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Review Article

Review on Cryptococcus Disease

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ABSTRACT

Fungal disease is the most important disease found in many part of the world. Cryptococcosis is one of important mycozoonosis that affecting human and animals. It is primarily caused by *Cryptococcus neoformans* and *Cryptococcus gattii*, which are mainly affecting human and animal. Agent is found in soil contaminated with avian droppings or eucalyptus trees and decaying woods. *Cryptococcus neoformans* can survive in pigeon drop for about 20 years. The inhalation is principal mode of entry of the pathogen. Cryptococcosis occurs in sporadic and epidemic form in susceptible hosts. The disease is most often found in cats but has also been reported in cattle, dogs, horses, sheep, goat and other animals. Cryptococcosis is the first manifestation of HIV infected patients to potentiate HIV infection. Diagnosis is application of Pal's sunflower seed medium and Narayan stain help in the study of this enigmatic mycosis in humans as well as in animals.

Keywords: *Cryptococcus gattii*; *Cryptococcus neoformans*; Cryptococcosis; Animals; Human

INTRODUCTION

Cryptococcosis is a fungal disease found worldwide in human and animal populations mainly caused by *Cryptococcus neoformans* and *Cryptococcus gattii*. *Cryptococcus neoformans* was first isolated from peach juice by Sanfelice in 1894 in Italy and was named Saccharomyces neoformans [1]. Around the same time, Curtis studied a yeast-like fungus isolated from a tumor in a patient's hip. Curtis' strain was later determined to be the first clinical isolate of C. *Gattii* [2]. The first description on animal cryptococcosis was in a horse and sheep in 1902 and 1924 respectively recorded [3].

There are 37 species of the genus Cryptococcus which are ubiquitous in nature and only two species namely C. *gattii* and C. *neoformans* are medically significant [4]. Their serotypes are classified Serotypes B and C belong to C. *gattii*, and C. *neoformans* has serotypes A, D and AD. The organism is non-motile, Gram-positive, non-fermenting, basidiomycetous, encapsulated yeast. It is recovered from the pigeon droppings, soil, bat guano, wood, parrot excreta, munia Bird droppings, other avian excreta, fruits, vegetables, wooden canary cages, unpasteurized milk, and Eucalyptus trees [5].

The disease is usually sporadic in occurrence. In temperate regions of the world C. *neoformans* is isolated from a variety of avian species excrement and at a lesser concentration in the soil [5]. On the other hand, in tropical and subtropical regions (where eucalyptus trees are found), C. *gattii* has been reported as a cause of cryptococcosis in people and animals. It isolated from only the bark and leaf litter of eucalyptus trees. C. *neoformans* has a worldwide distribution and infects immunosuppressed individuals, especially those suffering with AIDS. On the contrary, C. gattii causes 70% to 80% infections in immunocompetent hosts [6].

Man and animal acquire the infection from environment where fungus grows luxuriantly. The avian droppings are main reservoir of C. *neoformans*. It can survive for 20 years or longer in dry and old pigeon droppings in dark and humid sheltered site which is not exposed to direct sunlight [5]. Such natural sites may become a point source of infection to man and animals. The zoo attendants, pet bird keepers, pigeon breeder and persons engaged in the cleaning of historical buildings are more likely to expose to cryptococcal infection [7].

The disease in animals is usually sporadic in occurrence but outbreaks of cryptococcal infections. It is particularly common in cats that are immunosuppressed by feline leukemia virus or feline immunodeficiency virus infections [8]. Cryptococcosis may also be more common in immunosuppressed dogs [6]. Aerosol transmission of the organism is common in laboratory workers and person exposed to pigeons or bird feces. Accidental cutaneous inoculation with C. *neoformans* causes localized cutaneous disease. There is also nosocomial transmission of cryptococcal infections in humans [9].

The clinical presentation of cryptococcosis in human varies from asymptomatic pulmonary colonization to severe pneumonia with respiratory failure and meningitis [10]. Infections in birds are rare and in ruminants mostly resulted in mastitis [11]. In cats and dogs, cryptococcosis can be either focal or disseminated. The most common site of localized infections is the nasal cavity. Nasal

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cryptococcosis is frequently seen clinical signs including sneezing, snoring or snorting, dyspnea, nasal deformities and a mucopurulent nasal discharge. Polyp-like masses sometimes protrude from one or both nostrils [12].

Diagnosis of cryptococcosis to locate the lesions in the organ is Radiography, CT scan and MRI. Wet smear preparation and impression are also useful to detect the pathogen. Pal's sunflower seed medium used as highly specific and sensitive for C. *neoformans*. For demonstration of cryptococcal antigen in the serum, CSF, urine and broncho-alveolar lavage is Immunological test mainly latex agglutination is employed. Molecular techniques (PCR, RAPD) have been used in the diagnosis particularly from epidemiological point of view [7]. Cryptococcosis is treated with antifungal drugs such as amphotericin B, flucytosine, itraconazole, fluconazole and ketoconazole. There are no any effective methods of prevention in cryptococcosis [13]. Cryptococcosis is causes healthy problem both in human and animals therefore, the objectives of this paper is to give highlight on the general cryptococcosis etiology, transmission and classification.

HISTORY OF CRYPTOCOCCOSIS

Cryptococcosis in humans and animals is mainly caused by *Cryptococcus neoformans* and *Cryptococcus gattii*. *Cryptococcus neoformans* was first isolated from peach juice by Sanfelice in 1894 in Italy and was named Saccharomyces neoformans [1]. In the same year, Busse provided the first description of a case of cryptococcosis and isolated a yeast culture from a sarcoma-like lesion in the infected young woman's tibia. Busse called the fungus Saccharomyces, while naming the disease Saccharomyces's hominies [14].

Around the same time, Curtis studied a yeast-like fungus isolated from a tumor in a patient's hip, and, noting its difference from the cultures of both Busse and Sanfelice, described the fungus as Saccharomyces subcutaneous tumefaciensn specious. Curtis' strain was later determined to be the first clinical isolate of *C. Gattii* [2]. Because the Busse and Sanfelice's strains lacked the sugar fermentation and ascosporic formation that are the hallmarks of the genus Saccharomyces, Vuillemin reclassified the yeasts as *C. hominis* and *C. neoformans*, respectively, in 1901 [15].

Characteristic neurotropism of *C. neoformans* was first recognized in 1914 by Verse [16], and 2 years later by Stoddard and Cutler [17]. However, Stoddard and Cutler called the etiologic agent Torula histolytica and the disease "torulosis" by misinterpreting the fungal capsule as evidence of fungal histolytic action in the host tissue [18]. Confusion about the identity of the cryptococcosis agent persisted until Benham performed comprehensive studies with clinical Cryptococcus strains and concluded that all of the strains from human infections belonged to one species with two varieties based on serological differences. She proposed to replace "torulosis/torula meningitis" with cryptococcosis and to conserve the fungal name *C. neoformans* [19].

Environmental source of *C. neoformans* was unknown until Emmons isolated *C. neoformans* from soil collected in Virginia in 1951, reporting that the pathogen was abundant in pigeon nests and droppings [20]. It took nearly 40 more years to discover the environmental source of *C. gattii* as trees when Ellis reported isolation of serotype B strains from Eucalyptus camaldulensisin Australia in 1990 [21]. The first description on animal cryptococcosis was in a horse by Frothingham in 1902 [3] and Sheep in 1924 recorded. The first report of cryptococcosis in cat and dog was described by Holzworth and Seibold and co-workers [22] in 1952 and 1953, respectively. Pal is credited to elucidate the etiological significance of *C. neoformans* in mastitis of dairy goat and buffalo in 1975 and 1980, respectively [23].

The laboratory diagnosis of *C. neoformans* was drastically simplified by the early 1960s when Seeliger and Staib discovered that *C. neoformans* could be distinguished from other white clinical yeasts by their urease activity and melanin formation besides the presence of capsule [24]. By the mid-1970s, the complete life cycles of *C. neoformans* and *C. gattii* became known when heterothallic sexuality was discovered in both species. The discovery of a heterothallic life cycle ushered Cryptococcus into the modern era, facilitating the development of the tools for classical genetic analysis and providing evidence that virulence factors such as capsule and melanin formation followed Mendelian inheritance [25].

ETIOLOGY

The genus Cryptococcusis classified in the Kingdom- Fungi, Phylum-Basidiomycota, Class-Tremellomycetes, and Order Tremellales. There are 37 species of the genus Cryptococcus which are ubiquitous in nature and only two species namely *C. gattii* and *C. neoformans* are medically significant [4]. However, occasional infections due to other species such as *C. adeliensis*, *C. albidus*, *C. curvatus*, *C. flavescens*, *C. humicolus*, *C. laurentii*, *C. luteolus*, *C. macerans*, *C. magnus*, *C. uniguttulatus* and *C. uzbekistanensis* have been recorded in man and animals. *C. gattii* and *C. neoformans* have been divided into serotypes [26].

The serotypes are classified on the basis of immunologic reactivity of the cryptococcal capsule with immune sera [4]. Serotypes B and C belong to *C. gattii* and C .neoformans have serotypes A, D and AD. The organism is non-motile, Gram-positive, non-fermenting, basidiomycetous, encapsulated yeast. It is recovered from the pigeon droppings, soil, bat guano, wood, parrot excreta, munia Bird droppings, other avian excreta, fruits, vegetables, wooden canary cages, unpasteurized milk, and Eucalyptus trees. *C. neoformans* can survive for more than 20 years in pigeon dropping [5].

EPIDEMIOLOGY

Cryptococcosis is a fungal disease found worldwide in human and animal populations. The disease is usually sporadic in occurrence but outbreaks of cryptococcal mastitis in cows and cutaneous cryptococcosis in sheep are also documented [7]. The unusual outbreaks of cryptococcosis have also been recorded in cats, dogs, ferrets and a bird. It causes considerable morbidity and mortality in humans as well as animals [27].

In temperate regions of the world *C. neoformans* is the most often causes clinical disease. It has been isolated from a variety of avian species in addition to pigeons, including chickens, parrots, sparrows and sites contaminated by pigeon excrement and at a lesser concentration in the soil [5]. On the other hand, in tropical and subtropical regions (where eucalyptus trees are found), *C. gattii* has been reported as a cause of cryptococcosis in people and animals. It isolated from only the bark and leaf litter of eucalyptus trees [6].

C. neoformans has a worldwide distribution and infects immunosuppressed individuals, especially those suffering with AIDS. On the contrary, C .gattii causes 70% to 80 % infections in immunocompetent hosts [6]. In-sub-Saharan Africa, 15%-30% of all patients with AIDS develop cryptococcal disease. However, in some areas, such as Zimbabwe, 88% of patients with AIDS have cryptococcal infection. The disease due to *C. gattii* is mainly reported

from tropical and subtropical regions such as Australia, Papua New Guinea and South America. However, *C. gattii* infection can also occur in temperate climate. The global incidence of cryptococcal meningoencephalitis in AIDS patients is recorded 2%-33% [28].

The avian droppings are considered the main reservoir of *C. neoformans*. It is important to mention that *C. neoformans* can survive for 20 years or longer in dry and old pigeon droppings in dark and humid sheltered site which is not exposed to direct sunlight [5]. There are evidences to believe that man and animal usually acquire the infection from the environment where the fungus grows luxuriantly. It is estimated that 1gram of dry pigeon excreta may contain up to 50 million viable cells of *C. neoformans*. Such natural sites may become a point source of infection to man and animals [6]. The zoo attendants, pet bird keepers, bird enthusiast, pigeon breeder and persons engaged in the cleaning of historical buildings, old monuments etc. are more likely to expose to cryptococcal infection [7].

Vectors can disperse the spores from an endemic area to a previously unaffected area [26]. Healthy persons with a history of exposure to pigeons or bird feces and laboratory workers exposed to an aerosol of the organism have a higher rate of positive delayed hypersensitivity skin reactions to cryptococcal antigen or cryptococci. Occasionally, laboratory accidents result in transmission of *C. neoformans*, but pulmonary and disseminated disease is rare in this setting. Accidental cutaneous inoculation with *C. neoformans* causes localized cutaneous disease [5]. There are also reports of nosocomial transmission of cryptococcal infections in humans [9].

The disease in animals is usually sporadic in occurrence but outbreaks of cryptococcal infections are also documented in literature [29]. Clinical cryptococcosis is reported most often in cats. It is particularly common in cats that are immunosuppressed by feline leukemia virus or feline immunodeficiency virus infections [8]. Cryptococcosis may also be more common in immunosuppressed dogs. The prognosis is guarded, especially in cases with CNS disease. Untreated infections are usually fatal [6].

CLINICAL SIGNS

Clinical sign animal

Cryptococcus infections in bovines mostly associated with mastitis. It isolated from samples where no visible changes were noted in either the gland or milk, and the cases with visible signs varied from mild and transient swelling of one or more quarters of the udder to severe swelling and distention of the affected glands. In sheep and goats it also causes mastitis and unlike pneumonia, meningitis and abortion. The infection resulted in mastitis with gross and microscopic lesions being restricted to the infected udder halves only and there was no dissemination of infection to the opposite uninfected udder halves as well as to other organs of the body [12].

In equines, cryptococcosis is uncommon and sporadic cases. It appears that nasal cavity is the most common site if equine gets cryptococcosis. Cases have been associated with granulomatous pneumonia, nasal granuloma, endometritis and placentitis with neonatal cryptococcal pneumonia, abortion, mesenteric lymph node abscesses, intestinal polypoid granulomas, osteomyelitis and meningitis [30].

Infections in birds are rare. *C. neoformans* has been isolated from the faeces of carrier pigeons and other birds apart from domestic poultry [11]. Infection associated with the trachea of fowls, isolated from broilers of a poultry-processing plant. The bird exhibited patchy feather loss, especially around the back and beak area, and greyish crusts sticking quite firmly to the underlying skin. The feathers had a greasy appearance and disseminated a musty odour [31].

In cats and dogs, cryptococcosis can be either focal or disseminated. The most common site of localized infections is the nasal cavity. Nasal cryptococcosis is frequently seen clinical signs including sneezing, snoring or snorting, dyspnea, nasal deformities and a mucopurulent nasal discharge. Polyp-like masses sometimes protrude from one or both nostrils [12]. Cutaneous or subcutaneous swellings and nodules may be seen on the face, particularly the bridge of the nose, side of the face, upper lip or nostril. Some of these lesions may ulcerate. In addition, the submandibular lymph nodes are often enlarged. With time, infections involving the nasal cavity can spread to adjacent structures and disseminate to other organs including the brain and eyes and even the skin [12,29,32,33].

Clinical sign in human

The clinical presentation of cryptococcosis in human varies from asymptomatic pulmonary colonization to severe pneumonia with respiratory failure and meningitis. The patients exhibit the signs of cough, sputum, fever, pleuritc chest pain, and shortness of breath, chest tightness, fatigue, discomfort, malaise, sweating, tachycardia, hypoxia, and weight loss [11]. The frequency of occurrence of clinical signs and symptoms observed. Pulmonary cryptococcosis can also occur in HIV positive patients [34].

Acute respiratory failure may develop in one third of non-AIDS patients with pulmonary cryptococcosis. Pulmonary involvement in non-AIDS patients has been reported in 10% to 29 % in which the disease was diagnosed. In immunocompromised patients, complications of pulmonary cryptococcosis may have pleural effusion, and meningoencephalitis [35]. A presence of acute respiratory failure with cryptococcosis is a grave prognostic sign, and can represent a marker of systemic disease. Hence, it is pertinent to mention that in high risk patients, pulmonary cryptococcosis should be considered in the differential diagnosis of acute respiratory failure [36].

DIAGNOSIS

Clinical signs are not very characteristic to warrant the diagnosis of cryptococcosis. Therefore, mycological examination is recommended to provide a more definitive diagnosis. Radiography, CT scan and MRI may help to locate the lesions in the organ [5]. Clinical specimens such as CSF, sputum, skin exudates, nasal exudates, urine, pus, and tissue aspirate should be examined in India ink or nigrosin for the presence of thick, wide, circular, encapsulated budding yeast cells [7].

Wet smear preparation and impression are also useful to detect the pathogen. Affected tissue biopsies should be macerated with a sterile clean scalpel and be treated with 10% Potassium Hydroxide (KOH) solution before examination. Pal's sunflower seed medium should also be used as it is highly specific and sensitive for *C. neoformans*. In this medium, the diagnosis of cryptococcosis can be easily and rapidly confirmed by observing light to dark brown colonies of *C. neoformans*. The organism can also be recovered on Sabouraud medium at 370°C [5].

The morphology of the cultural isolates could be studied on "Narayan" stain [37]. Microscopically, most clinical isolates appear as thick, spherical, budding, encapsulated (1 µm-30 µm) yeast cells in both tissue and culture. Immunological test mainly latex agglutination is employed for demonstration of cryptococcal

antigen in the serum, CSF, urine and broncho-alveolar lavage. Molecular techniques (PCR, RAPD) have been used in the diagnosis particularly from epidemiological point of view [7]. Animal pathogenicity is performed into the Swiss albino mice by inoculating the culture through intracerebral or intraperitoneal route. The inoculated mice usually die within 7-10 days [38].

TREATMENT

In animal

Cryptococcosis in animals is treated with antifungal drugs such as amphotericin B, flucytosine, itraconazole, fluconazole and ketoconazole. Flucytosine is not used alone, as these results in rapid development of resistance; instead, it is typically combined with amphotericin B. The choice of antifungal agent varies with the species of animal and drug side effects, and with the ability of the drug to penetrate into the affected site. Cost considerations can also be a factor, especially in larger animals. Short courses of anti-inflammatory drugs have been prescribed concurrently in certain cases, to decrease inflammation in critical sites such as the brain. Drug treatment is sometimes combined with surgical excision of a mass. Two upper respiratory tract infections in horses, which are challenging to treat, were apparently eliminated with such combination therapies [13].

In human

Cryptococcosis can be treated with various antifungal drugs including amphotericin B (fluorocytosine), fluconazole and itraconazole. Standardized treatment recommendations have been published for illnesses caused by *C. neoformans* and *C. gattii*. The recommended drugs and duration of treatment vary with the site affected and the immune status of the individual. Supportive therapy may be needed to treat conditions such as dangerously elevated intracranial pressure in patients with CNS disease. Surgery is occasionally used to reduce the size of a mass lesion [39].

Immunocompetent, asymptomatic patients may or may not be treated if the infection is confined to the lungs, as these infections are usually self-limiting. There is still little experience in treating infections with other Cryptococcus species, but antifungal drugs were used successfully in some cases. Removal of any predisposing cause, such as an indwelling catheter, is expected to help the condition resolve [13].

Immune reconstitution syndrome can sometimes complicate the treatment of cryptococcosis. This syndrome occurs when immunity is boosted in a patient who was previously immunosuppressed (e.g., a pregnant patient after delivery or an HIV-infected person treated with antiviral drugs). The subsequent overly robust immune response to Cryptococcus can exacerbate the symptoms and may even be fatal. Concurrent anti-inflammatory medications are sometimes needed to treat this condition. After treatment, some immunosuppressed patients must be maintained long term or lifelong on antifungal drugs, to prevent latent infections from recurring [39].

PREVENTION AND CONTROL

In animal

Whether there are no any effective methods of preventing. cryptococcosis is uncertain, as *C. gattii* and *C. neoformans* are widespread in environments such as avian feces, rotting wood and soil, and risk factors for illness are still poorly understood. Although some factors (e.g., soil disturbances) seem to increase the risk of cryptococcosis, clinical cases occur even in pets kept indoors. It should be kept in mind that many animals are probably exposed frequently, but do not become ill [13].

Environmental modifications may be considered in certain situations. Some sources suggest that eucalyptus tree should be avoided with kiwis, as *C. gattii* caused fatal cryptococcosis. Environmental modification was also used at the Antwerp Zoo, when cryptococcosis occurred in an indoor exhibit, and *C. neoformans* was detected in a tree trunk, tree-stumps, and decaying wood in that exhibit, but not in surrounding areas. In this case, the contaminated objects were removed and replaced. Cryptococcal mastitis in cattle is usually associated with treatment of the mammary gland for another condition. Care should be taken not to contaminate syringes, cannulas or antibiotic preparations. The teat ends should also be adequately prepared before treatment [40].

In human

Complete prevention of exposure is probably impossible. *C. neoformans* is ubiquitous, while *C. gattii* has now been identified in a variety of climates, in and around many species of trees. Despite the frequency of exposure, most people do not become ill. In some circumstances, it might be possible to decrease the level of exposure from some environmental sources, such as bird droppings (especially pigeon droppings), trees during logging and cutting, eucalyptus trees in bloom, and soil disturbances [13].

Removal of guano should be preceded by chemical decontamination or wetting with water or oil to decrease aerosolization. Although no cases of animal-to-human transmission have been reported (except *via* avian feces in the environment), it is prudent to use caution when handling animals with cryptococcosis. People handling such animals should use appropriate barrier precautions, including avoidance of accidental inoculation into breaks in the skin. Cages and litter boxes should be decontaminated regularly. Targeted screening of immunosuppressed individuals, using tests that detect cryptococcal antigens, might identify disseminated infections in the early stages when they are most readily treated [41].

ROLE OF INTERNATIONAL ORGANIZATIONS

The World Health Organization (WHO) released "rapid advice" guidelines for cryptococcal disease among persons living with HIV which are focused on RLS. Early diagnosis is keys to reducing mortality due to cryptococcal disease. A major WHO recommendation is to consider implementation of cryptococcal antigen screening and pre-emptive anti-fungal therapy in those with a positive diagnostic test [42]. The recommendation is supported by epidemiological and clinical studies demonstrating a high prevalence of cryptococcal antigenemia increased one-year mortality in patients with cryptococcal antigenemia, and the cost effectiveness of screening and treatment of HIV-infected patients with cryptococcal antigenemia. Additionally, data demonstrating cryptococcal antigenemia may precede the development of CM by up to 22 days add to the scientific rationale of a screen and treat strategy [43].

CRYPTOCOCCOSIS STATUS IN ETHIOPIA

There is no any research done on animal criptococcus in Ethiopia but in human, over all prevalence of cryptococcal antigenaemia ranges from 6% to 11.7% among HIV/AIDS patients [44-48]. The prevalence of Cryptococcosis among HIV/AIDS patients attending two Western Oromia hospitals was (7.7%) another study conducted in Addis Ababa was 8.4% [45]. But this result is higher

Table 1: Prevalence Cryptococcosis disease among hospitalized HIV infected in Ethiopia.

Diseases	Population	Prevalence	Reference
Cryptococcosis	Cryptococcal antigen HIV infected persons <150 CD4 cells/L	6.20%	[44]
	Cryptococcal antigenemia among HIV-infected patients receiving antiretroviral therapy in Ethiopia	8.40%	[45]
	Cryptococcal disease among hospitalized HIV infected adults in Ethiopia	9.10%	[46]
	Cryptococcal antigenemia ART-naïve and experienced HIV-infected persons	10.20%	[47]
	Cryptococcal antigenemia among HIV-infected patients at a referral hospital	11.70%	[48]

than a study conducted in North West Ethiopia (0.5%) However, it lowers than the reported prevalence of 10.2% from South East Ethiopia [47] (Table 1).

CONCLUSION

Cryptococcosis is infectious opportunistic mycosis disease that affects both human and animals, chiefly caused by *C. neoformans* which occurs as a saprobe in wide variety of environmental substrates. The infection is acquired through respiratory tract by inhalation of highly infectious yeast cells from saprobic reservoirs. Cryptococcal meningitis is common among patients with immune-suppression. It could be the initial manifestation of HIV infection and should be suspected in any potential HIV infected patient with neurological symptoms especially headache and fever. Early diagnosis and prompt chemotherapy is necessary to reduce the morbidity and mortality due to this life threatening fungal zoonosis.

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