CASE REPORT

Disseminated cryptococcosis in an apparently immunocompetent patient presenting with primary intraventricular haemorrhage

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Accepted 8 October 2015

SUMMARY

Disseminated cryptococcosis is uncommon and almost always occurs in HIV-infected patients. However, cryptococcosis can also be found in patients of organ transplantation, in those on disease modifying agents for rheumatological conditions and in patients with underlying immunodeficiency. Cryptococcal infection may occur in an immunocompetent patient, but the pathogenic strain is usually *Cryptococcus gattii*, and not *C. neoformans*. However, disseminated disease, especially cerebral involvement in the form of primary intraventricular haemorrhage, is exceedingly rare. We report a case of disseminated cryptococcosis with cutaneous, cerebral and bone marrow involvement in an HIV-negative, apparently immunocompetent patient. Although the patient did not have the usual immunocompromising diseases, there were clinical signs possibly indicating a weakened immune system. This report highlights the need for awareness of disseminated cryptococcosis among patients with no apparent immunocompromising conditions.

BACKGROUND

Cryptococcosis is a disease caused by the *Cryptococcus* spp, an encapsulated yeast organism. Disseminated cryptococcosis commonly occurs in immunocompromised patients, particularly those with HIV infection, and is very rare in immunocompetent patients.^{1 2} These yeast organisms have five serotypes: *Cryptococcus neoformans* var. *grubii* and *C. neoformans* var. *neoformans* have been assigned serotypes A and D, respectively, whereas serotype AD strains are hybrids and serotype B and C strains belong to distinct but related pathogenic species called *C. gattii*.^{3 4} *C. neoformans* is the species predominantly reported from immunocompromised patients, while *C. gattii* infection has been associated with immunocompetent patients.⁴⁻⁶ Contiguous spread from paranasal sinuses may lead to fungal mycotic aneurysms, the rupture of which may cause intraventricular or subarachnoid haemorrhage.^{7 8} The manifestations of cutaneous cryptococcosis may be varied and may also mimic other skin diseases.⁹ Owing to varied presentation, a high clinical suspicion and early initiation of therapy is needed to recognise and treat patients effectively. We describe a case of disseminated cryptococcosis in an apparently immunocompetent boy presenting with fever and primary intraventricular haemorrhage; final diagnosis came from bone marrow aspiration.

CASE PRESENTATION

A 14-year-old boy with a 20-day history of intermittent low-grade fever with evening rise of temperature, presented with sudden onset headache associated with vomiting and disorientation. The boy belonged to a rural farming family from a nearby village, was involved in agricultural activities and lived in an earthen house. There was no history of otorrhoea, recurrent sinusitis, cough, increased sputum production, chest pain or weight loss. The patient did not give any history of recurrent childhood infections. Examination revealed meningeal signs, bilateral mild papilloedema, bilateral cervical and axillary lymph nodes (the largest measuring 2×2 cm) and a non-tender hepatomegaly. Strikingly, there were widespread polymorphic, scaly, confluent macular lesions all over the trunk and arms suggestive of pityriasis versicolor (figure 1A). The boy's body mass index was 16.5 kg/m², triceps skin fold was 10 mm, mid-arm muscle circumference was 26 cm and mid-arm muscle area was 31.6 cm² indicating undernutrition and depletion of lean body mass.

INVESTIGATIONS

Initial laboratory investigations showed microcytic hypochromic anaemia, serum albumin was 3.5 g/dL and serum creatinine was 0.86 mg/dL. Non-contrast CT of the brain showed primary intraventricular haemorrhage (figure 1B) in the lateral ventricles, from the third extending up to fourth ventricle. The patient improved symptomatically following conservative management. Cerebrospinal fluid (CSF) analysis showed normal pressure, 5 cells/mm³, normal protein and sugar. No organism was detected in Gram stain, acid-fast bacilli stain, Indian ink, or in routine CSF and fungal culture.

A chest radiograph revealed no abnormality. Biochemical parameters, coagulopathy screen, tests for malaria antigen, hepatitis serology, urine for microscopy and reducing substances were unremarkable. Axillary lymph node biopsy showed reactive hyperplasia. Repeat blood count showed worsening anaemia (haemoglobin 8 g/dL) along with a low platelet count (1.2 lakhs/mm³). Ultrasound of the abdomen and two-dimensional echocardiography were unremarkable. At this point, we sent blood cultures and bone marrow aspiration was performed. Bone marrow study revealed widespread myelonecrosis and clusters of small, refractile, encapsulated, budding organisms,

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To cite: Pal P, Ray S, Patra SK, et al. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2015-210250

Figure 1 (A) Hypopigmented and hyperpigmented patchy skin lesions over the trunk and arms. (B) Non-contrast CT scan of the brain showing intraventricular haemorrhage. (C) Bone marrow aspiration finding: the fungal microorganisms were budding yeast cells with demarcated capsules (Leishman stain, $\times 1000$). (D) Photomicrograph of slit skin smear showing dermal accumulation of encapsulated yeast forms (black arrowheads) (Leishman-Giemsa stain, $\times 400$).

morphologically consistent with cryptococci (figure 1C). The fungi were demonstrated by periodic acid-Schiff and Mucicarmine stains. A test for bone marrow cryptococcal antigen was positive in 1:32 dilution but negative in CSF and blood. *C. gattii* was cultured from the bone marrow aspirate. Colonies of isolate were first grown on conventional Sabouraud's dextrose agar media, and were mucoid and sticky in texture, non-fermentative, inositol accumulating and urease producing, and differed from *C. grubii* and *C. neoformans* based on growth on L-canavanine-glycine-bromothymol blue (CGB) agar, which turned cobalt blue and remained colourless in the latter two. The result of a tuberculin skin test showed 12 mm induration (the boy had received BCG vaccination in childhood). Absolute lymphocyte and absolute neutrophil count, and CD4 cell count, were normal. This indicated normal cell-mediated immunity. Serum immunoglobulin levels for humoral immunodeficiency screen were normal and complement levels were also within normal limit. ELISA for HIV antigen was negative. These tests excluded usual immunodeficiency diseases. Most surprisingly, slit skin smear from the newly appeared body rashes showed clusters of capsulated budding organisms, a morphology similar to that seen in the bone marrow (figure 1D). Skin culture was also positive for *C. gattii* by the same method used for bone marrow culture.

TREATMENT

Disseminated cryptococcosis was diagnosed according to the central nervous system (CNS), bone marrow and skin involvement. Amphotericin B was started (0.5 mg/kg/day) based on the bone marrow and skin biopsy typical of *Cryptococcus*. Owing to the concerns for bone marrow suppressing effects of flucytosine, it was not considered earlier as there was worsening anaemia and thrombocytopaenia with widespread myelonecrosis

on bone marrow study. Later, the patient, on a single dose of amphotericin B deoxycholate, showed substantial improvement, and with continued treatment, improvement in sepsis-related cytopenias was seen. The fever subsided and blood counts were normalised in 2 weeks and, as flucytosine was not initially given, amphotericin was continued for another 1 week and discontinued after third weeks due to side effects even after substituting by liposomal amphotericin B (febrile reaction after infusion and hypokalaemia). Amphotericin B was later substituted by oral fluconazole (12 mg/kg, ie, 400 mg/day) based on clinical improvement and biochemical improvement of sepsis markers.

OUTCOME AND FOLLOW-UP

At 2-month follow-up, the skin lesions had faded, and the patient's skin lesions disappeared markedly at 3 months. He had no further complications and fluconazole was stopped after 6 months.

DISCUSSION

On the basis of antigenic properties of polysaccharide capsule, *C. neoformans* has four serotypes, namely, A (*C. neoformans* var. *grubii*), D (*C. neoformans* var. *neoformans*) and AD (hybrids of serotypes A and D), and B and C (*C. neoformans* var. *gattii*). The members of serotypes B and C are true pathogens. *C. gattii*, a basidiomycetous yeast, grows mainly as an asexual budding organism, and is found in the environment and within human and animal hosts. *C. gattii* was isolated first from *Eucalyptus camaldulensis* trees and later found to grow in more than 50 tree species, especially as a fungus in decaying hollows in trunks and branches. This fungus has also been found in the air, soil and water, in heavily infested areas. The fungus has not been recovered from pigeon guano, as has *C. neoformans*.⁴

In conventional mycological agar media, *C. gattii* colonies are almost always more mucoid and sticky than *C. neoformans*. Yeast cells of *C. gattii* are elliptical or tear-shaped, which is not the case with *C. neoformans*. The two species can be more specifically distinguished by their reaction to CGB agar, as strains of *C. gattii* react positively and *C. neoformans* do not react at all; this is based on the ability of *C. gattii* to use glycine as the sole source of nitrogen and carbon, and its susceptibility to L-canavanine, an arginine analogue.³ Differentiation of *C. neoformans* varieties and *C. gattii* can also be achieved using CAP59-based loop-mediated isothermal DNA amplification.⁴ Usually, *C. gattii* causes severe lung disease and death without dissemination in the immunocompetent host; it also has a sub-acute course of disease; whereas *C. neoformans* disseminates readily to the CNS and can rapidly cause death from meningo-encephalitis in the immunocompromised patient.³

C. neoformans has been identified in cultures from blood, CSF, sputum, ascites, urine, bone marrow and skin.^{2 10} Patients with haematological malignancies, solid organ transplants, chronic organ failure, those on immunosuppressive medications and patients with diabetes, in addition to HIV infection, are at risk of cryptococcosis.⁶ Disseminated cryptococcosis is defined by (1) a positive culture from at least two different sites or (2) a positive blood culture.¹⁰ In the present case, positive cultures were obtained from two sites. Although our patient did not have the usual immunocompromising diseases, he had clinical signs of undernutrition, which could be the most plausible explanation for a weakened immunity leading to disseminated fungal infection.

Bone marrow cryptococcosis is a rare finding and has been reported in AIDS¹¹ and advanced histiocytic lymphoma¹² treated with antineoplastic agents. Disseminated cryptococcosis

involving the skin, pulmonary and CNS in immunocompetent patients initially diagnosed by fine-needle aspiration cytology has been described by Suchitha *et al*,¹³ and was also described in a recent case of chronic lymphocytic leukaemia treated with chemotherapeutic agents.¹⁴ Bone marrow cryptococcosis in an apparently immunocompetent patient has rarely been reported.

Cutaneous cryptococcosis may be one of the first manifestations of disseminated cryptococcosis or primary disease both in immunocompetent and immunocompromised hosts. Diagnosis of cutaneous cryptococcosis depends on skin histopathology and cultures.^{9 15} In our case, split skin smear revealed the organism and there was complete disappearance of skin lesions after treatment.

Diagnosis of fungal mycotic intracranial aneurysm (described with *Aspergillus* spp., *Candida* spp. and *Zygomycetes* spp. infections) is extremely rare and often established at autopsy. Cerebrovascular involvement of large vessels can occur from haematogenous spread from fungal endocarditis, following surgery (in immunocompromised patients) and from contiguous spread from paranasal sinuses (in immunocompetent patients).⁷ Cryptococcal antigen tests may be helpful, but the diagnostic gold standard for *C. neoformans* infection is growth of the organism in culture, from an otherwise sterile site of infection. The treatment option for cryptococcosis depends on the site of infection and the underlying condition of the patient. In non-HIV-infected, non-transplant hosts with meningoencephalitis without neurological complications, induction therapy includes amphotericin B deoxycholate (0.7–1.0 mg/kg/day intravenously) plus flucytosine (100 mg/kg/day orally in 4 divided doses) for 4 weeks. Induction therapy can be extended for a total of 6 weeks, and liposomal amphotericin B may be given for the last 4 weeks of the prolonged induction period in patients with neurological complications. In patients at low risk for therapeutic failure (ie, an early diagnosis by history, no uncontrolled underlying disease or immunocompromised state, and excellent clinical response to initial 2-week antifun-

gal combination course), induction therapy with combination of amphotericin B deoxycholate plus flucytosine can be given for only 2 weeks, followed by consolidation with fluconazole 12 mg/kg/day orally for 8 weeks. After induction and consolidation therapy, maintenance therapy includes fluconazole 3 mg/kg/day orally for 6–12 months. For non-HIV-infected, non-transplant children with cryptococcosis, the treatment length and schedule are the same as for adults. For CNS and disseminated disease due to *C. gattii*, induction, consolidation and suppressive treatment are the same as for *C. neoformans*.¹⁶

Conclusively, in our case, the cause of primary intraventricular haemorrhage remained elusive even after angiography, which may be due to cryptic mycotic aneurysm caused by disseminated cryptococcal disease. CSF antigen may be negative in *C. gattii* infection. Disseminated cryptococcosis was diagnosed only after bone marrow aspiration and slit skin smear from the cutaneous lesions, which showed budding yeasts with morphology suggestive of cryptococci. The diagnosis was confirmed by fungal culture.

Contributors PP and SKP contributed to the conception and design of the study. SR and PP were involved in the drafting of the manuscript. PP performed the literature search. SR and SKP participated in the analysis and interpretation of data. DM was responsible for the critical revision of the manuscript for important intellectual content. All the authors gave final approval of the manuscript.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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Learning points

- ▶ Disseminated cryptococcosis can, though rarely, occur in apparently immunocompetent patients, and is often misdiagnosed.
- ▶ The causative species in immunocompetent patients is mostly *Cryptococcus gattii*, which can be differentiated from *C. neoformans* by differential growth on specialised media such as L-canavanine-glycine-bromothymol blue (CGB) agar.
- ▶ It should be recognised as a possible cause of long-standing fever with infectious skin lesions even in HIV-negative patients.
- ▶ The manifestations of cutaneous cryptococcosis may masquerade as other skin diseases.
- ▶ A systematic investigation of disseminated infection is necessary and bone marrow analysis may be rewarding in difficult cases.
- ▶ Early diagnosis of cryptococcosis and introduction of appropriate antifungal therapy may improve clinical outcomes.

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