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Cryptococcus gattii as an important fungal pathogen of western North America

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Abstract

Cryptococcus gattii, a pathogenic fungus historically appreciated to be endemic to tropical regions, was recognized to emerge in a more temperate zone of North America in the 1990s. Early reports focused on an outbreak that was first apparent on Vancouver Island (BC, Canada), involving both the veterinary and human population. More recently, it has been recognized that this organism is endemic to a wider geography in western North America, with recognized disease caused by unique molecular subtypes in both healthy and immunosuppressed human hosts and a variety of domestic and wild animals. A number of cases of disease caused by *C. gattii* isolates that are unrelated to the Vancouver Island–Pacific Northwest outbreak strains have also been recognized in different parts of the USA. As microbiology laboratories have historically not identified these organisms to the species level, our current understanding of the scope of this infection is probably an underestimate. Ongoing public health epidemiologic efforts will be facilitated by increased attention towards culture-confirmed diagnosis and species identification in clinical microbiology laboratories. Early experience presents a strong rationale for increasing diagnostic attention, with multiple clinical features that are unique to this infection, including variability in antifungal susceptibilities and a heightened need for aggressive management of inflammatory responses. Larger prospective studies to evaluate and optimize clinical management are needed.

Keywords

cryptococcosis; *Cryptococcus gattii*; North America

Cryptococcal disease is a serious threat to the health of both humans and animals, with the bulk of infections caused by the cosmopolitan member of the genus, *Cryptococcus neoformans*. This organism is particularly prevalent as a cause of severe CNS disease in HIV-infected people who reside in resource-poor areas of the world. A recent report that estimated the global burden of cryptococcosis using published studies found that there are over 600,000 attributable deaths each year, with the highest case rate in sub-Saharan Africa,

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which approximates 1 million per year [1]. As such, cryptococcosis is defined as one of the most important worldwide opportunistic fungal infections.

Although *C. neoformans* has the widest geographic distribution, increased attention has been drawn to another species, *Cryptococcus gattii*, which holds the distinction of more frequently causing infection in people who have apparently healthy immune systems. Both of these yeasts are free-living in nature, with some variable environmental prevalence. Pigeon guano or other avian fecal matter is considered to provide a habitat conducive for *C. neoformans* growth, although the organism can be found in other soil and decaying wood [2,3]. *C. gattii* has been considered to be more geographically restricted, with associations typically reported from tree and plant materials in tropical regions that are rich in Eucalypts [4]. The tropical restriction and epidemiologic link to Eucalyptus trees has been challenged more recently with the emergence of a unique *C. gattii* subtype in the more temperate climates of western North America, and recovery of these organisms in other regions with more diverse vegetation [2,5,6]. Emergence of a multispecies outbreak of *C. gattii* infections in British Columbia (BC) and the Pacific Northwest (PNW) region of the USA defines it as a recently recognized ‘endemic mycosis’ in North America.

Microbiology

Pathogenic cryptococci are categorized into one of four subtypes (A–D) based on capsular antigens. Serotype A, the most common worldwide pathogen, is *C. neoformans var grubi* and D is *C. neoformans var neoformans*. Serotypes B and C are considered the distinct species, *C. gattii*. This species is further divided into molecular ‘VG’ types, with isolates falling into one of four different VG groups (VGI–IV), or, less commonly, intraspecies or intravarietal hybrids [7,8].

Understanding the epidemiology of cryptococcosis is made difficult by the fact that diagnoses are not routinely established with complete identification of the species involved. In some cases, diagnosis is only supported by antigen results, lacking culture. When the isolate is recovered from the site of disease, many clinical microbiology laboratories do not typically distinguish between *C. neoformans* and *C. gattii*. Some laboratories have started to use specialized screening methods to distinguish between *C. gattii* and *C. neoformans*, but this is not common despite commercial availability of L-canavanine glycine bromothymol blue medium. Growth on this medium allows for easy identification of *C. gattii* by virtue of colony color; one recent study showed that 25 out of 27 (93%) of *C. gattii* strains induced a blue color change, in contrast to none out of 86 of *C. neoformans* [9]. Hence, our current understanding of the distribution between *C. neoformans* and *C. gattii* is probably incomplete.

It is also important to note that there is some controversy over genotyping. In general, diagnostic laboratories use DNA finger-printing methods (e.g., M13 fingerprinting) that result in the so-called ‘VG’ fingerprints. However, this method of genotyping has a relatively low resolution; for instance, the VGIV genotype was actually found to contain two very distinct AFLP genotypes called AFLP7 and AFLP10 (and serotype C and B isolates, respectively) [10]. It is clear that our understanding is limited by the methods used in prior investigations, and much needs to be learned.

The Vancouver Island outbreak

A unique *C. gattii* isolate emerged as a cause of disease on Vancouver Island (BC, Canada) in humans and animals, with the first cases of this outbreak recognized in 1999. Very quickly after the first cases were reported on Vancouver Island, the Canadian public health department enabled reporting and tracking that would prove critical in capturing the scope

and nature of development of this new multispecies outbreak. Investigators documented that the outbreak, which is currently ongoing and geographically spreading, caused disease with an unusually high incidence. It was noted that the incidence of *C. gattii* infection among people of Vancouver Island from 1999 to 2003 was between 8.5 and 37 cases per million residents per year, compared with a reported 0.94 cases per million residents in Australia [11,12].

Environmental scientists recovered *C. gattii* isolates from tree sources, soil, air, and fresh- and sea-water, with 'hot spots' noted in areas around the southern, coastal regions of Vancouver Island, especially Parksville [5]. The bulk of isolates type as VGII; analysis of isolates recovered from humans, animals and the environment demonstrated a 'major' VGII genotype (VGIIa) and a 'minor' genotype (VGIIb), with the VGIIa isolate molecularly unique compared with prior isolates worldwide [11,13,14]. VGI isolates were also recovered, albeit at a lower frequency [5].

By 2004, the infection was noted to have emerged on mainland BC as well, with cases documented in people who had no prior exposure to Vancouver Island, and the isolate was recovered from multiple environmental sources [5,12]. By 2010, 281 human cases had been recognized by the British Columbia Centres of Disease Control. The multispecies nature of the outbreak has also been notable. Infection and colonization has been documented in aquatic mammals, small wild and large animals, and domestic dogs and cats.

Why, and how, this infection emerged in this area of the world has been a matter of debate. Some investigators postulated that the VGIIb/minor genotype, which is similar to those previously recognized in Australia, may have been transported into the region in association with typical vegetation, with same-sex recombination yielding the unique VGIIa/major variant [11,13,14]. These isolates then found themselves in a temperate region that was made more hospitable to a 'tropical' fungus, possibly as a result of a warmed environment. It was also shown that these isolates may disperse geographically by transportation of people and objects, potentially on feet and tires of travelers in the region, and that forestry practices probably affect airborne concentrations and spread [5].

When did this outbreak first become appreciated in the USA? Despite documented 'spread' of the Vancouver Island isolate to mainland BC, early efforts to recover the isolate in the USA, by sampling on the Gulf islands as well as inland regions around the Puget Sound (WA) and northern Washington, failed to recover *C. gattii* from the environment [Marr KA, Personal Observations] [15]. Canadian investigators did recover the isolate from the environment in northern Washington, just south of the USA–Canadian border [12]. Some people first believed that this infection was limited to Canada. However, our understanding of the epidemiology of disease in the USA has been limited by diagnostic bias; although some local clinicians were aware of the outbreak in Canada, microbiology laboratories in US states had not routinely identified isolates to the species level, instead reporting '*C. neoformans*' without serotype/species typing (to this day, this is the usual practice in most clinical microbiology laboratories). In response, we initiated efforts to identify cases in Seattle in 2005 [16]. We screened cases that were available from local hospitals to identify isolates that could be further evaluated to species level, with attention placed on evaluating isolates from people that were not infected with HIV; results of these efforts recovered one case of focal pulmonary disease, documented to be caused by *C. gattii* VGIIa, from a patient with a myelodysplastic syndrome who resided on Orcas Island [16]. Despite surveillance, we failed to recover the isolate from his home or surroundings on the north part of the island [Marr KA, Unpublished data]. Two cases of human disease also became apparent to the Oregon state department of health; these cases, dating back to 2004 and 2005, were subsequently shown to be *C. gattii* [12].

Although these cases were only first recognized in the USA in the mid-2000s, there is evidence that these isolates have been in our environment in western USA for a longer period of time. The outbreak strain of VGIIa is genetically similar to a *C. gattii* isolate that was submitted to the American-type culture collection (ATCC) from the CDC several decades ago, and another highly related isolate recovered from environmental sampling in the San Francisco Bay area in California in the 1990s (NIH444/CBS6956) [13]. The origin of the ATCC isolate is not clear. In way of anecdote, I was contacted (along with K Bartlett) several years ago by a patient from the Seattle area, who claimed to have been treated for *C. gattii* disease in the 1970s by physicians who were practicing at a local private hospital. Although he claimed to have contributed this isolate to the CDC, and hence ATCC, we were unable to confirm this history. Either way, I, and others, believe that *C. gattii* may have been 'emerging' for a longer period of time in a broader geography of the PNW. The detailed studies that our Canadian colleagues performed in BC were a critical step that served to initiate the awareness that has now generated an understanding of a more complex emerging infection involving western North America.

Current epidemiology of cryptococcal disease in North America

What we know about the current epidemiology of cryptococcal disease is largely the result of voluntary reporting of cases and submission of isolates. In 2008, we were asked to convene a group to write a 'white paper' summarizing the state of disease emergence in the PNW [17]. This group of academics and clinicians from the USA and Canada (including public health officials from the British Columbia Centres of Disease Control) were joined by representatives from the CDC and Washington and Oregon state public health systems to generate the *C. gattii* Public Health Working Group [18]. In 2009, this group took the critical step of formalizing surveillance of infections and developing an isolate repository housed at the CDC. In my opinion, the critical pieces that allowed for generation of an increased understanding of this outbreak included: establishment of reference laboratories in US states to distinguish *C. gattii* from *C. neoformans*; and multidisciplinary collaboration between medical and veterinary clinicians and public health officials. However, the limitations to our methods and data are obvious; most laboratories are still not routinely identifying these isolates to the species level, and all surveillance has been contingent on voluntary reporting. Hence, most of what we know still comes from case recognition from interested and aware clinicians, and communication to academic and public health reference laboratories. For this reason our understanding of the scope and distributions of this outbreak – and our understanding of the epidemiology of disease in the USA – is still critically incomplete.

Despite limitations in our knowledge and methods, many human and animal cases have now been documented in a broad geography of the PNW, and detailed molecular typing, including whole genome sequencing, has documented that there are two unique VGII genotype isolates that have demonstrated clonal expansion, as well as multiple other *C. gattii* types observed to cause disease in the region [14,19]. The VGIIa (Vancouver Island)/major genotype causes the bulk of human and veterinary disease and has been recovered from the environment in BC, Washington and Oregon. Other cases have been reported in states in which there has been some question regarding the origin of the infection. Another unique VGII isolate, dubbed VGIIc, has been recovered from humans and the environment in Oregon; this isolate also appears to be expanding clonally [11,20]. Human infections have now been documented in people residing in other states, although the molecular type of the isolates recovered have been variable and unrelated to the outbreak strain, spanning VG-I, -II and -III genotypes (Figure 1) [21–24]. Some of these cases have had travel exposure, some have not. Hence, the outbreak is the complex result of multiple variables. There has been clonal expansion of the original VGIIa/major isolate from Vancouver Island, and

establishment of another unique VGII strain, VGIIc, as well as identification of other *C. gattii* isolates having 'non-outbreak' strain types from distant states.

Closer examination of culture collections has now documented that *C. gattii* disease has been underappreciated as a cause of disease in HIV-infected people as well. A series of isolates recovered from AIDS patients in southern California was studied in detail to identify species; although the isolates were first identified as *C. neoformans*, a relatively large proportion were actually *C. gattii* [25,26]. These isolates were then recently examined by multilocus sequence typing and found to be VGIII, which is likely to be endemic to the region. Recent cases of CNS disease caused by *C. gattii* VGIII have been observed in people with HIV infection as well as in people with no recognized immunosuppression [Filler S, Pers. Comm.].

Our understanding of the outbreak is further enhanced by veterinary evaluations; detailed case reporting and surveillance studies have led to a critical understanding of the endemicity of the isolates. Early studies performed in the Vancouver Island outbreak region found *C. gattii* as a cause of disease and nasal colonization in both domestic cats and dogs, horses and wild animals (e.g., gray squirrels) [27]. Outbreaks and cases have been reported among domestic cat and dog populations in Washington in Oregon, llamas, horses and numerous aquatic mammals [5,12,27–30]. One interesting case of horizontal transmission in a pregnant porpoise was recently described [31].

Environmental scientists have now recovered *C. gattii* in both soil and water in tropical and temperate regions. In western North America, much of the distribution appears to overlap with the Coastal Douglas Fir and Coastal Western Hemlock biogeo-climatic zones, and *C. gattii* isolates have been recovered from decayed tree products representing over 50 different species [2,5,26]. Thus, it is likely that this infection is more globally distributed than previously appreciated.

Finally, a very interesting report described a case of *C. gattii* infection in a Japanese man who developed infection caused by a strain identical to the Vancouver Island VGIIa outbreak strain [32]. This occurred despite lack of travel to the endemic region in North America, raising the possibility that this isolate has spread to other regions of the world. Indeed, other investigators have isolated *C. gattii* from the environment in The Netherlands [33] and in a patient in southern Italy [34]. It appears evident that there is much more to learn about the epidemiology of this pathogenic fungus.

C. gattii causes a unique clinical syndrome

There is a large body of evidence that suggests that the disease caused by *C. gattii* is unique relative to that caused by *C. neo-formans*, with consideration of the hosts at risk, clinical presentation, antifungal susceptibilities and optimal management. Historically, this 'tropical fungus' was noted to cause disease proportionately more frequently in people who have no apparent cause of immunosuppression. Recent studies describing the clinical conditions in people who have developed *C. gattii* disease in North America suggests that roughly half do have some degree of immunosuppression, albeit different types and less often involving HIV compared with *C. neoformans*. In one Canadian study, risks involved receipt of oral corticosteroids, lung disease, older age, smoking, as well as underlying HIV and cancer [35]. The case patients identified in the USA have had variable underlying conditions, including receipt of solid organ transplants, hematological malignancies and rheumatologic conditions [22]. There are people who have developed this infection despite no apparent defect in immunity, both young and old. Some believe that there may be underlying subclinical immunological defects and/or 'differences' leading to an enhanced risk. Antibody responses to *Cryptococcus* were studied in one otherwise healthy 38-year-old woman. Although her

total anti-Cryptococcus antibody levels increased months after treatment of disease, she failed to develop potentially protective *Cryptococcus*-specific IgG2 antibodies [36]. This observation evokes the hypothesis that some otherwise healthy people may have more subtle immunologic differences, such as specific antibody deficiencies, as an underlying risk for invasive disease.

While *C. neoformans* most frequently presents as a symptomatic meningoencephalitis, there appears to be much more diversity in the clinical presentation of *C. gattii* disease, in both immunocompromised and immunosuppressed hosts. While presentation after CNS disease development is common, *C. gattii* also frequently presents with underlying pulmonary disease, with concurrent pneumonia and focal lung masses, as well as pulmonary nodules [22,36,37].

There may be clinically significant differences in anti-fungal susceptibility of *Cryptococcus* species, with more apparent variability in azole *in vitro* susceptibilities among *C. gattii* isolates, especially those of the VGII lineage. Specifically, minimal inhibitory concentrations to fluconazole can be high (≥32 ug/ml) in VGII (a–c) isolates that have been recovered from humans and animals [10,38–41]. Whether this causes true microbial 'resistance' has not yet been clarified, although my anecdotal observation has been of frequent failure with *C. gattii* infection treated with fluconazole alone. There is also evidence that the clinical syndrome caused by *C. gattii* is unique with consideration of pressure management needs and neurologic outcomes. Cases of *C. gattii* infection presenting as fulminent intracranial hypertension have been reported [42]. Also, many of these patients present needs for longer-term CNS drainage and administration of corticosteroids in order to control recurrent symptoms and sterile arachnoiditis [43,44]. Anecdotally, I have found that persistent elevated CNS pressures are common, and people do well with short-term courses of steroids, especially in the setting of prolonged CNS inflammation. The reported outcomes in clinical series support this observation, with high numbers of people developing neurologic morbidity [22]. More systematic studies need to be performed to evaluate the course of disease and optimize management strategies.

Expert commentary

Several academic and public health efforts are ongoing to enable an understanding of the scope of this infection, both worldwide and in North America. Many critical questions have arisen regarding where these organisms have come from, how prevalent they are, overall risks, as well as optimal management of disease (and prevention). Although steps have been taken to enhance identification and reporting of cases, I believe that there are critical limitations in our approach to diagnosis, especially with regards to our widespread failure to identify this organism to the species level. It is important for clinicians to understand that most laboratories do not distinguish between *C. neoformans*/*C. gattii* species complex. As evidence accumulates that these species cause unique syndromes, with potential differences in antifungal and pressure management, there arises an increased need to be more precise with consideration of Cryptococcal diagnosis.

Five-year view

The Canadian public health department responded swiftly with consideration of enabling case identification and reporting, and the CDC is coordinating critical efforts to understand the microbial epidemiology of this disease. In the next 5 years, there needs to be more efforts established to capture accurate diagnoses, track cases, and enable prospective clinical cases to evaluate specific immunologic risks and management needs, especially with consideration of optimizing antifungal management and other therapeutic approaches. I

believe that this infection will become more widely known as not only increasingly important in North America, but also in other regions of the world.

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Key issues

- A unique variant of *Cryptococcus gattii* has emerged as an important cause of pulmonary and CNS disease in humans and animals in western North America.
- Our epidemiologic understanding is limited by current (and historic) lack of routine testing to distinguish *Cryptococcus* species in clinical microbiology laboratories.
- Disease caused by this species appears to require a unique approach, with observation of variable susceptibility to azole antifungals and excessive inflammatory responses associated with neurologic morbidity in human hosts.
- Effective prevention and treatment of disease caused by *Cryptococcus* species requires incorporation of diagnostic testing in clinical microbiology laboratories, interaction with public health agencies, and prospective studies focused on specific host risks and outcomes.

Figure 1. States in which human cases of *Cryptococcus gattii* infection have been recently documented

Some of these may indicate travel-related exposure.

Adapted with permission from [45].