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Emerging role of *Aspergillus flavus* in human and animal disorders

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Fungi have emerged as a major public health problem both in developing as well developed countries. Among the fungi, *Aspergillus flavus*, is recognized as an important pathogen that has the potential to cause infections in plants, humans and animals including birds. The infection due *to A. flavus* can occur in sporadic and epidemic form, and is recorded from many countries of the world including India. *A. flavus* can produce disease both in immunocompetent,and immunocompromised hosts. The fungus is widely distributed in the environment, and is recovered from the soil, air, water, and plant materials. The source of infection is exogenous; and humans and animals can acquire the infection by inhalation of the infectious fungal spores from the saprobic environment. The fungus can attack on various tissues including the skin, eye, heart, brain and joint. The tissue damage is more severe in those whose immunity is compromised due to any reason. The disease in animals and plants has economic implications. The help of laboratory is needed to confirm the diagnosis of disease. The direct microscopic detection of pathogen in clinical specimens and its isolation in pure growth still remains the simple and cheap gold standard method for diagnosis of fungal infection. The pathogen is highly virulent and more resistant to antifungal drugs. However, itraconazole and voriconazole have been tried in clinical management of the disease. It is advised that immonocompromised persons must avoid dust environment and use face mask to prevent the exposure to *A.flavus*. The early diagnosis and prompt therapy is imperative in immunocompromised patients to prevent the fatal outcome of disease. The additional studies on the pathogenesis, chemotherapy and epidemiology of *A.flavus* infection would be rewarding. It is emphasized that the role of *A. flavus* in various clinical disorders of humans and animals should be established. The wider application of "NARAYAN" stain in all the microbiology and public health laboratories to study detailed morphology of fungal isolates for identification of the pathogen is recommended.

Key words: Animal, *Aspergillus flavus*, emerging pathogen, human, Narayan stain, public health

INTRODUCTION

Fungi constitute a very diverse group of organisms that are adopted in a wide variety of environmental and ecological niches. There are about 1.5 million species of fungi that inhabit our planet (Hawksworth, 1991).Currently, as many as 300 fungal species have been associated with humans and animals infections (Pal *et al.*, 2011).Fungi are ubiquitous in distribution ; and are recovered from

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diverse types of substrates such as fruits, vegetables, cereals, rice husk, straw, plant, wood, milk, butter, cheese, red meat, fish, white meat (chicken), compost, sewage, litter, soil, bat guano, pigeon dropping, water , and air (Pal and Matsusaka,1990; Paterson *et al*,1997;Pal,2004a; Pal,2007).Some of the fungi such as *Cryptococcus neoformans* can survive in the pigeon droppings for about 20 years (Pal *et al.*,2014).They are mainly acquired through exposure to a point source in environment where they grow as a saprobe (Pal *et al.*,2011).The respiratory tract is recognized as the primary mode of transmission in most of the fungal infections (Pal, 2007).

In the last decade, many fungi such as *Cryptococcus gattii, Geomyces destructans, Fusarium solani, Aspergillus terreus, A. flavus,Candida glabrata, Batrachochytrim dendrobatidis,* etc. have emerged as significant cause of morbidity and mortality in humans and animals (Nucci and Marr, 2005; Pal *et al.*,2011;Pal, 2014). The term "emerging infection" can be defined to describe an infection which has newly appeared in the population, or one that is rapidly increasing in incidence of geographic range (Morse, 1995; Pal, 2013). In recent years, *Aspergillus flavus* has emerged as a predominant pathogen in keratitis and sinusitis in humans in many regions of the world (Jiujiang *et al.*, 2005; Hedayati et al., 2007). In Middle East, *A. flavus* accounted for 80 % of the total *Aspergillus* keratitis infection (Khairallah *et al.*, 1992).In postoperative Aspergillus endocarditis, 11.2 % of cases were resulted due to *A.flavus* (Pasqualotto and Denning, 2006).Moreover, after *A. fumigatus*, *A. flavus* is the second leading cause of invasive aspergillosis (Denning, 1998).In one study, Mehgoub and El-Hassan (1972) reported that *A. flavus* is one of the main pathogens responsible for pulmonary aspergillosis in Africa. Outbreaks of aspergillosis involving the skin, oral mucosa and subcutaneous tissues are more often associated with *A. flavus* than other species of *Aspergillus* (Myoken *et al.*, 2003; Heinemann *et al.*, 2004).It is also an important species in wound aspergillosis accounting for 41% of cases as confirmed by culture (Pasqualotto and Denning, 2006). A plethora of risk factors for *Aspergillus* infection include neutropenia, cancer, HIV/AIDS, sarcoidosis, cystic fibrosis, asthma, prolonged use of corticosteroid therapy besides hospital stay as the fungus has been isolated from hospital environment (Pal, 2007; Pal *et al.*, 2011).Neutropenia is considered the major risk factor which predispose the host to invasive *Aspergillus* infection (Nucci and Marr,2005). The lung is involved in almost 75 % of *Aspergillus* infection in HIV patients. The haematogenous dissemination of *Aspergillus* from lungs to other sites may occur in 30 % of patients (Pal *et al.*, 2011).The invasive aspergillosis was identified by autopsy in 45 % of allogenic solid organ, and haemopoietic stem cell transplantation (Nucci and Marr, 2005).

In animals, the disease due to *A.flavus* is diagnosed in buffalo, cattle, goat and poultry from India. Pal (1997) is credited to elucidate the etiologic role of *A. flavus* in keratitis of a buffalo calf. The animal received traumatic injury in the eye while grazing in the pasture. The fungus was demonstrated in the corneal scrapings both by direct microscopy and cultural isolation. The pathogen was also implicated as the cause of caprine pneumonia (Pal *et al.*, 1995). Pal and co-investigators (1989) reported systemic aspergillosis in chicks due to *A. flavus*. In addition, it can cause disease in economically important crops such as maize and peanuts, and produce aflatoxins. The ingestion of aflatoxins contaminated products can cause serious health risks to humans and animals (Pal, 2002).The present communication delineates the growing significance of *A. flavus* as an important mycotic agent in human and animal health.

Etiology

There are approximately 600 species of *Aspergillus* of which about 27 have been identified as pathogen causing disease in humans and animals (Pal,2007;Pal *et al.*, 2012).The disease is chiefly caused by *A. fumigatus*, however, other species such as *A. amstelodami, A. candidus, A. chevallieri, A. clavatus, A. deflectus, A. flavus, A. glaucus, A. nidulans, A. phialisepticus, A. niger, A. oryzae, A. restricus, A.sydowii, A. terreus,*etc. are also implicated in disease (Pal,1991; Pal *et al.*, 2002; Pal and Dave,2006;Pal,2007; Pal *et al.*, 2012). *A. flavus* belongs to the genus *Aspergillus*, and it is a haploid filamentous fungus which is found worldwide in the soil (Pal and Matsusaka,1990; Pal,2007). The ability of *A.flavus* to survive in harsh conditions allows it to easily compete with other organisms for substrates in the soil .The fungus can grow in a wide range of temperature from 12 to 48 °C but its optimum temperature for growth is 25-37 °C. The heat tolerance nature of *A. flavus* contribute to its pathogenicity on humans and other warm blooded animals (Jiujiang *et al.*, 2005).The fungus has been recovered from drinking water as it can even survive water disinfection with chlorine (Gonclaves *et al.*,2006).

Host

Naturally occurring aspergillosis due to *A.flavus* has been recorded in humans (Pal and Torres-Rodriguez , 1990; Pal,2007).The infection is also diagnosed in animals which include buffalo, cattle, dog, goat, horse ,and poultry (Pal and Dave, 2006; Pal, 2007; Pal *et al*, 2012). It is emphasized that the etiologic role of *A.flavus* should be investigated in other species of animals.

Transmission

Inhalation *of A. flavus* spores through respiratory tract from the saprobic environment is the chief cause of disease. Direct inoculation of the fungus at the sites of skin injury due to wound, burns, surgical operation, intravenous catheter sites, occlusive dressings can also result infection. *A .flavus* can also enter through cataract surgery, and also laser therapy. Nosocomial infection is also recorded (Pal, 2007).

In animals, besides inhalation of infectious *A.flavus* conidia from the saprobic reservoirs, the use of contaminated semen for artificial insemination, introduction of fungal contaminated drug through intramammary route, traumatic injury with fungal contaminated objects in the eyes, nostril, and ingestion of mouldy feed containing aflatoxin produced by *A.flavus* can also produce disease (Pal, 2007).

Clinical Spectrum

Humans

The fungus *A. flavus* causes a broad spectrum of disease in humans, ranging from hypersensitivity reactions to invasive infections associated with angioinvasion. After *A.fumigatus*, this pathogen is considered the second most important cause of invasive and non-invasive aspergillosis .The fungus is implicated in rhinitis, sinusitis, otitis, keratitis, endophthalmitis, pericarditis, endocarditis, osteomyelitis, stomatitis, sinus granuloma (fungus ball) besides central nervous system infection , skin infection, and wound infection (Lance *et al.*,1988; Khirllah *et al.*,1992; Denning,1998; Rao and Saha, 2000; Alrajhi *et al.*, 2001; Myoken *et al.*, 2003). The clinical presentation of cutaneous *A. flavus* infection is characterized by macules, papules, plaques, nodules, pustules, subcutaneous abscesses, and ulcerations with central necrosis with or without eschar formation (Pal, 2007). Primary cutaneous aspergillosis due to *A. flavus* was diagnosed in a healthy, 45-year-old male agricultural farmer from India. The patient acquired infection following traumatic injury in his right hand while working in the field (P.Dave, Personal Communication).Rarely, *A. flavus* has been associated with chronic cavitary pulmonary aspergillosis ,and also with urinary tract infection (Kueter *et al.*, 2002). Invasive aspergillosis is often fatal in immunocomoromised patients (Pal and Dave, 2006).

The ingestion of *A.flavus* aflatoxin containing food can result into mycotoxicosis. The symptoms of aflatoxicosis in humans include vomition, abdominal cramps, pulmonary oedema, liver damage, convulsion, coma, and death. The ingestion of aflatoxin in low quantity for a prolonged time can produce cancer (Pal, 2002).The growing role of *A.flavus* in mycosis and mycotoxicosis should be further studied.

Animals

This filamentous fungus can produce natural infection in animals including birds (Pal, 2007). However, the infection is contained to cattle, dog, buffalo, goat, and poultry (Pal, 2007). *A. flavus* is one of the filamentous fungi involved in the etiology of mycotic abortion, and mastitis of dairy animals (Pal, 2007; Pal and Jadhav, 2013). Pal and co-workers in 1995 confirmed the etiologic significance of *A. flvaus* in pneumonia of a goat. The pathogen was identified as cause of rhinitis and sinusitis in dogs (M. Pal, Personal Communication).In addition, *A. flavus* was isolated from the nasal exudates of one young female horse and one adult male camel from India (M.Pal, Personal communication).This fungus was first time identified as the cause of keratitis in an Indian buffalo calf by Pal in 1997. The fatal systemic aspergillosis due to *A. flavus* in chicks was reported by Pal and co-investigators (1995). The birds affected with aflatoxicosis exhibit the signs of anorexia, loss of body weight, retarded growth, weakness, dullness, depression, paralysis, and decreased egg production (Pal, 2007). It seems imperative to undertake detailed studies to ascertain the etiologic role of *A. flavus* in other clinical conditions of domestic, farm, zoo, laboratory, and wild animals.

Epidemiology

The epidemiology of mould infections including aspergillosis has changed substantially in the last one decade. The incidence of invasive aspergillosis has increased significantly. Aspergillosis ,caused by mainly species of *Aspergillus* including *A.flavus* ,is one of the highly infectious, most frequently occurring, global mycotic disease of humans, and animals including birds (Pal and Dave, 2006; Pal, 2007; Pal *et al.*, 2012).The disease can occur in sporadic as well as in epidemic form ; and has public health , and economic implications (Pal *et al.*,2012).Among the many species of *Aspergillus* implicated in the etiology of aspergillosis, *A. flavus* has emerged as a predominant pathogen with several clinical syndrome of patients in many countries of the world (Jiujiang *et al.*, 2005; Hedayati *et al.*,2007).In India, the disease due to *A. flavus* has been recorded in humans as well as animals (Pal and Torees-Rodrigues,1990; Panda *et al.*,1998; Pal,2007). People with asthma and cystic fibrosis are more likely to have an allergic response to *A.flavus* , as it can produce many allergenic proteins (Hedayati *et al.*,2007).Many cases of craniocerebral aspergillosis due to *A.flavus* in immunocompetent subjects have been described from several countries including India (Panda *et al.*,1998).Likewise, one study in Saudi Arabia indicated that immunocompetent patients were often affected with rhinosinusitis caused by *A. flavus* (Alrajhi *et al.*,2001).The prevalence of *A.flavus* mould in the hospital environment such as surgical instruments, bedrails, potted plants, air cooler and air conditioner dust pose a serious risk to the people with a weekened immune system. *A.flavus* is the predominant species responsible for mycotic keratitis in tropical and warm climates; and the trauma mainly with plant material is considered the major predisposing factor for the development of keratitis due to *A. flavus* (Pal, 1987; Khairallah *et al.*, 1992). It is pertinent to mention that most cases of cutaneous aspergillosis, and also wound aspergillosis are attributed to *A. flavus* (Pasqualotto and Denning, 2006).Certain occupational groups such as poultry farmers, bird keepers, agricultural workers, garderners, etc. seem to be at a greater risk of acquiring aspergillus infection (Pal and Torres-Rodrigues, 1990; Pal and Dave, 2006) Nosocomial outbreaks of aspergillosis are traced near the hospital or construction work (Pal and Dave, 2006).

Diagnosis

As clinical symptoms are not pathogonomic, the help of laboratory is needed to confirm the diagnosis of aspergillosis. The radiography, computed tomography (CT), and magnetic resonance imaging (MRI) can help to detect the lesions particularly the aspergilloma (Pal, 2007). Slit lamp may be useful to have detailed examination of eye. Rhinoscopy can be performed in humans and small pet animals to reveal fungal mass in the nasal cavity. Fungi can be demonstrated in the clinical specimens by potassium hydroxide technique (Pal, 2007). Giemsa technique is found very useful to detect fugal elements in the corneal scrapings (Pal, 2007). The cytological examination of biopsied tissues with periodic acid Schiff (PAS) technique can reveal the presence of the fungal agent (Pal, 2007). *A. flavus* can be easily isolated from a variety of clinical samples such as ear swab, nasal exudates, corneal scrapings, pus, sputum, cerebrospinal fluid, milk, semen, lung, brain, trachea, skin biopsy, etc. on Sabouraud dextrose agar with chloramphenicol (Pal, 2007). It is important to mention that cycloheximide should not be incorporated in the medium as it inhibits the growth of *A .flavus* (Pal, 2007).The pathogen can also be recovered on Pal sunflower seed medium. This medium was originally formulated by Pal in 1980 to isolate *Cryptococcus neoformans* from clinical and environmental materials (Pal *et al.*,2014).The detailed identification of *A. flavus* is based on gross colony morphology, colour, and microscopic features in "PHOL" stain (Pal *et al.*, 1990) or "NARAYAN" stain (Pal,2004b). Hypersensitivity skin test is also performed to diagnosis aspergillosis. Serum antibodies against *A. flavus*, and other *Aspergillus* species are detected by agar gel immunodiffusion (AGID), counter immuno-electrophoresis (CIE), and enzyme linked immunosorbent assay (ELISA) both in humans and animals (Pal, 2007).Recently, use of molecular tools such as repetitive DNA probe has been tried for typing of *A.flavus* isolates from cutaneous lesions in a neonatal intensive care unit (James *et al.*, 2000).

Treatment

Surgery is recommended as the first option to remove the fungal mass from the sinuses and lungs. Medical management of *A.flavus* endocarditis is described by Rao and Saha (2000). Amphotericin B, itraconazole, and voriconazole have been used with varying success rate. Primary cutaneous aspergillosis due to *A.flavus* in an immunocompetent patient was successfully treated with intraconazole (P.Dave, Personal Communication).In canine nasal aspergillosis, ketoconazole has been tried (Pal, 2007). As all the systemic antifungal drugs show side effects mainly on the liver and kidney, it is, therefore, necessary that patients with weak immune system should be monitored by liver function and kidney function tests. Further research on the development of potent, safe and cheap drugs for the treatment of *A. flavus* and other fungal infections would be rewarding.

Prevention and Control

As *A.flavus* is abundantly and widely prevalent in nature, it seems impracticable to eradicate the infection from the world. Immediate attention to traumatic injury can prevent the fungi to show its pathogenic potential. In addition, early diagnosis and prompt therapy are helpful to mitigate the severity of disease The persons working in poultry farms, old monuments, construction areas, zoological gardens, composting plants, waste disposal grounds, hospital, litter cleaning sites, food grains store houses, and other dusty places should use face mask to prevent the entry *of A flavus* spores (Pal, 2007; Pal *et al.*, 2012).The immonocompromised individuals must stay away from the highly polluted sites that may pose hazard to them. Moreover, they are advised to wear protective clothing before entering to such risky areas. The periodical fumigation of such polluted sites can certainly reduce the chance of *A.flavus* infection in the immediate environment. Keeping of ornamental plants in the residence of compromised patients should be avoided, as several species of *Aspergillus* have been recovered from the soil of the potted plants (Pal, 2004a).

In animals, certain measures such as regular decontamination of hatchery, brooder pen, kennel, and feed store ,proper sterilization of dairy equipments, sanitary measures during intramammary infusion, avoidance of mouldy feed particularly to pregnant dairy animals, keeping the animals in properly ventilated pens, storage of animal feed in dry and clean well ventilated room, and mycological examination of semen before artificial insemination will certainly reduce the incidence of *A.flavus* infection in animals (Pal,2007;Pal *et al.*,2012).

Conclusion

In recent past, several fungi including *A. flavus* have emerged causing a great challenge to the medical and veterinary professionals. The early recognition and treatment are fundamental to modifying disease outcomes in many fungal infections, especially those in immonocompromised individuals. The active surveillance of the emerging mycotic pathogens is warranted to protect the human and animal health. The cordial association of many specialists such as physician, surgeon, veterinarian, pathologist and mycologist is highly imperative for the better management of the mycoses which pose a global threat. The continuous education programme of the public to create greater awareness about the increasing role of fungi in human and animal diseases is emphasized. As some of the mycoses are life threatening and fulminating, therefore, sincere attempts must be made to develop the safe and potent vaccine to protect the high risk groups, and the vulnerable population against the fungal diseases. It is recommended that simple, easy and low cost diagnostic techniques should be discovered that can be widely employed by poor resource countries to confirm the rapid and correct diagnosis of fungal infections both in humans and animals.

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