Cryptococcus gattii genotype VGIIb infection in Japan

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ABSTRACT

This report describes a case of Cryptococcus gattii VGIIb infection of the pulmonary and central nervous systems in an immunocompetent Japanese man with a travel history, and it hypothesizes the place where he was infected with C. gattii using the genotype information.

Key words: cryptococcosis, Cryptococcus gattii, genotype VGIIb

Introduction

Cryptococcus gattii causes a life-threatening infection of the pulmonary and central nervous systems and has traditionally been considered to be geographically restricted to the tropical and subtropical regions of the world. However, an outbreak in the Pacific Northwest of North America has changed our understanding of the epidemiology of C. gattii infection⁴. Sporadic cases have also been documented in other regions, including areas in Europe, Asia, Africa, and South America⁴.⁵. These reports have demonstrated a much less restrictive geographic range for C. gattii than previously thought.

There are four genotypes of C. gattii, VGI to VGIV, each containing subtypes as determined by several genotyping techniques. Genotypes VGI and VGII are prevalent worldwide, while VGIII and VGIV are less common⁶. VG genotypes indicate that their distribution and frequency vary among different geographic regions, although further studies are needed to explain possible connections between the distributions of various genotypes.

Since 2001, Japanese cases of C. gattii infection have sporadically been reported⁴−⁶. This report describes a case of C. gattii VGIIb infection of the pulmonary and central nervous systems in an immunocompetent Japanese man with a travel history, and it hypothesizes the place where he was infected with C. gattii using the genotype information.

Case

A previously healthy 41-year-old Japanese male was referred to the Shizuoka Cancer Center for a left lung mass. He complained of fever, cough, and headaches for two months. Six months before his symptoms started, he had traveled to Nanjing in China for one week. Additional travel history included trips to Hong Kong and Shanghai in 2013.
China, as well as Hawaii in the United States during his twenties. He was an office worker who had not been exposed to imported timber or animals.

Examination upon hospital admission revealed wheezes in his left lung. Chest computed tomography revealed a large consolidated mass in the lower left lung lobe (Fig. 1). Transbronchial biopsy demonstrated numerous fungal elements observed as encapsulated yeast with clear halos, a characteristic of *Cryptococcus* spp. A *Cryptococcus* sp. was later cultured from bronchoalveolar lavage fluid. Magnetic resonance imaging of the brain showed multiple small nodules throughout the cerebral parenchyma (Fig. 2). Lumbar puncture had a normal opening pressure at 19 cm H$_2$O, and the cerebrospinal fluid contained 276 nucleated cells, 84% of which were lymphocytes; no *Cryptococcus* spp. were isolated. Anti-HIV and anti-HTLV-1 antibody tests were negative. The cryptococcal strain isolated from the bronchoalveolar lavage was identified as *C. gattii* by analyzing the sequences of the internal transcribed spacer regions. Multi-locus sequence typing (MLST) based on the sequence analysis of a set of polymorphic loci revealed that the isolate was molecular type VGIIb.

After eight weeks of liposomal amphotericin B treatment, along with six weeks of flucytosine therapy, the patient began consolidation therapy with 800 mg of oral fluconazole daily for eight weeks, followed by maintenance therapy with 400 mg fluconazole daily for an anticipated 16-month course. One year after the initiation of antifungal therapy, the patient was asymptomatic and appeared healthy.

**Discussion**

We described a case of *C. gattii* genotype VGIIb infection in a Japanese male with a travel history to several cities in China and Hawaii. In 2001, Tsunemi et al. reported the first Japanese case in a healthy 71-year-old physician who had traveled to Australia for one week. Okamoto et al. reported a genotype VGIIa case in an immunocompetent 44-year-old sign painter who had traveled to Guam and Saipan. To the best of our knowledge, genotype VGIIb was first detected in clinical specimens from Japan.

VGII has been reported in the Western Hemisphere, Australasia, Asia, and Africa and is reportedly the most common and virulent strain responsible for infections in healthy and immunocompromised hosts. This strain is also associated with an ongoing outbreak of *C. gattii* cryptococcosis in Vancouver Island, British Columbia, Canada. These outbreak-related isolates have been genotyped as VGIIa, the major genotype, or VGIIb, the minor genotype. Additionally, a unique genotype, VGIIc, was recovered in Oregon in the United States. In this study, the MLST analysis was performed to determine the genetic relationship between the isolate and other various geographic strains. Overall, the sequence type of the isolate was ST7 (sequence type 7) based on the Fungal MLST database (http://mlst.mycologylab.org); it was identical to the se-
sequence type of the Vancouver Island minor genotype strain R272 (VGIIb). Although a small number of C. gattii cases have been documented in Hawaii, VGIIb has not been reported there\(^1\)\(^2\)\(^3\). However, several molecular epidemiologic studies have suggested that VGI is the most common genotype in China, with VGIIb being less common among C. gattii infections there\(^4\)\(^5\)\(^6\).

Since Australian eucalyptus were first reported in 1990 as natural habitats for Cryptococcus spp.\(^7\), C. gattii has been isolated from more than 50 tree species, including angiosperms and gymnosperms\(^8\). C. gattii has also been associated with native animals in Australia (koalas, echidnas), New Zealand (kiwi), Africa (cheetahs), and Canada (squirrels)\(^9\). The first reported Japanese case had close contact with koalas when traveling to Australia\(^9\). In Japan, no studies have reported isolation of C. gattii from the environment, although koalas kept in two different zoos were carriers of this pathogen\(^1\)\(^7\)\(^18\). Additionally, there have been no reports on the epidemiology of C. gattii genotypes in China, including their environmental profiles.

Understanding the length of the incubation period is critical to track the acquisition of C. gattii. A study of seven travelers to Vancouver Island revealed that incubation periods ranged from two to eleven months, with a median of six to seven months\(^1\)\(^9\). Other reports indicated a longer incubation period of several years following likely exposure, which suggests that C. gattii may be able to remain dormant\(^2\)\(^10\)\(^11\). Thus, the incubation period of C. gattii remains uncertain and needs more investigation.

Our patient had no exposure to imported timber or animals while living in Japan, and there have been only a few C. gattii clinical cases and no isolation of C. gattii from environmental niches in that country. Our patient had previously visited China three times and Hawaii once, and as previously mentioned, infections with the VGIIb C. gattii genotype have been reported in China\(^1\)\(^4\)\(^11\)\(^15\). Thus, the source of his infection appears to have originated in China, although we cannot rule out the possibility that he was infected in Japan. We acknowledge the limitation to infer the source of his infection from the MLST analysis because of a lack of comprehensive environmental and clinical surveillance samples from areas where the patient resides or traveled. Genotype information is not essential in routine clinical practice\(^1\)\(^2\)\(^19\), however, in terms of epidemiologic investigation, genotyping may be helpful for estimating where a patient was infected or for surveying which strains are common in a region.

References


