

Growing Significance of Non-Dermatophytic Fungi in Cutaneous Disorders of Humans and Animals

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Abstract

Fungi are versatile groups of eukaryotic organisms that have the potential to infect plants, humans and animals including birds. They can invade any organ of the body i.e. from skin to brain. Cutaneous mycoses, caused by dermatophytes, yeasts, and non-dermatophytic fungi, are important from public health and economic point of view; and are generally encountered both in medical and veterinary clinical practice. The cases of cutaneous mycoses are encountered in immunocompromised and also in immunocompetent subjects. The infection mostly occurs in sporadic form but rarely, small outbreaks are also observed. The growth of non-dermatophytic fungi on the cutaneous and external parts of the body of human beings and animals causes many dermatological problems. Non-dermatophyte fungi can colonize and invade the keratin of skin, nail, and hair. The natural infection is reported in humans, and also in a number of animal species. The source of infection in most cases is exogenous. The transmission occurs through the advent of the organism via superficial trauma, lacerated injury or punctured wound because of fungal infected objects from saprobic surroundings where these organisms exist as saprophytes. The symptoms depend on the species of fungus and health status of the host. The direct demonstration of the fungal agent in clinical specimens and its isolation in pure and luxuriant growth still remains the gold standard of diagnosis. A variety of chemicals and drugs are available to treat fungal dermatitis. Treatment depends upon the extent, site and severity of infection. Limited information is available on non-dermatophytic fungi affecting humans and animals. Therefore, researches, communications and thorough reviews are needed on non-dermatophytic fungi, which are implicated in cutaneous mycoses of humans as well as animals.

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Received: 27/05/2020

Accepted: 12/06/2020

Keywords: Animal, Cutaneous disorders, Human, Non-dermatophytic fungi, Traumatic injury.

1. Introduction

The skin is the largest organ of the body, which accounts for 16 to 20% of the total body weight. Human skin is of two types, one hair bearing and other non-hair bearing like sole and palm. Further, the skin is composed of epithelial tissue (epidermis and dermis), adipose tissue (hypodermis), and accessory structures (hair, nail, glands, and sensory receptors). The skin plays an important role in protecting the body against microbes that cause disease in humans and animals (Pal, 2015). The incidence of fungal infection is increasing at an alarming rate and therefore, poses a challenge to medical and veterinary professionals. Superficial cutaneous mycoses represent one of the most common dermatological diseases that affect around 20 to 25 % population of the world (Havlickova *et al.*, 2008). Cutaneous mycoses are mostly

encountered in sporadic form, and are observed both in immunocompromised as well as immunocompetent hosts (Dave and Pal, 2015a; Dave *et al.*, 2015). The superficial fungal skin infections of the skin caused by dermatophytes, yeasts and non-dermatophytes, constitute an important public health problem throughout the world (Pal, 2007; Pal, 2015). Dermatitis is an infectious, cosmopolitan, superficial mycosis of humans and a variety of animals (Rochette *et al.*, 2003; Baumgardner, 2017). Many cases of cutaneous mycoses revealed history of traumatic injury to the skin (Dave *et al.*, 2015). In this context, Dave and Pal (2015a) described a case of primary cutaneous mycosis in a parrot keeper due to *Cryptococcus neoformans*. The patient indicated that he received injury on the skin during the act of cleaning the wooden cage of parrot. The diagnosis was confirmed both by direct microscopic detection of *Cr.neoformans* in biopsied

tissue in India ink as well as isolation of the pathogen from cutaneous lesions on Pal sunflower seed medium. Retrospective epidemiological investigation confirmed that patient acquired the infection from the immediate environment as revealed by the presence of *Cr. neoformans* in the droppings and wooden cage of the caged parrot kept by the bird enthusiast (Dave and Pal, 2015a). Likewise, Dave and co-investigators (2015) diagnosed primary cutaneous aspergillosis due to *Aspergillus terreus* in an agricultural worker who gave a history of receiving traumatic injury with wooden splinter when planting in the field. Non-dermatophyte pathogens are filamentous fungi with recognized habitats in soil, avian excreta, wood, vegetables, decaying plant materials etc. (Gupta *et al.*, 1998). Historically, non-dermatophyte filamentous fungi have been taken as contaminant or secondary pathogens of the pores and skin and nails; but, some of them may behave as primary pathogens (Iorizzo *et al.*, 2007; Pal, 2015). The aim of this manuscript is to review the emerging role of non-dermatophytic fungi affecting humans and animals.

2. Etiology

A large number of non-dermatophytic fungi, such as *Absidia corymbifera*, *Acremonium kiliense*, *Alternaria alternata*, *Aphanoascus fulvescens*, *Aspergillus candidus*, *A. chevalieri*, *A. flavus*, *A. fumigatus*, *A. niger*, *A. tamarii*, *A. terreus*, *A. ustus*, *Aureobasidium pulluans*, *Batachochytrium dendrobatidis*, *Bipolaris spicifera*, *Candida albicans*, *C. guilliermondii*, *C. krusei*, *C. parapsilosis*, *C. tropicalis*, *Chaetomium globosum*, *Cladophialophora bantiana*, *Emmonsia pasteuriana*, *Exophiala attenuate*, *E. equina*, *E. jeanselmei*, *E. rostratum*, *E. spinifera*, *Fonsecaea compacta*, *F. multimorphosa*, *F. pedrosoi*, *Fusarium laceratum*, *F. oxysporum*, *F. solani*, *Geotrichum candidum*, *Locazia loboi*, *Malassezia furfur*, *M. globosa*, *M. pachydermatis*, *M. sympodialis*, *Microascus cinereus*, *Ochroconis humicola*, *Paecilomyces lilacinus*, *Phaeoannellomyces elegans*, *P. werneckii*, *Philophora bubakii*, *P. parasitica*, *P. repens*, *P. verrucosus*, *Phoma hiberica*, *P. eupyrena*, *Pseudoallescheria boydii*, *Pseudogymnoascus destructans*, *Rhizomucor pusillus*, *Rhizopus arrhizus*, *R. microspores*, *R. variabilis*, *Rhodotorula glutinis*, *Saksenaea vasiformis*, *Sarcinomyces phaemuriformis*, *Trichosporon beigilii*, *Ulocladium chartarum*, *Wangiella dermatitis*, and *Xylohypha emmonsii*, are found to be associated with dermatological/cutaneous disorders of humans as well as animals (Pal and Mehrota, 1983; Pal and Dahiya, 1984; Baes and Van Cutsem, 1985; Pal *et al.*, 1991; Pal and Lee, 1994; Pal, 1995; Walsh, 1995; Body, 1996; Pal and Lee, 1997; Romeo *et al.*, 1998; Pal and Rao, 1999; de Hoog *et al.*, 2000; Maser *et al.*, 2002; Pal *et al.*, 2002; Ungpakoran, 2000; Khander *et al.*, 2005; Robertshaw and Higgins, 2005; Padmaja *et al.*, 2006; Hay, 2007; Neoh *et al.*, 2007; Pal, 2007; Chander, 2009; Zhao *et al.*, 2009;

Brinca *et al.*, 2011; Dave and Pal, 2015a; Dave *et al.*, 2015; Guillot *et al.*, 2015; Pal *et al.*, 2015; Pin, 2017; Xiaoyan *et al.*, 2017; Sreepurna and Kindo, 2018; Pal, 2020).

Some of the systemic mycosis, such as blastomycosis, coccidioidomycosis, histoplasmosis, paracoccidioidomycosis and sporotrichosis also manifest with primary cutaneous lesions (Rutland and Horenstein, 2005; Pal, 2007; Chander, 2009; Pal and Dave, 2017).

Most of the causative agents of dermatitis are opportunistic pathogens, and are ubiquitously disbursed in nature. The organisms are recovered from a wide variety of environmental materials, which include air, soil, avian excreta, litter, bat guano, woods, fruits, vegetables, cereals, and different plant substrates. These opportunistic fungi develop, multiply and live in saprophytic materials (Pal, 2007; Dave and Pal, 2015a; Viegas *et al.*, 2015).

3. Host and Transmission

The natural infection due to non-dermatophilic fungi has been documented by several investigators in humans, and also in several animal species, such as alpaca, bear, bat, buffalo, camel, cat, cattle, chicken, donkey, frog, deer, dog, dolphin, goat, horse, leopard, pig, pigeon, rabbit, rhinoceros, toad, tortoise etc (English, 1968; Pal and Dahiya, 1984; Pal, 1995; Pal and Rao, 1999; Pal, 2003; Pal, 2007; Guillot *et al.*, 2015; Pin, 2017; Pal, 2019). In majority of instances, transmission occurs through the advent of the microorganism via superficial trauma, lacerated injury or punctured wound because of fungal infected objects from the saprobic surroundings where these organisms exist as saprophytes. However, yeast like *Candida* and *Malassezia* arise as normal inhabitants of the pores and skin, ear, gastrointestinal tract, and vagina. Both commensal yeasts can cause superficial fungal infection of the skin (Borges *et al.*, 2006). Minor breach or maceration of the skin might also permit the entry of the fungal agent into host. People who have the dependency of regularly contaminating the finger with saliva, are at a more risk of acquiring cutaneous candidiasis (Richardson and Edward, 2000; Gupta *et al.*, 2005).

4. Epidemiology

Dermatitis, a disorder of numerous etiologies, such as viruses, bacteria, fungi, algae, and parasites, is cosmopolitan in distribution (Dave and Pal, 2015a; Pal, 2017; Pal *et al.*, 2019). The prevalence of superficial fungal infections is rising in many parts of the world. A growing global immunocompromised population in the world has caused dramatic rise in incidence of fungal infections. The infection due to non-dermatophilic fungi are reported from many countries of the world including India (Pal, 2007; Chander, 2009; Dave and Pal, 2015a; Dave *et al.*, 2015). Cutaneous mycosis usually occurs in sporadic forms, but sometimes

outbreaks involving more number of persons or animals are also recorded (Songer and Post, 2004; Pal, 2007; Dave and Pal, 2015a). The infection has been reported from nearly every country of the world where the laboratory facilities of mycological investigation are available. Many cases of fungal dermatitis both in humans as well as animals are described from India (Pal, 1995; Pal, 2003; Pal, 2007; Dave *et al.*, 2014; Dave and Pal, 2015a).

The infection can be primary in origin or secondary to haematogenous dissemination. There is no racial predilection in the occurrence of disease. The infection seems to be more in adult males. All age groups are affected. Previous trauma, maceration to the pores and skin, hot humid climate, malnutrition, immoderate sweating, concurrent diseases (diabetes mellitus, HIV/AIDS), and immunosuppressive therapy may additionally act as predisposing factors for the flare up of infection (Richard *et al.*, 1994; Pal, 2007; Chander, 2009; Dave and Pal, 2015; Baumgardner, 2017).

Cutaneous candidiasis is recognized as the frequent cause of diaper rash in infants. Maceration and wet diapers predispose the infants to diaper candidiasis, which is also known as napkin candidiasis (Chander, 2009). Most instances of cutaneous candidiasis occur inside the skin fold or wherein occlusion from clothing or medical bandage produces extraordinary moist situations. The perianal candidiasis usually observed in young infants (Chander, 2009). Cutaneous zygomycosis generally described in patients who have ulcers in diabetes, severe burns, gangrenous cellulitis (Chander, 2009). Ledgard and co-workers (2008) reported primary cutaneous zygomycosis in a burn patient. Likewise, colonization of bun wound in cattle with *Trichosporon beigeli* is described by Pal and others (1991). Cases of primary cutaneous mycoses due to *Aspergillus terreus* and *Cryptococcus neoformans* are reported from India (Dave and Pal, 2015a; Dave *et al.*, 2015). There are evidences to believe that humans and animals may acquire the infection from the saprobic reservoirs (Pal, 2007).

Cutaneous mycotic diseases of animals cause heavy economic loss to the livestock industries because of poor quality of hide, skin, wool, and fur (Pal, 2007). The animals housed in dark, humid, ill-ventilated sheds are more susceptible to fungal contamination. The infection produces extensive morbidity however, fatality is reported minimum. In animals, the disorder is of superb monetary significance, as it consequences into heavy financial losses to the animal industry due to deterioration of the satisfactory of the skin, cover, wool, fur, hairs. The supply of infection is generally, exogenous because the organisms exist as saprophytes in surroundings, and extensively allotted within the soil, dirt, and decomposing natural be counted (Klotz *et al.*, 2000; Pal, 2007).

5. Clinical Spectrum

5.1 Humans

Clinical presentation of lesions may vary in patients depending on the species of fungus, and immune status of the host. In humans, the lesions may be discrete, multiple, flat, elevated, erythematous, scaly, crusted, ulcerated, nodule, macule, papule, vesicle, pustule, abscess, warty, hyperkeratotic, plaques, hyperpigmented, hypopigmented, circumscribed vegetative plaque, circular to irregular patches, verrucose, acneform, lichenified, eczematized, cyst, fistula, etc (Pal, 2007; Dave and Pal, 2015a; Dave *et al.*, 2015). The incubation period is highly variable, and lesions may occur on the arms, hands, legs, feet, back, face, neck or other body sites. The infection is mostly localized but sometimes generalized condition is also noticed (Pal, 2007). Signs and symptoms induced by various dermatophytic and non-dermatophytic infections are clinically indistinguishable from each other (Kaur, 2017).

5.2 Animals

The affected animals exhibit papule, vesicle, pustule, ulcer, erythema, nodule, abscess, exudation, scale, crust, pruritis, alopecia, etc. The lesion may be discrete or multiple and occur on any part of the body. Generalized skin lesions are also noticed. The disease may be primary or secondary. When it is mixed with dermatophytic fungi or other bacterial pathogens it may cause severe disease that may result in death of the affected animal (Pal, 2007; Pin, 2017).

6. Diagnosis

The diagnosis depends on the demonstration of organism in the skin scrapings, crusted material, pus, skin biopsy, exudates, aspirate from cysts, curettage of plaques and nodules in KOH wet mount under light microscope (Gupta *et al.*, 2003; Pal, 2015). The pathogen is isolated from clinical specimens on Sabouraud medium, brain heart infusion agar, blood agar, Pal's sunflower seed medium (Pal, 1997) and APRM (Anubha, Pratibha, Raj, Mahendra) agar (Dave and Pal, 2015b). The identification of the agent is made by studying cultural, morphological, physiological, and biochemical characteristic. The detailed morphology of the fungi isolated from cutaneous lesions can be easily studied in PHOL (Pal, Hasegawa, Ono, Lee) stain (Pal *et al.*, 1990) or Narayan stain (Pal, 2004). The biopsy tissue is subjected to histopathology for the detection of pathogen by staining with haematoxylin eosin (H, periodic acid-Schiff (PAS), Grocott methamine silver (GMS), Griedley (GS) methods (Pal, 2007; Guillot *et al.*, 2015). Fungal elements are stained black and pink by GMS and PAS technique, respectively (Pal, 2007). Immunological tests are of not of much significance in the diagnosis of fungal dermatitis (Elewski, 1998; Jaffe, 1998; Pal, 2007; Moreno and Arenas, 2010). Currently, molecular techniques are also applied for the diagnosis of fungal infections (Pal, 2007).

Identification and characterization of fungus by in vitro culture on mycological media is warranted for

proper diagnosis, treatment, and understanding of epidemiological characteristics of a region. Additionally, the importance of microscopy and culture is highlighted and it is stressed upon to understand and manage the locally prevalent fungi involved in the causation of disease and their control, helping in decreasing the drug resistance and morbid outcomes (Yehia *et al.*, 2010; Kaur, 2017). The set criteria for the diagnosis of mycosis due to non-dermatophytic moulds are: 1) observation of fungal elements in 20% KOH-preparations made from nail and skin scraping; 2) growth of the same mould in all three consecutive cultures of specimens taken three times from the same patient with one-week intervals; 3) no growth of a dermatophyte or yeast in three consecutive cultures (English, 1976; Pal, 2007; Pal, 2015). It should be differentiated from other cutaneous diseases like dermatophytosis, psoriasis, scabies, eczema, demodicidosis, Herpes simplex, dermatophilosis, bacterial folliculitis, impetigo, contact dermatitis, ecthyma, pyoderma, Herpes zoster, acne vulgaris, rosacea, leprosy, and leishmaniasis etc (Pal, 2007; Pal, 2015).

7. Treatment

Topical antifungal drugs play a significant role in the treatment of cutaneous mycoses, especially when infection is localized and uncomplicated. Further, topical agents are considered safe in infancy, pregnancy, lactation and systemic co-morbidities like severe renal and liver disorders. A variety of topical chemicals and drugs such as gentian violet, mercurochrome, tincture of iodine solution, nystatin, miconazole, clotrimazole, bifonazole, econazole, ciclopirox olamine, terbinafine, eberconazole, efinaconazole and are used in the chemotherapy of fungal dermatitis (Pal, 2007). In case of wide spread or generalized infection, systemic therapy with ketoconazole, fluconazole, itraconazole, posaconazole, voriconazole, and liposomal amphotericin B should be done (Pal, 2007; Dave and Pal, 2015; Dave *et al.*, 2015; Xiaoyan *et al.*, 2017; Sreepurna and Kindo, 2018; Sato *et al.*, 2019). Similarly, parenteral administration of these drugs is recommended in immunocompromised patients to save the life. In this context, Gupta and co-investigators (2005) reported in vitro activities of posaconazole, ravuconazole, terbinafine, itraconazole and fluconazole against dermatophyte, yeast and non-dermatophyte species. In untreated person, the infection may be severe (Ellis *et al.*, 1997; Pal, 2007).

8. Prevention and Control

It is very imperative to give immediate attention to traumatic injury on the skin to prevent implantation of infectious organisms from saprobic materials in environment. Certain occupational groups, such as

dairy farmers, agricultural workers, gardeners, brick manufactures, farm laborers, and others who have direct contact with the soil and other plant objects should avoid injury of their body, and also use protective wears while working. Prompt treatment is advised in immunocompromised patients. Excessive sweating and continuous moistening of the skin should be avoided (Pal, 2015). The people should be educated about the personal hygiene, especially the care of the skin. The animal should be housed in dry, well-ventilated, un-humid sheds. The overcrowding of the animals is also to be avoided (Jaffe, 1998; Pal, 2007; Pal, 2015).

9. Conclusion

The cutaneous mycoses caused by non-dermatophytic fungi, has been reported globally both in humans and animals. Most of the fungi, which are implicated in the etiology of cutaneous mycoses, occur as saprobe in wide variety of environmental materials including the soil, manure and plant materials. The source of infection in most cases is exogenous, transmission mainly occurs through superficial trauma, and lacerated injury. The fungi cause various cutaneous disorders in humans and animals mostly affecting the keratin layers of the body. Correct diagnosis requires the help of the laboratory. Topical and systemic therapy with antifungal drugs is needed to treat the patients. The early diagnosis and prompt treatment is advised in immunocompromised patients to reduce the complications of disease. The wider application of Pal sunflower seed medium and Narayan stain in public health and microbiology laboratories is recommended to studying fungi that are associated with fungal dermatitis. Further studies on the growing role of opportunistic fungi in the various cutaneous disorders of humans as well as animals should be conducted.

Acknowledgements

The authors are highly grateful to Prof. Dr. R.K. Narayan for his suggestions in manuscript. The computer help of Anubha Priyabandhu is very much appreciated

Author's Contribution

All the authors contributed equally. They read the final version, and approved it for publication.

Source of Financial Grant

There was no financial support.

Conflict of Interest

The authors declare that they have no conflict of interest.

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Cutaneous Fungal Infections mechanism - Free download as Powerpoint Presentation (.ppt), PDF File (.pdf), Text File (.txt) or view presentation slides online. tugas ppt sangat rahasia.Â Onychomycosis (infection of nails caused by non-dermatophytic fungi and yeasts). Most commonly caused by *T. rubrum*, then *E. floccosum* or other Trichophyton species. Resistant to treatment, rarely resolves spontaneously.Â Causes severer infections in humans on the scalp and beard. Very slow growing, no pigment on reverse to yellow. Grows best at 37 C. On unenriched media - chains of chlamydoconidia and antler-like hyphae. On thiamine-enriched media, produces many small microconidia and occasionally macroconidia are produced. Trichophyton verrucosum. Arthroderma insingulare is a geophilic fungus of worldwide distribution which may occur as a saprophytic contaminant on humans and animals. Durie and Frey (1957) first described this soil fungus as Trichophyton terrestre from New South Wales, Australia. Since then *T. terrestre* has been described as an anamorph of three different species of Arthroderma; *A. insingulare*, *A. lenticulare* and *A. quadrifidum* (Padhye and Carmichael, 1972).Â Aspergillus terreus occurs commonly in soil and is occasionally reported as a pathogen of humans and animals. RG-2 organism. Morphological Identification: On Czapek Dox agar, colonies are typically suede-like and cinnamon-buff to sand-brown in colour with a yellow to deep dirty brown reverse. The significance of these findings await further study since other investigators have found MAT1-2 strains switch more readily from mycelial to the yeast form. Guerra and colleagues reviewed forty reports of multiple Histoplasma infections in Brazil since 1946 [27].Â The authors rightly emphasize such accuracy is a pre-requisite for appropriate treatment choice with terbinafine, which is not effective for non-dermatophytic fungi. A Mycopathologica IMAGE by Wei et al.Â Schwartz IS, Wiederhold NP, Hanson KE, Patterson TF, Sigler L. Blastomyces helicus, a new dimorphic fungus causing fatal pulmonary and systemic disease in humans and animals in Western Canada and the United States. Clin Infect Dis. 2018;68(2):188â€“95.