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CASE REPORT

Cryptococcal meningitis relapse in an immunocompetent patient

Roya Ghasemian[1], Narges Najafi[1], Tahereh Shokohi[2*]
[1]North Iranian Research Center for Infectious Disease, Mazandaran University of Medical Sciences, Sari, Iran
[2]Department of Medical Mycology and Parasitology, Mazandaran University of Medical Sciences, Sari, Iran

ABSTRACT

Background: Cryptococcal meningitis is a common opportunistic infection in patients with underlying immunosuppressive state specially AIDS patients. However, it could be seen in immunocompetent patients mostly in tropical areas. There are scanty reports of such infection in healthy patients of non-tropical areas.
Patient: We report an immunocompetent 43 years old Iranian man who was in excellent health status until 3 weeks before hospitalization when he developed headache. He experienced a 5-week delay in diagnosis of cryptococcal meningitis which led to his blindness of right eye despite treatment.
Conclusion: We believed that the nonspecific clinical and laboratory finding of the present case and also the rarity of disease in our area especially in immunocompetent patients made his diagnosis confounding.

Keywords: *Cryptococcal meningitis; Immunocompetent state; Immunocompromised state*.
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INTRODUCTION

Cryptococcus is an encapsulated fungus found worldwide in soil contaminated with decaying pigeon roosts and bird droppings or on vegetables and fruits (1).This infection is usually seen in tropical and subtropical areas. In these areas eucalyptus trees appear to be the principle reservoir for the organism but the infection has been diagnosed in areas lacking eucalyptus, indicating that other environmental sources exist (1). In a survey of 480 eucalyptus trees of the two botanic gardens located in northern and central part of Iran, only two isolates of *C. neoformans var. gattii* were obtained (2).

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Reprint or Correspondence: Tahereh Shokohi, PhD. Department of Medical Mycology and Parasitology, Sari Medical School, Mazandaran University of Medical Sciences, Khazar Abad Road, Sari, Iran.
E-mail: shokohi.tahereh@gmail.com

However, prolonged incubation periods can make it difficult to identify the true source of exposure (3). Meningitis is the most common illness caused by Cryptococcus. The risk of infection is highest when T-cell (CD4+) counts are below 100. The most common underlying condition is: HIV/AIDS, other immunosuppressive stages like lymphoma, steroid use, complement deficiency and recently in patients using infliximab (1,4). However, this infection can occur rarely in immunocompetent patients, especially in older one in tropical and subtropical areas (5). There are few reports of cryptococcal meningitis in immunocompetent patients in temperate areas. To our knowledge, cryptoccocosis has been reported rarely from our country, Iran (6-8).

This is a report of cryptococcal meningitis in an immunocompetent patient without any underlying

condition, residing in northern Iran (Mazandaran province) a temperate area.

CASE PRESENTATION

A 43-year-old Iranian male was reported to be in excellent health status until 3 weeks before hospitalization when he developed headache which, over the next week, progressed to be worse along with some changes in mind. During the week prior to admission, the patient recommended to use NSAID to get relief of pain. The day prior to admission he developed gastrointestinal (GI) bleeding leading him to see the doctor who referred him to hospital. During the admission GI bleeding stopped but the headache continued and a neurologist requested a brain CT scan. Thereafter, his neck was supple and the other neurological examinations were within normal limit. Brain CT was normal, too. He discharged from hospital and referred to a psychiatrist. During the following days, he still had headache and gradually developed some temporary change in mental status in addition to low grade fever. On the day before his second admission (at the end of the fourth week), he was unable to walk and didn't have orientation to time and person until a tonic–clonic seizure occurred. The patient had no known pet or animal exposure, however, many pigeons were reported to live near his home. He was a simple construction worker. He reported no recent travels, denied any high risk behavior and had no history of blood transfusions. His recently prescribed medication was acetaminophen codeine, ibuprofen, omeprazole and imipramin. He admitted in neurology ward with presumed diagnosis of encephalitis. The patient was thin, moderately ill with an altered mental state, oriented only to person. He had an oral temperature of 38^{o}C, pulse of 110 beats/minute and a blood pressure of 115/70 mmHg. The patient had marked nuchal rigidity and diminished deep tendon reflexes but the physical examination was otherwise unremarkable.

The peripheral white blood cell count was 9600cells/mm^3 with 66% polymorphs, 32% lymphocytes and 2% monocytes. Analysis of the cerebral spinal fluid (CSF) revealed a white cell count of 20cells/mm^3 (20% polymorphs, 80% lymphocytes), a protein level of 57mg/dL and glucose of 17mg/dL. Gram stain and Ziehl–Nielsen stain of the CSF were negative. A tuberculin skin test was non-reactive. Human immunodeficiency virus serology tests were repeatedly negative, and all other laboratory indices of immune function, including CD4-cell count, were unremarkable.

A computerized tomography scan of the brain revealed only a mild ventricular dilatation.

A diagnosis of viral meningo-encephalitis was made and parenteral ceftriaxone and acyclovir along with dexamethasone were administered. During the next hours his level of consciousness diminished more and he transferred to ICU ward. In attention to low glucose level of initial CSF exam, with a presumed diagnosis of tuberculosis or fungal meningitis, lumbar puncture was repeated and CSF was tested again for cell count, acid fast and Indian ink stain. Second CSF analysis was as follow: WBC: 6% polymorphs, 94% lymphocytes; RBC: 3-5; Protein: 98 mg/dl; and sugar: 10mg/dl. Plenty of encapsulated budding yeasts were seen in Indian ink preparation and Gram stain. Acid fast staining was negative. The CSF was cultured on niger seed agar (NSA), sabouraud's dextrose agar (SDA), blood agar (BA) and brain heart infusion agar (BHIA) and incubated at 25 and 37°C. Two days later, brown colored, smooth and mucoid colonies were grown on NSA. The cream coloured and highly mucoid colonies were produced on other culture media. The yeasts were urease positive and assimilate inositol. The carbohydrate fermentation test was negative.

Therapy was changed to amphotericin B (0.5mg/kg/day), and over the ensuing 3 weeks the patient become afebrile, his mental status improved significantly, but unfortunately he lost his right eye vision to the level of finger count and also some

degree of hearing loss especially in right ear. CSF culture became sterile after 4 weeks of anti fungal therapy. At this time, the patient discharged from hospital with oral fluconazole. Three weeks later he came back again with fever, headache and agitation. Lumbar puncture was achieved and the CSF revealed recurrence of cryptococcal meningitis. After 3 weeks of amphotericin therapy, he was discharged with oral fluconazole for the next 6 months. During a 2-year follow up, he never experienced any further recurrence of fungal meningitis and got back his health except loosing of right eye vision.

DISCUSSION

Cryptococcal meningitis is a common opportunistic infection in patients with underlying immunosuppressive state specially AIDS patients. But it could be seen in immunocompetent patient mostly in tropical areas. Geographic and climate factors do play some roles in the underlying patient's status (1). *C. neoformans var. gattii* has usually been isolated from patients without any immune problems, unlike other varieties of *C. neoformans*, which more commonly seen in immunosuppressed patients, especially in HIV positive patients (3,5). Until now, this difference remains unexplained. Australian experiences of cryptococcal infection revealed that infection with *C. neoformans* var. *neoformans* always were in patients with some immunocompromised states while all the cases with *C. neoformans var. gattii* were judged to be free of underlying immune defects (9).

The present case was a healthy patient without any immunosuppressive state. There are scanty reports of such infection in healthy patients of non-tropical areas. In a study of 94 non-HIV infected patients with cryptococcal meningitis, only one patient didn't have any underlying disease (5). Case reports of cryptococcal meningitis in immunocompetent patients were reported from Singapore (10), Spain (11), Australia and other tropical and subtropical areas (1,9).

As described before, this infection was considered to be restricted to warm areas (tropical and subtropical climates), but this statement is under discussion after some outbreak of cryptoccocosis infection by *C. gattii* in the temperate climate like Vancouver Island (British Columbia, Canada) (9).

However, the present case is from a temperate climate in north part of Iran, where, to our knowledge, such infections are rare, especially in an immunocompetent patient. Unfortunately, we couldn't identify the serovar of the infectious fungus.

The first case of disseminated cryptoccocosis in Iran was reported by Alilou et al. in 1978 (6). Then, there are three reports of cryptococcal meningitis from our country (7,8). The underlying conditions and the immune states of those reported cases were unknown, except in one case with Hodgkin lymphoma. In the mentioned reports, the serotypes of infecting cryptococci were not detected.

There is usually a delay in diagnosis of cryptococcal meningitis (1,5), however, this delay is generally shorter in immunosuppressed patients. The disease has always a sub acute course of 2 to 4 weeks duration especially in normal patients. Headache is the most common initial presentation (86.2%), along with nausea/vomiting (72.3%) and fever (69%). The initial symptoms and clinical course was similar in patients with and without T-cell suppression in Thai study of 93 patients (5). The present case had a 5-week delay in establishing the diagnosis which led to complication such as blindness of right eye. However, with four weeks history of headache, chronic meningitis is the main diagnosis and tuberculosis, brucellosis and cryptoccocosis are the leading causes. Although complications are relatively common in cryptococcal meningitis, most of them are because of delay in diagnosis. In one study of 94 patients,

visual field defect or blindness were found in 21 subjects (5). Rates of visual loss in immunocompetent patients with *C. neoformans var. gattii* are significantly higher than immunosuppressed patients with *C. neoformans var. neoformans* (12). This difference may reflect immune mediated optic nerve dysfunction in *C. neoformans var. gattii* meningitis caused by either compression due to arachnoid adhesion or edema and inflammatory cell-mediated damage (12). We believed that the nonspecific clinical and laboratory finding of the present case and lack of notice to diagnosis of meningitis due to absence of nuchal rigidity led to such a long delay in establishing the right diagnosis. Also the rarity of the disease in our area especially in immunocompetent patients made the situation more confounding. Amphotericin B plus flucytosine remains the cornerstone of therapy for cryptococcal meningitis (13). The success rate in non-AIDS era is between 60% and 75%. Fluconazole is used for the suppressive phase of treatment to reduce the chance for relapse (13).

Despite treatment with amphotericin B plus flucytosine, 19.3% of patients with cryptococcal meningitis in Vietnam died during their first admission, at a median of 14 days. In addition, residual visual impairment was common, affecting 25 of 46 survivors (54.3%) (1).

To our knowledge, the present case is the first case of *C. neoformans* meningitis in a patient without any immunosuppressive state in our area.

In conclusion, cryptococcal meningitis should always be included in the differential diagnosis of chronic or subacute meningoencephalitis.

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