

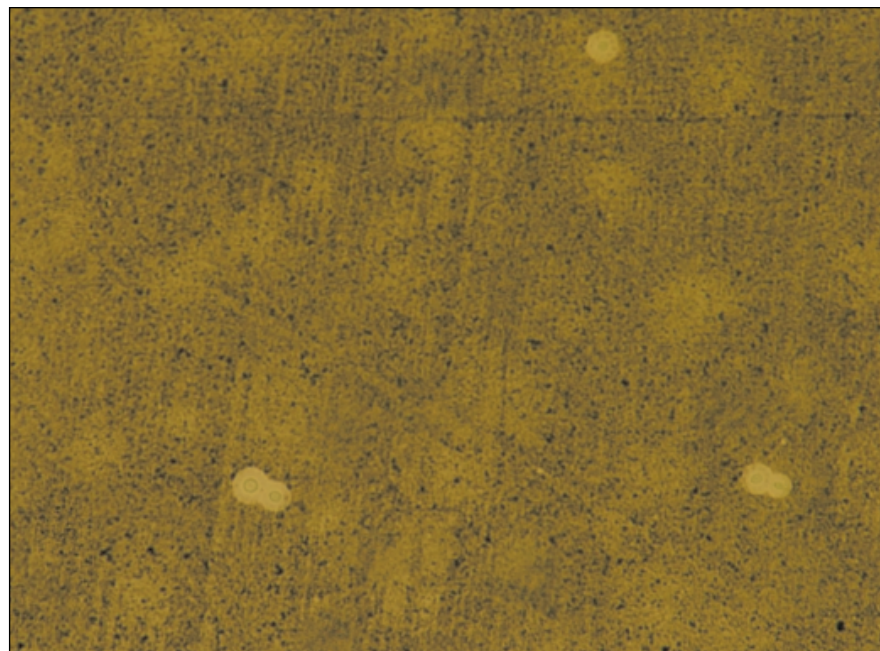
# The Creative Clinician

## Probing Past a Seizure

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**A 45 year-old man from the Ivory Coast was brought to the hospital after a witnessed grand mal seizure.** A mild headache for the past 2 months had been gradually worsening along with subjective fevers, mild photophobia and minimal neck pain. Mild papilledema had been recently noted on an outpatient ophthalmologic evaluation and the patient was scheduled to follow-up with his primary care physician for further work-up. The patient had no underlying medical conditions and no history of seizures. He had lived in the United States for 5 years since emigrating from West Africa. There had been an unintentional 5 lb weight loss over the past 2 months. He denied intravenous drug use.

On admission, the patient was afebrile and his physical examination was remarkable only for decreased neck flexion and slight photophobia. The neurological examination was normal except for papilledema. A CBC was normal except for mild lymphopenia; serum electrolytes, renal and liver function tests were normal. A urine toxicology screen was negative. A CXR was unremarkable. CT (with and without non-ionic IV contrast), MRI (with and without gadolinium) and MRV of the brain showed no abnormalities, and an EEG was normal. Blood cultures were negative. Examination of CSF showed 100 leukocytes, (79% lymphocytes and 21% monocytes), protein 67 mg/dl, glucose 11 mg/dl. The opening pressure was not recorded. A gram stain showed large budding yeast forms; an India ink preparation is shown below. *Cryptococcus neoformans* was isolated from CSF culture; the CSF cryptococcal antigen titer was >1:256.



India ink. Wet mount of CSF showing yeast forms of *Cryptococcus*.

A diagnosis of cryptococcal meningitis was made. Treatment with amphotericin B lipid complex (Abelcet) and flucytosine was started as well as valproic acid (Depakote). An HIV serology was positive; the CD4 count was 6/microL and viral load 20,349 copies/mL. After completing a 14-day induction course of anti-fungal therapy, consolidative treatment with fluconazole (Diflucan) was started. He had no further seizures. Anti-retroviral therapy (ART) with efavirenz, emtricitabine and tenofovir (Atripla) was started as an outpatient two weeks after hospital discharge, as well as trimethoprim/sulfamethoxazole (Bactrim) as prophylaxis for *Pneumocystis jirovecii* and toxoplasmosis. Serotyping by the Centers for Disease Control and Prevention showed that the isolate was not *C. neoformans* serotype B or C (var. *gattii*).

### DISCUSSION

Among HIV-infected patients with CNS infection with cryptococcus, this infection was the AIDS-defining illness in 60%. This infection rarely occurs with CD4 T-lymphocyte counts greater than 100/microL. Symptoms typically begin in an indolent fashion over a few weeks; the three most common are fever, malaise, and headache.<sup>1</sup> Seizures are a very rare clinical presentation of CNS cryptococcosis. In addition, CNS cryptococcosis produces a wide variety of MRI appearances including dilated Virchow-Robin spaces, leptomeningeal enhancement, focal enhancing lesions, focal lesions and hydrocephalus; however, a normal MRI does not exclude the diagnosis.<sup>2</sup>

The portal of entry most often is the lung. In the immunocompetent host, inhaled yeast are met by alveolar macrophages and killed in the resulting granulomatous inflammation. In immunocompromised hosts, infection in the lungs may not be halted and may directly progress to dissemination to the meninges or other organs. In some hosts, pulmonary infection may be halted but not eliminated and viable yeast may remain dormant. Reminiscent of the pathophysiology of tuberculosis, infection may recrudesce later under conditions of immune compromise with resulting dissemination to the CNS.<sup>3</sup>

Definitive diagnosis is by isolation from CSF; detection of cryptococcal capsular antigen is useful because it is quick, quite sensitive, and the titer can be measured during treatment and follow-up. Because the burden of organisms is usually high in AIDS patients, an India ink preparation from the CSF is frequently positive. India ink is a colloidal

dal suspension of carbon that is mixed in equal parts with the patient's CSF and then examined microscopically on high power under a coverslip. The yeast forms displace the carbon particles and are distinguished from lymphocytes and erythrocytes by the doubly contoured cell wall surrounded by the clear halo of the polysaccharide capsule.

*C. neoformans* can be classified into 5 serotypes (A, B, C, AD and D) which differ in their prevalence, geographic location and somewhat, their spectrum of clinical manifestations. Serotypes A (*var. grubii*) and D (*var. neoformans*) are the most common worldwide while serotype C (*var. gattii*) is rare in all localities.<sup>4,5,6</sup> In the USA and in AIDS patients, the vast majority of isolates are serotype A (*var. grubii*). In sub-Saharan Africa serotypes A, D, and AD are most common.

There are limited data relating the severity of CNS infection to the infecting serotype, and in most cases the host defense responses determine the clinical manifestations. However, some clinical presentations may depend on the serotype of the infecting strain. For example, in areas of the world with infections from different serotypes, cerebral cryptococcomas, hydrocephalus, increased intracranial pressure, and cranial neuropathies were found more commonly with serotypes B (*var. neoformans*) and C (*var. gattii*).<sup>7,8</sup> These observations suggest that some serotypes may have a greater propensity for invasion of brain parenchyma rather than limiting infection to the meninges alone. Serotyping is not performed routinely mainly because it does not inform decisions about treatment of cryptococcus infection; however, it may give insight into the virulence of a particular infection and might suggest where the primary infection was acquired.

The prognosis for patients diagnosed with AIDS-associated CNS cryptococcosis has improved dramatically over the past two decades, particularly when antifungal agents are combined with antiretroviral therapy.<sup>9</sup> Guidelines for the treatment of CNS cryptococcosis<sup>10</sup> in adults recommend aggressive management of high opening pressures with repeated lumbar punctures. Therapy includes induction with intravenous amphotericin B (a lipid formulation can be used) plus oral flucytosine for 14 days or longer depending on the patient's presenting prognostic factors. This should be followed by a consolidation and maintenance phase with fluconazole which can be given orally. Fluconazole alone should not be used for induction in HIV-infected patients, even in less severely ill cases, because relapse rates are unacceptably high.

Our patient had either serotype A (*var. grubii*) or D, and we do not know whether he had newly acquired infection in the US or relapse from a latent infection acquired previously in Africa. He initially did well and improved on his dual treatment regimen for both HIV infection and cryptococcus. His anticonvulsant was changed from valproic acid to levetiracetam. The patient then stopped taking levetiracetam because he said it was making him dizzy. Then, 8 weeks after initial presentation, he had a seizure. CSF examination showed cryptococci on Calcofluor stain but the culture was negative. His fluconazole dose was increased to 800 mg daily and the anticonvulsant was changed to phenytoin. Because of the potential drug interaction between phenytoin and efavirenz (a component in Atripla), the anticonvulsant was changed back to valproic acid two months later. In follow-up after seven months, he had had no further seizures. An HIV viral load was unde-

tectable and his CD4 count had risen to 97/microL. His CSF had 87 leukocytes, (76% lymphocytes, 7% neutrophils and 17% monocytes), protein 199 mg/dl, glucose 26 mg/dl, and CSF cryptococcal antigen titer was 1:256. Cryptococci were not seen on stain and culture was negative. He remains on valproic acid, fluconazole 800mg daily, Atripla, and trimethoprim/sulfamethoxazole. Valproic acid can be tapered off after 6 months of seizure-free activity and complete immune reconstitution (defined by CD4 T-lymphocyte counts greater than 200/microL). Whether fluconazole can eventually be stopped in AIDS patients is controversial. Some practitioners would consider discontinuing fluconazole after one year of complete immune reconstitution. Others would recommend lifelong treatment. A decision regarding this patient's fluconazole will be made after one year of treatment. He will require lifelong treatment of his HIV infection.

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## Disclosure of Financial Interests

The authors and their spouses/significant others have no financial interests to disclose.

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