CASE REPORT

CRYPTOCOCCAL MENINGITIS IN AN IMMUNOCOMPETENT CHILD: A CASE REPORT AND LITERATURE REVIEW

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Abstract. An immunocompetent 5 year-old girl presented with pyrexia of unknown origin associated with headache. Initial investigations showed leukocytosis and an increased erythrocyte sedimentation rate. A Widal-Weil Felix test, blood film for malarial parasites, mycoplasma IgM antibody, cultures from blood and urine, full blood picture, Mantoux test, and chest x-ray were all negative. A lumbar puncture was done as part of a work-up for pyrexia of unknown origin. *Cryptococcus neoformans* was seen on India ink examination and confirmed on culture. She was treated with 10 weeks of intravenous amphotericin B and 8 weeks of fluconazole. Further immunological tests did not reveal any defect in the cell-mediated immune system. *C. neoformans* meningitis may present with non-specific symptoms and should be considered in a work-up for pyrexia of unknown origin.

The menace of cryptococcosis has assumed global proportions over the years. The tropical climate in Malaysia offers a suitable environment for the growth of *C. neoformans*, which has a propensity to cause disease in immunocompromized hosts. The organism has a predilection for causing disease in the central nervous system. Cryptococcal meningitis is a chronic or subacute meningeal infection and is relatively rare in immonocompetent patients. The diagnosis is often delayed because of non-specific symptoms and the rarity of the disease. We report a case of cryptococcal meningitis in an immunocompetent child who presented with a 3-week history of fever and headache. The symptomatology, diagnosis and treatment of the disease are discussed.

The patient was a 5 year-old Indian girl who was previously well and first presented to a private pediatrician with a complaint of fever and occasional headache for 2 weeks duration. A peripheral blood film showed leukocytosis: a total white count of 27.9 x 10^9/l (neutrophil 88%, lymphocyte 10%, and monocytes 2%) and the urine culture showed no significant growth. She was given a 3-day course of Augmentin with no improvement. She was then referred to the local hospital for further investigations. Basic investigations were performed, including erythrocyte sedimentation rate, Widal-Weil Felix, and Chest x-ray, which were all normal. A further course of antibiotics comprised of oral penicillin and cloxacillin was given without success. The fever did not abate and she was then admitted for the work-up of pyrexia of unknown origin. There was mild loss of appetite and loss of weight. There was no history of night sweats. There was no contact with tuberculosis patients.

On examination, she was generally well but febrile on admission. She was thin with a body weight of 17 kg (at the 25th percentile of the NCHS chart) and there were shotty cervical lymph nodes present. A neurological examination was normal, with neither neck stiffness nor neurological deficits. An examination of the other systems was normal.

A repeat chest-xray showed no abnormalities. There was persistent leukocytosis with a predominance of neutrophils (TWC 21,900, neutrophils 74%, lymphocytes 18%) on the peripheral

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blood film. The full blood picture was reported as leukocytosis secondary to inflammation or infection. The erythrocyte sedimentation rate showed an increasing trend; 58 mm/hour rising to >170 mm/hour on two further results (normal<20). Skin testing with Mantoux was negative, mycoplasma IgM, the Widal-Weil Felix test, and blood for malarial parasites were all negative. Repeat blood and urine cultures had no growth. The urea, creatinine, electrolytes and liver function tests were also normal.

Further temperature spikes were observed. The child did not complain of headache while in the ward, though she was noted to be more lethargic. Further history revealed pigeons in the housing area where the family stayed. A lumbar puncture was carried out as part of a septic work-up.

The opening pressure was not noted during lumbar puncture. Analysis of CSF revealed the following: a normal cell count number (5 cells/ml), a low glucose compared to the random blood sugar (2.8 mmol/l in the CSF compared to 6.3 mmol/l in the serum) and a normal protein level of 0.3 mg/dl (normal 0.1-0.4 mg/dl). Ziehl-Neelsen staining for acid-fast bacilli and cultures for mycobacteria in the CSF were negative. India ink staining of the CSF was positive for a few capsulated yeasts. Cryptococcal antigen was present in the CSF at titers of >1:512. Subsequent cultures of the CSF yielded cryptococci and which was later identified as *C. neoformans*. The serum was not tested for the antigen and studies for cryptococcal antibodies were not done. The immunological work-up was normal; comprised of normal immunoglobulin levels, B and T-cell enumeration test, T-cell function test and normal phagocytic function.

She was treated with intravenous amphotericin B, with a test dose of 0.1 mg/kg, followed by 0.5 mg/kg the following day. She developed reaction with the low dose and was maintained at this dose for the next three days. This was stepped up gradually to complete a total cumulative dose of 738.2 mg (43.4 mg/kg) over a duration of 10 weeks.

Oral fluconazole (3 mg/kg) was added on day 22 of the amphotericin as fundoscopic examination revealed mild bilateral papilledema and a CT-scan of the brain showed mild hydrocephalus in the region of frontal and temporal horns of the lateral ventricles. Oral fluconazole was continued for a total of 8 weeks. Repeat India ink staining and cultures of the CSF were negative and subsequent CSF biochemistry was also normal. The repeat CSF cryptococcal antigen titer fell to 1:132 and was subsequently negative prior to the completion of anti-fungal therapy. The opthalmologic review was normal by six weeks of therapy. The patient's general condition gradually improved, and she was cheerful and back to her normal self prior to discharge.

A repeat CT-scan of the brain 4 months later showed no change from the first CT-scan findings. The patient has remained well after two years of follow-up.

Cryptococcosis is a systemic infection caused by the yeast-like fungus *Cryptococcus neoformans. C. neoformans* is an encapsulated, yeast-like fungus that reproduces by budding. It is a saprophyte in nature, with a world-wide distribution rather than any defined endemic area (Diamond, 1995). Because the organism is ubiquitous, it is presumed that exposure to *C. neoformans* is common. There must be a high natural resistance to infection because new cases were relatively rare before the arrival of acquired immunodeficiency syndrome (AIDS) and is rarely seen in immunocompetent patients.

Although pigeons have been associated with cryptococcosis, the organism resides in the feces, the birds are not infected. In a study of the seropositivity of *C. neoformans* in 185 immunocompetent children in the Bronx, the findings indicate that *C. neoformans* infects a majority of children after two years of age. The findings are consistent with several observations: the ubiquitous nature of *C. neoformans* in the environment, the large number of pigeons in urban areas, and the increased likelihood of environmental exposure for children who have learned to walk (Goldman *et al,* 2001) which predisposes them to cryptococcal infection. Few cases of human immunodeficiency virus (HIV) contracting cryptococcal meningitis in association with exposure to the excreta of birds have been reported (Fessel, 1993). A history of exposure to pigeons was helpful in our case.

Infection with *C. neoformans* is acquired by inhalation of the organism from environmental

sources, with no human-to-human transmission documented. Pulmonary infection with cryptococcosis is often asymptomatic. If uncontained, even in immunocompetent patients, there is hematogenous spread to other sites, in particular the central nervous system. Skin, bone, prostate, kidneys, eyes, liver, spleen, adrenals, and lymph nodes are also susceptible (Sabetta and Ariole, 1985; Perfect and Casadevell, 2002).

The most common symptoms associated with cryptococcal meningitis are headache and fever as in this case. Cryptococcal meningitis is often undiagnosed for several weeks and may manifest as pyrexia of unknown origin (Gelfand and Wolff, 1995). Although the onset is usually insiduous, it can be acute, especially in severely immunosuppressed patients. Less common symptoms are nausea, vomiting, and neck stiffness (Sarosi *et al*, 1969; Sabetta and Adriole, 1985; Diamond, 1995). In one of the most comprehensive studies of cryptococcosis in 171 cases from 24 health institutions in Brazil, neck stiffness was seen in 75% of those who were not immunocompromized, and in only 33% of those with AIDS (Rosenbuam and Goncalves, 1994). Other less frequent manifestations include visual disturbances, cranial nerve palsies, papilledema, cerebellar signs, seizures, and aphasia. It is important to note that some patients with cryptococcal meningitis are asymptomatic. For this reason, the CSF must be examined whenever *C. neoformans* is isolated from any site (Butler *et al*, 1964; Sarosi *et al*, 1969).

The differential diagnosis of cryptococcal meningitis includes tuberculosis, other mycoses, as well as viral meningoencephalitis or meningeal metastases. Tuberculous meningitis may be difficult to distinguish from cryptococcal meningitis, although patients with the former condition are more likely to have an abnormal mental status, nuchal rigidity, an abnormal chest radiograph and hyponatremia. Other mycoses, such as histoplasmosis, coccidiodomycosis, nocardia or aspergillus may mimic cryptococcal meningitis (Sabetta and Adriole, 1985; Diamond, 1995; Perfect and Casadevell, 2002). Meningeal metastases, including lymphoma or other secondaries in adults, may mimic cryptococcal meningitis.

Cryptococcal infection of the central nervous system is nearly always detected by abnormalities in the cerebrospinal fluid. In a study by Butler *et al* (1964) involving 40 patients with *C. neoformans* meningitis, the opening pressure was elevated in 64%. CSF glucose is typically depressed and CSF protein is elevated (Butler *et al*, 1964; Diamond and Bennett, 1964; Sarosi *et al*, 1969). The cell counts in CSF are usually abnormal with leukocyte counts exceeding 20/mm^3 or higher and lymphocytes generally outnumbering neutrophils. An eosinophilic pleocytosis may occur rarely (Schmidt *et al*, 1995). Unfortunately, none of these findings can provide a precise diagnosis.

Isolating the organism from the CSF can give a definitive diagnosis of cryptococcal meningitis. The organism is frequently isolated from culture after several sequential examinations of the CSF. A high yield from cultures is influenced by the collection and processing of the specimens. For the initial culture, Sabouroud and nigger seed agar media are used and the cultures are maintained at 30º-32 ºC. Cycloheximide should not be used, because it inhibits the growth of *C. neoformans*. Evidence of growth may accur as early as 3 days, but cultures should be held for 3 to 4 weeks before being considered negative (Edman, 1995).

The other classical method of diagnosis is demonstration of encapsulated yeast on India-ink preparations of the spinal fluid, as was illustrated in our patient. This test is easy to perform, but care should be taken not to confuse lymphocytes with fungal organisms. The yield rate by this method ranges from 40 to 79% in various series (Butler *et al*, 1964; Sarosi *et al*, 1969; Sabetta and Adriole, 1985; Dismukes *et al*, 1987).

Serologic methods to aid in the diagnosis of cryptococcal meningitis have been in use for years. The most useful serologic test for cryptococcosis is the latex agglutination test for cryptococcal antigen. This test detects as little as 19 ng of cryptococcal antigen per ml of body fluid (Wu and Koo, 1983). It has also been shown to be a useful diagnostic tool when CSF cultures and Indian ink preparations are negative (Snow and Dismuke, 1975; Godman and Kaufman, 1971). Occasionally, the latex test is positive before the appearance of cells in the CSF Snow and Dismuke, 1975). The CSF of patients with cryp-

tococcal meningitis is positive by latex agglutination in over 90% of cases; the serum is positive in 50% of cases. The test is also used to monitor progression of the disease; antigen titers usually decrease on therapy, and a falling titer has been used as a favorable prognostic indicator.

Both non-specific factors and rheumatoid factor can cause false positive reactions in serum and CSF. Many non-specific reactions can be eliminated by heating the serum samples to 56ºC for 3 minutes or the CSF samples to 100ºC for 10 minutes, now standard procedure in most laboratories (Sabetta and Adriole, 1985). Other serological methods include the complement-fixation test for cryptococcal antigen and the anti-cryptococcal antibody test.

It should be emphasized that there is no pathognomonic radiographic picture for cryptococcal meningitis. In fact, approximately half of CT scans are normal in cryptococcal meningitis (Perfect and Casadevell, 2002). Several findings on magnetic resonance imaging (MRI) or computed tomography are associated with cryptococcosis involving the central nervous system. These have been described in several studies involving small cohorts of immunocompromized patients as well as in case reports. Hydrocephalus is a common finding, as cryptococcal meningitis typically involves the basilar area. Cryptococcomas, with a propensity for the basal ganglia and brainstem and subsequent extension to the brain parenchyma are another finding in cryptococcal meningitis. Pathology reveals a collection of gelatinous material associatecd with the cryptococcal organisms (Miszkiel *et al*, 1996). Other rare reported findings include subarachnoid cysts, midbrain infarction and parenchymal calcification (Caldemeyer *et al*, 1997). These abnormal findings on CT-scan may persist years after completion of treatment in patients.

Cryptococcal meningitis is invariably fatal if untreated (Butlar *et al*, 1964). Amphotericin B had been used extensively for treatment since the 1950s and remains the most important therapeutic agent against cryptococcosis. Amphotericin, if used alone, should be given for at least 10 weeks at a dosage of 0.5-0.7 mg/kg. Double doses of amphotericin can be substituted on alternate days for convenience (Diamond, 1995). Amphotericin B can now be given in lipid preparations (Ambisome) if toxicities develop with standard amphotericin B.

Intrathecal therapy, as an adjunct to intravenous amphotericin B, has been advocated for very ill, refractory cases of cryptococcal meningitis. Intrathecal therapy produces higher drug levels in the CSF (Butler *et al*, 1964; Sarosi *et al*, 1969) but associated with a high risk of superimposed infection.

The azole anti-fungal group has shown promising results in the treatment of cryptococcal meningitis. Fluconazole, itraconazole and voriconazloe, the latter a newer oral triazole agent, are active against *C. neoformans* infection. Several studies have evaluated fluconazole and itraconazole alone or in combination with amphotericin therapy, consisting of amphotericin (0.3 mg/kg/d) and flucytosine (150 mg/kg/d) (Bennett *et al*, 1979; Wittner, 1995; Dromer *et al*, 1996). Combination therapy results in a more rapid CSF culture conversion from positive to negative, and several studies show fever relapses with the combination regimen (Perfect and Casadevell, 2002). This led to a definitive study using higher doses of amphotericin B (0.7 mg/kg/d) and lower doses of flucytosine (100 mg/kg/d) for a two-week induction period of treatment, then switching to fluconazole alone for 8 weeks. This strategy has become the recommendation for the treatment of cryptococcal meningitis. In our patient, fluconazole was added to the initial therapy of amphotericin, as there was clinical deterioration. Fluconazole is known to act synergistically with amphotericin and produces a good response.

As a learning point, a work-up for pyrexia of unknown origin should include a thorough history and examination. A child who has prolonged fever, headache and lethargy with a normal neurological examination warrants a lumbar puncture, provided there are no contraindications to the procedure. *C. neoformans* should be included as one of the possible causes in such a scenario, especially with a history of exposure to pigeons.

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