, only 11 patients had some laboratory investigation for cell mediated immunity abnormalities. The tests performed were not uniform and included delayed type hypersensitivity skin testing, rosette formation, lymphocyte response to mitogens, phytohemagglutinin transformation and interleukin-2 quantification. Only two other patients besides the one we report had T cell quantification (44,45). Fifty-six per cent (25 of 45) of patients had no obvious predisposing factor for this infection and on clinical grounds were 'immunocompetent'. Of these 25 patients, eight had laboratory investigations and 75% (six of eight) were found to have abnormalities of cell mediated immunity. This makes us question whether patients we assume are immunocompetent may have subtle, persistent or transient immunological defects that render them immunocompromised and thus at risk for the establishment of such infections.

TABLE 2
Predisposing factors among 45 cases of isolated skeletal cryptococcosis

Predisposing factor(s)	Cases
None noted	25
Sarcoidosis $\pm$ steroids	8
Diabetes mellitus	4
Cancer	3
?Sarcoidosis on basis of described CXR	2
Diabetes mellitus/sarcoidosis/steroids	1
Systemic lupus erythematosus/steroids	1
Trauma	1

CXR Chest x-ray

It is for the above reasons that an examination of cell mediated immunity is reasonable in all patients with cryptococcosis. It is difficult to recommend specific tests or panels of studies for assessment of cell mediated immunity given that many have variable specificity and sensitivity. However, evaluation of lymphocyte subsets including counts and stimulation studies are an important objective evaluating tool (46). Because absolute CD4 counts are fairly standardized and more easily available, they will undoubtedly be employed more often in future (46).

SUMMARY

We present a case of isolated temporal bone cryptococcosis in a patient with chronic hepatitis B and idiopathic CD4 lymphopenia who was treated successfully with surgical debridement and oral fluconazole. We also summarize the reported cases of isolated skeletal cryptococcosis in the English literature over the past 29 years. Our review suggests that 62% of patients have single site involvement, with the most common sites affected being the vertebrae, ribs, tibia and femur. Forty-four per cent of patients had obvious predisposing factors putting them at risk of this infection. Of those who did not and were investigated, 75% were found to have laboratory abnormalities of cell mediated immunity, suggesting that all patients with cryptococcosis should be investigated for evidence of immune dysfunction. Although no therapeutic regimen is standard, the most commonly employed is systemic amphotericin or a combination of local surgery and amphotericin.

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