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Cryptococcus gattii: Beyond Vancouver Island

When a BC patient presents with neurological findings suggestive of subacute meningitis, infection with *Cryptococcus gattii* should be included in the differential diagnosis, even if the patient has not lived on or visited Vancouver Island.

ABSTRACT: A previously healthy 30-year-old male presented to Royal Columbian Hospital in New Westminster, BC, with behavior disturbance and a history of headache, nausea, and vomiting. Serology, CT head scans, and culturing of bronchoscopy samples eventually confirmed meningitis due to disseminated *Cryptococcus gattii* infection. This case demonstrates the importance of including cryptococcosis caused by *C. gattii* in the differential diagnosis when patients present with neurological abnormalities. Although cryptococcal disease was first identified in patients who lived on or had visited Vancouver Island, the spread of *C. gattii* to other parts of mainland BC has been documented since 2004, and the possibility of infection with this fungal pathogen should be considered beyond Vancouver Island.

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Cryptococcus gattii is a fungal pathogen first documented on Vancouver Island in 1999.[1] The microorganism is found in soil and trees, and can infect humans through spore inhalation.[1] Though *C. gattii* is more prevalent globally in subtropical and tropical regions, Vancouver Island has one of the highest infection rates worldwide.[1] As a result, cryptococcal disease was made a provincially reportable disease in British Columbia in 2003.

Until 2004, all reported cases were among individuals who lived on or had visited Vancouver Island during the year before presentation. Since then, the spread of *C. gattii* to mainland BC has been documented.[1] However, despite multiple cases reported in Vancouver and other parts of the province, many physicians in BC mistakenly believe that travel to Vancouver Island is necessary for *C. gattii* infection.

Case data

A previously healthy 30-year-old male of First Nations descent was brought by his friends to the emergency department of Royal Columbian Hospital in New Westminster, BC, with a 4-week history of behavior disturbance. Before presentation to hospital, he had experienced a diffuse headache for 2 weeks and nausea and vomiting for 1 week. He reported decreased appetite and unintentional weight loss of 9 kg over the previous month. He had no history of fever or night sweats, and no history of travel, globally or locally. He was a nonsmoker and worked as a longshoreman. He lived alone in an apartment in Surrey, BC, but had previously lived on a reserve for 2 years during his childhood. He denied high-risk sexual behavior and illicit drug use.

A physical examination revealed neurological abnormalities, including disorientation to place and date with mental slowing, bilateral hyperreflexia with down-going plantars, papilledema on fundoscopy, and unsteady gait. Findings from preliminary laboratory investigations, including complete blood count, kidney function tests, and liver func-

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tion tests, were unremarkable except for a leukocytosis of 22.8 with left shift. Noncontrast and contrast CT head scans were performed. The contrast CT scans showed diffuse supratentorial and infratentorial nodules with meningeal enhancement, cerebellar edema with crowding in the foramen magnum, and mild hydrocephalus (**Figure 1**). Given these radiological findings, a lumbar puncture was deferred due to the risk of herniation.

The main differential diagnosis based on the lesions included malignancy and infection (fungal, mycobacterial, or parasitic) in a potentially immunocompromised host. Further workup included serology for HIV, hepatitis B and C, aspergillus, cytomegalovirus, and cryptococcus. CT scans of the chest, abdomen, and pelvis were performed to assess for underlying malignancy and other infectious foci. The CT chest scan revealed a 2-by-2.7-cm cavitating mass (**Figure 2**), which was subsequently investigated by bronchoscopy brush and wash. CT scans of the abdomen and pelvis revealed no abnormalities. Within days of presentation, serology results were found to be negative for HIV and hepatitis, but there was a strongly positive result for the cryptococcal antigen, with a titer of 1:1024. Shortly after, culturing the bronchoscopy samples permitted positive identification of *C. gattii*.

When cryptococcal infection was confirmed by serology, the patient was immediately started on induction therapy (amphotericin B and flucytosine), with serological monitoring for adverse effects, including renal insufficiency, hematological abnormalities (anemia, leukopenia, and thrombocytopenia), electrolyte disturbances (hypokalemia and hypomagnesemia), and hepatotoxicity. Adjunctive corticosteroids were also initiated to treat

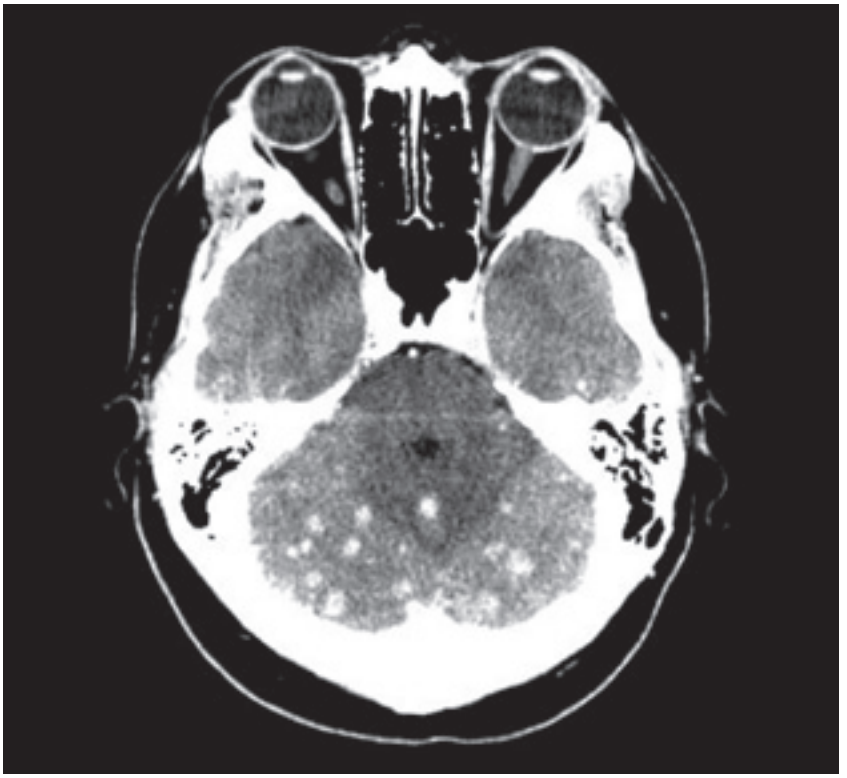

Figure 1. Image from CT head scan with contrast, cerebellar cut, showing diffuse enhancing nodules with cerebellar edema.

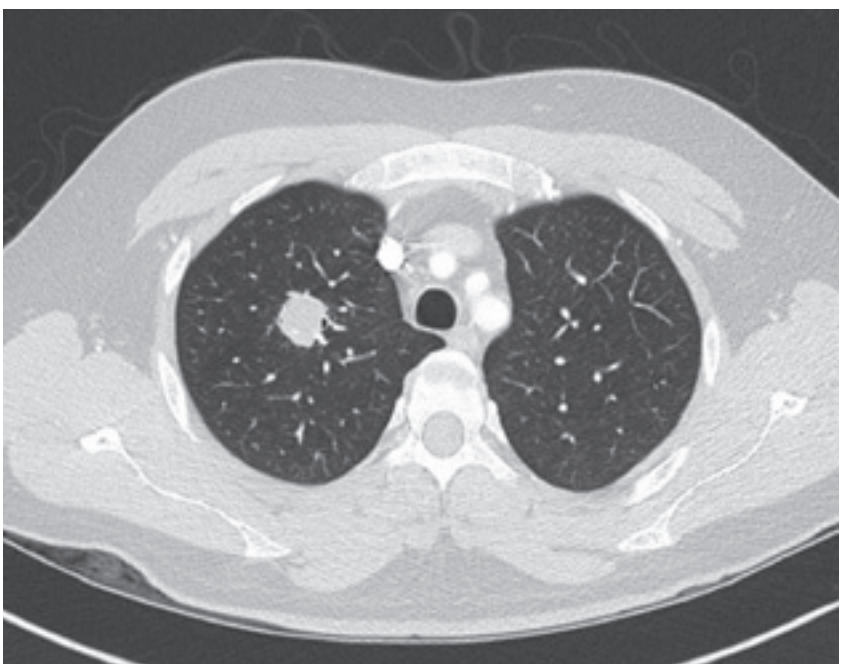

Figure 2. Image from CT chest scan showing 2-by-2.7-cm cavitating mass.

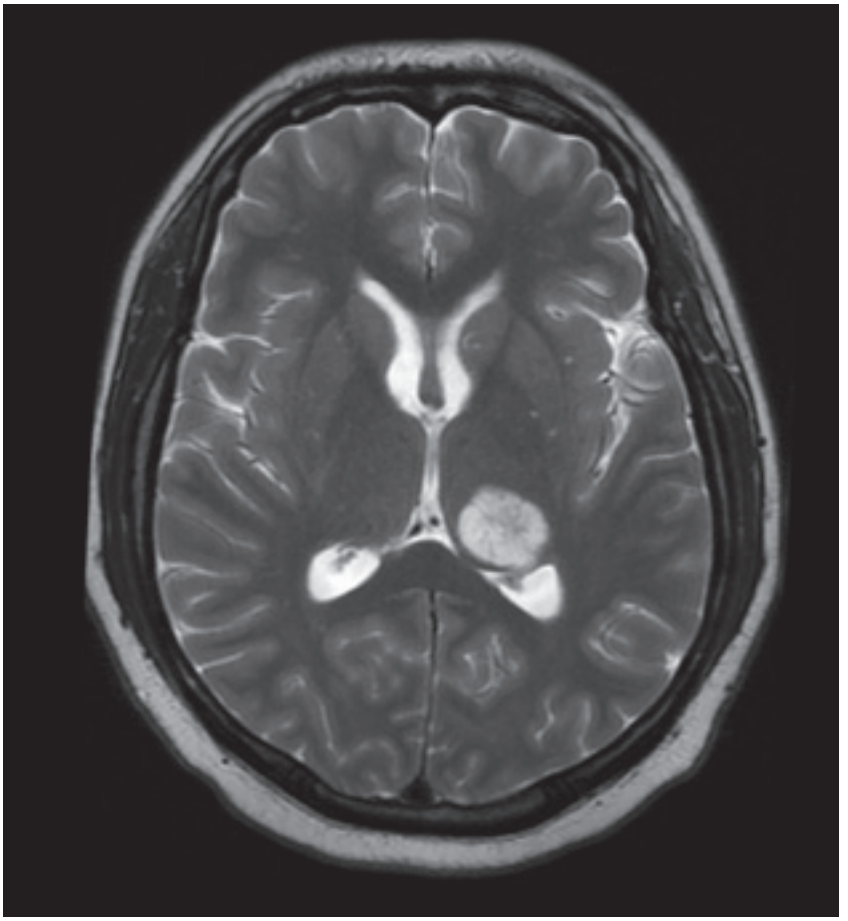

Figure 3. Image from T2-weighted MRI scan of head showing left thalamic cryptococcoma and leptomeningeal involvement.

cerebral edema. The literature recommends a repeat lumbar puncture after 2 weeks of induction therapy to confirm sterilization of cerebrospinal fluid and to reassess intracranial pressure (ICP).[2] After 2 weeks of induction therapy, we performed a repeat head CT scan that confirmed increased ICP and thus precluded lumbar puncture. Furthermore, the patient still had large cerebral lesions (cryptococcomas) that were well visualized on MRI (**Figure 3**).

Approximately 3 weeks following admission, when the patient had improved clinically and been tapered off corticosteroids, he suddenly deteriorated and experienced decreased level of consciousness, worsening headache, and persistent vomiting consistent with increased ICP. A repeat CT head scan revealed interval enlargement of the cryptoccomas, worsening hydrocephalus, and progressed cerebellar tonsillar crowding. As a result, an extraventricular drain was placed, corticosteroids were reinitiated, and the patient remained in hospital for ongoing treatment and monitoring. Following the standard 6 weeks of induction therapy, he had radiographic and clinical improvement and was stepped down to oral fluconazole, started on a glucocorticoid tapering schedule, and discharged home shortly after. He continues to improve clinically as an outpatient and has ongoing follow up in the community with the infectious disease team.

Discussion

Cryptococcus neoformans and *C. gattii* have important genetic, biochemical, and clinical differences. As demonstrated by this case, *C. gattii* generally infects immunocompetent hosts, whereas *C. neoformans* generally infects immunocompromised, predominantly HIV-positive, individuals.[1,3,4] *C. gattii* is believed to be more virulent and lead to more severe neurological sequelae.[3,5,6] Most commonly, *C. gattii* infection involves the central nervous system and lungs, often manifesting as cryptococcomas or circumscribed nodules, with occasional cutaneous manifestations.[2] *C. neoformans* infection presents similarly, but cryptococcomas are not often observed.[4,5] In addition to neurological abnormalities and clinical signs such as papilledema, an elevated ICP determined through lumbar puncture opening pressure generally occurs in more than 50% of patients at presentation, often at values upwards of 250 mm Hg (normal ICP is less than 20 mm Hg), and indicates a poor prognosis.[7,8]

The diagnostic process is the same for *C. gattii* and *C. neoformans* infection. Serum cryptococcal antigen has a reported sensitivity of 94% to 100% for central nervous system disease and 90% for pulmonary disease, and CSF cryptococcal antigen has sensitivity of 87% to 100% with specificity of 93% to 100%.[7-12] While India ink staining of the CSF sample can provide rapid detection of cryptococcal infection, sensitivity in HIV patients is only 75% and in immunocompetent patients is even less at 50%.[13-15] Culturing of CSF and/or bronchoscopy samples can provide definitive diagnosis and speciation; however, a lumbar punc-

ture, as demonstrated by this case, can be contraindicated.[13,16]

Management principles are also similar for infection with *C. gattii* and *C. neoformans*, and modifications are more dependent on clinical status than the subspecies of cryptococcus. Individuals will generally have induction therapy of amphotericin B (in liposomal form if there are renal concerns) and flucytosine for 4 to 6 weeks (longer if neurological complications exist).[2] Subsequently, they will have consolidation therapy of oral fluconazole for 8 weeks and then lower-dose fluconazole for maintenance therapy over 6 to 12 months.[2] Another important component of treatment is the use of serial lumbar punctures to reduce ICP.[2] However, if there is any concern about mass effect or risk of herniation, as in this case, lumbar puncture is generally avoided. Occasionally, surgical decompression is necessary.[2,8]

C. gattii infection is associated with more neurological complications than *C. neoformans* infection. Often patients will have a delayed response to therapy due to reduced drug penetration of the cryptococcomas. Consequently, these patients often require glucocorticoids for treatment of cerebral edema and have a higher incidence of neurosurgical intervention.[2] Neurosurgery is considered if there are large lesions (more than 3 cm in diameter), accessible lesions with mass effect, or compression of vital structures, or if 4 weeks of therapy fail to reduce the size of cryptococcomas.[2] Even though effective treatment exists for this infection, the mortality rate following appropriate management of acute cryptococcal meningoencephalitis has been reported to be as high as 30%.[5]

Cryptococcal immune reconstitution inflammatory syndrome (IRIS) is a paradoxical clinical worsening associated with an improvement of the host immune response. It has been well described in HIV-positive individuals who are beginning antiretroviral therapy. The viral load falls, the CD4 count rises, and a dramatic inflammatory effect occurs as the immune system strengthens in response to the antigen burden.[7,17] IRIS can occur in both immunocompetent and immunocompromised individuals and whether or not *C. gattii* or *C. neoformans* is involved. It presents as a clinical or radiological worsening approximately 6 weeks to 12 months following initiation of treatment[7,17,18] with a relapse of neurological symptoms. If symptoms are severe, the patient is generally treated supportively with the glucocorticoids.[17]

Summary

Cryptococcal disease should be considered in both immunocompetent and immunocompromised individuals presenting with subacute meningitis or meningoencephalitis. Although *C. gattii* infection is more commonly contracted on Vancouver Island, it can also be contracted by those living across British Columbia and elsewhere in the Pacific Northwest. As this case demonstrates, subtle neurological findings may be the only indication of this indolent infection prior to imaging. Unlike other causes of chronic meningitis, including tuberculosis and herpes simplex virus, which require lumbar puncture to confirm the diagnosis, a simple peripheral blood sample for cryptococcal antigen testing has a sensitivity of nearly 100% and should be performed routinely when patients present with neurological findings that might be attributable to a subacute meningitis.

Although *C. gattii* infection is more commonly contracted on Vancouver Island, it can also be contracted by those living across British Columbia and elsewhere in the Pacific Northwest.

Competing interests

None declared.

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As this case demonstrates, subtle neurological findings may be the only indication of this indolent infection prior to imaging.

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