Cryptococcosis, A Risk for Immunocompromised and Immunocompetent Individuals

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Abstract: The genus Cryptococcus includes at least 37 different species, of which, two are important human pathogens: Cryptococcus neoformans and Cryptococcus gattii. These fungi are opportunistic pathogens and etiologic agents of cryptococcosis disease in humans and animals. A variety of virulence factors interfere with the establishment of cryptococcal infection is usually acquired via inhalation of environmental basidiospores or desiccated yeasts. Cryptococcosis has gained medical importance over the last decade due to the AIDS pandemic, and become an emerging pathogen of immunocompetent individuals, especially in children. This disease in humans may involve every tissue, including cutaneous and pulmonary sites, but the most serious manifestation is central nervous system involvement with meningoencephalitis. In this review, we briefly described the taxonomy, the fungus biology, epidemiology and clinical manifestations of cryptococcosis in immunocompetent and immunocompromised individuals.

Keywords: Cryptococcus neoformans, Cryptococcus gattii, cryptococcosis, immunocompetent individuals, immunocompromised individuals.

1. INTRODUCTION

Cryptococcosis is caused by the basidiomycetous yeasts Cryptococcus neoformans and Cryptococcus gattii [1], which have a predilection for the pulmonary and central nervous systems [2, 3]. This considerable impact on human health can be attributed to the number of virulence factors found in C. gattii and C. neoformans which share structural and physiological characteristics that allow them to invade and survive in host tissues [3]. The major virulence factors associated with Cryptococcus are the ability to grow at 37°C [4], the production of the pigment melanin [5-7] and the formation of a polysaccharide capsule [8]. The number of infections caused by Cryptococcus has advanced considerably around the world in recent years. This perception comes from the rapidly increasing number of hospitalized patients due to complications caused by infections attributed to this type of microorganism [9, 10]. C. neoformans varieties are opportunistic pathogens, which mainly cause meningoencephalitis predominantly in immunocompromised individuals [11]. C. gattii has a more aggressive behavior and causes infections more frequently in immunocompetent humans and animals [12,13]. In recent years, several excellent recent reviews for further information about other aspects of cryptococcal virulence, sexual development and signaling, and immune response have been published. In this review, we briefly describe the taxonomy, the fungus biology, epidemiology and clinical manifestations of cryptococcosis in immunocompetent and immunocompromised individuals. We performed a comprehensive review of original research and reports regarding the cases of cryptococcosis in the world, covering publications up to 2013 using the databases PubMed, MEDLINE, Google Scholar and SciELO.

2. TAXONOMY

The genus Cryptococcus is classified in the order Tremellales, class Tremellomycetes, phylum Basidiomycota and the kingdom Fungi. It includes at least 37 different species, of which, two are important human pathogens: Cryptococcus neoformans and Cryptococcus gattii [1]. They are characterized as basidiomycetous encapsulated budding yeasts commonly involved in the etiology of infection affecting the pulmonary and central nervous systems [2, 14]. Typically, C. neoformans has been associated with severe cases of meningitis in immunocompromised patients, while C. gattii has been shown to be an important cause of infections in immunocompetent individuals [11, 15]. C. neoformans and C. gattii have now been divided into separate species, although most clinical laboratories will not routinely identify Cryptococcus to the species level [16].

C. neoformans was originally named Saccharomyces neoformans by Sanfelice in 1894 after the microorganism was isolated from peach juice [17]. Since then, several studies showed that the yeast was related to different
infections, which led to the creation of a different species names; however, this was later proven to be the same microorganism. In 1901, Vuillemin proposed a new genus, named Cryptococcus, to include these yeasts, based on the differences found in morphological aspects when compared to Saccharomyces sp. [18]. The teleomorph [sexual state] of C. neoformans was identified in 1975 by Kwon-Chung and described as Filobasidiella neoformans as a result of the mating of two strains of serotype D [19]. Currently, there are three recognized varieties of C. neoformans: C. neoformans var. grubii [serotype A], C. neoformans var. neoformans [serotype D] and hybrid serotype AD [20].

The matings between two other compatible strains [serotypes B and C] produced a different teleomorph named Filobasidiella bacillispora [21]. Several studies [12,22-25] then revealed the huge diversity not only in this teleomorph, but also in its anamorph, which was named Cryptococcus bacillispora, considering the differences found in aspects such as physiology, biochemistry, epidemiology, ecology and genetics [25]. Later, B. bacillispora was suggested as a variety of C. neoformans named C. neoformans var. gattii [26], which in 2002, was finally proposed to be the species Cryptococcus gattii [16].

Recently, molecular studies using different methods, such as PCR fingerprinting, Amplified Fragment Length Polymorphisms [AFLP] analysis, Restriction Fragment Length Polymorphism [RFLP] and Multilocus Sequence Typing [MLST], have shown that C. neoformans and C. gattii can also be grouped in at least eight cryptic species defined as molecular types, therefore characterizing intra-species and inter-species genetic diversity [27]. Thus, although other subgroups exist, the main genotypes recognized so far are: C. neoformans var. grubii, serotype A, molecular types recognized as VNI=AFLP1 and VNII=AFLP1A; the hybrid serotype AD corresponds to VNIII=AFLP3; and C. neoformans var. neoformans, serotype D, which consists of VNIV=AFLP2. In both serotypes B or C of C. gattii, the molecular types established are VGI=AFLP4, VGGI=AFLP6, VGGII=AFLP5, and VGV=AFLP7 [28]. The pathogenic implications of these molecular types will require more studies, since the epidemiological distribution is not completely known. However, it has recently been shown that the genotype VGIIa presents higher virulence than VGIIb isolates of C. gattii [29].

3. BIOLOGICAL CHARACTERISTICS AND VIRULENCE FACTORS

Cryptococcosis is a systemic mycosis that occurs in humans caused by either C. neoformans or C. gattii species, which has a predilection for the central nervous system and is generally believed to be acquired through the inhalation of airborne fungal propagules [30,31]. However, there are some intrinsic characteristics of each species that influence their epidemiology and ecological niche, as well as the clinical course of the disease. Typically, C. neoformans varieties cause disease predominantly in immunocompromised individuals [11]. C. neoformans var. grubii is distributed worldwide and is considered the main cause of cryptococcosis in HIV-infected patients, while C. neoformans var. neoformans is more prevalent in South America and Europe [32,33]. Bird droppings (mainly pigeons) and soil contaminated with avian fecal material are the main sources of transmission of C. neoformans [31,32,34], but this fungus was also isolated from decaying wood contained in hollow parts of living trees [35,36].

C. gattii has a more aggressive behavior and causes infections more frequently in immunocompetent humans and animals [12,13,31,37-39]. C. gattii infections are reported to be more resistant to antifungal chemotherapy and, thus, require more aggressive and prolonged treatment [12,13,37,40]. C. gattii was initially thought to be found only in tropical subtropical climates [13,16,31,40,41]; however, after the ongoing outbreak occurred in Vancouver Island in British Columbia, Canada it was determined that this species is also present in temperate climates [42,43]. In this regards, C. gattii has been found to be endemic in many regions such as Australia and New Zealand, Papua New Guinea, South and Southeast Asia (Cambodia, Malaysia, Thailand, Vietnam, People’s Republic of China, Taiwan, Singapore, Nepal, and the Indian subcontinent), parts of Latin America (Argentina, Brazil, Colombia, Uruguay, Paraguay, Peru, and Venezuela), southern California, Mexico, Hawaii, Central and South Africa, and certain parts of Europe (Austria, Germany, France, Italy, Greece, and Spain) [40].

C. gattii was believed to be restricted to the tropics and subtropical regions associated with species of Eucalyptus trees. The distribution of C. gattii has been associated with Eucalyptus trees from Australia that are exported throughout the world [31,40,41,44]. However, recent studies have also documented the dispersal of C. gattii through other trees, bird excreta, soil and human interactions with the environment [14,45-47]. Moreover, C. gattii serotypes frequently cause disease in healthy individuals and also show the ability to infect many kinds of animal, including wild felines, dogs, cats, and birds, among others [48].

These fungi can cause infection in humans and animals and have been reported sporadically in wild animals, including several exotic species [30,49-53], and in domestic animals [54-57]. However, infection is most common systemic mycosis in cats [55], with the most frequently isolated causative agent in these cases being C. neoformans. While cats and occasionally dogs can develop skin infections due to this yeast, the aerosols formed from these injuries do not appear to be a source of infection for people via touch. On the other hand, recent studies have reported that a Cryptococcus outbreak in a human Vancouver Island (British Columbia, Canada) was associated with the elimination of the yeast C. gattii in dogs and cats with asymptomatic infection or colonization of the fungus in the nose, suggesting that these pets can be possible carriers of this species to humans [57].

Although not well established yet, it is assumed that infection starts when humans inhale microscopic-size propagules of the fungi (basidiospores < 2 μm in size) found in the environment. The spores seem to be the most suitable for both air dispersal and survival in the soil and can be transferred to the alveoli of the lungs where they can cause pneumonia; subsequently, the microorganisms can spread to the central nervous system, causing meningoencephalitis [58]. However, it is also considered that desiccated yeasts play a role in transmission because of their small size (~3 μm compared with 4-10 μm for actively growing yeast cells) despite their fragility. For C. neoformans, the main source of
infectious propagules is pigeon guano, although the species can also be isolated from other avian guano, soil and decaying wood [35,44,59]. On the other hand, C. gattii has been mostly isolated from several species of trees in many countries, such as Eucalyptus camaldulensis and Eucalyptus blakelyi in Australia [60], Moguilea tomentosa [pottery tree] and Cassia grandis [pink shower tree] in Brazil [35,47] and Terminalia catappa [almond tree] in Colombia [61].

This considerable impact on human health can be attributed to the number of virulence factors found in C. gattii and C. neoformans which share structural and physiological characteristics that allow them to invade and survive in host tissues [3]. Moreover, differences in the presentation of infections caused by C. gattii and C. neoformans may be due, in part, to a deficiency in proteinase production by the former, which may limit the ability of C. gattii to disseminate locally and into circulation. C. gattii produces circumscribed lesions (cryptococcomas) more often than C. neoformans [62].

Cryptococcus is an encapsulated fungal organism and the cryptococcal capsule is one of the most important virulence factors to dissemination and survival of this microorganism inside immunocompetent and immunocompromized host tissue, according to studies that demonstrated a loss of virulence in acapsular strains or strains with defective capsule production [63, 64]. The capsule works like a physical barrier made of polysaccharides rich in mannan residues with important properties [8].

Fig. (1) shows the principal virulence factor of these species is the presence of a polysaccharide capsule which is basically composed of glucuronoxylomanan (GXM) with smaller proportions of galactoxylomanan (GalXM) and mannoprotein [65]. GXM and GalXM have weak antigenic functions and hide cellular components which could be recognized, like pattern molecular associated to pathogens (PAMPs) by the receptors of innate immunity, including Toll-like receptors, and can induce danger signals to the host immune response [3,66,68]. The capsule plays a major role in the immune response of the host by interference with phagocytosis and the recruitment of inflammatory cells (macrophages, DCs and neutrophils), decreasing antibody production in response to infection and activation of complement via the classical pathway, as well as suppressing the delayed-type hypersensitivity response [3,8,66-68].

Other virulence factors are the presence of melanin, which is shown to contribute to nervous system tropism [69] and protect against oxygen and nitrogen free radicals [6,70]; the growth at physiological temperature (37°C) which contributes to survival and persistence in the host [4,70]; and the production of extracellular enzymes such as laccases, which are the enzymes responsible for melanin biosynthesis in the cell wall and, together with urease, induce the macrophages to produce IL-10 and TGF-β [5-7,70,71]. Phospholipase B is involved in cell wall integrity and fungal invasion and dissemination in the host lung tissue. The Th2 polarization observed in cryptococcosis could be explained by phospholipase participation that induces pulmonary eosinophilia in mice infected with the wild type strain but not with the phospholipase-deleted mutant strain [72]. Urease, which catalyzes the hydrolysis of urea to ammonia and carbamate, increases the ability of C. neoformans to invade the central nervous system, among other roles [73]. The urease expression by virulent strains has been shown to be important in the traffic of DCs to lymph nodes in a murine model, with inadequate migration of immature DC resulting in Th2 response and pulmonary pathology in C57BL/6 mice infected with Cryptococcus [74]. Finally, phenomere production in sexual reproduction can generate hybrid organisms that are potentially more virulent [75, 76].

4. EPIDEMIOLOGY OF CRYPTOCOCCOSIS

Cryptococcosis occurrence has been considered sporadic, although of worldwide distribution. In non-HIV infected individuals, incidence rates of 0.2-0.9% have been reported in the United States, mainly in organ transplant recipients [77]. Nevertheless, the infection prevalence can reach 15% when considering patients with AIDS accessing antiretroviral therapy [78]. The percentages of disease can vary according to many factors such as clinical presentation. A study in Uganda showed that the prevalence of pulmonary cryptococcosis among HIV-infected patients hospitalized with pneumonia who underwent bronchoscopy was 11% [79]. Balkhair [80] reported that Cryptococcus menigitis accounted for 21% of the HIV patients, while Indian studies showed an incidence of cryptococcal infection (including meningitis) of 6-8%, 5-11% in the USA, 33% in Africa, and 28.5% in Thailand [80-82].

The prevalence ratings are also different for both species and their subgroups. In this regard, a lot of studies have reported the local distributions of cryptococcosis considering the etiological aspect in order to establish the real epidemiology of C. neoformans and C. gattii. In French Guiana, a retrospective study from 1998 to 2008 was performed on all patients with cryptococcosis who were admitted to hospitals, and showed that C. neoformans var. grubii was recovered with a frequency of 77.3% and was mainly isolated from patients with AIDS, whereas C. gattii was responsible for 22.7% of the cases and was strictly isolated from HIV-negative patients with no apparent risk factors [83]. In the Southeast and South regions of Brazil, human cryptococcosis is predominantly caused by C. neoformans serotype A, VNI and is associated with AIDS [84]. Conversely, British Columbia, Canada, has the largest reported population of Cryptococcus gattii-infected persons worldwide with the predominance of VGIIa strain, with a total of 218 cases reported [average annual incidence 5.8 per million persons] during the period from 1999 to 2007 [85]. Since 2005, the C. gattii outbreak has continued to expand throughout this temperate region, with outbreak isolates being reported in the United States involving both the VGIIa/major genotype and the novel VGIIe genotype, which are clonally derived and highly virulent in host models of infection [86]. A study realized in Brazil showed that C. gattii was the main causative agent of meningeitis in the HIV-negative patients with high frequency of cryptococcal meningitis in children (18.6%) suggesting that cryptococcal infection occurs early in life in this region [87]. Epidemiological studies in these regions showed that the molecular type VGII is the main agent for cryptococcal meningitis in young adults and children [87, 88].

The morbidity and mortality associated with cryptococcosis is very significant. It is estimated that C.
*Cryptococcus neoformans* causes about 1 million new cases of meningoencephalitis globally per year in patients with AIDS, leading to approximately 625,000 deaths [9]; a higher prevalence is found in sub-Saharan Africa [9, 20, 89]. A study conducted in the United States of America in the period from 1997 to 2009 analyzed the incidence of cryptococcal meningitis in 18 States using the Agency for Healthcare and Research Quality (AHRQ) State Inpatient Databases (SID) datasets and identified 30,840 hospitalizations. Of those, 24,151 (79.4%) were associated with HIV, while 6,689 (21.6%) were not associated with HIV/AIDS. In-hospital mortality was found to be 12.4% for women and 10.8% for men, with a total of 3,440 deaths [90].

Factors associated with high mortality of cryptococcosis include the presence of immunodeficiency, particularly HIV-1 infection. In these patients, mortality is even higher when they present low CD4+ cells counts (< 50 cells/mm³) [91, 92] In this regard, an important measure to reduce mortality due to cryptococcal disease is to implement early diagnosis, which can be achieved by antigen screening in order to establish anti-fungal therapy in those patients with a positive test in areas with a high prevalence of cryptococcal disease [93].

It is worrying that, despite access to advanced medical care and the availability of HAART, the mortality rate of acute cryptococcal meningoencephalitis after 3 months of treatment is approximately 20% [94,95]. Moreover, without specific antifungal treatment for cryptococcal meningoencephalitis in some HIV-positive populations, mortality rates may reach 100% within 2 weeks after the onset of clinical symptoms and access to health care [16]. Clearly, a careful evaluation of cryptococcosis is critical to the success of curing the disease [39]. Disseminated cryptococcosis is also commonly found in patients with AIDS; studies have reported that this form of cryptococcosis was identified in 8% of cases from India [96] 8-14% of cases from United States [97], 10% from Mexico [98], 3-19% from Africa [99,100], 3-4% from Brazil [84,101,102], and 14% from Japan [103].

The incidence of cryptococcal infection among all patients with malignant neoplasms receiving multiple cycles of combined chemotherapeutic regimens, including corticosteroids, has been reported to be 1.3-2.7% [104]. Infections with the cryptococcal species account for about 2% of all infections of the central nervous system complicating hematological malignancies [105]. Patients with lymphoproliferative disorders, including malignant lymphoma, are also in a state of suppression of cell-mediated immunity, and intercurrent cryptococcal infections complicated with Acute Lymphocytic Leukemia(ALL), Adult T-cell Leukemia(ATL), Hairy Cell Leukemia(HCL),
Chronic Lymphocytic Leukemia (CLL) and Hodgkin’s lymphoma have been reported [104,106-109].

5. CRYPTOCOCCOSIS IN IMMUNOCOMPROMISED PATIENTS

Cryptococcosis as a result of *C. neoformans* is cosmopolitan and is a rare fungal infection that existed before the AIDS epidemic which has emerged as an important cause of illness and death in people infected with HIV in both developed and developing countries [58,99,100]. *C. neoformans* is also an opportunistic pathogen, which can cause cryptococcosis in patients with HIV infection and HIV-negative patients with immunological conditions predisposing to this fungal infection, such as a history of systemic corticosteroid therapy, immunosuppressive treatments, organ transplant, chronic organ failure (liver, lung, and kidney), malignancy, rheumatic diseases, systemic lupus erythematosus and diabetes mellitus [104,106-110].

Infection occurs via inhalation and primary infection is localized to the lung where there is dissemination to other organs including brain. Thus, the most common sites of infection are the central nervous system (CNS) and lungs; usual manifestations that are most commonly reported are pulmonary, meningoencephalitis, sepsicaemia ocular and gastrointestinal [111-114]. Although the lung is the most likely point of entry of the fungus due to the inhalation of yeast cells or basidiospores by the patient, pulmonary cryptococcosis is diagnosed less frequently than meningitis in patients with AIDS [111]. Cryptococcus has a special tropism for the CNS, but the respiratory system is most commonly affected. However, these characteristics vary depending on the infecting strain and the host immune response, because some cryptococcal strains may be more virulent than others and the systemic inflammatory response varies from one patient to another [115].

Cryptococcal pneumonia may be either asymptomatic or symptomatic, with or without evidence of dissemination, and clinical manifestations include fever and cough that produces scant sputum, malaise, shortness of breath, and pleuritic pain; physical examination may reveal localized nodular lesions, with or without cavitations, segmental pneumatic infiltrate, patchy interstitial or alveolar infiltrates, pleural effusions, tachypnea, hilar masses and thoracic lymphadenopathy [115, 116]. Cryptococcal pneumonia in immunocompromised patients may have a completely different and more rapid clinical course; *C. neoformans* tends to disseminate rapidly from the lungs or to reactivate from a primary focus, to eventually establish infection within the CNS, and patients often present with a meningeal rather than a pulmonary syndrome [115, 116]. The clinical presentation of *C. gattii* in immunocompromised individuals is very similar to that of *C. neoformans*; however, the former is associated with more pulmonary and CNS cryptococcomas [117].

In this regards, pulmonary involvement by *C. neoformans* has been reported in 30-40% of patients with meningoencephalitis [118]. Visnegarwala et al. [119] reported that of 210 patients with HIV infection and cryptococcal disease, 29 (13.8%) had acute respiratory failure and the *C. neoformans* from at least one extrapulmonary or extraneural site was isolated of 10 patients, which carries an extremely high rate of mortality. Thus, these authors reported that acute respiratory failure associated with cryptococcal disease in AIDS patients is a marker of disseminated disease; this may suggest that the fulminating course of the disease in these patients was due to acute dissemination shortly after the acquisition of a primary pulmonary infection. However, it is unclear whether disseminated disease represents a progression or reactivation of pulmonary disease because many patients have no evidence of pulmonary involvement at the time of diagnosis of disseminated disease [120].

Disseminated disease is uncommon and when present almost always occurs in HIV-infected patients, but has also been reported in non-HIV-infected patients with alcoholic liver cirrhosis or those receiving chronic immunosuppressive medications [121-123]. The CNS is the most common site of disseminated cryptococcal infection; accordingly, Heyderman et al. [124] reported that the cryptococcal meningitis was the AIDS-defining illness in 78 (88%) out of 89 patients studied. CNS invasion may be secondary to hematogenous infection or may represent reactivation disease similar to histoplasmosis or tuberculosis. Infection in most patients is typically characterized as subacute meningitis or meningoencephalitis and presents signs and symptoms such as headache, fever, lethargy, coma, personality changes, and memory loss over 2 to 4 weeks [125]. Moreover, cranial nerve palsies and papillledema are the most common ocular manifestations seen in patients with cryptococcal CNS invasion and most patients have severe visual loss [125,126]. Complications of CNS cryptococcosis include diffuse atrophy, hydrocephalus, and diffuse edema, while mass lesions include hydrocephalus, motor or sensory deficits, cerebellar dysfunction, seizures, diffuse edema; mass lesions and dementia [127].

Cryptococcal peritonitis must be regarded as an unusual clinical manifestation and has been proposed as a potential site of disseminated cryptococcosis [9,112,113]. Cirrhotic patients with ascites and oral or upper gastrointestinal tract bleeding are at risk of developing spontaneous cryptococcal peritonitis [112-114, 128,129]. Singh et al. [130] reported that the overall mortality rate of 33 patients with *C. neoformans* infection and cirrhosis, including liver transplant candidates, was 81% cases, and that the median time to death from admission was 13 days. These authors evidenced that cryptococcal peritonitis was present in 45.4% cases and that intraabdominal infection with *C. neoformans* was the most common site of disease manifestation in these patients. In addition, meningitis was present in 39% of patients, and 18% had pulmonary infection; also, that a total of 16 patients was treated with antifungal therapy and only 37% of these patients survived the fungal infection. Husain et al. [131] reported that 2.8% of organ transplant recipients can develop cryptococcal infections, resulting in a 42% mortality rate.

The administration of highly active antiretroviral therapy (HAART) has resulted in a decrease in the number of cases of AIDS-related cryptococcosis in developed countries, but *Cryptococcus* is still a major problem in developing country where HAART is not readily available. However, studies have described that primary antifungal prophylaxis for cryptococcosis is not routinely recommended in HIV-
infected patients in the United States and Europe, but areas with limited HAART availability, high levels of antiretroviral drug resistance, and a high burden of disease might consider it or a preemptive strategy with serum cryptococcal antigen testing for asymptomatic antigenemia [39].

According to the World Health Organization (WHO), “early antiretroviral therapy (ART) initiation is the most important and cost-effective preventive strategy to reduce the incidence and high mortality associated with cryptococcal meningitis in HIV-infected adults, adolescents and children in resource-limited settings. Moreover, patients should ideally initiate ART at a CD4 count of 350 cells/mm<sup>3</sup>, and definitely before a decline in the CD4 cell count to less than 200 cells/mm<sup>3</sup>” [132].

6. CRYPTOCOCCOSIS IN IMMUNOCOMPETENT PATIENTS

Healthy individuals have been affected by <i>C. gattii</i> and <i>C. neoformans</i>, but these infections are more frequently caused by <i>C. gattii</i> [85, 86, 117, 133-137]. <i>C. gattii</i> may cause mild to severe clinical disease in the apparently healthy as well as in people with immunosuppressive conditions, including those with HIV infection, organ transplant recipients and patients with hematologic malignancies [133-137]. Thus, the major risk factor for acquiring <i>C. gattii</i> infection is a history of living in or travel to an endemic area, as well as an age greater than 50 years, smoking, the use of corticosteroids, and a history of cancer or chronic lung disease [138]. On the other hand, some studies have reported that approximately 25% of cases of cryptococcosis in immunocompetent individuals were associated with <i>C. neoformans</i> in the United States, and similar numbers have been found through the world [139-141].

Pulmonary cryptococcosis was described in apparently immunocompetent patients [142,143]. Pulmonary cryptococcosis caused by <i>C. gattii</i> usually presents as a regressive lung lesion which is usually undetected, or as a peripheral lung nodule which can be misdiagnosed as a malignant tumor. It typically evolves sub-acutely or chronically and is often confused with viral or bacterial meningoencephalitis or other infections, including tuberculosis [87]. In <i>C. gattii</i> infection, cerebral mass lesions and/or hydrocephalus, pulmonary mass lesions, increased neurological deficits, and a slower response to treatment are more common than in <i>C. neoformans</i> infection [134]. In addition, <i>C. gattii</i> disease is more often associated with neurologic sequelae, frequently requiring aggressive neurosurgical management [135].

Dora et al. [136] reported a case of disseminated cryptococcosis presenting as cutaneous lesions in an immunocompetent patient, which, after direct microscopy and culturing of cerebrospinal fluid, was found to be positive for <i>C. gattii</i>. In a study by Santos et al. [87] about infectious agents causing human disseminated cryptococcosis, it was shown that <i>C. gattii</i> was more frequently isolated from HIV negative patients and <i>C. neoformans</i> was predominantly isolated from the HIV-positive patients. Galanis et al. [137] have shown three case reports of cryptococcosis in HIV negative patients with confirmed infection by <i>C. gattii</i>. Georgi et al. [134] described a case report of a female patient who developed severe meningoencephalitis due to <i>C. gattii</i> infection. Gutierrez et al. [144] reported a case of an immunocompetent patient with a one-month history of meningoencephalitis caused by <i>C. gattii</i>. Okamoto et al. [145] related a HIV negative patient in Japan infected with <i>C. gattii</i>. To date, there is no effective vaccine to prevent cryptococcosis. In truth, the best way to prevent this disease is to not inhale the fungus. Therefore, the use of masks can be of help to prevent inhalation. This is even more useful in places where there are dried feces of pigeons, which are important sources of <i>C. gattii</i>. Moreover, forests with eucalyptus trees are an important area in which <i>C. gattii</i> lives and therefore constitute important sources of infection, mainly where logging operations occur; care regarding the inhalation of dusts is crucial in preventing the disease [146].

In the prevention of cryptococcosis, the serum or plasma containing the cryptococcal antigen is a good manner to identify on screening which, together with symptoms or signs associated with cryptococcal meningitis, indicate proceeding to a lumbar puncture with cerebrospinal fluid examination to exclude active cryptococcal disease [132].

7. CONCLUSION

Over the last decade, due to AIDS, cryptococcosis has increased and has become one of the major diseases of medical importance in both immunocompromised and immunocompetent individuals, particularly children. The major risk factors for <i>Cryptococcus</i> infection depend on the patient’s immune status and the severity of the infection; unfortunately, treatment failures and mortality remain high. Consequently, future research will need to consider target molecules for intracellular survival and growth and/or cryptococcal virulence factors expressed during a host’s parasitism to advance therapeutic schemes and also propose new strategies to improve anti-cryptococcal treatment.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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