Case Report

Cryptococcal meningitis with secondary cutaneous involvement in an immunocompetent host

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Abstract

Cryptococcosis is a potentially fatal fungal disease caused by variants of *Cryptococcus neoformans* species. The respiratory tract is the usual portal of entry, with a peculiar predilection to invade the central nervous system. The skin can be secondarily involved in disseminated infection or be exceptionally involved as primary cutaneous infection by inoculation. The disease is mostly seen in immunodeficiency states. The diagnosis is frequently unsuspected in immunocompetent patients.

We report a case of disseminated cryptococcal meningitis in an immunocompetent young adult. The cutaneous eruption prompted the accurate diagnosis. The patient, a 20-year-old female, had fever, cough, headache and intractable vomiting for the past two months and was being managed as a case of tuberculous meningitis. Two weeks after starting antituberculous treatment she developed umbilicated papules on the head and neck region. Necessary laboratory workup identified *C. neoformans* in cerebrospinal fluid (CSF) and skin specimens. The titers of cryptococcal antigen were measured in CSF and serum for diagnostic and prognostic purposes. Anti-fungal treatment resulted in regression of the cutaneous lesions and resolution of systemic complaints.

The case highlights the need for high degree of suspicion, especially in healthy young adults, in the diagnosis of cryptococcosis. The cutaneous eruptions can be the first manifestation or a diagnostic clue of enormous significance.

Key words: *Cryptococcus neoformans*; immunocompetent; skin involvement; meningitis; young adult

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Introduction

Cryptococcus *neoformans* is an encapsulated yeast present in the environment worldwide. It is found in soil contaminated with avian excreta, especially pigeon droppings, and in decaying wood, fruits, vegetables, and dust [1,2]. Primary cutaneous cryptococcosis occurs when skin is the portal of entry, usually after an injury. More commonly, skin is affected secondarily by hematogenous dissemination. Rarely observed in immunocompetent patients, cryptococcosis has been reported to be associated with AIDS in most cases, or with other immunodeficiencies [3]. *C. neoformans* is the most common CNS mycotic infection but rarely considered in the differential diagnosis in immunocompetent patients [4]. We report a case of disseminated cryptococcosis presenting with cutaneous lesions in an immunocompetent patient.

Case report

A 20-year-old female was referred to the dermatology clinic with four days' history of raised, skin-coloured to red lesions on the head and neck region. Nearly five weeks previously she had presented to the Department of Internal Medicine with a history for one and a half months of high-grade fever, dry cough, headache, and intractable vomiting. She had a documented weight loss of 8 kg during her illness. Her past medical history revealed that at the age of one and a half years she had tuberculous lymphadenitis for which she had completed antituberculosis treatment (ATT) of six months' duration. At the age of 13 years she was diagnosed and treated for tuberculosis (TB) of the spine at a tertiary care hospital for nine months. One of her siblings had also received a nine-month course of ATT on account of TB lymphadenitis.

Her baseline investigation included a complete blood count, revealing haemoglobin (Hb) of 8 gm/dl (normocytic normochromic anaemia) and total leucocyte count (TLC) 10.2 with marked eosinophilia (32%). Erythrocyte sedimentation rate (ESR) was elevated (43 mm fall after the first hour). Other investigations such as urine detailed report, chest X-ray, abdomen ultrasound, blood chemistry analysis, and liver and renal function tests were within normal limits. Her CSF study revealed clear fluid, without coagulum, slightly elevated proteins (50 mg/dL), decreased glucose (49 mg/dL), and occasional mononuclear cells (25/cmm). No microorganisms were detected on Gram and Ziehl-Neelsen (ZN) stains, nor did CSF culture reveal growth of any microorganism. Polymerase chain reaction (PCR) assay for detection of *Mycobacterium tuberculosis* in the CSF sample was negative. Magnetic resonance imaging (MRI) of the brain showed nonspecific changes of increased signal intensity in the periventricular region.

Anti-tuberculosis treatment was started empirically. She initially responded to treatment: after three weeks of therapy her fever became occasional and low grade, and vomiting settled. She was discharged on ATT and advised regular follow-up.

After two weeks of therapy, at home, her symptoms aggravated. She again developed high-grade fever, severe headache, vomiting, and pain in the neck radiating to the shoulders. New symptoms of diplopia and cutaneous eruptions on the head and neck region evolved. At this time dermatologic consultation was sought. Examination revealed discrete erythematous to skin-coloured papules with central umbilication on the face, nape of neck and upper back, resembling molluscum contagiosum, (Figure 1). The rest of the dermatological examination did not reveal any abnormality. Her nails, hair, and mucosae were normal. She was febrile with a temperature of 101˚F, and restless with intractable pain in the head, neck and shoulders. Her higher mental functions were intact. There was diplopia on the left lateral gaze depicting left lateral rectus palsy. The rest of the central nervous system was intact with normal fundii. Her abdominal, respiratory, and cardiovascular examinations were unremarkable.

Relapse of the symptoms together with molluscum contagiosum-like lesions led us to suspect crytococcal meningitis with secondary cutaneous involvement. The CSF study revealed low sugar (46 mg/dl), protein 35 mg/dl, red blood count 760/cmm and white blood count 160/cmm (polymorphonuclear leucocytes 45%, lymphocytes 55%). India ink preparation of CSF revealed characteristic round budding yeast cells with distinct halos, resembling a starry sky (Figure 2). Skin biopsy for histopathological examination showed encapsulated cells mixed with a network of connective tissue in the dermis. The large capsules of spores did not stain with hematoxylene-eosine (H&E), resulting in distinctive large surrounding clear spaces (Figure 3). CSF for fungal culture, grown on Saboraud's dextrose agar, yielded growth of *C. neoformans.* Due to limited resources, facilities for determining the exact taxonomical status of *C. neoformans* are not available in our laboratory. The patient was advised to send a sample to a reference laboratory but refused because of financial constraints. We believe *C. gatti* to be more likely in her case, considering the fact that this variant is more common in our part of the world. Serological tests for detection of cryptococcal capsular antigen in CSF yielded a titer of 1:256, by latex agglutination technique. The patient was thoroughly investigated for her immune status. She was non-reactive to human immunodeficiency virus (HIV). Serum protein electrophoresis, immunoglobulins, complement levels, and measurement of CD4/CD8 T-lymphocyte ratio were within the normal range. CT scans of chest and abdomen did not detect any pathology.

Finally, the diagnosis of cryptococcal meningitis with secondary cutaneous involvement in an immunocompetent host was made. Treatment was started with intravenous amphotericin B (AmB) in a dose of 0.7mg/kg/day for two weeks, followed by oral fluconazole 400 mg/day. The patient responded well to treatment and her CNS symptoms and skin lesions started settling. However, after two and a half months, the patient left treatment on her own, and her symptoms relapsed. The CSF routine examination revealed sugar 44 mg/dl, protein 38 mg/dl, no RBC, and occasional (10/cmm) WBCs. The cryptococcal antigen titer was 1:256, showing no decline. AmB and fluconazole were concomitantly started; however, AmB could not be continued for the complete duration due to refractory hypokalemia despite aggressive replacement. Her serum urea was 14 mg/dl and serum creatinine was 0.78 mg/dl. The hypokalemia reverted to normal once AmB was stopped. The patient responded well to fluconazole alone and is now in remission, doing well on a maintenance dose. Her cutaneous lesions have mostly resolved (Figure 4). After eight months of treatment the cryptococcal antigen titer was 1:128

Figure 1. Papulonodular umbilicated lesions on the neck and upper trunk

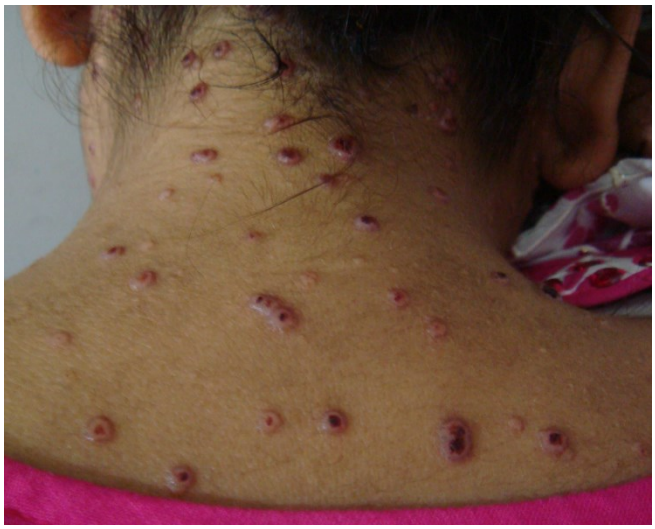


Figure 2. India ink preparation of CSF revealing budding yeast cells with surrounding halos

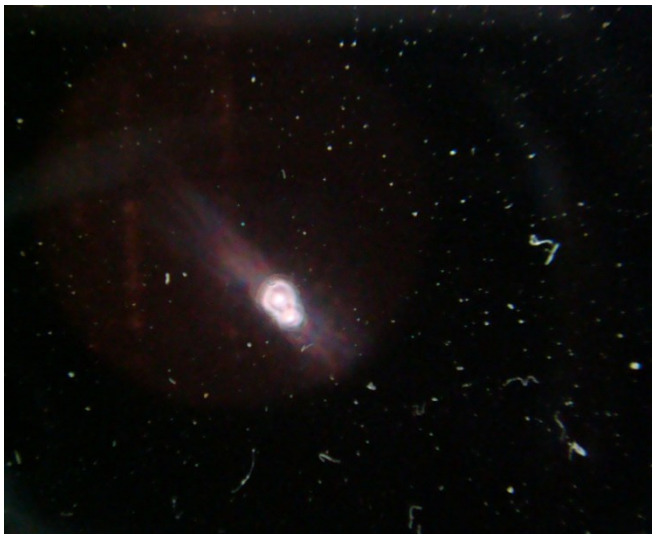


Figure 3. Histopathological examination of the cutaneous lesion showing encapsulated cells with distinctive clear surrounding spaces within the

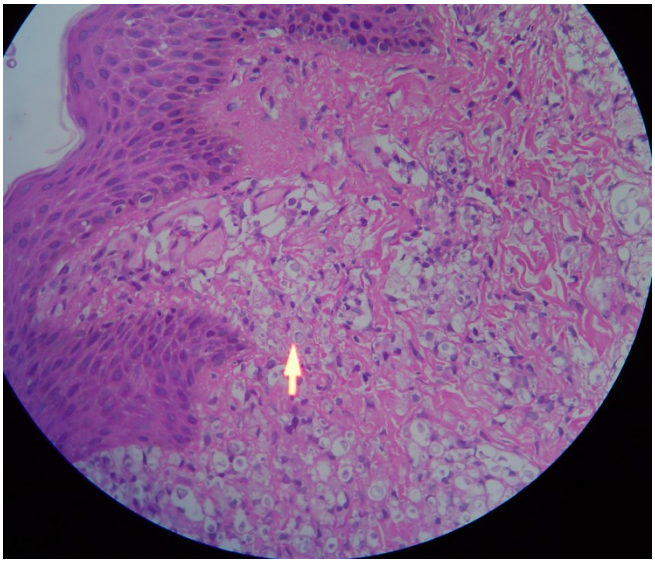
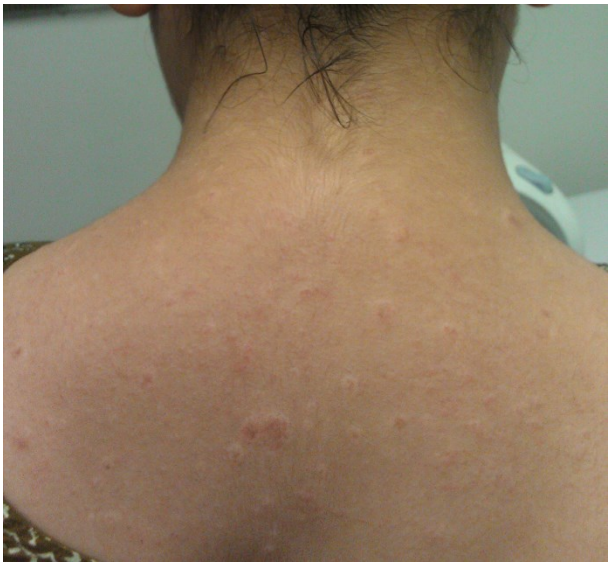


Figure 4. Resolution of cutaneous lesions with Amphotericin B and fluconazole therapy



Discussion

The genus *Cryptococcus* is a heterogeneous group of nonfermentative, encapsulated yeast species, distributed worldwide, which includes several important human pathogens. Among these, *Cryptococcus neoformans* has been increasingly reported from immunocompromised patients, particularly those infected with HIV [5]. In contrast, disseminated cryptococcosis in normal hosts has been reported sparingly, the diagnosis frequently being unsuspected [6].

The single species of fungus *C. neoformans* comprises two variants: *C. neoformans* var. *neoformans* and *C. neoformans* var. *gattii*. These correspond to cryptococcal serotypes known as A, D, AD and B and C, respectively [7]. Controversially, it has been suggested that var. *neoformans* should be split further into var. *neoformans* (serotype D) and a new variety, var. *grubii* (serotype A), although there is still discussion as to the validity of this split [8].

C. neoformans var. *neoformans* was initially thought to be the predominant variant in Europe and much of the United States, and *C. neoformans* var. *gattii* was thought to be limited to tropical and subtropical areas, including Africa. With the spread of HIV infection, the *neoformans* variety is overwhelmingly found in AIDS patients, as well as in other immunocompromised individuals distributed all over the world [3].

Bird droppings act as an excellent culture medium, and probably play an important part in promoting multiplication of the fungus in contaminated soil. The inhalation of small yeast forms that have been aerosolized is likely to be the main route of infection. Pulmonary infections are in most cases asymptomatic, but may lead to hematogenous dissemination. *C. neoformans* has a particular predilection for invasion of the central nervous system. Cryptococcosis of the central nervous system is life threatening and presents as meningitis or meningoencephalitis, with symptoms such as headache, increased intracranial pressure, fever, lethargy, coma, personality changes, and memory loss [4,9]. Other sites of hematogenous dissemination include skin, bones, joints, kidneys, adrenal gland, spleen, and prostate [7,10,11].

Secondary cutaneous cryptococcosis is not an uncommon entity, occurring in 10% to 20% of those with systemic involvement [12]. In its generalized forms, especially in patients with AIDS, the infection presents as multiple lesions, most of them simulating *molluscum contagiosum*. The skin lesions typically appear as pedunculated, dome-shaped papules with an umbilicated center. Acneiform, nodular, herpetiform lesions and lesions mimicking cellulitis are also recorded. Cellulitis, ulceration, and whitlow are the most common clinical features of primary cutaneous cryptococcosis [13,14]. The frequency of cutaneous involvement in disseminated infection is higher in liver transplant recipients receiving tacrolimus or in patients infected with serotype D [15].

The laboratory diagnostic workup includes detection of *Cryptococcus* in biological fluids, such as cerebrospinal fluid, stained with India ink. India ink mounts of urine, sputum and bronchoalveolar lavage specimens are almost impossible to interpret. With routine histopathologic eosin and hematoxylin stains, the yeasts are surrounded by empty spaces, which reflect the capsule. Stains such as mucicarmine and Alcian blue are used to identify the polysaccharide capsule. A fungal colony can be grown on culture media and the varieties *C. neoformans* and *C. gatti* can be identified by a colour reaction on concanavalin-glycine-thymol agar, by antibody kit for serotyping or by fingerprinting with DNA-based methods [16,17]. Cryptococcal polysaccharide antigen detection in CSF and serum is made by latex agglutination test or by ELISA.

Successful treatment of disseminated cryoptococcal infection is a challenging task. *C. neoformans* is a facultative intracellular pathogen of host cells. This intracellular location provides a slot to escape host immune mechanisms, such as complement and antibodies, and also renders antifungal agents less efficacious [3]. Additionally, the cryptococcal capsule itself has antiphagocytic properties and is an important determinant of virulence. The current guidelines of the Infectious Diseases Society of America (IDSA) recommend amphotericin B based combination therapy with flucytocine as the primary induction therapy for all severe forms of disseminated cryptococcal infections (cryptococcosis) followed by fluconazole consolidation therapy [18].

Due to the unavailability of flucytocine we managed our patient with induction therapy of AmB alone, followed by consolidation therapy with fluconazole. Fortunately, we saw a rapid clinical response to this regimen.

The treatment outcome depends not only on the duration and choice of antifungal therapy, but also on resistance of the organism to therapy. Several authors have reported disseminated cryptococcosis being refractory to antifungal chemotherapy [6, 19]. Serum antigen titers should be obtained in all immunocompetent patients who have cryptococcosis,

to monitor the progress of the disease [20]. A decrease in cryptococcal antigen titer can be used to monitor the antifungal therapy efficacy but cannot be used as an index of cure, as titer remains positive even when fungal culture and stain turn negative [21].

In our local setting, a 10-year study has been conducted in a tertiary care hospital to compare the differences in presentation and outcome of patients with tuberculous meningitis and cryptococcal meningitis [22]. No cutaneous eruption was mentioned in any of the patients. We have reported the disease in a twenty-year-old, previously healthy female and, to the best of our knowledge, cutaneous eruption with cryptococcal meningitis has not been previously reported from Pakistan.

Our patient is continuing with oral fluconazole and is being regularly monitored as an outpatient. Her serum cryptococcal antigen titer is still high. We foresee that she will have to continue her medication for a long duration.

Conclusion

Cryptococcal infection should be considered in the differential diagnoses in patients of meningitis, even in areas where the prevalence of infection is low, especially when laboratory and radiology aids do not support bacterial or viral causes. Cryptococcal meningitis should no longer be considered in elderly, debilitated immunocompromised patients only. Delay in diagnosis may lead to substantial morbidity and mortality. The cutaneous eruptions can be the first manifestation or a diagnostic clue of enormous significance.

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