

Cryptococcal epidemiology and clinical course among HIV-positive patients in Manitoba: A case series from 2006 to 2013. Can J Infect Dis Med Microbiol 2014;25:118-119.

To the Editor:

There has been limited research on the epidemiology of cryptococcosis in Canada. Here we present a case series of HIV-positive patients in Manitoba with cryptococcal meningitis between 2006 and 2013. Cryptococcosis remains a common etiology of life-threatening illness in HIV-infected patients. The central nervous system and the respiratory tract are the primary sites of involvement (1).

In the present case series, HIV-positive individuals hospitalized in Winnipeg, Manitoba, from 2006 to 2013 with a new diagnosis of cryptococcosis were identified and their charts were included in the review. Ethics approval was obtained through the University of Manitoba Research Ethics Board (Winnipeg, Manitoba).

A retrospective chart review of the Manitoba HIV program was performed; sociodemographic characteristics, blood, bronchoalveolar lavage and cerebrospinal fluid (CSF) cultures, cryptococcal antigen (CRAG) titres, CD4 cell count, viral load and clinical outcomes were recorded. Cryptococcal meningitis was defined as positive CSF culture or positive cerebrospinal CRAG. If lumbar puncture was not possible, the diagnosis was made with clinical signs and symptoms with a positive serum CRAG, positive blood cultures or positive extraneural site culture. Subspecies identification of *Cryptococcus neoformans* var. *grubii* and *C. neoformans* var. *neoformans* was performed by sequence analysis of the ribosomal RNA intergenic spacer region (2).

We identified seven cases of cryptococcal meningitis between 2006 and 2013. Six cases had positive cryptococcal CSF cultures, two of seven had positive serum CRAG, and four of seven had positive CSF CRAG. One patient refused a lumbar puncture and the diagnosis was made based on presentation with headache with associated fever and chills, and a positive blood culture. No cases of pulmonary cryptococcosis were identified. All cases were male and five of seven had self-reported Aboriginal ethnicities (including First Nations, Metis and Inuit). The other two cases were Filipino and Caucasian Canadian, respectively. The risk factors for HIV transmission were unprotected heterosexual intercourse (five of seven cases), intravenous drug use (three of seven) and men who have sex with men (two of seven). Three of the patients were newly diagnosed with HIV during their hospitalization with cryptococcal meningitis. The remainder of the patients had a previously established diagnosis of HIV. At hospitalization, all individuals had a CD4 count <200 cells/mm³, with a mean CD4 count of 44 cells/mm³. Six of the seven cases were *C. neoformans* var. *grubii* and one case was *C. neoformans* var. *neoformans*.

Six of the seven cases received induction therapy with amphotericin B and flucytosine followed by oral fluconazole. In one case, induction therapy was not given because the patient left the hospital against medical advice. Sterilization of CSF was confirmed in six of seven patients two weeks after induction therapy. One patient had elevated opening pressure of 50 cmH₂O, requiring repeat lumbar punctures, and eventually had an external ventricular drain placed. Two cases were complicated by cryptococcal immune reconstitution inflammatory syndrome. In the first case, antiretroviral therapy (ART) was initiated four weeks after the diagnosis of cryptococcal meningitis and the patient returned to hospital six weeks later with increasing headache and photophobia. Repeat CSF analysis showed negative CRAG and culture. Computed tomography scan of the brain showed

leptomeningeal enhancement. The patient was treated with a tapering dose of prednisone and continued on ART. In the second patient with cryptococcal immune reconstitution inflammatory syndrome, ART was initiated eight weeks after the diagnosis of cryptococcal meningitis. The patient returned to hospital two months later with an occipital headache and unsteady gait; repeat CSF analysis was negative for CRAG and culture. This patient was also treated with a tapering dose of prednisone and ART was continued. One patient was lost to follow-up; therefore, the outcomes are not known. One patient died from non-HIV-related bowel perforation. Another patient died from renal transplant-related complications.

The present case series describes several features of cryptococcal infections in Manitoba. Five of the seven patients were Aboriginal. According to the 2006 census, 15.5% of Manitoba's population identified as First Nations, Metis or Inuit. The Aboriginal population remains heavily over-represented in the HIV epidemic in the Prairie provinces of Alberta, Saskatchewan and Manitoba, with 36% of new HIV cases diagnosed between 2003 and 2007 being of Aboriginal origin; in Manitoba, >50% of new cases in 2010 were Aboriginal (3). Unprotected heterosexual intercourse was a risk factor for HIV acquisition in five of seven cases as well, which is consistent with unprotected heterosexual intercourse as the primary risk factor for HIV transmission in Manitoba. Furthermore, all patients in the present review were male, which is reflective of overall sex-related HIV trends in Manitoba. Previous studies have observed that being diagnosed with HIV in Manitoba is an independent risk factor for late presentation with HIV, and 67.9% of Manitoba's known HIV population is male (4).

Interestingly, six cases were *C. neoformans* var. *grubii* or serotype A, one case was serotype D or *C. neoformans* var. *neoformans*. This patient presented initially with a cutaneous cryptococcosis involving the nose, and subsequently developed cryptococcal meningitis. This is in accordance with studies showing a predilection of serotype D and skin involvement (5).

Cryptococcal meningitis presents the 'tip of the iceberg' of late presentation in HIV. This suggests that earlier testing and linkage to care may benefit individuals and improve outcomes. Overall, the present case series provides information on the epidemiology and trend of cryptococcal meningitis in HIV patients in Manitoba.

Karan Sharma MD, Aditya Sharma MD
Department of Internal Medicine
University of Manitoba

Kim Nichol MSc, James Karlowsky PhD
Diagnostic Services of Manitoba

Marissa Becker MD
Department of Internal Medicine
Department of Medical Microbiology
Department of Community Health Sciences

Ken Kasper MD
Department of Internal Medicine
Department of Medical Microbiology

Yoav Keynan MD
Department of Internal Medicine
Department of Medical Microbiology
Department of Community Health Sciences,
University of Manitoba
Winnipeg, Manitoba

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