REVIEW ARTICLE

The Frozen Brain State of *Cryptococcus gattii*: A Globe-Trotting, Tropical, Neurotropic Fungus

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Abstract

Initially reported in tropical regions, *Cryptococcus gattii* infection is now diagnosed globally. Methods: case report; Literature review. Although initial reports described outbreaks of pulmonary and central nervous system (CNS) disease in tropical regions such as Australia and New Guinea, it is now clear that *Cryptococcus gattii* is a global, neurotropic pathogen. In contrast with *C. neoformans*, *C. gattii* patients are more likely to present with cryptococcomas in the brain and lungs and are often HIV negative. Imaging findings can mimic cancer leading to delays in diagnosis and definitive treatment. Some experts have speculated that the spread of *C. gattii* is due to climate change, newly recognized genotypes that cause disease in temperate zones (genotype VGII), international travel, and improved awareness among physicians and veterinarians. We emphasize neurocritical and neurosurgical management, because patients with CNS involvement often have high intracranial pressures (ICP). *Cryptococcus gattii* patients often have elevated ICP without 'red flag' radiographic signs of elevated ICP such as ventriculomegaly, cerebral edema, or effaced basal cisterns. Therefore, diagnosis of high ICP should be suspected based on clinical symptoms such as incapacitating headaches, progressive visual loss and associated papilledema, and then confirmed by measuring the opening pressure with lumbar puncture (LP). Cerebral intraparenchymal deposition of the large cryptococcal polysaccharide capsule and cryptococcal organisms causes poor brain compliance leading to a 'frozen brain state'. Mortality rates and clinical outcomes are significantly improved with early diagnosis, antifungal therapies, steroids, and aggressive management of elevated ICP including cerebrospinal fluid (CSF) diversion by serial LP's, external ventricular drains and CSF shunts. Following institution of antifungal therapy, about 10% of patients can worsen due to immune reconstitution inflammatory syndrome which responds to steroids. We recommend neurocritical and neurosurgical management of *C. gattii* patients with CNS involvement and elevated ICP. There is often poor correlation between elevated ICP and neuroimaging due to the frozen brain state.

Keywords: *Cryptococcus*, *Cryptococcus gattii*, *Cryptococcus neoformans*, Meningitis, Brain abscess, Climate change, Lung abscess, Intracranial pressure, Valley fever, Low-pressure hydrocephalus, Frozen brain, Coccidioidomycosis

Key Summary Points

- *Cryptococcus gattii* is a naturally occurring fungus found throughout the world.
- Although initial reports indicated outbreaks of pulmonary and CNS disease in tropical regions such as

Australia and New Guinea, it is now clear that *Cryptococcus gattii* is a pathogen throughout the world.

- Specialized agar [L-canavanine-glycine-bromothymol blue (CBD) medium] is needed to distinguish *Cryptococcus neoformans* from *Cryptococcus gattii*.
- Molecular genotyping has identified 4 major lineages (VGI, VGII, FVIII, and VGIV).

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- It has been speculated that global warming/climate change may contribute to the rise in clinical infections due to *C. gattii*.
- Neurologic manifestations include headaches, visual loss, hearing loss, seizures, meningitis, ventriculitis, cryptococcomas, and elevated ICP.
- Neuroimaging may correlate poorly with elevated ICP measured by lumbar puncture or external ventricular drain. This paradoxical finding has been attributed to interstitial deposition of cryptococcal capsular polysaccharides and has been termed the 'frozen brain state.'
- Neurocritical and neurosurgical care for elevated ICP may include: serial LP, EVD, VP shunt, lumbar drains, and hyperosmolar therapy in addition to antifungal therapy and steroids.
- Delayed decline due to immune reconstitution syndrome (IRIS) has been reported in about 10% of patients and may respond to steroids.

Introduction

The purpose of this review is to increase awareness of *Cryptococcus gattii* as an emerging central nervous system (CNS) pathogen, discuss key differences between *C. neoformans* and *C. gattii*, and identify important clinical features that require neurocritical and neurosurgical management. In the 1950s, *Cryptococcal neoformans* was classified into serotypes A, B, and C, and serotype D was later recognized and added. Serotypes B and C were found to produce a blue discoloration when grown on L-canavanine-glycine-bromothymol blue (CBD) medium. The B and C serotypes were reclassified as *C. neoformans* var. *gattii*, and serotypes A and D reclassified as *C. neoformans* var. *neoformans*. Recent molecular studies have confirmed that *C. gattii* is a separate species from *C. neoformans*. As many clinical microbiology laboratories may not speciate *C. gattii* from *C. neoformans* by specialized CBD medium or genotyping, it is likely that *C. gattii* infections are underdiagnosed [1–12]. In this article, we will discuss neurocritical and neurosurgical management of a *C. gattii* patient with a complicated course and then conclude with an update on the ongoing *C. gattii* saga (Table 1).

Case Illustration

The authors obtained Institutional Review Board approval for retrospective case review. No informed consent was required. A 42-year-old woman presented to an outside hospital with right face and hand numbness and transient difficulty holding a pen in her right hand. She had no prior medical history and was not taking any medications. She had immigrated to the USA from Fiji 28 years prior and had returned to Fiji for a 1 month visit in the last year. She had no medical or social risk factors that would

increase concern for an immunocompromised state. Her neurologic examination did not reveal any deficits, and a non-contrast head computed tomography (CT) showed a small hypodensity in the left posterior frontal lobe. She underwent brain magnetic resonance imaging (MRI) and numerous ring-enhancing lesions were seen (Fig. 1a). She was started on levetiracetam for focal seizures. Due to concern for CNS metastatic disease, a chest xray and then chest/abdomen/pelvis CT were performed (Fig. 2). A right lung mass was seen and biopsied. Cytology was negative for malignancy, and granulomatous inflammation and fungal elements were seen. She then had a lumbar puncture. The opening pressure was 42 cm H₂O (31 mm Hg), white blood cell (WBC) 59/μL with 95% lymphocytes, RBC 255/μL, protein 220 mg/dl, glucose 45 mg/dl (serum glucose was 117 mg/dl), and cryptococcal antigen was positive at >1:2560. Subsequent cerebrospinal fluid (CSF) results are shown in Table 2. Her initial complete blood count showed 6.3 K/μL WBC with 64% neutrophils, 30% lymphocytes, 5% monocytes, and 1% eosinophils, absolute neutrophil count 4.0 K/μL, hemoglobin 14.2 g/dl, and platelets 358 K/μL. Serum serologies were positive for cryptococcal antigen at >1:2560, and negative for human immunodeficiency virus (HIV), HTLV-1 +2, Bartonella henselae, Bartonella quintata, Coccidioides immitis, cysticercus, echinococcus, trichinella, histoplasmosis, Schistosoma, toxoplasmosis, Treponema pallidum, and T spiralis.

She started on liposomal amphotericin B (5 mg/kg/day) and oral flucytosine (25 mg/kg po q6 h). During the first week of treatment, she developed rapidly progressive, bilateral visual loss, right VI n palsy, right facial weakness, bilateral hearing loss, and somnolence. A repeat lumbar puncture demonstrated persistent high opening pressure (42 cm H₂O) which improved with large volume drainage. She was then transferred to our center and underwent external ventricular drain (EVD) placement with neuronavigation due to small ventricles. Maintaining patency of her EVD and tubing was challenging due high CSF protein levels and thick, gelatinous material in her CSF. With intracranial pressure (ICP) controlled and antifungal therapy, her level of consciousness and her vision improved significantly, and she had partial recovery of hearing. She failed EVD weaning due to high ICP without ventriculomegaly, and a ventriculoperitoneal shunt was placed.

After 2 months of antifungal therapy, a repeat MRI showed marked improvement in the ring-enhancing lesions (Fig. 1b). She was then transitioned off amphotericin and maintained on high-dose fluconazole. After 4 weeks, *C. gattii* was isolated from her CSF. Given uncertainties about where her exposure occurred, California Department of Health determined that she had the VGIII genotype.

Table 1 Highlights from the *C. gattii* literature

Year	Event	Comments
37–80 million years	<i>Cryptococcal gattii</i> species divergence [4, 10, 11]	Genetic analysis of <i>C. gattii</i> and <i>C. neoformans</i>
1964	Early analysis of rodent brain implantation with cryptococcal capsular polysaccharide [18]	Basic research of effects of <i>Cryptococcus</i> on brain edema
1970	<i>C. neoformans</i> var. <i>gattii</i> isolated from leukemia patient in Congo, Africa [4]	Strain ATCC 32269
1982	Culture medium developed to distinguish between <i>C. neoformans</i> and <i>C. gattii</i> [4]	<i>C. gattii</i> growth has blue coloration when grown on CGB medium
1980s	Frozen brain state in cryptococcal patients [14–16]	Poor correlation of brain imaging with high ICP
1996	Pathology recognizing parenchymal component of cryptococcal infections [13, 19]	Cryptococcal infections often affect brain parenchyma, not just meninges
1997	Visual loss and elevated ICP treated with CSF shunts in AIDS patients with cryptococcal infections	Severe loss of brain compliance noted clinically [15–17] and termed the ‘frozen brain state’ [17]
2002	<i>C. gattii</i> recognized as separate species [4]	No genetic recombination found when interbreeding sexual spores from <i>C. neoformans</i> and <i>C. gattii</i>
1999–2010	<i>C. gattii</i> outbreak in the Pacific NW [2]	Approximately 200 cases; Data collected on 52 cases by <i>C. gattii</i> Public Health Working Group; 20% mortality from <i>C. gattii</i> ; 92% of cases were from three clonal strains (VGIIa, VGIIb, VGIIc)
2000–2007	Nationwide study of <i>C. gattii</i> in Australia [1]	86 cases; No underlying predisposing diseases in 72%; only 1 HIV+ patient. Occupational exposure to Eucalyptus trees identified in 43% (ecological niche for <i>C. gattii</i>); 85% had CNS involved and 42% had elevated ICP; IRIS occurred in 11%
2009–2012	25 cases reported to CDC from US states that are not in the Pacific NW [3–6, 9]	24% case-fatality rate; States with reported cases: Alabama, California, Florida, Georgia, Hawaii, Michigan, Montana, New Mexico; multiple non-clonal genotypes identified
2011–2015	Whole genome sequencing studies [10, 11]	Four major lineages (VGI, VGII, VGIII, VGIV) identified globally. In the Pacific NW, VGII is the major pathogen; VGI and VGIII arising in other US regions
Ongoing	Global reports of <i>C. gattii</i> in the environment and causing clinical disease [1–12]	Basic and clinical research indicate that <i>C. gattii</i> is a global species that may flourish with climate change

AIDS acquired immunodeficiency syndrome, *CDC* Centers for Disease Control, *CGB* L-canavanine-glycine-bromothymol blue, *CNS* central nervous system, *CSF* cerebrospinal fluid, *ICP* intracranial pressure, *IRIS* immune reconstitution inflammatory syndrome, *NW* Northwest

Fig. 1 Despite subtle neurologic deficits at presentation, the initial MRI imaging in our patient showed numerous ring-enhancing lesions with minimal vasogenic edema and mass effect and no meningeal inflammation (**a**). A repeat MRI after 2 months of antifungal treatment and CSF diversion showed marked improvement in the ring-enhancing lesions (straight arrows; **b**). Meningeal enhancement (curved arrow) seen in the lower images is due to venous engorgement following a lumbar puncture to confirm her response to antifungal therapy

Fig. 2 A right pulmonary mass (arrow) was identified on CT chest, abdomen, pelvis imaging in our patient with multiple ring-enhancing lesions (Fig. 1). Needle biopsy showed granulomas and fungal elements consistent with pulmonary cryptococcoma. Initial *C. gattii* presentation and imaging can masquerade as malignancy, and tissue biopsy and CSF analysis including cryptococcal antigen and microbiologic testing to speciate *C. gattii* from *C. neoformans* lead to a definitive diagnosis

Table 2 CSF parameters

Days of illness	CSF source	WBC/ μ l	RBC/ μ l	Glucose (mg/dl)	Protein (mg/dl)
35	LP	59	255	45	220
43	LP	52	159	45	220
59	EVD	53	0	73	208
65	EVD	19	1	74	193
70	EVD	6	0	87	110
120	LD	4	1	194	635
127	LD	6	2	138	326

Samples are indexed to the time of the patient's first emergency department visit. *C. gattii* was isolated from CSF sampled on days 35 and 43 only with no positive bacterial or fungal cultures after this time. CSF protein samples are higher from lumbar samples. Serum glucose was elevated due to steroids administered for immune reconstitution inflammatory syndrome (IRIS) initiated on day 119, and this is reflected in the higher CSF values on days 120 and 127

CSF cerebrospinal fluid, EVD external ventricular drain, LD lumbar drain, LP lumbar puncture, RBC red blood cells, WBC white blood cells

She remained stable during the third month of treatment on high-dose oral fluconazole and then rapidly worsened over 2 days with refractory headaches, then progressive lethargy. A non-contrast head CT demonstrated slit ventricles and increased cerebral edema. She was intubated, received mannitol and decadron, resumed amphotericin and flucytosine, and was transferred to our facility. Her shunt was tapped, the valve and tubing were patent, but minimal CSF was aspirated due to slit ventricles. Therefore, a lumbar drain was placed, and an opening pressure of >53 cm H_2O was measured. MRI brain showed new vasogenic cerebral edema around the brain abscesses (Fig. 3). CSF WBC count and fungal culture did

not indicate relapse of *C. gattii* infection (Table 2), and bacterial cultures did not demonstrate superimposed secondary infections. The elevated CSF protein in the CSF sampled from the lumbar thecal sac was higher than her initial CSF profile. After steroids were started, the CSF protein decreased (Table 2). Therefore, her diagnosis was immune reconstitution inflammatory syndrome (IRIS). Despite neurocritical care management with steroids, hyperosmolar therapy, sedation, continuous electroencephalography, ventilator support, and CSF drainage via lumbar drain, she had further neurologic decline from uncontrollable ICP. The family requested hospice treatment, and she died 4 months after her initial *C. gattii* diagnosis.

Background Summary

Historically (Table 1), *C. gattii* infections were first reported in tropical and subtropical regions in non-HIV infected patients such as Australia and Papua New Guinea [1]. This changed following a rising incidence of cases in British Columbia, Canada (including Vancouver Island), Washington, and Oregon beginning in 1999 [2]. The *C. gattii* Public Health Working Group was organized to collect epidemiologic information on patients and send isolates to the Centers for Disease Control (CDC). In 2010, the group reported on 52 patients diagnosed with *C. gattii* infections. Only 8% of patients had HIV infection and 21% had solid organ transplants. *Cryptococcus gattii*, like *C. neoformans*, is neurotropic, but nasal and pulmonary exposure likely precedes neurologic involvement. For example, in the Pacific Northwest outbreak [2], key clinical findings of *C. gattii* infections were:

Fig. 3 The initial T2 MRI sequence showed no perilesional edema (a). After 3 months of antifungal therapy, the patient had marked worsening and repeat MRI imaging showed new perilesional edema (b, T2 MRI sequence, arrows). Immune reconstitution inflammatory syndrome (IRIS) was diagnosed, and relapse of *C. gattii* and secondary infections were excluded. Steroids were administered

pneumonia (57%), lung cryptococcomas (34%), meningitis (43%), encephalitis (22%), and brain cryptococcomas (25%), and similar findings have been reported in a large Australian case series [1]. Initial clinical imaging of brain and lung can mimick malignancy as in our patient. Overall case fatality from the Pacific Northwest outbreak was 33%, and 20% of deaths were directly attributed to *C. gattii* infection. With 1-year follow-up in the Australian *C. gattii* case series (Chen et al. [1]), mortality was 13%. Fatal outcome correlated with intensive care unit (ICU) admission and immunocompromise on univariate analysis and CSF titers ≥ 256 on multivariate analysis. Unfortunately, our patient met two of these three criteria. *Cryptococcus gattii* cases have now been reported in California, Idaho, Utah, Arizona, upper Michigan peninsula, the coastal Southeastern USA and globally as well [1–12].

Whole genome sequencing has identified four major lineages globally (VGI, VGII, VGIII, and VGIV) [10, 11]. In the Pacific Northwest [2], VGII is the major pathogen (78%), while VGI (41%) and VGIII (44%) are responsible for most infections in other US regions [9]. Our patient had VGIII which indicates that it is more likely that she acquired the organism in California [9]. Some researchers anticipate that the genetic and geographic features differ enough between these lineages to warrant classification into separate species [10, 11]. There is emerging information that the molecular types have different clinical manifestations. For example, the VGIIa subtype has higher virulence and is the predominant isolate found in the Pacific Northwest outbreak [2, 9].

Basic and clinical understanding of this emerging fungal pathogen is rapidly increasing (Table 1). A PubMed search using *C. gattii* as the search term showed the

following publication trend: 1998–2002 $n=68$; 2003–2007 $n=139$; 2008–2012 $n=305$; 2013–2017 $n=378$. Based on genetic studies, we now know that *C. gattii* likely emerged as a separate species 37–80 million years ago [10]. Key virulence genes are shared between *C. gattii* and *C. neoformans* including 91% of the 35 genes regulating cryptococcal polysaccharide capsule formation. Both *C. gattii* and *C. neoformans* grow at 37°, which is a key contributor to their human pathogenicity. *Cryptococcus gattii* is found in over 50 tree species, particularly in decaying wood, and in air, soil, and water in areas with heavy infestation [4]. The eucalyptus tress is an important niche in Australia. While eucalyptus is non-native to California, it has been widely planted in rural areas as wind breaks and for erosion control. In the Pacific Northwest, *C. gattii* is found in the Douglas fir and Western hemlock. Veterinarians have isolated *C. gattii* from the nasal cavities of asymptomatic cats and dogs [2].

Current *C. gattii* Disease Model

The current working model for clinical infection is that humans inhale *C. gattii* in regions favorable for its growth, such as Mediterranean, tropical, or subtropical climates [2, 4, 8]. The fungus colonizes the nasal passages with subsequent spread to other regions such as the lungs, brain, and muscle. It is possible that many patients have subclinical disease, as people in Papua New Guinea, an area endemic for *C. gattii*, can have antibody responses to *C. gattii* without any clinical disease [4]. Development of clinical disease is likely determined by host factors, such as burden of exposure and host susceptibility such as defective cellular immunity in HIV-negative patients. For example, idiopathic CD4 leucopenia was noted in the

Australian case series [1] and solid organ transplant in the Pacific Northwest outbreak [2]. Another factor contributing to *C. gattii* infections in patients without known immunocompromise may be related to defective neutrophil recruitment and infiltration [4]. The *C. gattii* model that incorporates environmental exposure and infection in susceptible individuals has many similarities to other fungal infections with CNS involvement such as coccidioidomycosis (Valley fever).

Case Discussion

We would like to emphasize a few key details about our patient. At her initial presentation with transient symptoms, she did not appear clinically ill or toxic. Her initial MRI imaging showed numerous ring-enhancing lesions with minimal vasogenic edema and mass effect and no meningeal inflammation (Fig. 1a). Given the associated lung mass, the initial working diagnosis was metastatic cancer. In the Australian case series [1], the most common neurologic abnormalities at presentation were: abnormal mental status, cerebellar signs, focal weakness, seizures, cranial nerve deficits including optic nerve, abducens palsy, and hearing loss. Our patient never had signs of meningeal irritation. The late finding of meningeal enhancement in Fig. 1b is due to meningeal venous engorgement after a lumbar puncture was repeated to monitor her treatment response to antifungal therapy. Restricted diffusion on MRI is expected for a pyogenic infection but is uncommon with granulomatous infections. In *C. neoformans* patients, pathologic studies [14] are more likely to find parenchymal disease such as cryptococcomas and gelatinous pseudocysts [6] in immunocompromised patients and isolated meningitis in patients without immunocompromise. In contrast, *C. gattii* patients without known immunocompromise commonly present with cryptococcomas in the brain and lungs.

Throughout the clinical course of our patient, there was poor correlation between high ICP and neuroimaging. The disconnect between imaging and elevated ICP was first recognized in patients with *C. neoformans* [14–17]. During the acquired immuno deficiency syndrome epidemic in the 1980s, it was observed that patients with papilledema and high ICP from cryptococcal meningitis did not show radiographic signs of hydrocephalus [14, 16, 17]. In our patient, the initial CT and MRI brain imaging did not correlate with the markedly elevated ICP measured by lumbar puncture, and subsequent malignant clinical course with rapidly progressive visual loss and impaired level of consciousness. In all case series of *C. gattii* [1, 2], high ICP is reported and is associated with irreversible visual loss and mortality. For example, in the Australian case series [1], 64% of patients with elevated ICP required placement of CSF drains and/or shunts.

Previous authors have emphasized the importance of serial lumbar punctures, lumbar drains, and ventriculoperitoneal shunts in selected patients, particularly where vision and level of consciousness are threatened. While implanting shunts in the setting of chronic CNS infection should be avoided when possible, our literature review did not find reports of peritoneal seeding of *C. gattii* or *C. neoformans* after shunt placement. In our patient, we temporized initial treatment with EVD placement. Since early EVD patency was complicated by the gelatinous cryptococcal polysaccharide, we delayed internalization of the EVD in our patient until the CSF sludge and protein levels dropped.

Poor Correlation Between ICP Elevations with *C. gattii* and Neuroimaging "Frozen Brain State"

To understand why *C. gattii* and *C. neoformans* CNS infections can lead to the frozen brain state [17], it is helpful to consider other chronic CNS infections and to review earlier pathologic studies [13, 18, 19]. The most common fungal CNS infection that we encounter at our center is coccidioidomycosis (Valley Fever). Early on, these patients develop typical clinical and radiographic signs of communicating hydrocephalus and basilar meningeal enhancement. Later in their course, they can paradoxically develop clinical and radiographic signs of worsening communicating hydrocephalus or isolated 4th ventriculomegaly [19, 20] with low ICP and abnormally high brain compliance [20, 21] necessitating negative pressure EVD drainage and subsequent low-pressure shunt systems (Fig. 4). Like polar opposites of coccidioidomycosis patients, *C. gattii* patients may have elevated ICP without radiographic signs of high ICP such as mass effect or ventriculomegaly (Fig. 4) indicating poor brain compliance. The severe and striking loss of brain compliance was termed the "frozen brain state" by Bach, Tally, and Godovskys [17]. One explanation for this abnormal brain rigidity is the poor CSF absorption caused by the CNS infection combined with widespread deposition of cryptococcal capsular polysaccharide throughout the brain [18, 19]. This can be clinically appreciated from the marked CSF protein elevations and accumulations of gelatinous material in the CSF collection devices and radiographic findings of cryptococcomas and gelatinous pseudocysts (Fig. 1) [1, 6, 13]. It is our hypothesis that this interstitial deposition alters brain poroelastic properties in addition to impeding CSF resorption.

Late Complication-Immune Reconstitution Inflammatory Syndrome (IRIS)

The delayed worsening of our patient after an initial clinically favorable response was due to IRIS and occurred in 11% of patients in a large case series from Australia [1].

Fig. 4 Miscorrelation of imaging and ICP can be seen with fungal CNS infections. The highly compliant, “floppy” low-pressure hydrocephalic state associated with Valley Fever (**a**, coccidioidomycosis) is the polar opposite of the poorly compliant “frozen brain state” [17] associated with *C. gattii* (**b**). **a** Initial CT scan in an HIV-negative, non-immunocompromised 51-year-old Asian male in coma. EVD was placed but there was no CSF drainage until it was lowered to 0 cm relative to the external auditory canal. He was diagnosed with coccidioidomycosis. He made a full recovery following extended negative pressure ‘subzero’ drainage by EVD, subsequent ventricular shunt, and antifungal therapy [20]. **b** Initial CT scan in an HIV-negative, non-immunocompromised 26-year-old Samoan woman with papilledema and visual loss. Opening pressure on lumbar puncture was 53 cm H₂O (40 mm Hg). Her CSF profile showed: WBC 88/μL, 83% lymphocytes, 13% monocytes, 4% polymorphic neutrophils, RBC 53/μL, glucose 45 mg/dl, protein 316 mg/dl, cryptococcal antigen 1:1280, and *C. gattii* isolated. She fully recovered following extended antifungal therapy, EVD placement for ICP control, and a ventricular shunt. The frozen brain state [17] has been attributed to parenchymal deposition of cryptococcal capsular polysaccharide with subsequent impaired CSF resorption and altered poroelastic brain properties

IRIS is most often encountered in HIV patients with low CD4 counts who are started on antiviral therapy. Therefore, it is important for clinicians to recognize that IRIS can occur in *C. gattii* patients without known immunocompromise. In the Australian case series [1], 5/7 of the IRIS patients were not immunocompromised, and the onset of symptoms occurred 16 weeks after initial diagnosis (range 6–52 weeks).

We refer readers to the extensive review by May et al. [22] for details regarding how cryptococcus alters host immunity. Briefly, cryptococcus produces glucuronoxylomannan and galactoxylomannan which directly suppress the nuclear factor-κB pathway and downstream production of inflammatory cytokines such as tumor necrosis factor. Through an effect on dendritic cell maturation, additional inflammatory cytokine production (IL-12, IL-23) is inhibited. Phagocytosis of cryptococcus does not kill macrophages or dendritic cells, and there is evidence that the fungus can penetrate the blood–brain barrier when housed within host phagocytes using a ‘Trojan Horse’ strategy. Additional mechanisms have also been described. Therefore, despite pulmonary and CNS infection with *C. gattii*, our patient did not appear to be clinically ill due to reduced host response to infection,

and her initial MRI appearance did not show vasogenic edema despite numerous cryptococcomas (Fig. 3).

IRIS is a clinical diagnosis and it is important to exclude progression of the initial infection or development of a superinfection. In our patient, the delayed worsening while on maintenance fluconazole was re-evaluated with CSF analysis and culture and repeat neuroimaging. Dexamethasone was started and amphotericin and flucytosine were resumed while awaiting test results and cultures. The lack of vasogenic edema on initial MRI and subsequent development on delayed MRI imaging without new or expanding cryptococcomas (Fig. 3) is consistent with IRIS. CSF fungal and bacterial cultures remained sterile. Her CSF WBC count remained low (Table 2). The elevated CSF protein on day 120 may also reflect immune-mediated disruption of the blood–brain barrier due to IRIS and fell when steroid therapy was started (Table 2). For example, there is an inverse relationship between response to antifungal therapies for cryptococcal meningitis and CSF protein where high CSF protein correlated with better outcomes [23]. The elevated CSF protein was attributed to a higher intensity of the host inflammatory response to infection. Unfortunately, our patient did not survive this late complication despite prompt diagnosis

and treatment with steroids and aggressive ICP management. Management of refractory pulmonary cryptococcomas is another important detail when managing *C. gattii* patients. Antifungal therapy is the cornerstone of treatment, but thoracic surgery may be necessary in some refractory patients [24]. Extended treatment with azoles after induction with amphotericin and flucytosine for pulmonary cryptococcomas is a common strategy by infectious disease colleagues.

Conclusion

Cryptococcus gattii is an emerging pathogen which shares important differences from *C. neoformans*. It is more likely to present in non-immunocompromised patients, have intracerebral and pulmonary cryptococcomas, and can masquerade as cancer. The frozen brain state [17] due to intraparenchymal deposition of the gelatinous cryptococcal capsular polysaccharide can mislead clinicians due to poor correlation between clinical symptoms of life threatening, elevated ICP, and the relatively benign appearance of neuroimaging studies. Patients with clinical symptoms of high ICP and confirmation of high ICP by lumbar puncture will benefit from neurocritical and neurosurgical care and often require both temporary and long-term CSF diversion. Because of this clinical/radiographic disconnect, remote monitoring by teleneurology is not recommended, and we advise transfer to tertiary care centers with neurocritical and neurosurgical expertise.

Compliance with ethical standards

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Conflict of Interest

The authors declare that they have no conflict of interest.

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