AIDS RESEARCH AND HUMAN RETROVIRUSES
Volume 27, Number 4, 2011

DOI: 10.1089/aid.2010.0167

A Case of Cryptococcal Lymphadenitis in an HIV-Infected Child

Eva Natukunda, Victor Musiime, Francis Ssali, Hilda Kizito, Cissy Kityo, and Peter Mugyenyi

Abstract

An 8-year-old HIV-positive antiretroviral therapy-naive child developed severe headache and generalized lymphadenopathy. The serum cryptococcal antigen (CRAG) test was positive, the histology on the lymph node biopsy revealed budding yeast cells, and *Cryptococcus neoformans* was isolated on culture of his cerebrospinal fluid. He was treated with intravenous amphotericin B followed by oral fluconazole with a good response. Therefore cryptococcal lymphadenitis should be considered in the differential diagnosis of children presenting with lymphadenopathy and a positive serum CRAG.

An 8-year-old HIV-positive antiretroviral therapy (ART)-naive child was referred to our center in March 2009 with a 4-day history of a severe headache that was preceded by a painful ear. The headache was frontal with no fever, seizures, or vomiting. He had been treated with amoxicillin–clavulanic acid. This was his second admission. His mother was HIV positive and was on highly active antiretroviral therapy (HAART) and his father was not tested. The couple have two children. Their second child is 1 year old and is HIV negative.

At the time of presentation, he was moderately wasted with a weight of 18 kg (third percentile of weight for age), had moderate pallor, and no peripheral lymphadenopathy. His temperature was 37°C. In the central nervous system (CNS), he was fully conscious, had a stiff neck, and a positive Kernig's sign, as well as hypertonia in the left lower limb. The abdominal examination revealed a nontender hepatomegally of 6 cm below the costal margin.

A brain computerized tomography (CT) scan was done and it revealed normal features (as shown in Fig. 1).

The serum cryptococcal antigen (CRAG) test was positive (4+).[1] A lumbar puncture was then done and the cerebrospinal fluid (CSF) findings were protein, 30 mg/dl; glucose, 50 mg/dl; cell count, 15 wbc/mm^3 (lymphocytes 95%, neutrophils 5%); CSF CRAG, positive 4+ [1]; Indian ink, positive; gram stain, yeast cells 4+; CRAG, 4+ [1]; Ziel–Neelsen (ZN) staining, no acid-fast bacilli (AFB) seen; *Cryptococcus neoformans* was isolated on culture. The complete blood count (CBC) showed WBC, 4900/μl; neutrophils, 3220/μl; lymphocytes, 1140/μl; hemoglobin (Hb), 8.9g/dl; and platelets, 488,000/μl. The serum creatinine was 0.43 mg/dl, serum urea was 17.89 mg/dl, alanine aminotransferase (ALT) enzyme was 18.7 IU/liter, aspartate aminotransferase (AST) enzyme was 59.2 IU/liter, total bilirubin was 0.31 mg/dl, and albumin was 3.78 mg/dl, all being within normal range except for AST, which was slightly above normal. His CD4 was 15 cells/μl (2%) and the HIV-1 viral load was 62,072 copies/ml.

At this point, a diagnosis of cryptococcal meningitis was made and he was started on intravenous amphotericin B at 1.0 mg/kg/day, with oral morphine. A therapeutic lumbar puncture with tapping of 10 ml of CSF was done on the fifth day of treatment. The CSF analysis on day 14 and the day 21 of amphotericin B treatment showed gram-positive yeast cells but no growth on culture, a result that prompted us to give amphotericin B for 28 days. The decision to give the amphotericin B for an extra 14 days was based on our clinical observations of several cases of recurrence of cryptococcal meningitis after 2-week courses of the drug in the presence of gram-positive yeast cells even when cultures are negative for *C. neoformans*. The renal function tests carried out twice a week remained normal throughout the course of amphotericin B.

On day 14 of his treatment with amphotericin B, he developed a painful neck swelling and abdominal discomfort associated with a low-grade fever. He was febrile (temperature = 37.6°C and had a tender mobile supraclavicular lymph

Joint Clinical Research Centre, Kampala, Uganda.

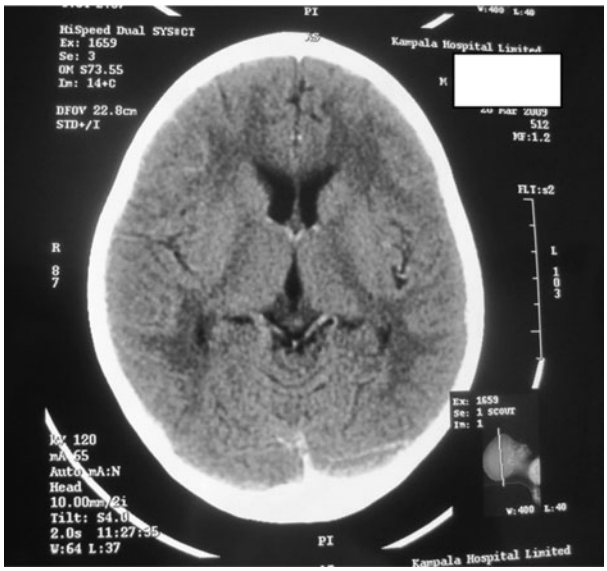

FIG. 1. Brain computerized tomography (CT) scan of the child at admission.

node. The abdominal ultrasound scan showed multiple discrete enlarged lymph nodes along the celiac trunk measuring 8–24 mm, as well as peritoneal fluid of 5 mm thickness in Morrison's pouch (Fig. 2). The chest X-ray showed normal features. The tuberculin skin test (Mantoux) was 00 mm after 48 h (negative).

A presumptive diagnosis of disseminated tuberculosis (TB) (abdominal TB and TB lymphadenitis) was made and hence he was started on anti-TB medication (rifampicin, isoniazid, pyrazinamide, and ethambutol with pyridoxine for 2 months to be followed by 7 months of isoniazid and ethambutol). Although the response was good with his fever subsiding and his appetite improving, we went ahead and did a lymph node biopsy with histology on the 21st day of treatment with amphotericin B, which showed budding yeast cells (Fig. 3). It should be noted that both ZN (Fig. 3b) and the hematoxylin and eosin (H&E) (Fig. 3a) stains of sections of the lymph node did not show acid-fast bacilli, granulomas, or giant Langahans giant cells, which would have been confirmatory of TB,[2] but rather showed budding yeast cells suggestive of *C. neoformans,* which had earlier been cultured on the child's CSF.

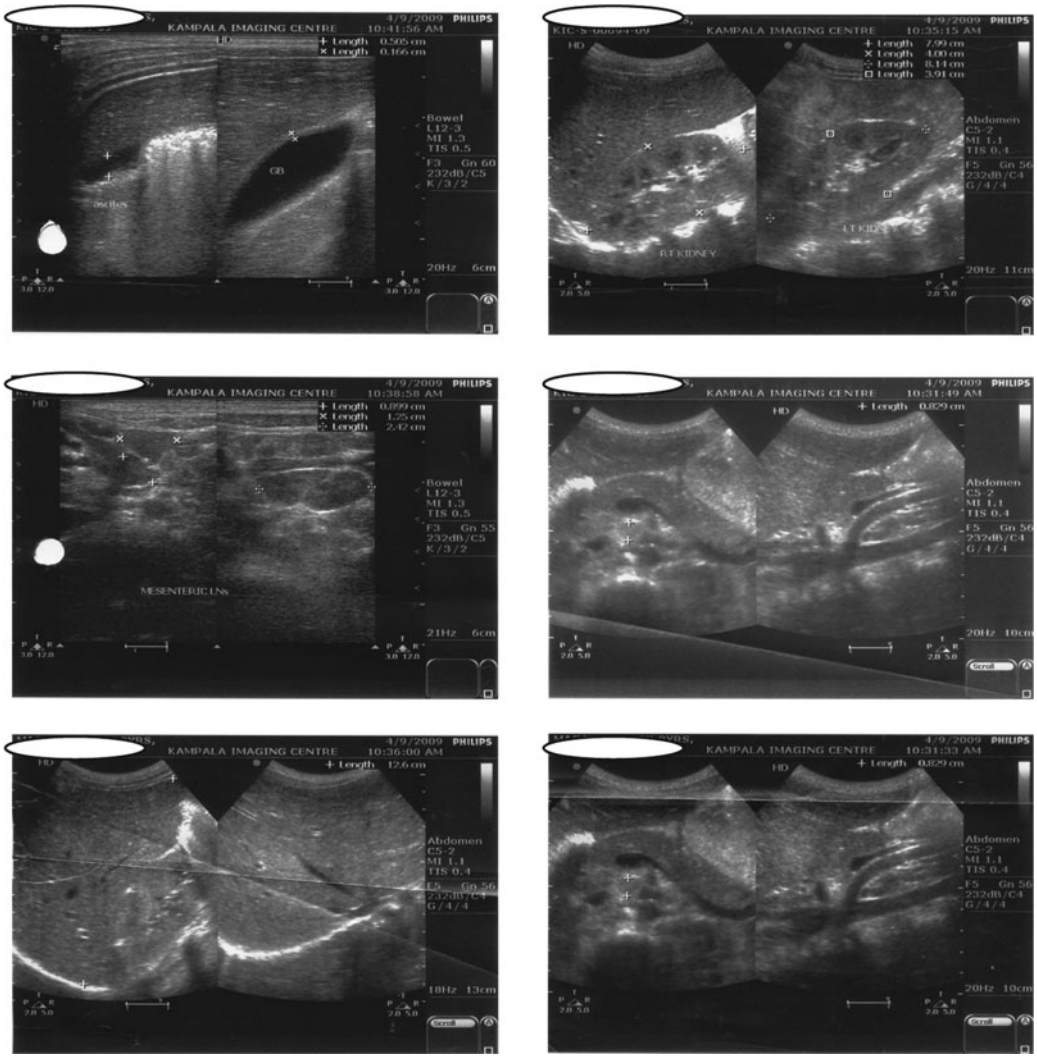

FIG. 2. Abdominal ultrasound showing multiple lymphadenopathy along the celiac trunk.

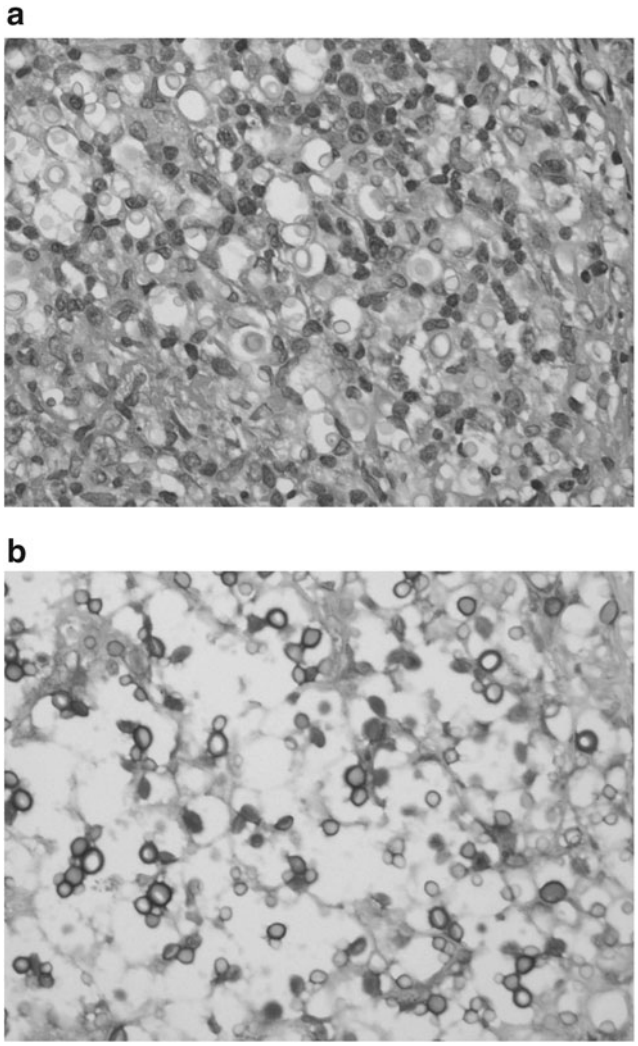

FIG. 3. Histology of a section of a lymph node showing budding yeast cells **(a)** stained with hematoxylin and eosin (H&E) stain and **(b)** stained with Ziehl–Neelsen (ZN) stain.

A 28-day course of amphotericin B was completed after which he was switched to oral fluconazole 200 mg once daily.

Antiretroviral therapy (ART) with abacavir (ABC), lamivudine (3TC), and efavirenz (EFV) was started on day 32 of his treatment for this disseminated cryptococcal disease. His CD4 after 24 weeks of ART was 164 cells/μl (12%).

At week 8 following initiation of treatment for cryptococcal disease, he developed nodules on his feet, and at week 24 the headache recurred and the CSF analysis showed the following: protein, 20 mg/dl; glucose, 50 mg/dl; cells <5 wbc/hpf; CSF CRAG, positive $(4+)^1$; Indian ink, positive; gram stain, gram positive yeast cells 2+; culture, no growth, prompting a 6-week course of amphotericin B followed by fluconazole 200 mg once daily.

Anti-TB drugs were given until January 2010 (the total course was for 9 months). This is because we considered this as a case of possible dual infection of TB and disseminated cryptococcal disease given that the child responded well clinically to the antituberculous medications and Uganda being a country with high TB endemicity.[3] Such cases of TB and cryptococcal disease coinfection have been reported.[4,5]

Currently, 12 months after initial presentation, he is symptom free. The cervical lymph nodes and the nodules on the lower limbs completely resolved. The last CSF analysis was done in November 2009 and it revealed improvement: CSF CRAG, $1+^1$; Indian ink, positive; gram stain, gram-positive yeast cells 2+; culture, no growth. His current weight is 22.5 kg (third percentile weight for age). He is on fluconazole 200 mg (as a secondary prophylaxis for cryptococcal disease), ART (ABC, 3TC, EFV), and cotrimoxazole for primary prophylaxis of pneumocystis pneumonia. This boy presented with advanced HIV disease with disseminated cryptococcal disease (cryptococcosis).

Cryptococcosis occurs in HIV-infected individuals, especially those with advanced disease (at low CD4 counts) and usually in adults.[6] It is rare in children,[7] although a few cases of cryptococcal meningitis have been reported.[8,9]

Given that cryptococcal lymphadenitis is a rare presentation even in adults with only a few reported cases,[10] this boy's presentation was surprising to us. This presentation is similar to the case of mesenteric lymphadenitis that was reported elsewhere.[11] The recurrence of symptoms at week 24 was probably a case of immune reconstitution inflammatory syndrome (IRIS).[12] We propose that cryptococcal lymphadenitis should be considered in the differential diagnosis of children presenting with lymphadenopathy and a positive serum CRAG.

Author Disclosure Statement

No competing financial interests exist.

References

1. Immuno-Mycologics, Inc., Norman ,OK. Latex–Cryptococcus Antigen Detection System. www.immy.com/cryptococcus. Accessed 16 August 2010.
2. Mfinanga SG, Sviland L, Chande H, *et al.*: How does clinical diagnosis of mycobacterial adenitis correlate with histological findings. East Afr J Public Health 2007;4(2): 47–50.
3. WHO Global Tuberculosis Control: Estimated burden of TB in 2005. http://www.who.int/tb/publications/global-report/2007/xls.xls. Accessed 16 August 2010.
4. Huang CT, Tsai YJ, Fan JY, *et al.*: Cryptococcosis and tuberculosis co-infection at a university hospital in Taiwan, 1993–2006. Infection. 2010 Jul 27 (Epub ahead of print).
5. Siber E, Sonnenberg P, Koornhof HJ, *et al.*: Dual infective pathology in patients with cryptococcal meningitis. Neurology 1998;51(4):1213–1215.
6. Wadhwa A, Kaur R, and Bhalla P: Profile of central nervous system disease in HIV/AIDS patients with special reference to cryptococcal infections. Neurologist 2008;14(4); 247–251.
7. McCarthy KM, Morgan J, and Hajjeh RA: Population based surveillance for cryptococcosis in an antiretroviral naïve South African province with a high HIV seroprevalence. AIDS 2006;20(17);2199–2206.
8. Kaur R, Rawat D, Kakkar M, *et al.*: Cryptococcal meningitis in Pediatric AIDS. J Trop Pediatr 2003;49(2):124–125.
9. Ma AL, Fong NC, and Leung CW: Cryptococcal meningitis in an immunocompetent adolescent. Ann Trop Paediatr 2008;28(3):231–234.

10. Mohanty SK, Vaiphei K, Dutta U, *et al.*: Granulomatous cryptococcal lymphadenitis in immunocompetent individuals: Report of two cases. Histopathology 2003;42(1):96–77.
11. Karaquezel G, Kilicarslan-Akkaya B, Melikoglu M, *et al.*: Cryptococcal mesenteric lymphadenitis: An unusual cause of acute abdomen. Pediatr Surg Int 2004;20(8):633–635.
12. Michelet C, Arvieux C, François C, *et al.*: Opportunistic infections occurring during highly active antiretroviral treatment. AIDS 1998;12:1815–1822.

Address correspondence to:
Eva Natukunda
Joint Clinical Research Centre
Plot 893 Ring Road, Butikiro House–Mengo
P. O. Box 10005
Kampala
Uganda

E-mail: evnatu@yahoo.co.uk