Rare disease

Disseminated cryptococcosis in an HIV-positive boy

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Summary

Cryptococcosis is rare among children, only occurring in about 1% of children with HIV. We report the case of a 12-year-old boy with disseminated cryptococcosis. He had a history of recurrent pneumonia. He then developed meningeal symptoms and was found to have disseminated *Cryptococcus neoformans* by cerebrospinal fluid and bone marrow aspirate culture. He was treated with amphotericin B for 2 weeks (1 mg/kg/day), and then with fluconazole orally for 8 weeks (12 mg/kg/day). He also received a new diagnosis of HIV and was started on antiretroviral therapy 2 weeks after starting antifungal treatment. At follow-up 8 weeks later, he was doing well.

BACKGROUND

Cryptococcosis is a rare disease in children, affecting only 1–1.4% of children with HIV.¹ It is caused by *Cryptococcus neoformans*, a monomorphic encapsulated yeast. Concurrently, *C. neoformans* and *Cryptococcus gattii* are now considered separate species, although many labs do not report them as such.² It is thought that cryptococcosis is acquired from inhalation of fungal spores or acapsular yeast cells in the environment, although direct association between environmental exposure and the infection is difficult.¹ *Cryptococcus* has the potential to infect any organ in the human body, but pulmonary disease, disseminated infection and meningitis are the most common clinical manifestations.^{1–3} About half of children who develop cryptococcosis are immunocompetent, and cryptococcal meningitis often does not have the classic severe, acute meningeal signs that are common among other forms of meningitis.^{3–5} This case is unique in that the boy developed symptoms while hospitalised, and the meningitis symptoms and signs were acute and severe.

CASE PRESENTATION

A 12-year-old Thai boy presented to Chiang Mai University Hospital (CMUH) with a 3-day history of high fevers, dyspnoea and productive cough, as well as a 1-day history of vomiting. The sputum was green without any evidence of blood. Three months prior to admission, he had a cough without fever or dyspnoea, which resolved. One month prior, he had fever and dyspnoea associated with cough. He was taken to a provincial hospital and diagnosed with pneumonia for which he was treated with intravenous antibiotics. However, the caregivers were not sure which antibiotics were given. The fever and dyspnoea improved, but the productive cough remained. He had been living with his grandmother from a very young age because his mother was in prison for drug abuse and drug trafficking. Her medical history is not known. The grandmother is HIV-positive and did prechew his food when he was young as she was his sole caregiver. His grandmother did not think that he had received all of his immunisations according to the Thai

guidelines, but was not sure which ones he had received and his records were not available. Physical examination showed a boy in mild respiratory distress. He had a temperature of 38.1°C, a pulse of 128 beats/min, a respiratory rate of 40 breaths/min, a blood pressure of 94/50 and an oxygen saturation of 96% on room air. He weighed 16.7 kg and was 117 cm tall, both much less than the third percentile for age on the Thai growth charts. His body mass index was 12.2 kg/m.² He had dry lips, mildly sunken eyes and oral thrush. His lung exam showed crepitations in the left lower lobe and right lower lobe. He had no wheezing. He did have mild suprasternal notch retractions, but no intercostal or subcostal retractions. He had no murmurs or gallops on cardiovascular exam. He had mild tenderness to palpation at the right upper quadrant on abdominal exam, and hepatosplenomegaly with a liver edge 3 cm below the right costal margin and the spleen was palpable 2 cm below the left costal margin. He had no rash, and his extremities had no oedema or clubbing. His neurological exam was intact and he had no meningeal signs.

INVESTIGATIONS

His laboratory tests showed a haemoglobin level of 8.1 with a mean corpuscular volume of 78.9. His white blood cell (WBC) count was 4800/mm³ with 70% neutrophils and 27% lymphocytes. His platelet count was 196 000/mm³. His peripheral blood smear showed hypochromic, microcytic red blood cells with anisopoikilocytosis, no band forms, no toxic granules and no vacuolisation. The blood cultures were negative for bacteria and fungi. Serum iron was low at 46 µg/dl and total iron binding capacity was low normal at 250 µg/dl. His reticulocyte count was 3%. His electrolytes showed hyponatraemia at 131 mEq/l, hypokalaemia at 3.1 mEq/l and hypochloridaemia at 97 mEq/l, but were otherwise within normal limits. His albumin level was low at 2.5 g/dl, but otherwise his liver function tests were within normal limits as well. His urinalysis was within normal limits. A potassium hydroxide smear from his oral cavity showed budding yeast. Mycoplasma immunoglobulin M (IgM) and IgG were negative. His HIV antibody screen

Figure 1 Chest x-ray obtained on admission showing diffuse patchy infiltrates with right-sided hilar lymphadenopathy.

was positive. His viral load was 125 545 and his CD4 count was 1% or 14 cells/ μ l. Acid-fast bacilli stains of the sputum were negative 3 days in a row. A chest x-ray showed diffuse perihilar infiltrates and right-sided hilar lymphadenopathy (figure 1).

DIFFERENTIAL DIAGNOSIS

- Pneumonia in an HIV-infected child:
 - Bacterial causes: *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, tuberculosis, *Mycobacterium avium* intracellulare complex (MAC) and *Nocardia*.
 - Viral causes: respiratory syncytial virus, measles, influenza, adenovirus, parainfluenza, herpes simplex virus, varicella zoster virus, cytomegalovirus (CMV) and Ebstein-Barr virus.
 - Fungal causes: *Cryptococcus* spp., *Pneumocystis jirovecii*, aspergillosis, histoplasmosis and coccidioidomycosis.
 - Parasitic causes: strongyloidiasis, toxoplasmosis and malaria.
 - Other causes: lymphoma and lymphocytic interstitial pneumonia.
- Protein-energy malnutrition and stunting: HIV, tuberculosis, recurrent infections and poor nutrition.

TREATMENT

The boy was started on antibiotics, including cefotaxime (150 mg/kg/day), amikacin (15 mg/kg/day) and azithromycin (10 mg/kg/day). He also received nystatin for his thrush. Because of his dyspnoea he was not eating well; so he received intravenous fluids. He also received albuterol nebulisations to try to help with his dyspnoea. His clinical symptoms resolved after 4 days of treatment. He did not have fever or dyspnoea, and had good appetite. We assumed that he had suffered from bacterial pneumonia and had responded well to the antibiotic treatment.

Figure 2 India ink staining on the cerebrospinal fluid showing encapsulated budding yeast.

OUTCOME AND FOLLOW-UP

Five days after admission, the boy developed headache, nausea and vomiting. He had a stiff neck on exam. An ophthalmologist was consulted given his HIV infection, who found no papilloedema and no evidence of CMV retinitis. He did not have abnormal neurological signs and weakness of extremities. He then underwent lumbar puncture. His opening pressure was 35 cm H₂O. Cell count showed many budding yeast cells, 6 neutrophils/mm³ and 2 lymphocytes/mm³. Cerebrospinal fluid (CSF) India ink stain showed budding encapsulated yeast cells (figures 2). CSF protein level was 89 mg/dl and glucose level was 48 mg/dl, with a serum glucose of 83 mg/dl at that time. Gram stain of the CSF showed no organisms, but the Wright's stain showed many budding yeasts (figure 3). His *Cryptococcus* antigen of the CSF was positive at 1:10 000. Rapid CSF latex agglutination was negative for *N meningitidis*, *S pneumoniae*, *H influenzae* and *S agalactiae*. Culture of the CSF showed no bacteria, but grew *C neoformans*. A bone marrow aspiration was done that was also positive for encapsulated organisms and grew both *C neoformans* and *Salmonella enteritidis* group D. Due to the diffuse nature of the disease, he was diagnosed with disseminated cryptococcosis, an AIDS-defining illness. Amphotericin B was started at 1 mg/kg/day and given for 2 weeks. During this time, he had therapeutic lumbar punctures in order to relieve symptoms when needed. He then started fluconazole (12 mg/kg/day (200 mg)) by mouth. His cryptococcal antigen titre decreased to 1:100. Two weeks after starting antifungal therapy, he started treatment with antiretroviral

Figure 3 Giemsa staining of bone marrow biopsy showing encapsulated yeast as well.

therapy (ART) consisting of a combination of lamivudine, stavudine and efavirenz. According to the national 2010 guidelines on HIV/AIDS diagnosis and treatment in Thailand,⁶ efavirenz-based regimens are the preferred regimens for the treatment of children aged more than 3 years because they have shown to be more efficacious, easier to administer and have fewer side effects than nevirapine-based regimens.

DISCUSSION

A retrospective database review of 5 years of data from 42 children's hospitals in the USA showed a rate of 6.2 cases of cryptococcosis per one million hospitalisations.⁵ In this study, HIV-infected patients made up only 16% of the cases of cryptococcosis, with immunocompetent children, children with malignancy and children with other immunosuppressive conditions making up the rest.⁵ Our patient was not only HIV-infected, but severely immunocompromised given his CD4 count of 1%, as well as co-existent stunting and malnutrition. He was relatively older than the median age of 8 years in one study of children with cryptococcosis, but within the range of 2–17 years.⁴ Unlike the children in this study who rarely had meningeal signs or acute mental status changes,⁴ his cryptococcal meningitis was accompanied by prominent meningeal signs. His India ink stain, as well as his culture and cryptococcal antigen latex agglutination (CRAG) titres were positive. Preferred methods of diagnosis include culture, which usually turns positive in 48–72 h, but can take up to 2 weeks or CRAG. CRAG has a sensitivity and specificity of around 90%, and any positive titres over 1:1 024 suggest a high burden of yeast.¹ Our patient's initial CRAG was quite high at 1:10 000. India ink staining is helpful, especially in resource-limited settings; however, it is only positive about 50% of the time in non-HIV-infected patients, and 80% of the time in AIDS patients.¹ It also requires skill because lymphocytes with proteinaceous debris can sometimes resemble the encapsulated yeast. Chest radiography in cryptococcal pneumonitis can show diffuse infiltrate, hilar lymphadenopathy, discrete nodules, cavitation or even pleural effusion, and so can mimic many other causes of indolent pneumonia, such as tuberculosis and *P jirovecii*. This can make the diagnosis of pneumonia in severely immunocompromised children quite challenging, especially in resource-limited settings. While dual treatment with amphotericin B plus flucytosine is preferred,² flucytosine can be difficult to obtain and requires laboratory monitoring due to its association with bone marrow suppression

and renal toxicities. ART can be started 2–10 weeks after starting antifungal therapy, and maintenance therapy may be able to be stopped once the CD4 count is over 100 cells/ μ l, the viral load is very low or undetectable for at least 3 months, and the patient has had antifungal therapy for at least 1 year.² Mortality is often still quite high even with treatment, with one meta-analysis showing a death rate ranging from 0% to 20% in North America, Europe and Southeast Asia, and 27–83% in Africa.⁷

Learning points

- ▶ Paediatric disseminated cryptococcosis is a rare, but severe disease, and can mimic many other opportunistic infections associated with HIV.
- ▶ Cryptococcosis usually has an insidious onset and can involve any organ in the body, but can have more acute presentations.
- ▶ Lumbar puncture is one of the most important procedures for the diagnosis of cryptococcosis in children.

Competing interests None.

Patient consent Obtained.

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