Management of *Cryptococcus gattii* meningoencephalitis

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Cryptococcosis is a fungal disease caused by *Cryptococcus neoformans* and *Cryptococcus gattii*. By inhalation and subsequent pulmonary infection, it may disseminate to the CNS and cause meningitis or meningoencephalitis. Most cases occur in immunosuppressed hosts, including patients with HIV/AIDS, patients receiving immunosuppressing drugs, and solid organ transplant recipients. However, cryptococcosis also occurs in individuals with apparently healthy immune systems. A growing number of cases are caused by *C gattii*, with infections occurring in both immunosuppressed and immunocompetent individuals. In the majority of documented cases, treatment of *C gattii* infection of the CNS requires aggressive management of raised intracranial pressure along with standard antifungal therapy. Early cerebrospinal fluid evacuation is often needed through placement of a percutaneous lumbar drain or ventriculostomy. Furthermore, pharmacological immunosuppression with a high dose of dexamethasone is sometimes needed to ameliorate a persistently increased inflammatory response and to reduce intracranial pressure. In this Grand Round, we present the case of an otherwise healthy adolescent female patient, who, despite aggressive management, succumbed to *C gattii* meningoencephalitis. We also present a review of the existing literature and discuss optimum clinical management of meningoencephalitis caused by *C gattii*.

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Introduction

Cryptococcosis is one of the most common invasive fungal diseases in human beings, with more than 1 million cases per year and around 650 000 deaths in sub-Saharan Africa.[1,2] Of the more than 30 species of the genus *Cryptococcus*, *Cryptococcus neoformans* and *Cryptococcus gattii* are the only species that are commonly pathogenic because of their ability to grow at 37°C and the presence of other virulence factors such as production of melanin and a protective capsule.[3] The epidemiology and clinical features of infections caused by *C neoformans* have been previously described. Infections occur worldwide, affecting predominantly patients with HIV/AIDS or other immunocompromising conditions, although infections do occur among apparently immmunocompetent individuals.[1,4–8]

Many aspects of the epidemiology and clinical features of infections caused by *C gattii* are relatively less well defined.[9,10] *C gattii* is a fungal pathogen that grows preferentially in soil around various kinds of trees.[7,11] Similar to *C neoformans*, it causes pulmonary and CNS disease in people.[8,12,13] The initial recognition of *C gattii* as a pathogen was reported in a patient with a lumbar tumour by pathologist Ferdinand Curtis in 1896.[11] Historically, most cases due to *C gattii* have been seen in tropical and subtropical regions, but it is now regarded as an emerging fungal pathogen in other geographical settings.[9] Cases of *C gattii* meningoencephalitis occurring among otherwise healthy, immunocompetent individuals have predominated in the literature.[14–16] However, recent reports from the USA have shown that those infected frequently have some underlying condition that could potentially be associated with immunosuppression.[12,17,18] *C gattii* tend to produce severe CNS manifestations, including meningitis, encephalitis, or, more frequently, meningoencephalitis. These manifestations might lead to excessive neurological morbidity due to the associated intracranial hypertension.[8,12,13]

C gattii was previously thought to be a subtype of *C neoformans* (subtype B and C, referring to capsular antigens), but is now recognised as a unique species.[19] The species is divided into four unique molecular types (variety gattii; VGI-IV).[5,9] There is endemicity of VGI and VGII strains in Australia, VGII and VGIII strains in South America, VGI strains in India, and VGIV strains in Africa.[9,10,20] In the USA, cases of *C gattii* have been noted in southern California and Hawaii. Typing of isolates recovered from human beings and animals in those regions suggested similarity to other strains arising in more tropical regions, specifically VGI and VGIII.[9,10,20] Since 2004, an outbreak of infection has been identified in the Pacific northwest region in North America, involving primarily clonal VGII strains (clonal VGIIa and VGIIb in Canada, and clonal VGIIc in the USA).[21–25] These isolates, first recognised on Vancouver Island, have now been documented to have expanded onto western mainland Canada as well as several Pacific northwestern states in the USA.[22] Many of these cases have presented predominantly with respiratory symptoms and have occurred in immunocompromised hosts (38% of British Columbia cases and 59% of the USA cases; table).[9] Moreover, since 2009, more than 25 autochthonous (non-outbreak) cases of *C gattii* have been documented in other parts of the USA, the most common molecular types being VGI or VGIII.[34–37]

Much of our knowledge on cryptococcosis has been derived from studies focused on *C neoformans* infection in people with HIV. We now appreciate several unique features of CNS disease caused by *C gattii*. Herein, we present an illustrative case and review the existing medical literature to address the optimum medical management of meningoencephalitis caused by *C gattii*.

Case description

A previously healthy 18-year-old woman was admitted to a hospital in Georgia, USA, with a 1-week history of severe headaches, altered mental status, and new onset seizures.

	C gattii			*C neoformans*
	US Pacific northwest region	Other US regions	Australia, New Zealand, Papua New Guinea	Worldwide distribution
Molecular epidemiology	Clonal VGIIa, VGIIb, VGIIc (USA)	Sporadic VGI,VGIII	Endemic VGI, (outbreak VGIIc)	Endemic
Host risk factors	Chronic lung disease, chronic diseases associated with immunosuppression (ie, diabetes, chronic kidney disease, end stage renal disease), and others	Chronic lung disease, chronic diseases associated with immunosuppression (ie, diabetes, chronic kidney disease, end stage renal disease) and others (20%); 64% of infections occur in otherwise healthy people	Idiopathic CD4+ lymphocytopenia; granulocyte macrophage colony-stimulating factor antibodies	HIV/AIDS, corticosteroids, organ transplantation, idiopathic CD4+ lymphocytopenia, diabetes, chronic kidney disease, end stage renal disease
Predominant clinical manifestation	Pulmonary nodules, infiltrates, cryptococcomas; CNS (meningitis, meningoencephalitis)	CNS (meningoencephalitis); pulmonary nodules/infiltrates/ cryptococcomas	CNS (meningoencephalitis); pulmonary nodules, infiltrates, cryptococcomas	CNS (meningitis, meningoencephalitis, IRIS, cryptococcomas); pulmonary nodules, infiltrates, cryptococcomas; others (ie, skin and soft tissues)
Antifungal treatment	Same as *C neoformans* recommendations for CNS and pulmonary (fluconazole)[26]	Same as *C neoformans* recommendations for CNS and pulmonary (fluconazole)[26]	Amphotericin B formulations 6 weeks or longer for CNS infection;[32] amphotericin B formulations 2 weeks or pulmonary forms followed by azole (fluconazole)[32]	Duration of antifungal therapy depends on whether patient has HIV/AIDS, or is a transplant recipient[26]
Benefit of steroids	Clinical benefit by decreasing intracranial hypertension and neurological manifestations in case series and case reports[27–30]	Case reports show benefit[17,24]	Only randomised trial benefit in decreasing vision loss in Papua New Guinea;[33] case series and case reports show substantial benefit[27–30]	The use of steroids might be indicated in the setting of IRIS CNS cryptococcomas with mass effect and surrounding oedema[26]
Intracranial hypertension management	Lumbar punctures until clinical improvement or decreased intracranial pressure; consideration for CSF drains or shunts for those patients with persistent symptoms or elevated intracranial pressure[26,31]	Lumbar punctures until clinical improvement or decreased intracranial hypertension; consideration for CSF drains or shunts for those with persistent symptoms or elevated intracranial pressure[26,31]	Early aggressive CSF drainage including CSF drains and shunts[32]	Lumbar punctures until clinical improvement or decreased intracranial hypertension; consideration for CSF drains or shunts for those with persistent symptoms or elevated intracranial hypertension[26–28,31]

IRIS=immune reconstitution inflammatory syndrome. ICP=intracranial pressure. CSF=cerebrospinal fluid.

***Table*: Features associated with *Cryptococcus gattii* and *Cryptococcus neoformans* in different settings**

She was a college student with no previous medical history, including no history of recurrent infections, no travel history outside the state, and was not taking any medications before her admission to the hospital. Her parents and sister were healthy. On admission, CT scan imaging of the head without contrast was unremarkable, and because of intermittent fever episodes and headache during a 5-day inpatient course, she underwent a lumbar puncture. The finding of budding yeast in the cerebrospinal fluid (CSF) as well as CSF pleocytosis prompted transfer of the patient to our regional hospital (Phoebe Putney Memorial Hospital, Albany, GA, USA) for management of fungal meningitis. On admission to the hospital, the patient suffered a generalised tonic-clonic seizure. She was stuporous and unable to provide any medical history. Her blood pressure was 130/77 mm Hg, pulse 106 beats per min, respiratory rate 18 breaths per min, and her temperature was 37°C. Her neck was supple with no signs of meningeal irritation. She did not have any skin lesions or rashes and was able to open her eyes to painful stimuli. Her pupils were symmetrical and equally reactive with intact oculocephalic and corneal reflexes. No facial asymmetry or grimace was noted. She had normal tone in her upper and lower limbs and withdrawal to painful stimuli. Her lung, cardiac, and abdominal examination were judged normal.

The patient was admitted to the intensive care unit, and because of progressive neurological deterioration she needed endotracheal intubation with ventilator support. A lumbar puncture was repeated, disclosing an opening pressure exceeding 60 cm of water. A lumbar drain was placed for CSF drainage and pressure monitoring. CSF analysis revealed a glucose concentration of 3·22 mmol/L, protein concentrations of 2·43 g/L and 860 white blood cells per field (61% mononuclear cells). The titre of cryptococcal antigen by enzyme immunoassay of CSF was greater than 1/512. *Cryptococcus* spp was isolated in CSF standard fungal culture media, while blood and urine cultures revealed no growth. An ELISA for HIV was negative, and her chest radiograph did not show evidence of any abnormalities. Liposomal amphotericin B (5 mg/kg) and flucytosine were given immediately. An MRI of the brain revealed multiple non-enhancing cystic masses within the bilateral basal ganglia and head of the caudate lobes, consistent with gelatinous pseudocysts (dilated Virchow-Robin perivascular spaces; figure 1).[38]

Despite aggressive intensive care support, the patient died about 48 hours after admission. A necropsy revealed marked asymmetry of the cerebral hemispheres, with midline shift from left to right and thickened meninges. Downward displacement of brainstem and cerebellum also showed evidence of central and tonsillar herniation (figure 2). Microscopic examination revealed many pseudocysts bilaterally throughout the basal ganglia, which contained multiple fungal organisms histologically consistent with

Cryptococcus spp (figure 3). Focal areas of inflammation, oedema, and haemorrhage were found in areas where these organisms appear to be diffusely infiltrating the brain parenchyma (thalamus, periventricular white matter, midbrain, and the cerebellum). These areas were defined as small, and in some areas, confluent cryptococcomas (cryptococci inside parenchyma with associated oedema and inflammation).[39,40] The actual number and distribution of lesions that were identified pathologically were underestimated by MRI images.[39]

Our initial management focused on treating her case as *C neoformans* presenting in a patient without HIV, with the use of amphotericin B and flucytosine, in accordance with treatment guidelines. We concomitantly addressed her raised intracranial pressure by placing a lumbar drain to drain CSF and monitoring her intracranial pressure. When she began to deteriorate despite these interventions, she received a dose of 4 mg of dexamethasone. At this point, on the basis of her progressive course and MRI findings, we also suspected the possibility of *C gattii* meningoencephalitis.[24] Before her death, vascular flow studies with ^{99m}Tc pertechnetate were consistent with photopenia, which, in turn, was consistent with decreased vascular supply to the cerebral hemispheres and diencephalon. 3 days later, culture of her CSF on agar containing canavianine, glycine, and bromothymol blue (CGB) (figure 4) and dihydroxyphenylalanine/birdseed agar revealed growth of *C gattii*.[41] Multilocus sequence typing conducted at the Fungal Reference Laboratory at the US Centers for Disease Control and Prevention identified *C gattii* molecular type VGIII, with the isolate having genetic similarity to other isolates from patients residing in the southeastern USA.[42]

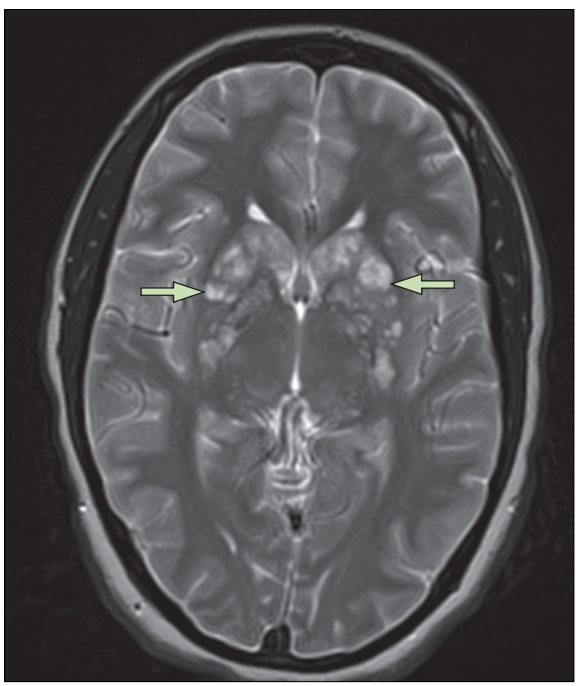

Figure 1: **T2-weighted axial images demonstrating hyperintense lesions (arrows) at the basal ganglia consistent with multiple gelatinous pseudocysts in the perivascular spaces (dilated Virchow-Robin spaces with mucoid capsular material of *Cryptococcus* spp)**

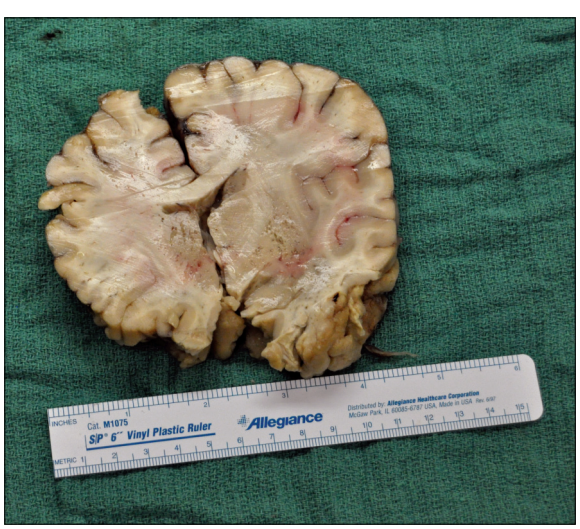

Figure 2: **Coronal sectioning through the brain showing numerous pseudocysts throughout the basal ganglia bilaterally containing fungal organisms histologically consistent with *Cryptococcus* spp**

Review and discussion

Cryptococcal meningoencephalitis is the most severe clinical manifestation caused by *C gattii*.[1,5,43] We postulate that infection of the CNS by *C gattii* molecular type VGIII in our patient produced a severe inflammatory response. This was demonstrated by the histopathological evidence of severe meningoencephalitis, with substantial thickening of her meninges, diffuse infiltration of *Cryptococci* spp in the parenchyma, and associated inflammation and oedema, similar to necropsy reports of individuals without HIV.[39,40] Elevated titres of cryptococcal antigen in the CSF,[44] positive CSF culture,[17] and high CSF pleocytosis were markers of high fungal burden and severe inflammation.[18,24]

We postulate that the elevated intracranial pressure experienced by our patient jointly resulted from an increased volume of brain tissue, caused by parenchymal inflammation and interstitial oedema (identified in necropsy), and an augmented CSF volume, caused by outflow resistance. Decreased outflow of CSF was possibly triggered by the presence of yeast and its capsular polysaccharide at the arachnoid granulations, where arachnoid villus cells resorb CSF and meningeal inflammation.[45–50] Compensatory mechanisms that ensued to accommodate for the increased brain CSF volume were exhausted, leading to mass effect producing pathological consequences by displacing surrounding tissue and cerebral herniation. Although there are important pathogenic differences between acute bacterial meningitis[51] and cryptococcal meningoencephalitis, we can infer from evidence of the association of acute bacterial meningitis and lumbar puncture that most

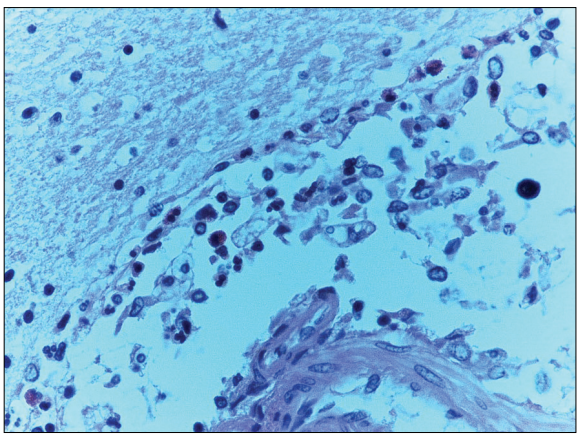

Figure 3: **Micrographs of brain parenchyma showing a pseudocyst**
Cryptococcus spp was identified in the perivascular space where it induced marked oedema, inflammation, and necrosis of the surrounding parenchyma. Haematoxylin and eosin staining 40× magnification.

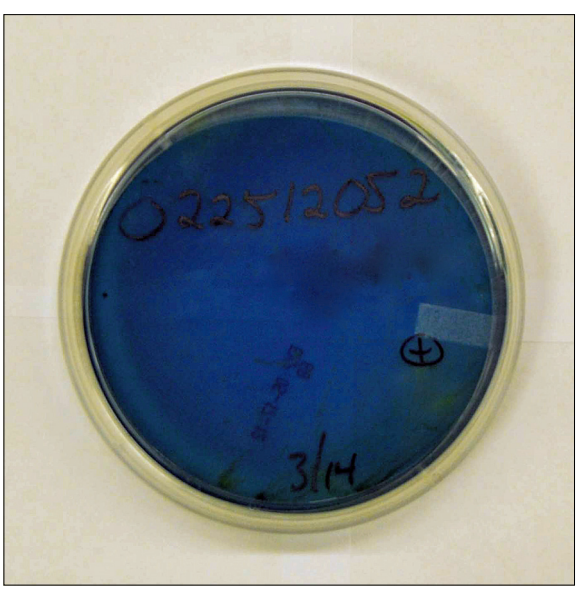

Figure 4: Cryptococcus gattii **isolated on canavanine-glycine bromothymol blue (CGB) agar**
C gattii turns the medium blue by assimilation of glycine, which changes the pH. *Cryptococcus neoformans* does not grow in the presence of canavanine and will not affect the colour change.

reports of herniation occur shortly after a lumbar puncture. Thus, our patient's progressive neurological decline and the timing of lumbar puncture relative to her time of death, suggest that iatrogenic cerebral herniation syndrome due to CSF drainage was unlikely. Only a scant number of necropsy reports are available to allow us to assess the rate of occurrence of brain herniation syndromes associated with CNS cryptococcosis.[39,40]

While ongoing research continues to elucidate the epidemiology, pathogenesis, and clinical expression of *C gattii* infection in human beings, evidence from animal models and clinical reports suggest that susceptibility to infection and clinical expression depends on host, site of infection, strain, and endemic or sporadic versus outbreak settings (table).[9,12,18] *C gattii* can affect both immunocompromised as well as otherwise immunocompetent individuals and can affect both the lungs and the CNS.[1,12,44] Host risk factors for infection include HIV/AIDS,[52] idiopathic CD4+ lymphopenia,[44] chronic lung diseases,[1,12,19] or immunosuppression associated with diabetes or chronic kidney disease.[12,18] Many of the individuals previously identified as otherwise immunocompetent might actually have a predisposing phagocyte dysfunction, as suggested by the recent identification of antibodies against granulocyte macrophage colony-stimulating factor in patients with *C gattii* meningoencephalitis.[53,54]

Evidence suggests that in some settings, and depending on the host factors and strain, *C gattii* tend to produce more severe CNS manifestations compared with *C neoformans*.[14–16] Reports from Australia and Papua New Guinea[14–16] first suggested that CNS disease caused by *C gattii* is characterised by severe CNS inflammation, high intracranial pressure complications, cryptococcomas, and poor prognoses in terms of neurological sequelae. During the past few years, reports[1,10,18,24,27,33,55] have also suggested that the immune response to *C gattii* among individuals without HIV and who are otherwise immunocompetent can paradoxically present with more severe CNS disease, with an immune reconstitution inflammatory syndrome (IRIS)-like syndrome, or with sterile arachnoiditis. The molecular type and strain are probably important in the spectrum of disease caused by *C gattii*. As illustrated by case series from Australia,[45] Papua New Guinea,[33,56,57] and Colombia,[58] infection with *C gattii* molecular types VGI, VGII, and non-outbreak strain VGII usually presents as severe meningoencephalitis.[17,18,24] Similarly, most sporadic (non-outbreak) cases reported from the USA that are caused by either VGI or VGIII types frequently present with severe meningoencephalitis, similar to our patient.[17] However, infections in the Pacific northwest region of the USA and British Columbia, Canada, which are caused mostly by VGIIa, manifest more likely as pulmonary disease.[12,43,59]

Mechanism of CNS disease

Most of what is known about the pathogenesis of cryptococcosis has been derived from studies of *C neoformans*. *Cryptococcus* spp establish pulmonary infection when spores or dessicated cells are inhaled.[7–9] Once in the lung, the yeast can reach the bloodstream and travel to the CNS, entering the CSF via transcellular migration across the microvascular endothelium of the blood–brain barrier.[4] Other mechanisms for crossing of the blood–brain barrier include a so-called Trojan horse mechanism, whereby *Cryptococcus* spp cross the endothelium by hiding inside mononuclear cells or by using paracellular migration pathways.[4] Three hypotheses have been proposed to explain fungal neurotropism.

First, neuronal substrates in the basal ganglia are thought to promote cryptococcal growth and survival. The CNS, and particularly the perivascular spaces (Virchow-Robin spaces), might serve as a niche for *Cryptococcus* spp.[4,38] Our patient showed evidence of *Cryptococcus* spp infection within perivascular spaces of the parenchyma supplied by the perforating lenticulostriate branches of the middle cerebral arteries. Further signs of infection were found at other perivascular spaces, including the thalamus, periventricular white matter, cerebellum, and midbrain (figure 2).[60] Second, there seem to be specific neuronal receptors that might attract this fungal pathogen to the CNS.[4] Finally, once in the CNS, *Cryptococcus* spp use substrates such as the neurotransmitters dopamine or adrenaline, which aid in the synthesis of melanin, a cell wall component that enhances protection from oxidative stress and phagocytosis.[3,4]

The precise mechanism leading to intracranial hypertension in cryptococcal infection remains to be elucidated. Circulation of the CSF is a dynamic process, and its regulation is responsible for cerebral homeostasis.[47] Under regular conditions, CSF is produced in the choroid plexus at a rate of 20 mL/h to reach a volume of about 125–150 mL, of which roughly 20% is contained in the ventricular system and the rest circulates in cranial and spinal subarachnoid spaces.[47] Most CSF is continuously resorbed in the arachnoid villi located in the intracranial venous sinuses, and the rest is resorbed by spinal nerve and some cranial nerve sheaths.[61] The Monro-Kellie hypothesis states that the expansion of one of the intracranial components of the brain, CSF, or intravascular blood, is at the expense of a reduction in the other component.[62] As CSF accumulates in the subarachnoid spaces and the compensatory mechanism becomes exhausted, pliable blood vessels are compressed and cerebral blood flow is reduced.[47,62] When intracranial pressure reaches 50–60 mm Hg, pressure in the arteries of the circle of Willis becomes compromised, producing global cerebral ischaemia and potentially leading to brain death.[62] Because the cranium is a fixed vault, the increase in the volume produces herniation of brain tissue, causing central and tonsillar herniation, similar to what occurred to our patient.[45,63–65]

The reduced rate of removal of CSF is a central aspect of cryptococcosis of the CNS. A report from 1968 described a patient with longstanding cryptococcal meningitis and a substantial increase in intracranial pressure compared with 11 controls, and in whom artificial CSF was infused.[45,63] Subsequently, many reports have emphasised the possibility that accumulation of CSF and intracranial hypertension in cryptococcosis arise as secondary features to fungal or capsular blockage of CSF outflow at the level of the arachnoid villi.[45,47,50,51,66] Cryptococcal polysaccharide molecular weight is high (range 2×10^7–2×10^8 Da) and can spread rapidly through the brain, as shown by implantation experiments in rats.[45,46] Furthermore, animal models using intracerebral injections of purified cryptococcal polysaccharide caused interstitial oedema.[45,46] This interstitial oedema may not be as visible as in other conditions, due to the concurrent marked accumulation of CSF.[45] Thus, coating of the brain parenchyma by large cryptococcal polysaccharides has been suggested[45,46] to result in a so-called frozen brain with decreased compliance that leaves ventricles unable to accommodate additional CSF that is inadequately resorbed.[48–50] This process has been proposed to explain the frequent lack of enlargement of ventricles identified in some patients with either *C neoformans* or *C gattii* infection, despite the documented presence of elevated intracranial pressure.[48] An alternative explanation for this process is that, in view of the frequent subacute clinical nature of cryptococcal CNS infection,[67] the distribution of high quantities of the fungus and its polysaccharide in the CNS might allow the gradual establishment of pressure equilibrium between the ventricles, the subarachnoid space, and the interstitial space in the parenchyma.[45,47,49] The absence of any decompression in the ventricles after the insertion of ventriculoperitoneal shunts confirms this possible mechanism.[49]

We further speculate that the presence of *Cryptococci* spp, mucinous material, and capsular polysaccharide deposition[46,48,49] might facilitate this pressure equilibrium, given that the CSF moves freely with interstitial fluid in the brain parenchyma via the Virchow-Robin perivascular spaces.[47] In this sense, cerebral oedema associated with cryptococcal infection is mostly interstitial due to decreased CSF outflow,[64,65] whereas the cerebral oedema leading to increased intracranial volume in acute bacterial meningitis is a combination of interstitial (decreased outflow caused by meningeal inflammation) and vasogenic (by disruption of the blood–brain barrier by polymorphonuclear infiltration) components.[51,64] The heavy deposition of capsular cryptococcal polysaccharide antigen in brain tissue might result in persistence of antigen in CSF months or years after completion of adequate antifungal therapy.[30,45,49,50]

Management of intracranial hypertension

Treatment guidelines for cryptococcosis have historically distinguished therapeutic approaches based on the presence or absence of HIV infection and whether treating pulmonary or CNS disease.[66] Although treatment guidelines have historically lacked specific recommendations for management of severe *C gattii* disease, recent experiences illustrate the need for consideration of more aggressive management of CNS inflammatory complications, including procedures to address intracranial hypertension and, in some cases, early use of dexamethasone.[17,24]

Intracranial hypertension is associated with poor clinical outcomes, and it is often a potentially remediable component of cryptococcal disease.[45,66] Thus, prevention of secondary brain damage from intracranial hypertension is a central focus in management of

Search strategy and selection criteria

Data for this Grand Round were identified through searches of PubMed with the following search terms: "*Cryptococcus gattii*" AND "meningoencephalitis" OR "meningitis" OR "central nervous system" OR "neurological complications" AND "treatment". The search was limited to articles published in English from Jan 1, 1960 to Aug 31, 2014.

cryptococcal meningitis, with serial lumbar punctures needed as an adjunct to antifungal therapy.[26,31,68,69] Daily lumbar puncture is currently recommended to relieve intracranial pressure until pressure is below 25 cm of water and symptoms (ie, headache, seizures, improved cognition, or improvement of any focal sign) are stabilised for two consecutive days.[26,31] If pressure remains raised, lumbar percutaneous drains or ventriculoperitoneal shunts are currently recommended.[70] Our experience is that ventriculostomy should also be considered in severe cases of *C gattii* meningoencephalitis to allow for removal of more CSF than can be safely removed by daily lumbar puncture. Ventriculoperitoneal shunt placement should also be considered in people who have uncontrollable intracranial hypertension, even in the setting of normal ventricular size.[45,48,70]

Steroids are potentially an important adjunct to antifungal therapy in cases of *C neoformans* infection with suspected IRIS, although randomised trials have not proven their benefit.[26] Dexamethasone is postulated to inhibit the secretion of cryptococcal glucuronoxylomannan-induced vascular endothelial growth factor A by mononuclear cells, which can cause damage to the blood–brain barrier. Dexamethasone can thus reduce meningeal inflammation caused by *Cryptococcus* spp and decrease sterile arachnoiditis during episodes of IRIS.[27–30,33,57,68,69] A retrospective study[33] of 16 patients with *C gattii* infection of the CNS from Papua New Guinea reported that those who received steroids had decreased rates of vision loss and blindness, with improvement in vision in three patients. Other studies have reported substantial clinical improvement in patients with severe cases of meningoencephalitis receiving dexamethasone.[27–30,57] However, our patient's neurological status was rapidly deteriorating by the time we initiated the use of dexamethasone, and this intervention probably took place too far into her clinical course to provide any substantial benefit. Therefore, although more clinical studies are necessary to define optimal treatment guidelines, we suggest that on the basis of existing literature, steroids be considered for patients with intracranial hypertension caused by *C gattii* infection, particularly in severe cases of meningoencephalitis, and for patients with persistent or worsening symptoms, despite improvements in parameters of fungal burden (antigen titres and CSF sterility).

Antifungal therapy

Microbial control in CNS disease caused by *C gattii* can often necessitate prolonged courses of amphotericin formulations (plus flucytosine). A recent report from Australia suggested that improved outcomes among those with CNS disease were associated with a 6-week course of amphotericin and flucytosine (table).[32] Recent epidemiological studies demonstrate that some strains of *C gattii*, especially those of the VGII molecular type, have relatively low susceptibilities to fluconazole, with sustained susceptibility to voriconazole and posaconazole.[71–74] Although no reported data correlates low susceptibility to fluconazole by minimal inhibitory concentration to clinical outcomes, our experience is that these other azoles might have relatively improved activity when used during the continuation phase of therapy, during which the goal is to maintain oral azole therapy for weeks to months (average 6 months) after the patient completed the induction phase of treatment with amphotericin B-based formulations. Therefore, further research is needed to prospectively evaluate treatment outcomes of *C gattii* infections and minimal inhibitory concentration values with fluconazole.

Conclusion

Our case illustrates an unfortunate and dramatic clinical outcome of severe infection caused by this emerging fungal pathogen. While we await further research to guide the optimum care of *C gattii* meningoencephalitis, we suggest that our experiences support a therapeutic approach that considers aggressive CSF drainage to manage intracranial hypertension with percutaneous lumbar drain or ventriculostomy placement early in the course of the disease. Some cases need placement of ventriculoperitoneal shunts.[70] The concomitant use of dexamethasone to decrease (or modulate) a potentially harmful inflammatory response might be an important consideration, although we lack definitive clinical data documenting utility or defining an optimum drug, dose, or timing. Finally, prolonged courses of amphotericin-B-based regimens with flucytosine appear to be needed. Despite the lack of randomised trials, growing clinical experience as well as epidemiological and microbiological data support the use of expanded-spectrum azoles during the continuation phase of treatment.

Contributions

CFP and TW wrote the initial draft and performed the review of the literature. CFP was also the attending infectious diseases clinician caring for this patient. KP participated in drafting original manuscript and was also the attending neurologist of this patient. BS, SL, and TB reviewed and edited the manuscript. BS and SL also participated in the processing of microbiological specimens. TB provided images of necropsy and was also the attending pathologist of this case. WS edited the manuscript and reviewed the literature. JL and KAM reviewed and edited the manuscript, and were consulted on the clinical management of this case and others of *C gattii* meningoencephalitis.

Declaration of interests

KAM discloses that she has participated in advisory boards for Astellas, Merck, and Pfizer and received grants from Astellas, Merck, Pfizer, Enzon, and Schering Plough. All other authors declare no conflicts of interest.

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