Review

Medical Mycology Seen Through a One Health Approach

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ABSTRACT

In clinical settings, the number of immune compromised patients have increased as a result of developments in medical technology (e.g., organ transplantation, anticancer drugs, steroids, TNF inhibitors, etc.). However, patients with fungal diseases are also increasing globally. In recent years, the distribution and pathogenicity of fungi worldwide have been changing, with reports that new fungi are emerging, and antifungal-resistant fungi are spreading globally. Global warming, globalization, human activities, and other factors have been suggested as contributing to the emergence of new fungi. Some of the antifungals against which resistant fungi have emerged are commonly used not only for human but also for animal health care and crop protection. Consequently, the occurrence of antifungal-resistant fungi has become a clinical issue. Solving these problems entails continuing the “One Health” approach, which in turn requires updating medical mycology information with regard to the emerging pathogenic fungi. In particular, this paper reviews the recent information on *Cryptococcus gattii*, *Candida auris*, and azole-resistant *Aspergillus fumigatus*.

Key words : azole-resistant *Aspergillus fumigatus*, *Candida auris*, *Cryptococcus gattii*

Introduction

Currently, more than 600 fungal species are known to cause infections in humans. In recent years, the distribution and pathogenicity of fungi worldwide have been changing, and the frequency of fungal infections in animals and plants has been increasing. In particular, plant diseases caused by fungi are threatening to cause species extinction, leading to food shortages. Global warming, globalization, and other factors are contributing to these problems¹⁾.

Among the emerging fungal diseases, those caused by *Cryptococcus gattii*, a new species that appeared on Vancouver Island, British Columbia, Canada in 1999, and *Candida auris*, which was discovered in Japan in 2009 and has since become a clinical concern worldwide, are noteworthy. Antimicrobial resistance has also become a worldwide problem, leading to the promotion of antimicrobial stewardship programs. Trends in antifungal drug resistance have also become of concern. The U.S. Centers for Disease Control and Prevention (CDC) 2019 Antibiotic Resistance Threats Report²⁾ lists drug-resistant *Ca. auris* among the urgent threats

and drug-resistant *Candida* spp. among the serious threats; while azole-resistant *Aspergillus fumigatus* is on its watch list.

This article addresses *Cr. gattii*, *Ca. auris*, and azole-resistant *A. fumigatus* as fungi of interest in the last two decades and reviews the causes of their emergence and spread from a “One Health” perspective.

I. *Cryptococcus gattii*

Cr. gattii is found in eucalyptus trees in tropical and subtropical regions such as Papua New Guinea and Australia and is mainly known to be a pathogen of koalas, and human infections are rare. However, starting with an outbreak on Vancouver Island, British Columbia, Canada in 1999, 218 cases of human infections were reported over an eight-year period through 2007, with a high average incidence of 27.9 cases per 1 million inhabitants on Vancouver Island between 2002 and 2006³⁾. It then spread to the adjacent U.S. Pacific coast (Washington, Oregon, and California), where 96 cases were reported between 2004 and 2011⁴⁾.

Cr. gattii is further subdivided into four genotypes; namely, VGI to VGIV (VGII is further subdivided into VGIIa to

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VGIIc), with VGI being widely distributed in Australia, Papua New Guinea, Asia, and Europe. VGII is prevalent in North and South America, particularly in British Columbia, where the outbreak of VGIIa occurred, and VGIIa, VGIIb, and VGIIc are found on the Pacific coast of the U.S., especially VGIIc, which is a new genotype that has not been reported outside the U.S.^{5,6}. It has been determined that VGIIa and VGIIc are highly pathogenic⁷.

Human-mediated *Cr. gattii* dispersal

In British Columbia, where *Cr. gattii* is not prevalent, it has been detected in the tires of 35% (22/63) of cars. A total of 8 million cars travel between Vancouver Island and the BC Mainland every year, suggesting that the fungus was carried by car tires. *Cr. gattii* was also detected in 54% (43/80) of footwear (confirmed to enable survival up to 333 days), suggesting that it may have spread due to human activity⁸.

It has been contended that the spores of *Cr. gattii* detected on Vancouver Island are smaller than those of plant origin, which may have facilitated the spread of the infection, that same-sex mating of *Cryptococcus* may have occurred and altered its characteristics, and that habitat expansion may be associated with global environmental changes such as global warming⁹.

Cr. gattii (VGII) has also been detected in cats with cutaneous cryptococcosis in an urban area in Brazil, suggesting that the spread of *Cr. gattii* can occur through animals¹⁰. These reports suggest the spread of new *Cryptococcus* genotypes. *Cr. gattii* infections involve human and animal activities; thus, emerging fungal diseases should be considered from the perspective of a One Health approach in the future.

Cr. gattii infections in Japan

Cases in Japan are rare. A male patient in Tokyo with underlying diabetes mellitus presented with headache and right homonymous hemianopia and underwent craniotomy due to a mass of approximately 4 cm in size that was recognized in the left frontal lobe on a head computed tomography (CT) scan. Brain lesions caused by *Cr. gattii* were diagnosed by histopathological examination and genetic testing of the strain obtained through culture¹¹.

In another case, a man in Aichi Prefecture with no underlying disease presented with headache and low-grade fever, and bronchoscopy and cerebrospinal fluid examination were performed as the chest CT scan revealed a mass shadow of approximately 5 cm in size in the right lower lobe, and head MRI revealed multiple brain lesions. Histopathology of the transbronchial lung biopsy and the cerebrospinal fluid by India ink revealed yeast-like fungi suggestive of *Cryptococcus*, and heterogeneity testing of the strain obtained in culture led to the diagnosis of disseminated cryptococcosis due to *Cr. gattii*¹².

II. *Candida auris*

Ca. auris is a new species of the genus *Candida* described by Sato et al. in 2009¹³. Of the 1468 strains collected from all over Japan by the Japan Antifungal Surveillance Program (JASP), only one strain, which could not be identified, was determined to be a new species by molecular phylogenetic analysis. Since this strain was detected in the ear canal discharge of a patient, it was named *Ca. auris*, after the Latin word “auris”, which means “ear”.

Originally, *Ca. auris* was not noted clinically because of its low detection rate and preserved antifungal susceptibility; however, in 2009, it was reported in a Korean patient with otitis media¹⁴. In 2011, it was reported in three hospital-onset fungal infections¹⁵. These strains showed reduced susceptibility to fluconazole (FLCZ). Transmission and epidemics have been reported in India¹⁶, South Africa¹⁷, the United States^{18,19}, and Europe²⁰. Moreover, recent reports have shown that some strains have poor susceptibility to antifungals such as amphotericin B (AMPH-B), voriconazole (VRCZ), and caspofungin, and some strains are multidrug-resistant. Thus, the existence of multidrug-resistant strains, the difficulty in identifying species by standard laboratory assays, and the need for identification by molecular biological techniques and mass spectrometry have been reported, in addition to three cases of local colonization and outbreaks in healthcare facilities. Therefore, *Ca. auris* infection is now a major public health issue.

In an epidemiological study of *Ca. auris* in Japan (2019)²¹, only 3 of the 13 isolates, all of which were isolated from the periauricular region, were resistant to azoles (FLCZ and VRCZ), and all isolates remained susceptible to AMPH-B and echinocandins. Thus, multidrug-resistant *Ca. auris* is currently not a clinical concern in Japan. However, because *Ca. auris* possesses a high biofilm-forming ability, has high environmental viability and high transmissibility, and multiple clades exist worldwide, there is a risk of colonization by multidrug-resistant *Ca. auris* in the future and the possibility that the East Asian-type of *Ca. auris* may acquire secondary resistance in Japan. These trends should therefore be monitored.

Ca. auris is broadly classified into East Asian (Japan/Korea), South Asian (India/Pakistan/Malaysia), South African, and South American (Venezuela) types, with each clade having a different tendency toward antifungal resistance²². *Ca. auris* is currently spreading rapidly worldwide, and although it is likely that *Ca. auris* has been established as infectious in Japan and Korea since around 2000 and elsewhere since the late 2000s, it is likely that it emerged simultaneously in different regions rather than solely from East Asia, which is thought to have been the region of its first occurrence.

The cause of the nearly simultaneous emergence of each genetically distinct clade on three continents is unknown; however, it has been suggested that azoles present in the environment may be involved in the acquisition of resistance and that the possible acquisition of temperature tolerance may be involved in the acquisition of human pathogenicity²³⁾.

Regarding the origin of pathogenic *Ca. auris*, Casadevall et al. cited factors such as global warming, multidrug resistance due to HSP90 overexpression, changes in pathogenicity, and temperature sensitivity as reasons why *Ca. auris*, traditionally considered an environmental fungus, has acquired pathogenicity in humans²⁴⁾.

III. Azole-resistant *Aspergillus fumigatus*

A. fumigatus, the causative fungus of aspergillosis, is originally susceptible to azoles, echinocandins, and AMPH-B; however, azole-resistant *A. fumigatus* has recently received increased attention²⁵⁾. There are two main strains of azole-resistant *A. fumigatus*: human-derived and environmentally derived strains. Human-derived strains are mainly detected in patients receiving long-term treatment with azoles. The long-term use of azoles induces genetic mutations in the target enzyme Cyp51A, resulting in resistance to the drug. Some strains are not cross-resistant to other azoles (e.g., resistant to itraconazole and susceptible to VRCZ) depending on the site of the mutation. In contrast, among environmentally derived strains, a particular strain is known to have a mutation in the Cyp51A gene (L98H) with a 34-nucleotide tandem repeat sequence (TR34) in the promoter region. Environmentally derived strains with this resistance mechanism are resistant to more than one azole-based drug (multi-azole-resistant). Environmentally derived, azole-resistant strains were first reported in the Netherlands in 2008²⁶⁾; however, several azole analogs have been used as pesticides in Europe since the 1990s and have been suggested to be associated with the emergence of multi-azole-resistant *A. fumigatus*^{27, 28)}. Initially, multi-azole-resistant *A. fumigatus* was detected mainly in Europe; however, in recent years, it has also been detected in many other countries²⁹⁾. One of the possible reasons for this worldwide spread is that azole-resistant *A. fumigatus* may have adhered to and spread by tulip bulbs exported from the Netherlands³⁰⁾.

The azole drug VRCZ is the first recommended treatment for aspergillosis, whereas echinocandins and liposomal amphotericin B (L-AMB), which have different mechanisms of action, are used for the treatment of azole-resistant *A. fumigatus*. Therefore, in areas where azole-resistant *A. fumigatus* is isolated in more than 10% of cases, experts suggest opting for a combination of VRCZ and echinocandins or L-AMB as the initial treatment and changing antifungal drugs after confirming antifungal susceptibility outcomes³¹⁾.

Isolation status of Japanese Azole-resistant *A. fumigatus*

In Japan, multi-azole-resistant *A. fumigatus* was first reported in a patient's specimen in 2016. However, this patient had the infection in 2013, suggesting that multi-azole-resistant strains had existed in Japan for some time³²⁾. In 2017, multi-azole-resistant *A. fumigatus* was detected in Hokkaido³³⁾. In regard to local epidemiology, it has been reported that 12.7% of *A. fumigatus* strains are resistant to azoles in the Kyoto and Shiga regions, and some multi-azole-resistant strains with the TR34/L98H mutation have been detected among them³⁴⁾. However, no national surveillance for the drug susceptibility of *Aspergillus* spp. has been conducted to date. Antifungal susceptibility testing should be conducted in each region to clarify the actual situation in Japan.

A causal investigation by Nakano et al. of azole-resistant *Aspergillus* imported into Japan found that 7.8% (13/167) of *A. fumigatus* isolates from tulip bulbs imported from the Netherlands (*Gladiolus*, *Hippeastrum*, *Tulipa*, etc.) were azole-resistant but only found azole resistance in 1.2% (1/86) of isolates from bulbs in Japan (*Ipheion*, *Narcissus*, *Tulipa*, etc.)³⁵⁾.

These results suggest that drug-resistant fungi are being introduced into Japan via agricultural products imported from abroad.

At present, azole-resistant *Aspergillus* strains are not considered prevalent in Japan; however, it is important to keep an eye on future trends. Especially, azole-resistant organisms have been isolated from patients with long-term azole use³⁶⁾. A nationwide survey is therefore necessary.

In filamentous fungal infections, antifungal drugs should ideally be selected on the basis of accurate species identification and antifungal susceptibility testing. In Japan, only a limited number of facilities are able to perform genetic identification and antifungal susceptibility testing for filamentous fungi. In addition, antifungal susceptibility testing for filamentous fungi is not covered by the Japanese health insurance system (as of September 2021). Antifungal susceptibility testing of filamentous fungi is also considered more time-consuming and more difficult than testing of yeasts; this is believed to be the reason why the test is not widely used. In the future, it will be necessary for laboratories to acquire competencies in antifungal susceptibility testing and establish a system for consultation with specialized facilities in each region.

In conclusion, these findings suggest that the evolution of antifungal resistance is caused by an increase in the number of susceptible patients due to population growth, urbanization, and immunosuppressive and anticancer drug treatments. In addition, there is a limited selection of antifungal drugs, wherein prophylaxis and empiric treatment with the same antifungal drugs is leading to the development of resistant fungi. Likewise, the movement of people and products with

the development of transportation networks is leading to the dispersal of resistant fungi on a global scale³⁷⁾. There is a limit to what we can do to influence population growth, urbanization, and the prevention of the dispersal of resistant strains and new emerging pathogenic fungi. What we can do is to search for the causative fungus, which is the basis of infectious disease treatment, confirm its antifungal susceptibility, and select the appropriate antifungal drug according to the condition and pathology of the host. The current state of hospitals, however, indicates that they do not have an adequate testing system in place. Proactive introduction of state-of-the-art technology is also necessary to promote antifungal stewardship.

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Conflicts of interest

None.

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