CLINICOMORPHOLOGICAL STUDY OF MYCOTIC INFECTIONS OF SKIN IN IMMUNOCOMPETENT AND IMMUNOCOMPROMISED PATINETS: A 7-YEAR RETROSPECTIVE STUDY

A DISSERTATION SUBMITTED IN PART FULFILMENT OF

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Clinicomorphological study of mycotic infections of skin in immunocompetent and immunocompromised patients: A 7-year retrospective study.

A dissertation submitted in part fulfilment of the regulation for the award of the degree of M.D. Pathology Branch III.

CERTIFICATE

This is to certify that this dissertation “Clinicomorphological study of mycotic infections of skin in immunocompetent and immunocompromised patients: A 7-year retrospective study” is the bonafide work done by Dr.Rushni.S, in part fulfilment of the rules and regulations for the M.D. Branch III (Pathology) Degree Examination of Tamilnadu Dr.M.G.R. Medical university, to be held in April 2017.

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Clinicomorphological study of mycotic infections of skin in immunocompetent and immunocompromised patients- A 7 years retrospective study

ORIGINALITY REPORT

%13	%7	%11	%2
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	Priya Venkatesan. "Evaluation and management of Fungal infections in Immunocompromised patients", Dermatologic Therapy, 1/2005 Publication	%2
2	cmr.asm.org Internet Source	%1
3	www.ncbi.nlm.nih.gov Internet Source	%1
4	www.science.gov Internet Source	%1
5	Gupta, E. Bhalla, P. Khurana, N. Singh, . "Histopathology for the diagnosis of infectious diseases.(Review Article)", Indian Journal of Medical Microbiology, April-June 2009 Issue Publication	<%1
6	Sangoi, Ankur R., William M. Rogers, Teri A. Longacre, Jose G. Montoya, Ellen Jo Baron, and Niaz Banaei. "Challenges and Pitfalls of	<%1

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ABBREVIATIONS

H&E - Haematoxylin & Eosin

PAS - Periodic Acid-Schiff

GMS - Gomori Methinamine Silver

CONTENTS

INTRODUCTION

Introduction

Cutaneous mycotic infections are a common universal problem. Fungal infections of skin are seen in 20-25% of the world's population .(1) The incidence of cutaneous mycoses is rising at an alarming rate, presenting a huge challenge to the healthcare professionals. Increasing population of immunocompromised patients is directly related to increase in the frequency of fungal infection. Fungi occur in the form of yeast, hyphae or dimorph. All fungi may not be pathogenic and the infection may occur in severely ill, immunocompromised or hospitalised individuals. Histopathological examination of tissue for mycotic infection is a rapid and cost-effective means of giving a preliminary or definitive diagnosis of fungal infection (2). Since the immunocompromised population continues to grow, the incidence of fungal infections is increasing. Fungal infections in this patient population signify challenges in diagnosis and management due to atypical clinical presentation. Histopathological examination can offer timely provisional diagnosis of infectious fungal organisms and also remains the only accessible consistent means to identify certain pathogens (3). This study focuses on the dermatopathological aspects of superficial and invasive mycoses with cutaneous manifestation that occur in the immunocompetent and immunocompromised population. Mycoses are classified as superficial, dermal/cutaneous, subcutaneous, or systemic infections depending on the type and degree of tissue involvement and the host response to the pathogen. (4) Superficial mycoses are limited to the stratum corneum and basically elicit no inflammation. Cutaneous infections involve the integument and its appendages, including hair and nails. Infection may involve the stratum corneum or deeper layers of the epidermis or

dermis. Subcutaneous mycoses include a variety of different infections characterized by infection of the subcutaneous tissues generally at the point of traumatic inoculation. Systemic mycoses involve the lungs, abdominal viscera, bones and or central nervous system.

AIM AND OBJECTIVES

Aim

In our current study we aim to classify and assess the prevalence of cutaneous mycoses in our setting and to compare the clinicomorphological features in immuncompetent and immunocompromised patients.

Objectives

1) To do a detailed retrospective histomorphological study of cases diagnosed as cutaneous mycoses over a period of 7 years (January 2008 to December 2009 & January 2011- December 2015) in the department of General Pathology, Christian Medical College Hospital, Vellore.

2) To classify those cases into two groups namely immunocompetent and immunocompromised individuals**.**

3) To compare the cliniomorphological features of mycotic infections of skin between immunocompetent and immunocompromised individuals.

4) To find out the correlation between histopathology and mycological culture report in the diagnosis of cutaneous mycotic infection.

REVIEW OF LITERATURE

Review of literature

Cutaneous mycotic infections of the skin and nails are a common global problem. They are observed commonly in the recent years due to the expansion of at-risk population and use of various treatment modalities that let longer survival of these patients. (2) Cutaneous mycoses affect a large proportion of the elderly population due to metabolic changes which favours these infections in this population (5). Children are commonly affected due to predisposing factors such as overcrowding and low socioeconomic factors (6).

In general, two populations have been at risk for acquiring fungal infections. Individuals who are at increased susceptibility of infection because of their geographic location; and they are referred to as endemic mycoses. The other population includes persons with increased host susceptibility like immunocompromised individuals who develop opportunistic infections. Many immunosuppressed individuals present to the hospital with fungal infections and others develop them while hospitalized (7).

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The increase in solid-organ transplantation and increase in patient survival rate post-transplant has been accompanied by emergence of unusual infections. Cutaneous fungal infections in solid-organ transplant patients present in a variety of nonspecific ways, requiring a high index of suspicion to diagnose correctly and they are a major cause of morbidity and mortality.(8) More effective and newer immunosuppressive regimens and widespread use of antifungal drugs has changed the

type of fungal infections in these populations. Non-albicans species and non-Aspergillus molds infections have become more established. Depending on the type of solid organ transplant the frequency and types of fungal infections varies. Liver transplant recipients commonly present with candidial infections and lung transplant recipients commonly presents with Aspergillus infections. (9) (10) GVHD and infections are the major sources of mortality in bone marrow transplant recipients. (10) In a study done in India by George B Mathew et al at CMCH Vellore in 2004, on infections among allogenic bone marrow transplant recipients, fungal infections formed 15.9%, which included Aspergillus species (69.7%), Candida (22.2%) and Zygomycetes (8.1%) (11). Cutaneous manifestations are common in human immunodeficiency virus (HIV)-infected patients and are connected with significant morbidity and mortality (12). In a study done in HIV infected individuals cutaneous candidiasis were found to be seen in (47%) of the patients and dermatophytoses were seen in 30% of the patients. (13) Mucosal candidiasis is the most common mycoses in HIV-AIDS patients, however the common invasive mycoses affecting them include cryptococcosis, histoplasmosis, coccidiomycosis and penicilliosis (14). The prevalence of fungal infection seems to be higher among diabetic patients. Foot infection accounted for 38% of the mycotic infections in these patients, mostly due to dermatophytes (94%) (15).

Cutaneous fungal infections may be classified as primary and secondary. Primary cutaneous fungal infections involves the sites of skin injury, at or near intravenous access catheter sites and at sites associated with occlusive dressings, burns, or surgery.

Secondary coetaneous fungal infections result either from contiguous extension to the skin from infected underlying structures or from other systemic site through haematogenous spread. Primary infection may further be classified as superficial, cutaneous and subcutaneous infection. Superficial infections are limited to the epidermis, hair, nails and the mucous membrane. Cutaneous mycoses are those disorders that involve the skin and its appendages to a greater degree than do the disease classified as superficial mycoses. Subcutaneous mycoses are fungal infections that primarily involve the dermis and subcutaneous tissue and rarely disseminate in immunocompetent hosts (4). Secondary cutaneous fungal infections are caused by pathogens those that usually cause systemic disease and only secondarily involve the skin. (16) Superficial mycoses include tinea versicolor, piedra and tinea nigra. Cutaneous mycoses includes onychomycosis, tinea capitis, tinea corporis, tinea pedis and candidiasis of skin, mucosa and nails(4). Subcutaneous mycoses include mycetoma, phycomycosis, chromomycosis and sporotrichosis. Systemic invasive fungal infections such as candidiasis, histoplasmosis, cryptococcosis and coccidiomycosis may disseminate to the skin through the blood stream producing a wide variety of cutaneous lesions (17) .

Superficial fungal infections affect millions of people worldwide with an estimated risk of 10–20%.(18) The three most common types are dermatophytoses, tinea versicolor and candidiasis. (19) Dermatophytes are the most frequent causative agents of superficial fungal infections, leading to tinea infections, and they are generally classified according to the body site affected.(18)

Dermatophytoses:

Dermatophytes have a worldwide distribution, being responsible for most of the cutaneous mycoses in both healthy and immunocompromised patients (20). They are a group of fungi that invade the keratinized tissue (skin, nail & hair) of humans and animals. Their infection is commonly referred to as ringworm. Infection is restricted to the dead cornified layers because of the inability of the fungi to penetrate the deeper tissues or organs in case of immunocompetent hosts. (21) This group consists of the genera Epidermophyton, Trichophyton and Microsporum, forming approximately 40 species. Migration of populations has resulted in changes in the distribution of the different dermatophytes. Dermatophytes are acquired through contact of an individual with conidia present in soil, animals or objects. Certain occupations that allow longer contact between conidia and skin for example in farmers and stock breeders, and presence of appropriate humidity and temperature for example in interdigital areas predispose to harbour these infections. (2)

Epidemiology: The prevalence of dermatophytoses has increased worldwide in recent years, mainly in immunocompromised patients.(22) They are the most common agents of superficial fungal infections in the developing countries, particularly in the tropical and subtropical countries like India, where the environmental temperature is relatively high (23). A study in Japan revealed that dermatophytoses was the most prevalent cutaneous fungal infection (89.1%), followed by candidiasis (8.4%) and Malassezia infections (2.4%)(24). In three studies done by Watanabe S, et al , Elmegeed A, et al and Teklebirhan et al, they found that tinea pedis and tinea capitis

(28.6%) were the most common clinical presentation and the least common presentation were tinea cruris (6.6%) and tinea unguium.

There is geographic variation in the distribution of the fungi. Some of the species are widely distributed throughout the world. Trichophyton rubrum accounts for 40% of all dermatophyte infections worldwide. (25) T. rubrum, T.interdigitale, M. canis, M. audoui-nii, T. tonsurans and T. verrucosum are the most common dermatophytoses worldwide. The highest incidence of T. rubrum was reported in Europe, whereas T. mentagrophytes was more commonly reported in Asia (26).

In a study done in India by V K Bhatia et al in 2014, on dermatophytes reveals that the distribution and causative agents of infection are influenced by environmental factors like temperature, humidity and socio-economic factors like poverty, overcrowding and poor hygiene. (27) In one study Trichophyton mentagrophyte was the predominant dermatophyte (63.5%) involved followed by T. rubrum (34.6%). Microsporum gypseum was involved in 1.35% cases (27). In solid-organ transplant population dermatophytoses has been estimated to affect about 40% of renal transplant recipients. T. rubrum infection involving dermis is not common but may occur as a result of immunosuppression(14). In a study done in north India by Sunil Dogra et at al, tinea capitis was found to be most common (46%), followed by pityriasis versicolor (23.6%), tinea corporis (19.2%), and tinea pedis (11.2%)(28) . In a study done on paediatric patients in India by Bhatia V et al, infections contributed 63.5%, of which pediculosis capitis was seen in 20.4% of children, followed by pyoderma in 16.07%

and dermatophytoses in 6.61% (29). In a study done by B Devi et al, at Impala in India it was found that fungal infections (17.19%) was the second most commonest dermatological disorder after eczema in which dermatophytoses (13.82) was the commonest fungal infection followed by pityriasis versicolor (3%) , candidiasis(0.33%) and deep mycosis (0.02%) (30).

Etiology & Pathogenesis: Many predisposing conditions for dermatophytoses include mucocutaneous candidiasis, AIDS, treatment with corticosteroids, malnutrition and disorder of the immune system. Xerosis was one of the most common factor leading to dermatophytoses.(31) School children between the age group 4-16 years, public bathers, athletes, military men and diabetics are prone for dermatophytoses. (32) Dermatophytes are fungi that invade the keratin of immunocompetent and immunosupressed hosts by virtue of their keratinolytic proteases (2). After inoculation at the skin site, adherence and penetration are the two important stages which are necessary for the infection to progress (33). The fungi express carbohydrate-specific adhesions that allow attachment to epithelial cells, and they produce multiple serine- subtilisins and fungalysin that allow digestion of the keratin network .(2) The mucolytic enzymes help in penetration and they also provide nutrition to the fungi, the mechanism of which is unknown. The alkaline metabolic products of fungus diffuse through the malphigian layer and cause erythema, vesicle or even pustule formation along with pruritis. Acute dermatophytoses is associated with a delayed type hypersensitivity reaction against them, while persistent disease is associated with immediate hypersensitivity response and with high levels of IgE and

IgG4 antibodies, and the production of Th2 cytokines by mononuclear leukocytes (33).

Clinical presentation: Dermatophytoses have been named depending on the anatomic locations, as 1) tinea pedals (feet), 2) tine barbare (beard and mustache, 3) tinea corporis (glabarous skin) 4) tinea cruris (groin) etc. (34) The tissue reactions also varies from erythema and scaliness to extensively crusted, suppurative or rarely granulomatous lesions. The lesions may be pruritic, painful or asymptomatic (4). Tinea capitals typically presents with mild erythematic, patchy areas of scaling, kerion formation or with extensive areas of scarring and alopecia. Tine corporis, usually involves the trunk, shoulders, or limbs. The common clinical presentation is annular, scaly patches with sharply marginated and raised erythematous lesions. In tine cruris the lesions are erythematous to tawny brown and covered with thin and dry scales. They are usually bilateral extending down the sides of the inner thigh and exhibiting a raised, sharply marginated border that is frequently studded with small vesicles. Tinea pedis commonly involves the soles and toe webs and the most common clinical manifestation is the intertriginous form, which presents with peeling, fissuring and maceration. There are two main types of nail involvement namely superficial white mycotic infection and invasive subungual and superficial white mycotic infection. T. rubrum and T. mentagrophytes are the most common dermatophytes causing onychomycosis. (21) In the immunosuppressed population, the clinical presentation of dermatophytoses is often atypical and hence it is difficult to diagnose (35)

Diagnosis: The gold standard for diagnosis of dermatophytoses is the microscopic examination of the clinical specimen with potassium hydroxide and culture. The identification of species relies on culturing the organism, which may take up to weeks. Rapid diagnostic tests using current molecular methodology have been developed for the diagnosis of dermatophytes(36). Histological detection of fungi with PAS staining possesses a high sensitivity (37). Histological and mycological examinations are the most widespread diagnostic techniques for onychomycosis. Nail clipping is not a most favourable technique for fungal culture and a large proportion of non-pathogenic and contaminant moulds can grow on culture medium. Polymerase chain reaction (PCR) and PCR–restriction fragment length polymorphism techniques have been developed for the identification of fungal organisms. Molecular methods are however cost-intensive and require highly skilled staff (38).

Histopathology: In Haematoxylin and Eosin (H&E) stained sections, dermatophytes appears as hyphae and round to oval spore forms ranging in size from 1-2 microns in size within the stratum corneum and hair follicles (4). To detect dermatophytes in the keratin skin layer, Gomori's methinamine silver (GMS) or Periodic acid Schiff (PAS) stains may be used. Host reaction to fungus is very variable (2). Microscopically epidermal changes consists of hyperkeratosis and varying degrees of acanthosis. Spongiosis and vesicle formation may also be seen. These changes may be associated by an inflammatory infiltrate in the dermis (4). Histology was the most sensitive test for the diagnosis of onychomycosis, with the sensitivity of 80.8%. Both histology and smear were significantly more sensitive than culture (53.2%) (39)

Pityrosporum infections

Pityrosporum ovale, also known as Malassezia furfur is a lipophilic yeast seen as cutaneous flora in adults. It is associated with pityriasis versicolor, pityrosporum folliculitis, seborrheic dermatitis and atopic dermatitis. Pityrosporum folliculitis is characterized by pruritic follicular papules and pustules located on the upper trunk, upper arms and neck. (40) Pityriasis versicolor is distributed worldwide and it has been reported to be 30-40% in tropical countries and 1-4% in temperate countries (41). Pityrosporum folliculitis is more common in tropical countries and in a study done by Faergemann et al at Sweden, it was reported to be prevalent in 16.5% of patients attending the dermatology clinic. Seborrheic dermatitis has a prevalence range of 2-5% worldwide (42) Pityrosporum ovale was found to be positive in skin prick test of patients with atopic dermatitis especially involving head and neck areas (41). Immunocompromised hosts such as organ transplant and bone marrow transplant recipients are at risk of pityriasis infection and they may present with disseminated skin rash. (10). In a study done in India on HIV patients by P.K.Kaviarasan et al, pityrosporum infection was found in 13.5% of their cases.

Clinical presentation: Pityriasis causes pigmentary changes in the skin, hence the term versicolor and hypopigmentation of the skin occurs in most individuals. It is more common in oily areas of the skin. The classic distribution involves the chest, back, neck, and face. The lesions are well-defined, slightly scaly hypo pigmented or hyper pigmented macules and patches (5). In seborrheic dermatitis skin lesions are usually distributed on the scalp, eyebrows, nasolabial fold, cheeks and groins. Lesions

are erythematous and covered with greasy scales and itching is the common presentation in the scalp (41). In a study done in south India by N Tabaseera et al, the type of lesions seen in their study were predominantly of hypopigmented variety followed by hyperpigmented and mixed types in 80% and 15.2% and 4.7% respectively and chest was the commonest site to be affected in the study (43).

Diagnosis: The diagnosis can be made clinically or by visualizing the Pityrosporum yeast on skin biopsy. Pityrosporum is difficult to be cultured with normal fungal culture medium (5). Special media containing fatty acids and lipids, such as Leeming-Notman medium, should be used if Pityrosporum is suspected (14). The diagnosis is made microscopically by observing the etiologic agent in epidermal scales. M. Furfur appears as short somewhat curved and bent hyphal elements, 2.5 to 3 micrometer in diameter, associated with clusters of oval or round thick walled cells 3-5 micrometer in diameter. These round or oval cells are considered to be phialospores (4). There may be mild to moderate hyperkeratosis and acanthosis. The hair follicles may be dilated and plugged with keratinous debris. There may be mild chronic inflammatory cell infiltrate around the infundibular portion of the follicle. Disruption of the follicular epithelium is sometimes noted, with basophilic granular debris, keratinous material, neutrophils and other inflammatory cells in the perifollicular dermis. (44)

Candidiasis

The clinical forms of candidiasis can be divided into three broad

categories as follows i)cutaneous ii) mucocutaneous and iii)invasive candidiasis (4). Cutaneous candidiasis is most commonly caused by Candida albicans, a yeast that is part of the normal flora of the skin, gastrointestinal tract, and genitourinary tract of humans. A unique balance keeps it in check and when that is disturbed, it can cause clinical infection of the skin, mucous membranes, and nails (5) Cutaneous candidiasis is less commonly seen than the oral form in those with HIV infection. The transplant population is less likely to develop superficial candidiasis compared to AIDS patients, but organ transplant recipients are more likely to develop disseminated mycoses with Candida. Disseminated candidiasis presenting as skin lesions are evident in approximately 10–13% of affected individuals (14) (45) .

Epidemiology: A Population-based surveillance study reported the yearly incidence of Candida infections as eight per 100,000 population. (46) Superficial candidiasis is an important fungal infection with varying clinical presentations. In a study done by Razzhagi-Abyaneh et al, they confirmed candidiasis on histopathology and culture in 173 clinical samples, of which 61.8% were from skin, nail scrapings and 4% from oral swabs, it was found that Candida albicans (61.8%) was the most prevalent species followed by C. Parapsilosis (11.5%). A study done by Arendrup et al in USA revealed Candida species as the infectious agent in 8% to 10% of nosocomial blood stream infections. (45) In a study done in a tertiary institute in India by Kathari A et al, Candida spp. accounted for 18% of all nosocomial bloodstream infections, of which, 45% were caused by C. tropicalis , 23% by C. albicans and 32% by other Candida spp. In western literature C. albicans is associated with 50-70% episodes of

candidemia, whereas in the Indian setting C. tropicalis is the most common (46). In a study done in our institution on infections among bone marrow transplant recipients by B George et al in 2008, 19.7% were fungal infections of which 22.2% were caused by Candida. (47) Candidial yeast forms are the normal commensal of skin and mucosal surfaces, however invasive infections arise only when barrier leakage happens or when the immune function is impaired. (48) Cutaneous and mucocutaneous candidiasis, although common in children, is often under-reported.

C. albicans predominates in mucocutaneous and cutaneous candidiasis, with

C. dubliniensis also contributing substantially in the paediatric population (49).

Pathogenesis: The pathogenesis of Candida species is facilitated by a number of virulence factors, one of which is the adherence to host tissues and medical devices, biofilm formation and secretion of hydrolytic enzymes. Relatively little is known about the pathogenesis of non-albicans species other than Candida albicans (50).

Clinical presentation: Mucocutaneous candidiasis frequently involves the skin of the entire body, mucous membranes and nails. Cutaneous candidiasis involves the intertriginous areas of the skin such as the interdigital areas of the hand, groin, and the axillae. The lesions are typically erythematous, scaly, inflammed and moist. (15) Vesicles and pustules may also develop in the centre of the affected areas. Itching is a common complaint. Intertriginous and paronychial candidiasis is frequently seen among individuals whose work involves prolonged immersion of their hands in water.(4)

Diagnosis: Histological examination of the specimens is important to define invasion into the tissue and vessels, because growth from skin is only indicative of colonization The organisms can be visualised using routine H&E stain and/or by using special stains like GMS and PAS stains(2). The diagnosis of candidiasis is also supported by a KOH preparation of mucous membrane scrapings that reveals budding yeasts with or without pseudohyphae. Culture is useful if there is a clinical suspicion of a non albicans species or azole resistance (14).

Histopathology: In tissues Candida organisms appear as yeast forms measuring 3 to 5 mm in diameter intermingled with pseudohyphae. The pseudohyphae may show periodic constrictions. The predominant Candida species that does not produce pseudohyphae is Candida glabrata (2). Associated histological features like marked hyperkeratosis, acanthosis and pseudoepitheliomatous hyperplasia of the epidermis, dense collections of lymphocytes, plasma cells, neutrophils, macrophages and foreign body giant cells in the dermis may also be seen (4). Granulomas with giant cells and coagulative necrosis may also be evident. Necrosis with haemorrhage and sparse infiltrates of lymphocytes and macropahges is seen in candidiasis associated with neutropenia (2).

Subcutaneous infection: Subcutaneous mycotic infections primarily involve the dermis and subcutaneous tissue and rarely disseminate through the bloodstream and presents as systemic disease (47). Mycetoma, sporotrichosis, chromomycosis, zygomycosis, candidiasis, pheohyphomycosis and lobomycosis are the commonly

encountered subcutaneous mycotic infections. (51) Infection occurs most commonly by the accidental inoculation of the etiological agent into the subcutaneous tissue (52). It affects both immunocompetent and immunocompromised individuals. In immunocompromised individuals it can disseminate widely (53).

Epidemiology: A meta-analysis study on the global burden of mycetoma was done by van de Sande et al in 2013, in which it was found that 8763 mycetoma cases were documented in 23 countries since 1944. Thus the globally reported number of cases is 127 cases/year. The prevalence numbers ranges from <0.01 cases per 100,000 inhabitants (several countries) to 1.8 cases per 100,000 inhabitants (Sudan) and an average of cases reported per year ranging from 0.9 Tunesia to 106 Sudan (54) . A study done in Mexico by Lopez Martinez et al, revealed out of 3933 mycetoma cases reported over a period of 54 years, 75.6% of infection is seen in men and 24.4% of infection was seen in women. Farmers are the most commonly affected group followed by housewives. The most commonly affected body part is extremity (60.29%) followed by trunk (19.75%). Eumycetoma comprises 3.48% and it is predominantly caused by Madurella grisea (28.47%) and followed by Madurella mycetomatis (26.28%) (55). The dematiaceous fungi cause a wide range of diseases namely phaeohyphomycosis, chromoblastomycosis and eumycotic mycetoma. Most commonly seen human pathogens are Alternaria species, Cladophialophora bantiana, Curvularia species, Exophiala species, Fonsecaea pedrosoi, Madurella species, Phialophora species, Scedosporium prolificans and Scytalidium dimidiatum. (52) These organisms are present in the environment like soil, wood and plant debris .

Subcutaneous infections with dematiaceous fungi occur worldwide, but are more common in tropical and subtropical climate. Immunocompetent individuals are affected more commonly. The incidence of disseminated infection is increasing, especially in immunocompromised individuals (56). A study done in India by Bhat RM et al, revealed that chromoblastomycosis was the most commonly seen subcutaneous infection followed by mycetoma, sporotrichosis and rhinoentomophthoromycosis . Most common site of involvement was lower extremities. Male patients were more commonly affected than females and most patients were farmers (52).

Aspergillus species are omnipresent in the environment, seen in air, decaying matter and soil. Aspergillosis may occur as a primary cutaneous infection or may occur as secondary to disseminated aspergillosis (53) The lesions of primary cutaneous aspergillosis are usually found at an intravenous infusion site. (57). It is seen especially in immunocompromised patients and it is one of the serious condition requiring early diagnosis and treatment (58). Primary cutaneous aspergillosis has been recognized in 12 cases from a tertiary care centre in northern India. Aspergillus flavus is the commonest causative agent in India unlike the western world where Aspergillus fumigatus is the chief pathogen (59).

Cutaneous zygomycosis appears to have increased incidence in recent years. They constitutes a group of infections caused by members of the class Zygomycetes, which is divided into two orders namely i) Mucorales and ii) Entomophthorales (60). In

review by Roden et al, the most common types of zygomycotic infection were sinus (rhinocerebral sinus & sino-orbital sinus) (39%), pulmonary (24%) and skin (19%). 78 out of total 176 cutaneous infection were complicated by dissemination or deep extension (61). In India a meta-analysis study done by Kaushik et al, described 130 cases of cutaneous zygomycosis with an overall mortality of 35 %. The commonest zygomycete identified was Apophysomyces elegans. Among these patients diabetes was reported only in 36 patients (27.69 %). The commonest cause for the infection was breach of the skin (62).

Histoplasmosis is found all over the world, with the largest endemic focus in the Central eastern United States, where 85% to 90% of the population has positive skin tests for histoplasmin. Histoplasmosis usually occur in three forms namely, primary cutaneous histoplasmosis caused by inoculation, primary pulmonary histoplasmosis caused by inhalation, and disseminated histoplasmosis. Primary cutaneous inoculation of histoplasmosis is a rare event which is usually benign and self-limited. In a survey done in Europe, of 118 cases reported 62 patients had disseminated disease, 31 had acute pulmonary infection, chronic pulmonary infection in 6 and localized disease in 2 patients.(63) Primary cutaneous histoplasmosis is rare, usually cutaneous involvement is the manifestation of disseminated systemic disease. Cutaneous involvement is reported in almost 10% of HIV-associated histoplasmosis cases. (64) In India, West Bengal and Assam are endemic to histoplasmosis, especially in the Gangetic delta.(66) The first case of disseminated histoplasmosis was reported in Calcutta by Panja and Sen in 1954 (65).

Clinical presentation: Mycetoma has a long insidious course upto 5 years or more with pain and swelling being the most common clinical presentation followed by suppurative nodules with draining sinuses.(66) During active phase of the disease grains may be seen discharging from the sinuses, which may aid in the diagnosis of particular infectious agent (66). Chromoblastomycosis clinically manifests as papillomatous lesions that usually ulcerate. The infection spreads through lymphatics and presents as satellite lesions. (4) In immunocompromised individual's cutaneous aspergillosis is usually a primary form rather than a disseminated disease and it usually present as ulcerative nodules associated with other systemic symptoms like fever. Primary cutaneous aspergillosis seen in HIV individuals present as pustules, papules mimicking molluscum contagiosum and verrucous plaques (14). Neonates present with pustules and with purulent discharge. Erythema and induration are the common presentation for infections arising from the intravenous catheter puncture site (57). Subcutaneous phaeohypomycosis is characterized by asymptomatic nodular lesions especially on the extremities. They are also referred to as mycotic cysts and the average size of the cysts is 2.5 cm (67). Sporotrichosis is caused by the dimorphic fungus. Sporothrix schenckii and it can enter the subcutaneous tissue by traumatic inoculation. They are characterized by papules or nodules, erythematous lesions with a smooth or verrucous surface and some may show ulceration.

Diagnosis: Specimen collection and transport are the most important factors in the diagnosis of subcutaneous infection. Specimen collection is particularly important because many of these lesions are open and rapidly colonized by nosocomial

pathogens that may not be involved in the infection. Most reliable specimens for diagnosis are of ulcers and nodules obtained by surgical biopsy of the deep tissue without contact with superficial layers of skin (55).

Histopathology: In mycetoma the affected area enlarges as a result of the interaction of host and parasite and because of formation of fibrotic tissue. Gross examination of the biopsy specimen is necessary to look for the presence of granules which are variable in shape, size and colour. The colour of the granules varies to black, white, red or yellow depending on the type of infecting organisms. Madurella mycetomatis, Curvularia and Exophiala jeanselmai are the causative agents of black grain mycetoma. Acremonium spp and Pseudallescheria boydii are causative agents of white grain mycetoma.(68) Eumycotic mycetomas are composed of septate mycelial filaments that are atleast 2-4 micrometer. The typical grains are found in the center of zones of suppuration and within suppurative granulomas in the dermis or subcutis. Surrounding the areas of suppuration there may be a palisade of histiocytes admixed with multinucleate giant cells. An eosinophilic fringe, similar to the Splendore–Hoeppli phenomenon found around some parasites, is present around the grains. (44)

In chromoblastomycosis regardless of the genus and species of mould involved, the tissue form of fungus seen in the body is in the form of 6- 12micro meter, thick walled, dark brown muriform cells, generally referred to as sclerotic bodies. Chromoblastomycosis generally produce mixed purulent and granulomatous inflammatory reaction. The similar type of tissue response may also seen in other infections like blastomycosis, coccidiodomycosis, paracocodiodomycosis and

sporotrichosis the latter with increased plasma cells. Blastomycosis has broad-based budding yeasts, with the yeast forms ranging in size from 10-14 microns. (2) The histological diagnosis of coccidiomycosis is established by identifying spherules of C.immitis measuring 20-200 micrometer in diameter. Mature spherules contains many uninucleate endospores ranging in size from 2-5 micrometer in diameter (4). The yeast forms of Histoplasma capsulatum var. duboisii are round to oval and 2-4 micrometer in diameter; that may show narrow based buds. The basophilic yeast cytoplasm is separated from the surrounding tissue by a clear zone corresponding to the cell wall. Overlying pseudoepitheliomatous hyperplasia of the epidermis has been reported in cutaneous aspergillosis. Secondary cutaneous aspergillosis and mucormycosis results from haematogenous seeding from a lesion elsewhere in the body. Those patients may have underlying diabetes, neutropenia, leukemia, lymphoma or other immunoocompromised condition. (44)

Systemic mycoses: Many dimorphic fungi cause systemic mycoses in immunocompromised persons. Cutaneous manifestations of systemic mycotic infection may be misdiagnosed as cutaneous neoplastic lesions (69) Cutaneous manifestation of systemic mycosis is uncommon and limited to a few species of fungi. Disseminated candidiasis is a frequent and serious complication in the immunocompromised host and they may present as cutaneous nodules. Ulcerative plaques and necrotic pustules in immunocompromised host may raise the suspicion of candidial sepsis, which signifies the importance of skin biopsy. (70) Opportunistic fungal infections cause significant morbidity and mortality in immunocompromised

patients and cutaneous lesions may be the first clinical manifestation which give the clue to early diagnosis. (71)

Epidemiology: Candida, Sporothrix and Aspergillus are the common causative organisms with systemic mycoses presenting as cutaneous lesions. The typical clinical presentations include nodular lesions, papules, plaques, macules and ulcers. In immunocompromised hosts with atypical skin findings, clinical suspicion is very important since failure to diagnose systemic mycoses causes significant morbidity and mortality. (72) Approximately, 15-20% of AIDS patients with cryptococcocal meningitis may have cutaneous involvement. However cutaneous manifestation with no signs of meningeal involvement is an unusual entity happening in only about 6% of already diagnosed HIV-infected cases (73). In bone marrow transplant individuals most common site of fungal infection was lung (51.5%) followed by systemic disseminated form (15.5%), central nervous system (6%), isolation from blood (6%), gastrointestinal tract (7.5%), skin, catheter related and sinus (13.5%) (11).

Diagnosis: Biopsies of skin lesions for histological examination, including special stains and culture are critical for the diagnosis of invasive mycoses. Any of the suspicious lesions should be biopsied, however relatively new skin lesions will have a higher yield. The skin should be cleansed with alcohol before sampling to decrease contamination with bacteria, commensal organisms and spores of airborne saprophytic fungi. In case of multiple different looking lesions it is advisable to do biopsy from all the different types of lesions in order to identify more than one infection. Blood

cultures are diagnostic in disseminated Candidial infections and are usually positive in disseminated Fusarium, Cryptococcus and P. marneffei infections. Antibody detection assays, polymerase chain reaction (PCR), enzyme-linked immunosorbent assay (ELISA) for antigen detection, or direct immunofluorescence are preferred tests. Serum antigen testing is very sensitive for cryptococcosis. (14)

Treatment : Sertaconazole has a broad-spectrum antifungal activity against dermatophytes of the Trichophyton, Epidermophyton and Microsporum genera and yeasts of the genera Candida and Cryptococcus (74) . Topical formulation of griseofulvin is an effective treatment for interdigital dermatophyte infections (75) .

Tinea versicolor can be treated with selenium sulfide 2.5% shampoo which should be applied over the affected areas for 7 days twice monthly for 6 months. Topical azoles such as clotrimazole 1% and ketoconazole 2% for 2 weeks are also recommended. Oral therapy ketoconazole 400 mg or fluconazole 400 mg can also be given to the elderly (5). Superficial candidiasis can be treated with topical preparations like clotrimazole or nystatin or systemic agents like fluconazole or voriconazole. (2). Invasive mycoses have been increasing in prevalence. Many drug-resistant fungi are also appearing in patients; however developments in antifungal therapy have emerged to address these concerns. Fluconazole has excellent activity against C. albicans, Cryptococcus, and Coccidioides spp but not against the invasive molds. Itraconazole is effective against molds as well as Blastomyces and Histoplasma spp. Voriconazole, the newest extended spectrum azole, has excellent anti-Aspergillus activity (14).

Histopathological examination is one of the chief investigative tools in mycology as it permits rapid presumptive detection of fungal infections. Histopathological examination can also make available insight into the diagnostic significance of culture isolates.

Demonstration of an inflammatory reaction or tissue invasion can assist to determine whether an organism represents contamination, colonization, or true infection.

Histopathological examination remains the only reliable means to identify certain pathogens, like Pneumocystis jiroveci (formerly Pneumocystis carinii), and Loboa loboi . Many studies have demonstrated fungal detection by histopathological examination, but very few have investigated the diagnostic specificity of histopathological examination versus mycological culture (3).

Histopathology provides quick and commercial means of providing diagnosis of fungal infection. Histopathological diagnosis of fungi depends on the morphology and the tissue reaction. However, unless special techniques such as immunofluorescence, immuohistochemistry are used, or the infecting fungus possesses exclusive structures such as spherules detection of the aetiologic agent by histopathology is complicated. Histopathology is the only way to diagnose infections caused by L. Loboi as cultivation techniques have to date been ineffective. Many histological stains are available that are routinely used to visualize fungi in tissue sections. Some of these are special fungal stains. H and E stain is useful to visualize the host's response. It does not stain most of the fungi, except a few like Aspergillus spp. and the

Zygomycetes. Thus, a combination of GMS, PAS and H &E is usually in use to visualize both the tissue reaction and the infecting fungus. The main growth forms of the fungi that help in histopathologic diagnosis are the yeast cells, hyphae, pseudohyphae, arthroconidia, chlamydoconidia and spherules. The typical features like shape, size, location and colour assist in identification of the fungus. The morphology of the fungus may be distorted due to type of biopsy, crush artefacts and processing. Although GMS and PAS are useful in delineating fungal morphology, they have restrictions when the material is very little, and the number of fungal elements is sparse. These limitations lead to misinterpretation and misdiagnosis on histopathology. There are very few studies that correlated histopathology and culture diagnosis of which a study done by R Kaur et al, found culture correlation to be 52%. In the present study, we analyzed the correlation and discrepancy between histological and culture diagnosis.

MATERIALS AND METHODS

Materials and Methods

All the procedures carried out in the present retrospective study were approved by the Institutional Review Board of Christian Medical College, Vellore. Department Of General Pathology, Christian Medical College and Hospital diagnosed a total of 249 cases of cutaneous mycoses between January 2008 – December 2009 &

January 2011- December 2015, of these 232 cases were included in the study group. Haematoxylin and Eosin (H&E) stained and mounted slides and paraffin embedded tissue blocks were retrieved from the departmental archives.

Inclusion criteria:

1. The cases of cutaneous mycotic infections diagnosed between January 2008 to December 2009 & January 2011-December 2015. These cases were obtained from the oracle based pathology work station in Christian Medical College Vellore.
2. Those cases referred from elsewhere for review of slides and blocks were also included provided the clinical details and blocks were available.

Exclusion criteria:

1. Slides and blocks handed over to the patients.
2. Slides on review in which fungal organisms could not be identified

Clinical details of the case:

The clinical details of these patients from the charts retrieved from the Medical Records Department and the hospital records through the clinical work station, Department of General pathology. The clinical features that were analysed included age, gender, symptoms and its duration, type of skin lesion, site of the biopsy, associated comorbidities and if present treatment history for the same and prior anti-fungal treatment.

Histopathological assessment of cutaneous fungal infection:

Microscopic features: The slides were reviewed by two pathologists and the features were assessed as described in the proforma (Appendix -1).

Special stains: Two special stains were done in our study, PAS and GMS. Special stains were performed manually using the technique described in (Appendix-2).

Each fungus was identified by the following features:

Dermatophytes: Yeast forms or hyphal forms ranging in size from 1-3 microns are seen in the stratum corneum and may also be seen within the hair follicle. The stratum corneum may show hyperkeratosis, parakeratosis, spongiosis, neutrophilic microabscess and sandwich sign. It refers to presence of hyphae 'sandwiched in' between an upper but normal basket-weave stratum corneum, and a lower layer of recently produced stratum corneum which is abnormal in being compact

orthokeratotic or parakeratotic in type. The dermis may also show mild perivascular chronic inflammation and dermal edema is also been described.

Pityrosporum: Spherical or oval yeast forms ranging in size from 2-4 microns in size may be seen. There may be budding yeast forms too. Involved follicles are dilated and usually plugged with keratinous material. There is mild chronic inflammation around the hair follicle.

Candida: They are seen as yeasts measuring 3 to 5 microns in size admixed with hyphal and pseudohyphal forms. The peudohyphal forms may show periodic constrictions.

Cryptococcus: Cryptococcus is encapsulated, spherical to oval yeasts that measure 5 to 10 microns in size and have narrow-based budding. A thick polysaccharide capsule gives these organisms the distinctive appearance of having a clear space around them that can be seen in tissue sections with H&E stains or Alcian blue stain.

Histoplasma: Histoplasma in tissue is seen as oval 2-4 microns yeasts that may show narrow-based buds. With H&E stain, the basophilic yeast cytoplasm is seen separated from the surrounding tissue by a clear zone corresponding to the cell wall.

Chromomycosis: Round, thick-walled, golden brown cells ranging in size from 5-12 microns (sclerotic bodies) may be seen lying free or within the multinucleate giant cells. Septate hyphal forms may also be seen.

Aspergillosis: Aspergillus spp are seen as thin septate acute angled branched hyphae ranging in size from 3-12 microns in size.

Zygomycosis: The hyphae are broad, non-pigmented wide and usually non-septate and ranges in size from 5to 20 microns. The branching is usually seen at right angles. The hyphae are ribbon like in appearance and vary in width.

Subcutaneous phycomycosis: Broad hyphal forms ranging in size from 6-25 microns in size are seen surrounded by an irregular deposit of eosinophilic Splendore-Hoeppli material.

Eumycetoma: The segmented mycelial filaments ranging in size from 2-4 microns are seen. Large granules up to 5 mm or more with interlacing hyphae embedded in interstitial brownish matrix, hyphae at periphery arranged radially with numerous chlamydospores may also be seen.

Statistical analysis:

The study data were summarized using descriptive statistics. Pearson's Chi square test was used to evaluate associations between categorical variables using SPSS software. In all the statistical analysis a P value of <0.05 was considered to be statistically significant.

RESULTS

Results:

A total of 249 cases of cutaneous fungal infection were diagnosed in the department of pathology, CMC Vellore between January 2008-Decemeber 2009 & January 2011-December 2015. The year 2010 was exempted from our study since maximum number of blocks of that year were not available. The archived slides and blocks were retrieved from the pathology records, Department of General Pathology, CMCH, and Vellore. 232 cases satisfied our inclusion criteria. Eight cases were eliminated because both slides and blocks were not available and nine cases were eliminated because on review of the slides fungal organisms could not be identified. The clinical, morphological features and histochemical staining features were analysed for all the 232 cases. Restaining of the slides were done if they were poorly stained or had artefact due to storage.

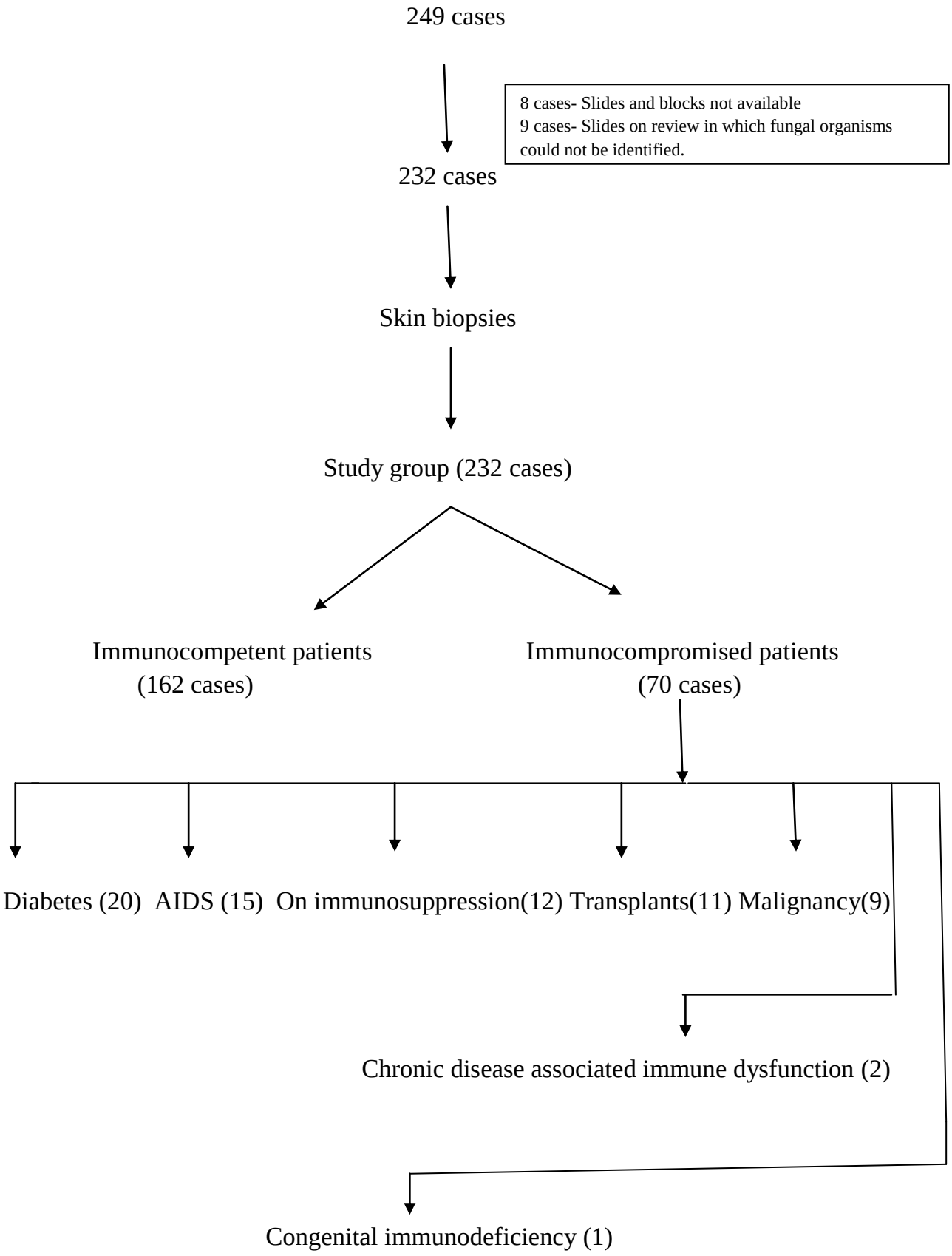


Fig 1: Cases included in our study.

Clinical features:

Age: The mean age at diagnosis of the cases of cutaneous fungal infection in our study was 38 (range 1-83 years). The median age was found to be 42 years. Among the 70 cases of immunocompromised patients the mean and median age were found to be 43 years with the (Range 9-77) in contrast to those immunocompetent patients that showed a slightly lower mean and median age of 35 years and 42 years (Range 1-83). The following charts depict the age distribution of all the cases and age-wise distribution of fungi observed in our study. (Figure 2 & Figure 3)

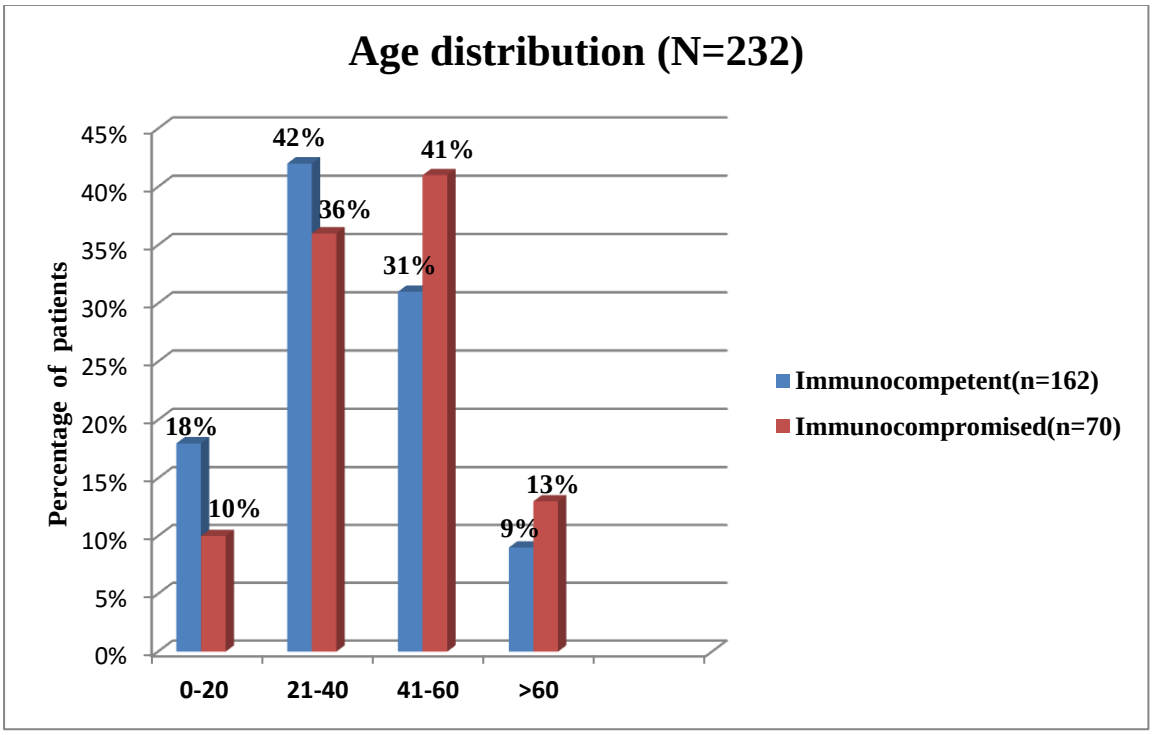


Figure 2: Age distribution of all cases of cutaneous fungal infection among both the groups.

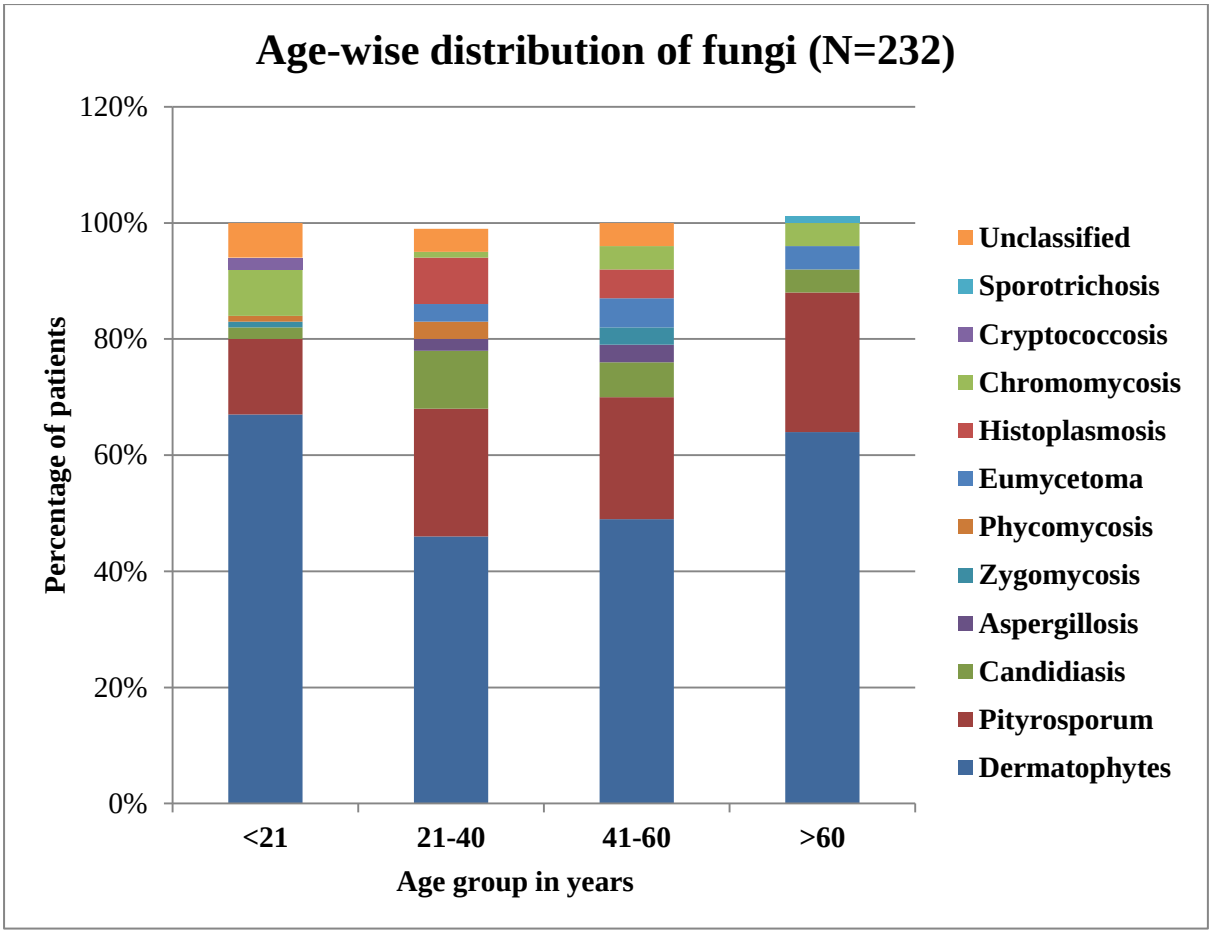


Figure 3: Age-wise distribution of all fungi.

Gender distribution: Overall cases of cutaneous fungal infection showed a male predominance (1.72:1). Among the total 70 immunocompromised patients 40 were males and 30 were females. The following charts depict the gender distribution in all the cases and gender-wise distribution of all fungi. (Figure 4 & Figure 5)

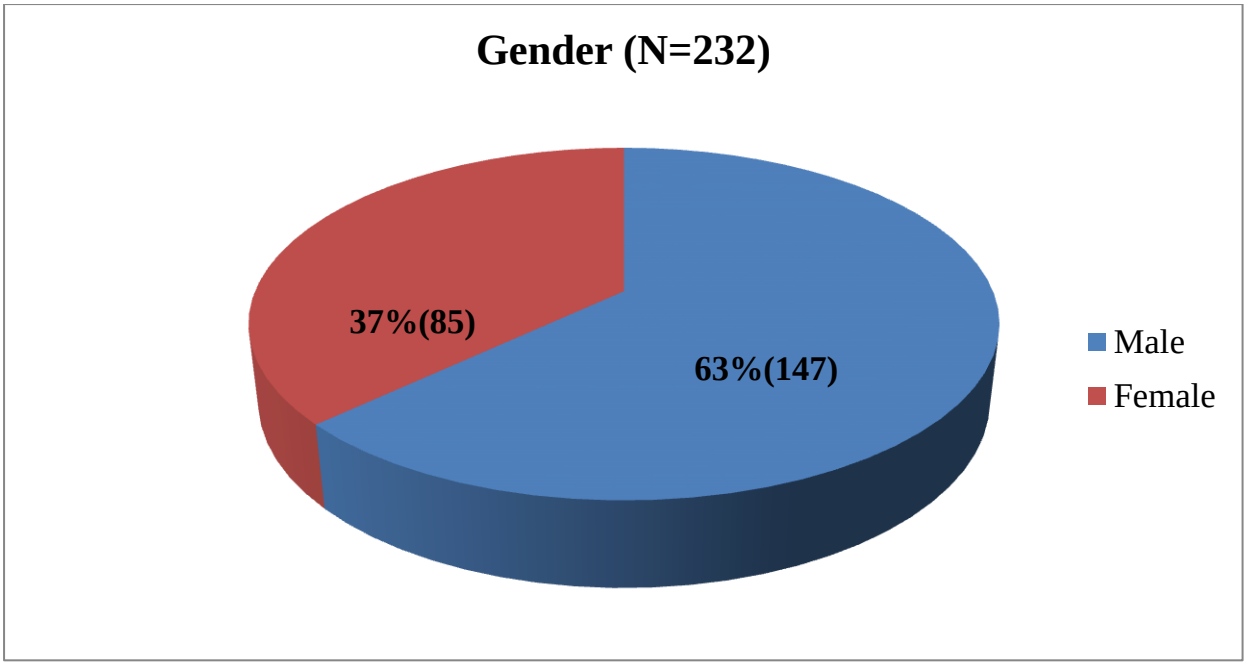


Figure 4: Gender distribution of all cases of cutaneous fungal infection.

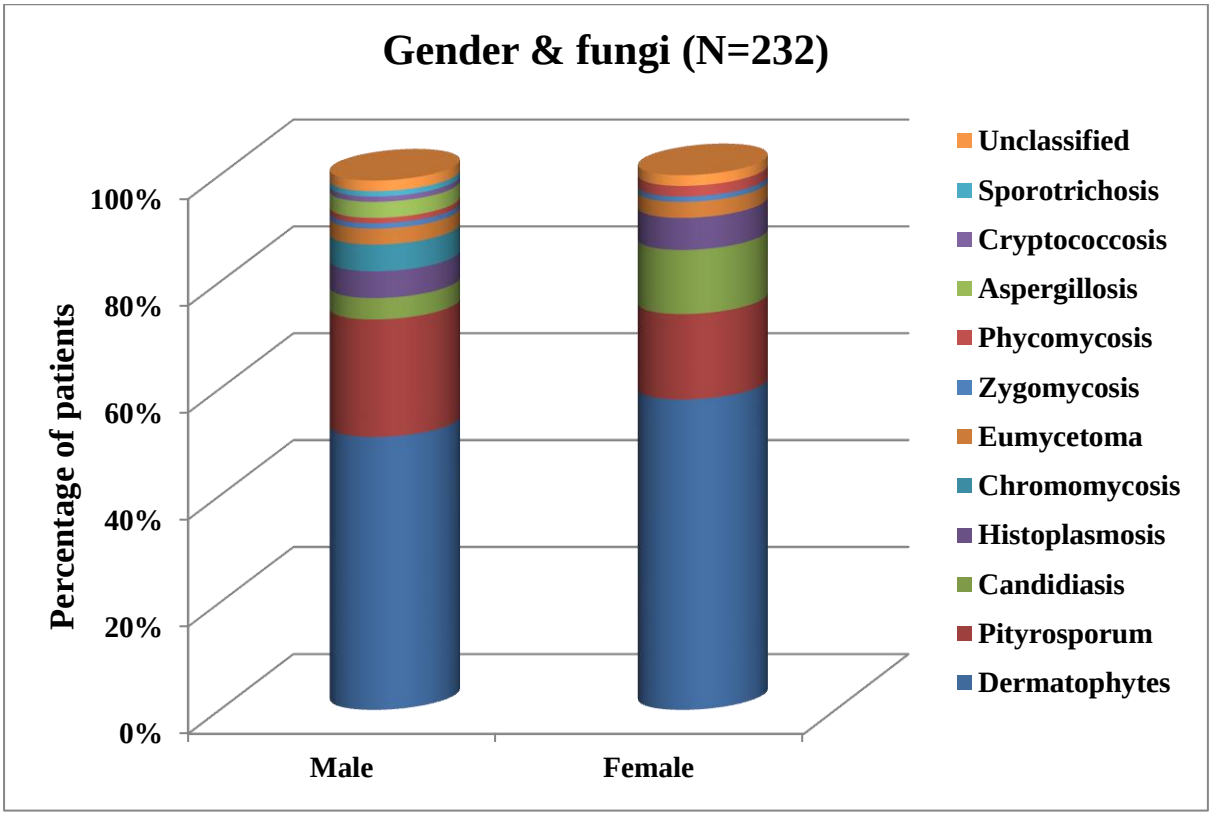


Figure 5:Gender-wise distribution of all fungi.

Patient demographic:

The following chart depicts the geographical distribution of all cases in this study. (Figure 6)

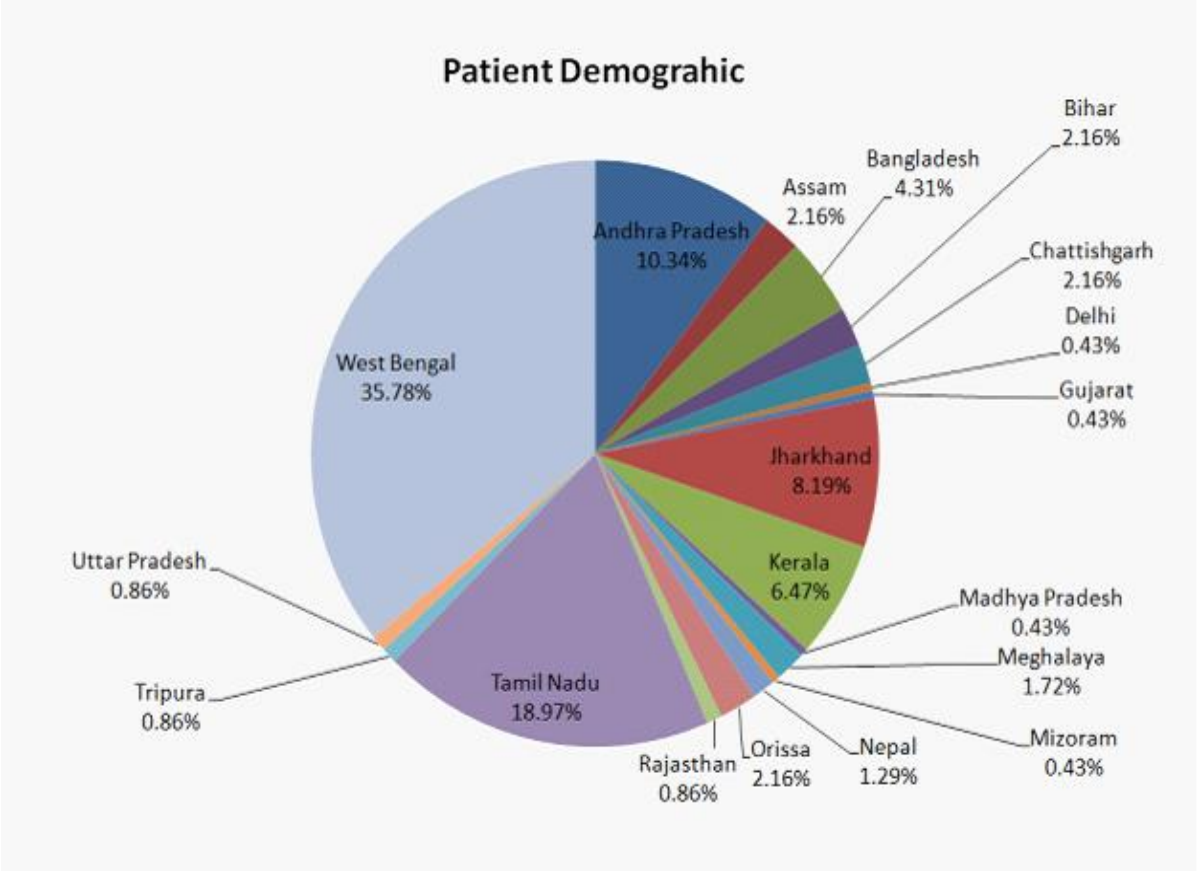


Figure 6: Patient demographic for all cases in this study.

Occupation: The following chart depicts the occupation of all the cases in this study. In this study agricultural workers were found to be most commonly affected group, 25% followed by house wives 22%. (Figure 7)

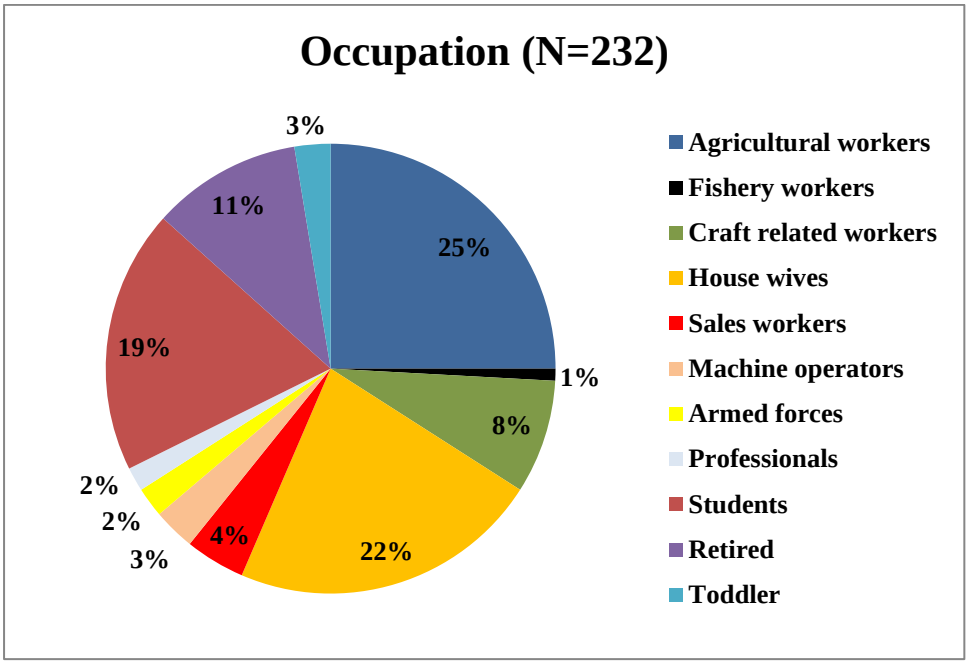


Figure 7: Occupation of all cases

Immunocompromised patients:

Among the total 232 cases, 70 (30.2%) were found to be immunocompromised. The following charts depict the various immunocompromised conditions observed in this study and associated fungi with different immunocompromised condition. Diabetes was found to be the most common immunocompromised condition with 20 cases (29%) followed by HIV-AIDS 15 cases (21%) (Figure 8) & (Figure 9)

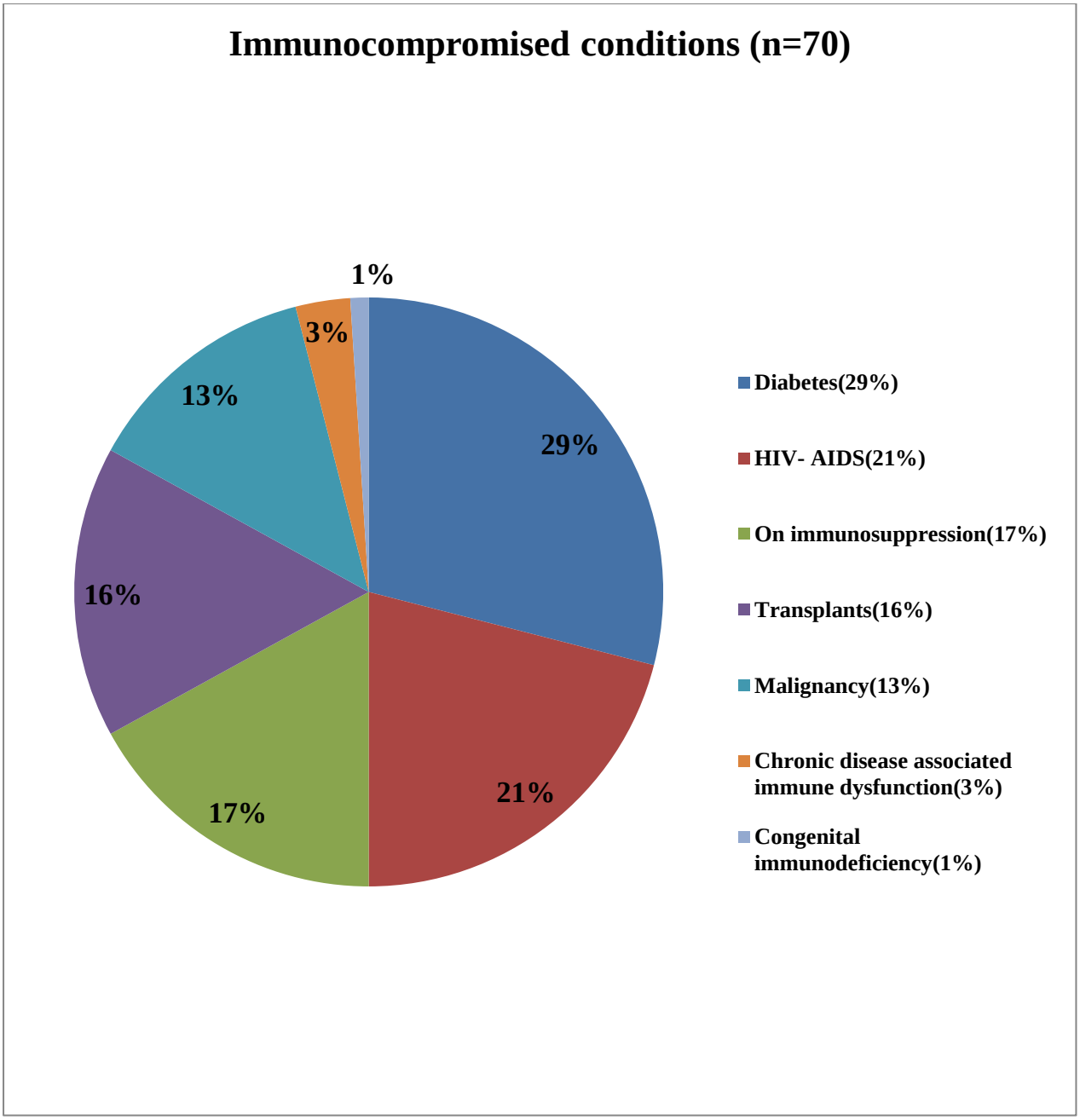


Figure 8: Various immunocompromsied conditions observed in this study.

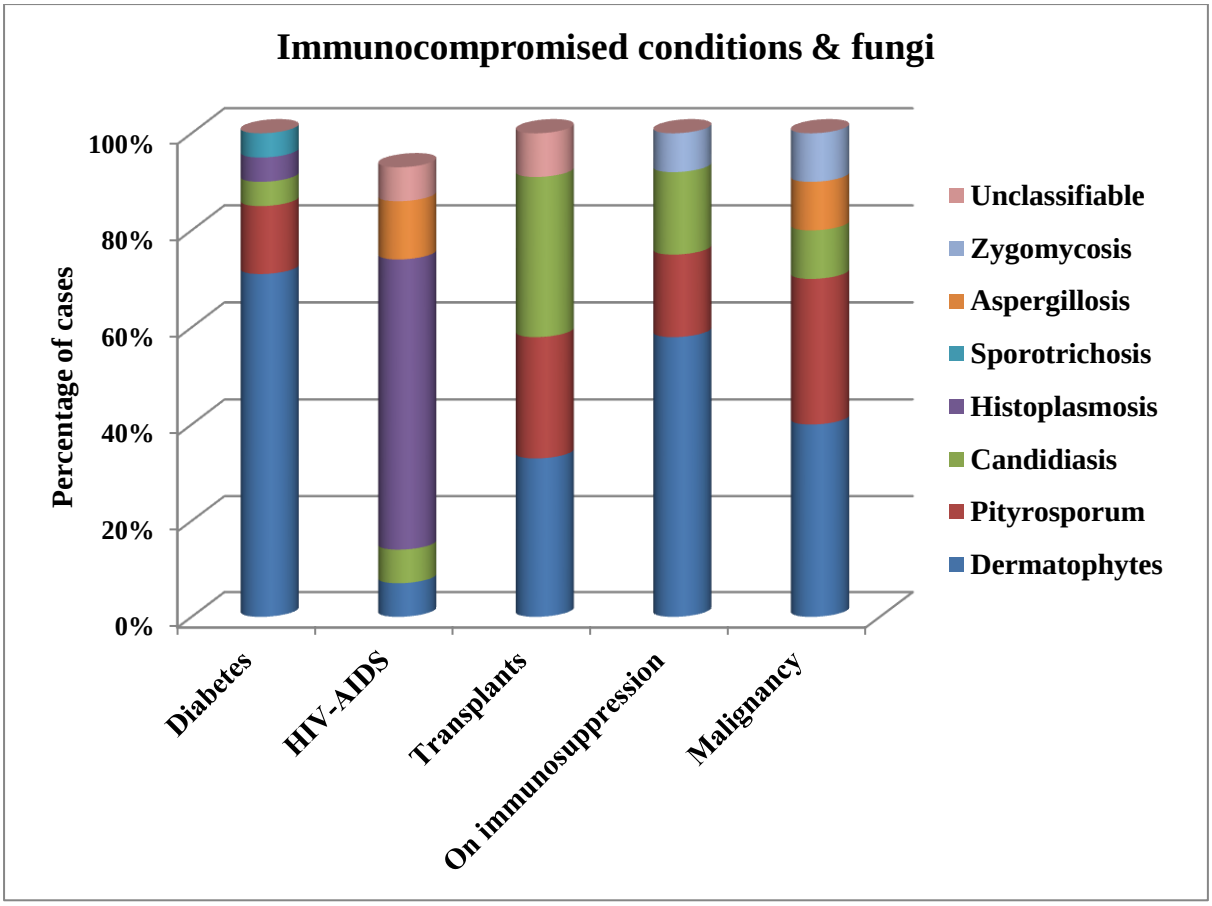


Figure 9: Various immunocompromised conditions and associated fungi

Associated comorbidity: Diabetes, autoimmune disease and inflammatory bowel disease who were on immunosuppressive therapy has been included in immunocompromised state. Excluding the above conditions, 13 cases were found to have associated comorbidity like hypertension (11), cardiovascular disease (1) and bronchial asthma (1).

Clinical Presentation: Most of the patients presented with skin lesions in both immunocompetent (59.25%) and immunocomprosmised (72.85%) groups. A minority of patients presented with nail discolouration, pigmentary lesions and swelling. (Figure 10)

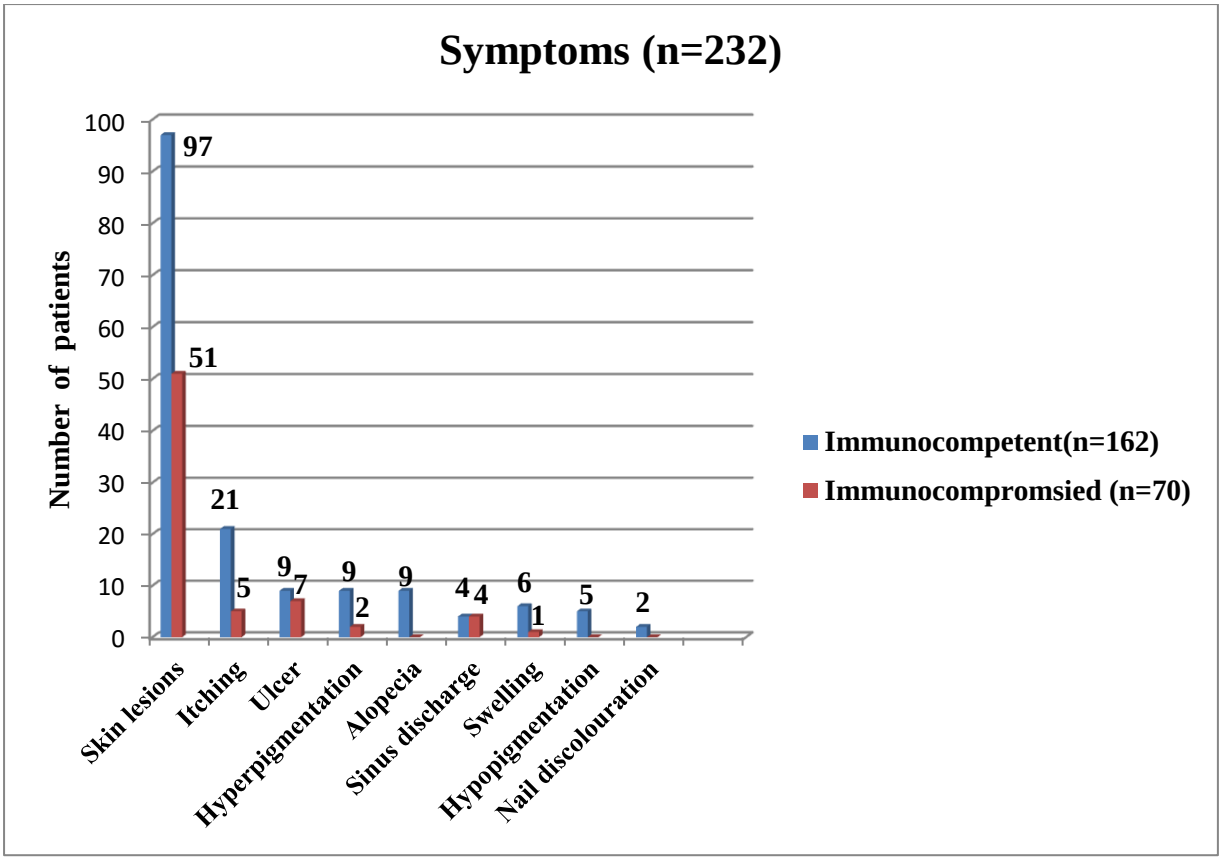


Figure 10: Symptoms in both the groups.

Duration of symptoms:

The following chart depicts the duration of symptoms among both the groups. The symptomatic presentation was found to be more acute (<6 months) in immunocompromised patients (65.71%), when compared to immunocompetent individuals (27.77%). (Figure 11)

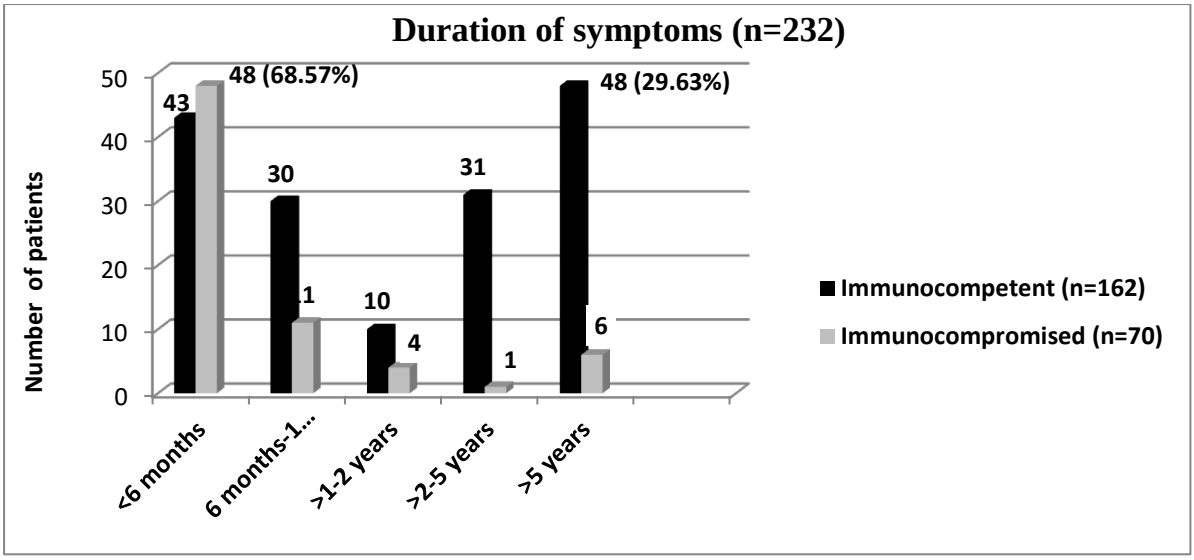


Figure 11: Duration of symptoms among both the groups

Site: The most common site involved was lower extremity 52 (22.41%). Among immunocompromised patients the most common site involved was face and neck region 20 (28.57%), followed by lower extremity 18 (25.71%). (Figure 12)

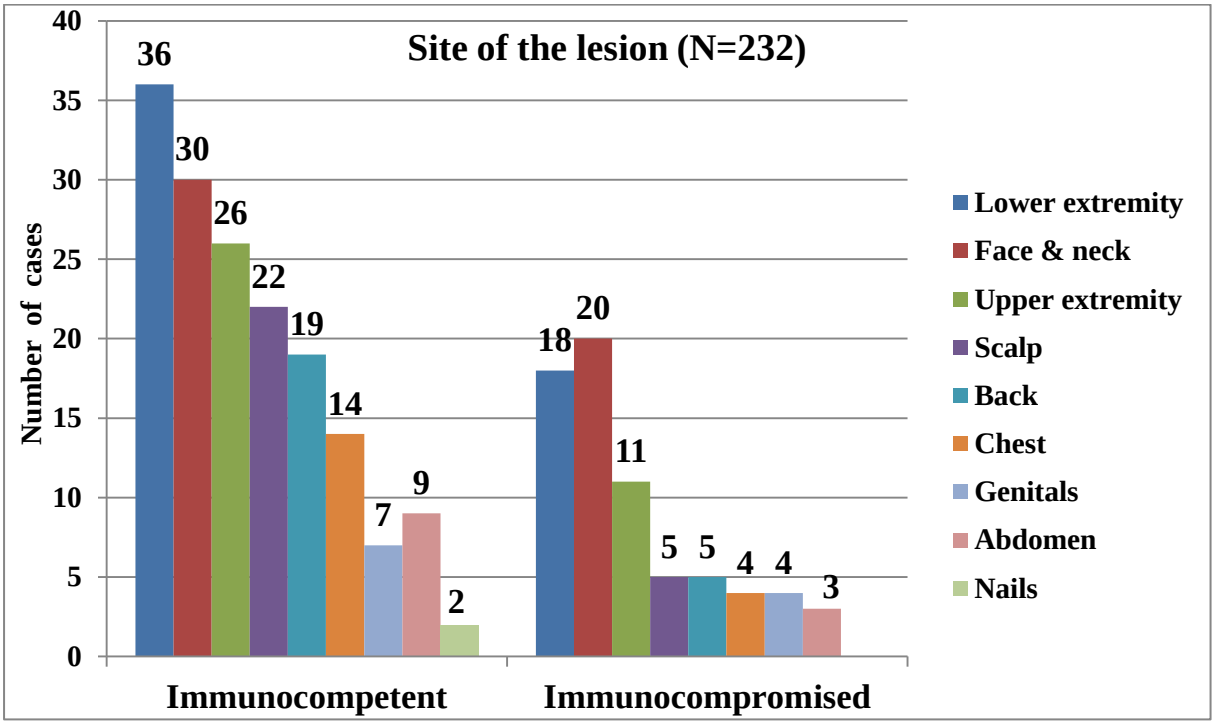


Figure 12: Site predilection of cutaneous fungal infections in both the groups

Nature of lesion: The most common type of skin lesion observed in both the groups were macule/papule (44%) followed by plaque (29%). There is no significant difference in the type of lesions among both the groups.

Histological features: Based on the histomorphological features cutaneous fungi seen in all the 232 cases were classified into four categories**.** Superficial fungi were the most common category seen in both immunocompetent, 120 (74.08%) and immunocompromised, 34 (61.4%) patients. Dermal/cutaneous fungi, 22 (31.43%) and disseminated fungi, 2 (2.86%) was found to be seen more commonly in immunocompromised patients. (Figure 13)

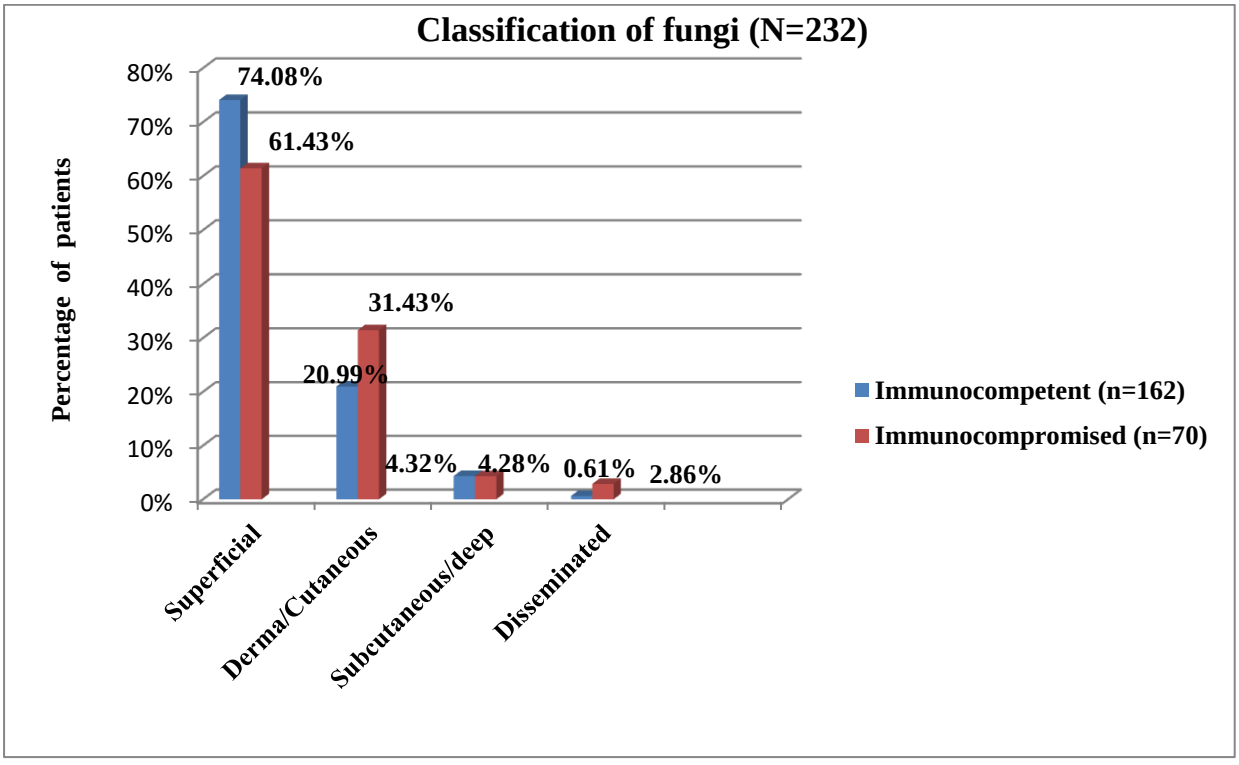


Figure 13: Classification of fungi among two groups

Site of fungi: The following figure depicts the location of fungi in both the groups. In both the groups fungi were seen most commonly in the epidermis followed by dermis and subcutaneous tissue. (Figure 14)

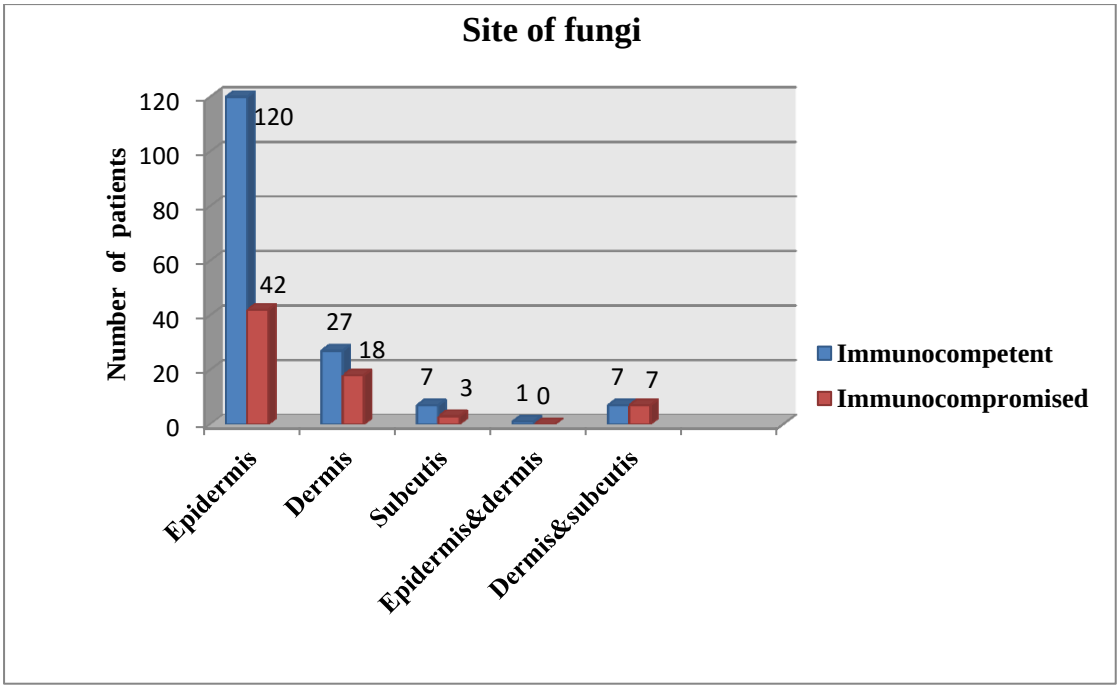


Figure 14: Site of fungi seen in both groups

Superficial fungi: Superficial fungi were observed in 163 cases (70.26%). Dermatophytes were the most common organisms observed in 114 cases (48.27%), of which 86 cases (51.85%) were immunocompetent and 28 cases (40%) were immunocompromised. One superficial fungus could not be categorized as it had occasional yeast forms ranging in size from 1-5 microns in size. (Figure 15)

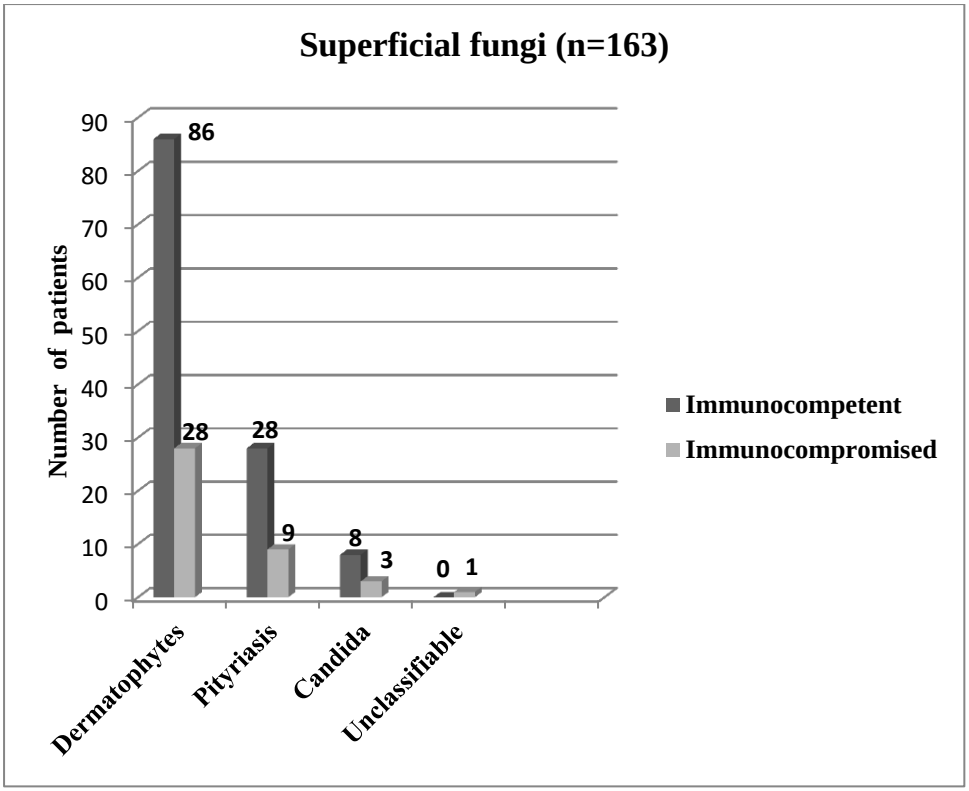


Figure 15: Superficial fungi seen among both the groups

Dermal/cutaneous fungi: Among total 56 cases (24.1%) with dermal/coetaneous fungi, further categorization based on histomorphology was made for 51 cases. (21.5%) The following two figures (Figure 16 & Figure 17) depict dermal/cutaneous fungi seen with and without granulomas among immunocompetent and immunocompromised patients. Chromomycosis was most commonly associated with granulomas whereas histoplasmosis was most commonly associated without granulomas.

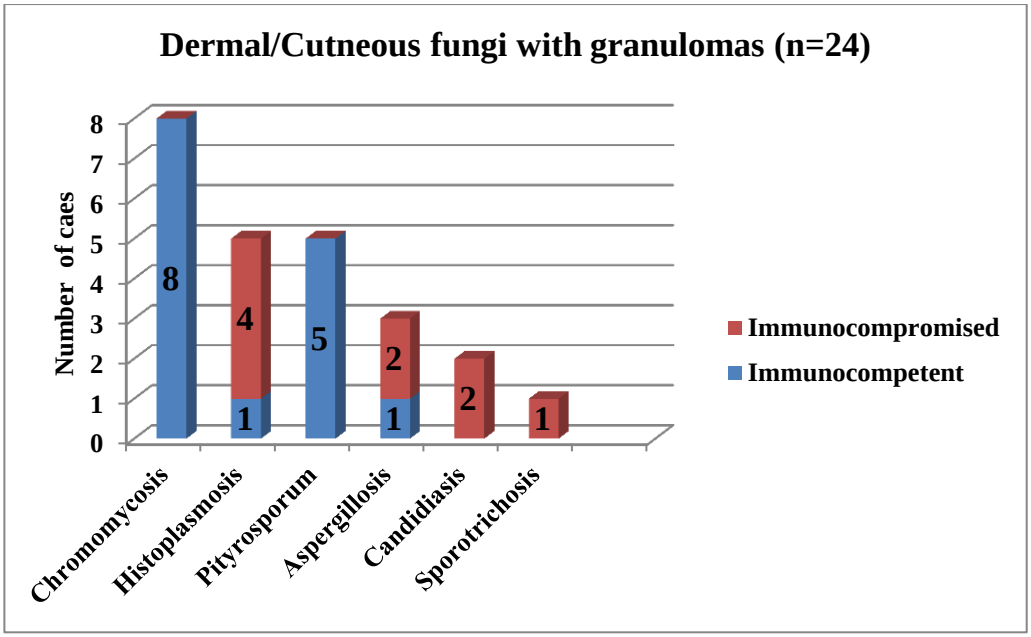


Figure 16: Dermal/cutaneous fungi with granulomas

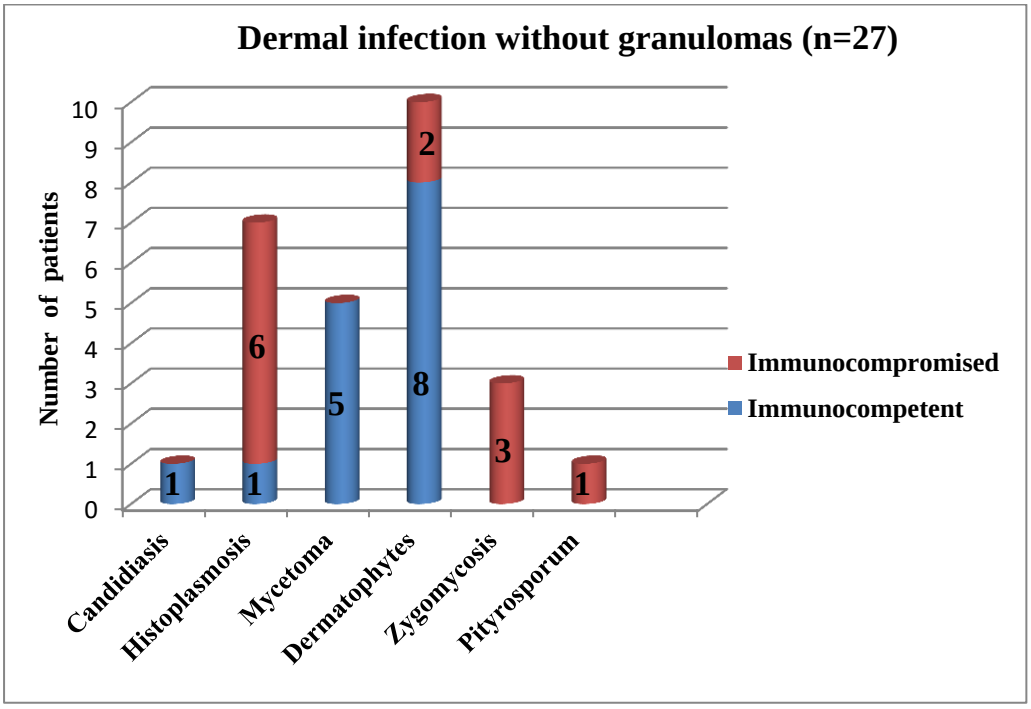


Figure 17: Dermal/cutaneous fungi without granulomas

Subcutaneous/deep fungal infections:

Among 10 cases (4.3%) with subcutaneous/deep fungal infection, further categorization based on morphology was possible for 9 cases (3.88%). The following figure depicts the subcutaneous fungal organisms seen in both the groups. (Figure 18)

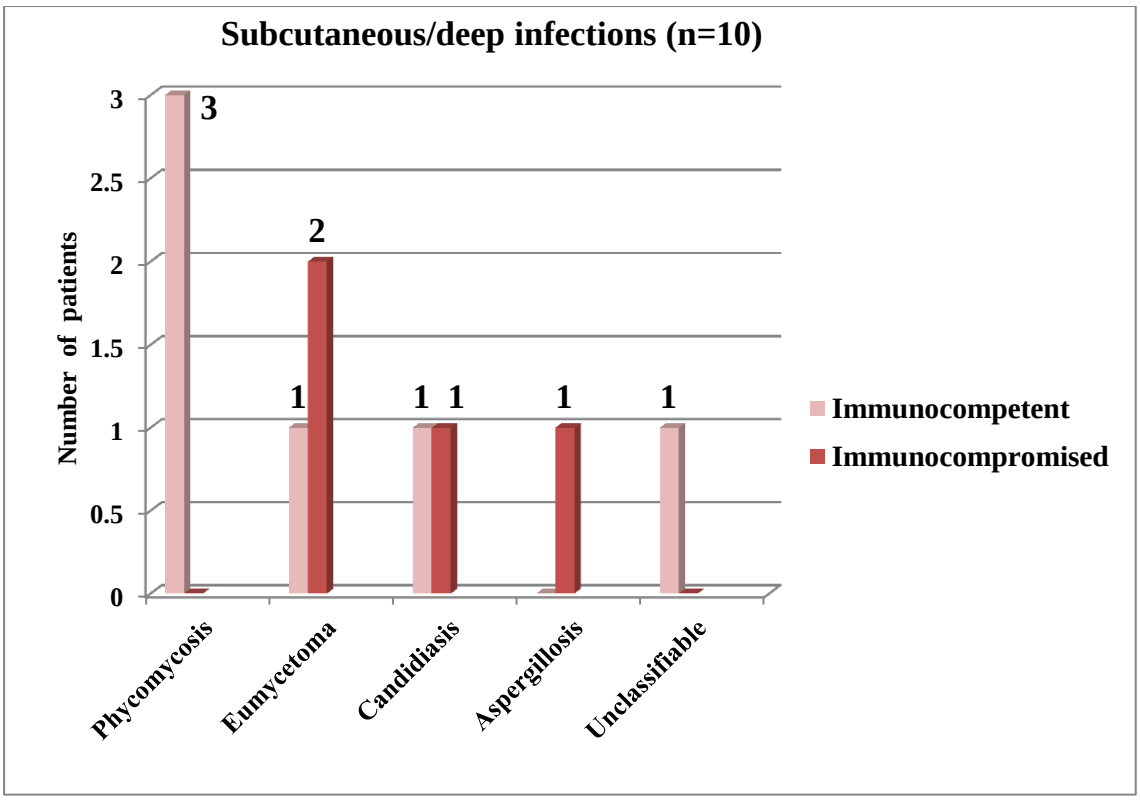


Figure 18: Subcutaneous/deep fungal infections in both the groups.

Disseminated fungal infection:

Among total 3 cases (1.3%) with disseminated fungal infection, further categorization based on histomorphology was made for 2 cases (0.86%). One immunocompetent patient had cryptococcosis and 1 immunocompromised individual had candidiasis.

Morphology of fungi: Fungal organisms were seen in various structural forms like yeasts, spore forms, hyphal, pseudohyphal forms, pigmented hyphal forms, sclerotic bodies and as granules. The dimension of these fungi varies from 1-20 microns in size.

.

Yeast forms of fungi: The following two figures depict the fungal organisms with yeast forms seen among immunocompetent (Figure 19) and immunocompromised patients (Figure 20).Dermatophytes was most commonly seen in both the groups. Candida and Histoplasma were found to be seen more among immunocompromised patients. Candidial organisms also show budding yeast and pseudohyphal forms along with yeast forms.

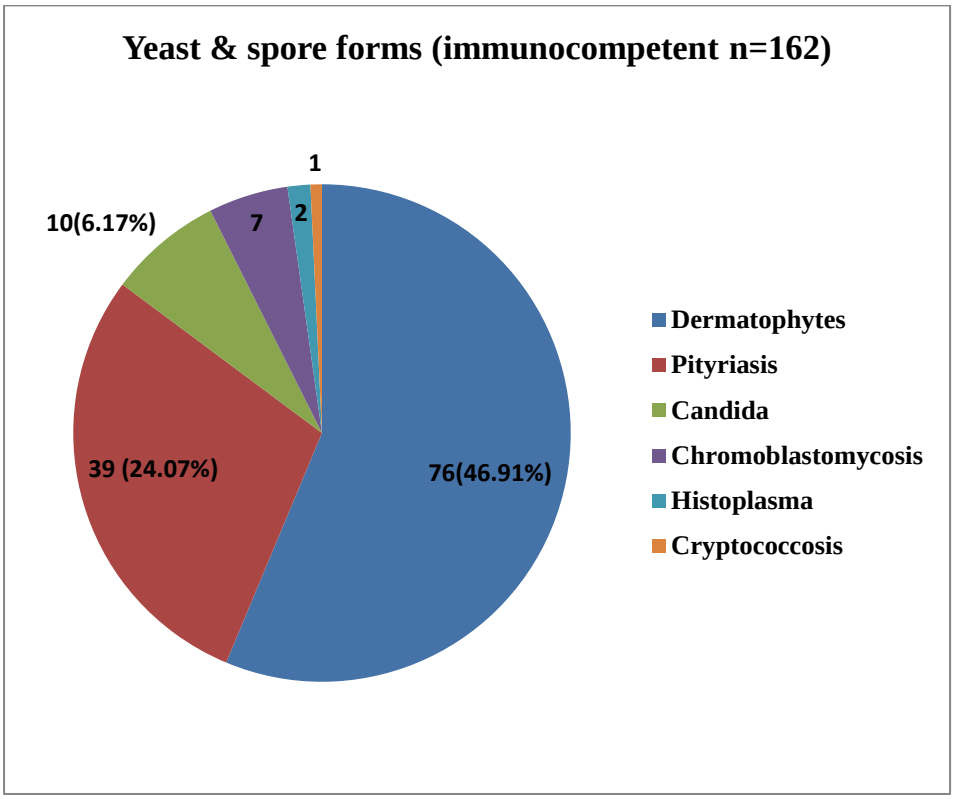


Figure 19: Yeast forms of fungal organisms seen in immunocompetent patients

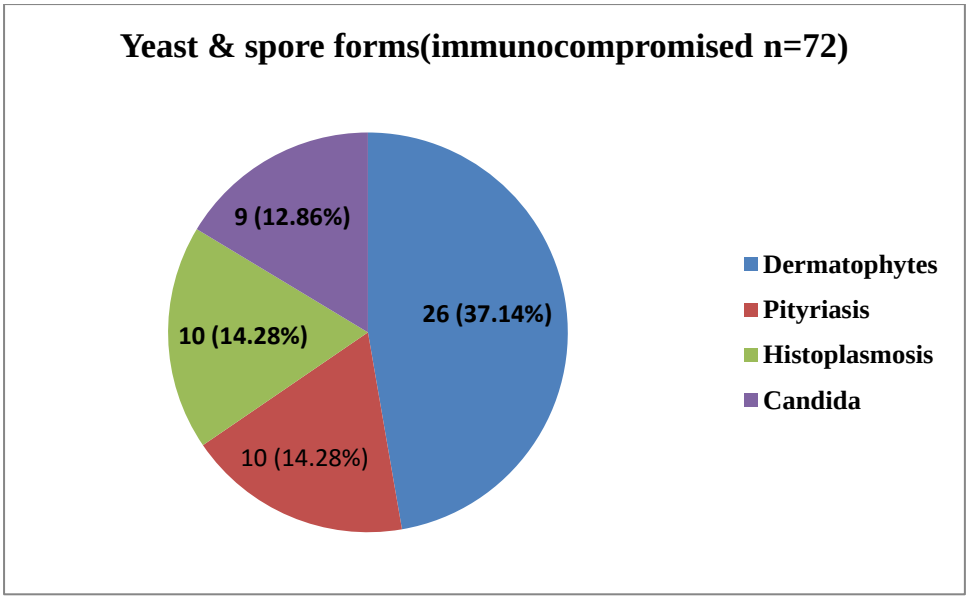


Figure 20: Yeast forms of fungal organisms seen in immunocompromised patients.

Hyphal forms of fungi: In this study hyphal forms of fungi are seen in 37 cases (15.94%). The following chart depicts various morphological forms of hyphae observed in this study. (Figure 21)

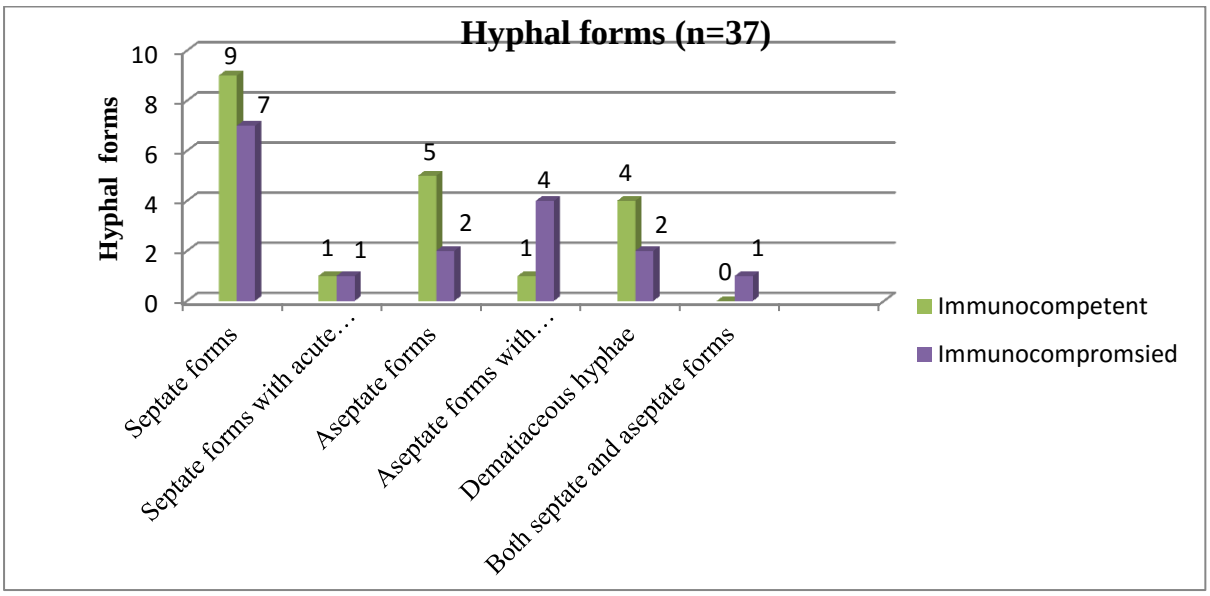


Figure 21: Various structural forms of hyphae seen in both the groups

Fungal organisms with granules: In this study totally 8 cases (3.88%) were found to have eumycotic mycetoma granules. 6 of these patients were immunocompetent and 2 were immunocompromised. Based on histomorphology 4 cases were further categorized as Madurella species. For none of the cases colour of the granules was available in the database.

Associated histological features:

Epidermal changes: A majority of cases in both the groups showed epidermal changes like hyperkeratosis (68.53%) and hyperplasia (62.06%). However in immunocompromised category spongiosis (17.14%), neutrophilic crusting (12.86%) and surface ulceration (17.14%) were present only in few cases but spongiosis was alone found to be significantly more commonly seen in immunocompromised patients as compared to immunocompetent patients ($p < 0.05$).

In the superficial fungal category the most commonly observed histological features in both the groups were epidermal hyperkeratosis (74.8%), hyperplasia (61%), chronic dermal inflammation with lymphocytes and histiocytes being the predominant inflammatory cells (76.6%). Few cases also showed other features like spongiosis (15.3%), dermal edema (16%) and dermal telangiectasia.

In the superficial fungal category the presence of epidermal hyperplasia was significantly associated with immunocompetent individuals, while spongiosis was significantly associated with immunocompromised individual with a p value of <0.05.

Accordingly the presence of epidermal histological features like hyperkeratosis hyperplasia and parakeratosis gives us the clue to look for fungal organisms. Similarly according to our study absence of eosinophilic microabscess, intraepidermal neutrophilic microabscess, sandwich sign and presence of spongiosis, neutrophilic exocytosis and neutrophilic crusting could not exclude cutaneous fungal infections. This was not statistically significant. The following table depicts the epidermal changes observed in all cases of cutaneous fungal infection. (Table 1)

Table 1: Histological features observed in epidermis of all the cases

Epidermal changes	Immuno competent patients (n=162) (n/%)	Immuno compromised patients (n=70) (n/%)	Total patients (n=232) (n/%)
Hyperkeratosis			
1. Present	**115 (70.98)**	**44 (62.86)**	**159(68.3)**
2. Absent	47 (29.02)	26 (37.14)	73(31.4)
Parakeratosis			
1. Present	65 (40.12)	25 (35.71)	90(38.8)
2. Absent	97 (59.88)	45 (64.29)	142(61.2)
Hyperplasia			
1. Present	**106(65.43)**	**38(54.28)**	**144(62.6)**
2. Absent	56(34.57)	32(45.72)	88(37.94)
Papillomatosis			
1. Present	27 (16.66)	3 (4.28)	30(12.93)
2. Absent	135 (83.34)	67 (95.72)	202(87.7)
Pseudoepitheliomatous hyperplasia			
1. Present	7(4.33)	4(5.72)	11 (4.74)
2. Absent	155(95.67)	66 (94.28)	221(95.6)
Spongiosis			
1.Present	19 (11.73)	12 (17.14)	31(13.36)
2.Absent	143 (88.27)	58 (82.86)	201(86.4)
Vesicle/bullous formation			
1. Present	2 (1.23)	1 (1.42)	3(1.3)
2. Absent	160 (98.77)	69 (98.58)	229(98.0)
Exocytosis			
1. Lymphocytic	23(14.19)	7 (10)	30(12.95)
2. Neutrophilic	**28(17.28)**	**19 (27.14)**	**47(20.25)**
3. Absent	111 (68.52)	44 (62.86)	155(66.8)
Epidermal neutrophilic microabscess			
1.Present	10 (6.17)	4 (5.71)	14 (6.03)
2.Absent	152 (93.83)	66 (94.29)	218(93.7)
Neutrophilic crusting			
1.Present	20 (12.34)	9 (12.86)	29 (12.5)
2.Absent	142 (87.65)	61 (87.14)	203 (87.5)
Eosinophilic microabscess			
1.Present	1 (0.6)	1 (1.43)	2 (0.86)
2.Absent	161 (99.4)	69 (98.57)	230(99.4)

Epidermal changes	Immuno competent patients (n=162) (n/%)	Immuno compromised patients (n=70) (n/%)	Total patients (n=232) (n/%)
Surface ulceration			
1.Present	18 (11.11)	12 (17.14)	30(12.93)
2.Absent	144 (88.89)	58 (82.86)	202(87.7)
Sandwich sign			
1.Present	6 (3.7)	3 (4.28)	9 (3.88)
2.Absent	156 (96.30)	67 (95.72)	223(96.2)
Follicular plugging			
1.Present	70 (43.2)	20 (28.57)	90(38.79)
2.Absent	92 (56.8)	50 (71.43)	142(61.2)

The following table depicts all the histological features except granulomas, observed in dermis and subcutaneous tissue. **(Table 2)**

Table 2: Histological features observed in dermis and subcutis of all the cases

Dermal & subcutaneous changes	Immuno competent patients (n=162) (n/%)	Immuno compromsied patients (n=70) (n/%)	Total patients (n=232) (n/%)
Type of dermal inflammation			
1. Acute	1 (0.61)	1 (1.43)	2 (0.86)
2. Chronic	**116 (71.6)**	**49 (70)**	**165 (71.12)**
3. Combined	45 (27.79)	20 (28.57)	65 (28.02)
Degree of inflammation			
1.Mild	**95 (58.64)**	**25 (35.71)**	**110 (47.41)**
2.Moderate	63 (38.89)	40 (57.14)	103 (44.40)
2.Severe	4 (2.47)	5 (7.14)	9 (3.89)
Perifollicular inflammation			
1.Present	27 (16.66)	12 (17.14)	39 (16.81)
2.Absent	135 (83.34)	58 (82.86)	193 (83.19)
Periadnexal inflammation			
1.Present	4 (2.47)	8 (11.42)	12 (5.18)
2.Absent	158 (97.53)	62 (88.58)	220 (94.82)
Follicularbinfection pattern			
1.Ectothrix	2 (1.23)	2 (2.86)	4 (1.72)
2.Endothrix	3 (1.86)	1 (1.43)	4 (1.72)
3.Nil	157 (96.09)	67 (95.71)	224 (96.56)
Types of inflammatory cells			
1.Lymphocytes & histiocytes	**109 (67.28)**	**45 (27.78)**	**154 (66.40)**
2.Lymphocytes, histiocytes & neutrophils	39 (24.07)	19 (27.15)	58 (25)
3.Lymphocytes, histiocytes & plasma cells	10 (6.17)	5 (7.15)	15 (6.46)
4.Lymphocytes, neutrophils & eosinophils	4 (2.48)	1 (1.42)	5 (2.14)
Dermal edema			
1.Present	15 (9.26)	13 (18.58)	28 (12.07)
2.Absent	147 (90.74)	57 (81.42)	204 (87.93)
Dermal telangiectasia			
1.Present	25 (15.44)	6 (8.58)	31 (13.36)
2.Absent	137 (84.56)	64 (91.42)	201 (86.64)
Fibrosis			
1.Present	6 (3. 70)	0	6 (2.58)
2.Absent	156 (96.30)	70 (100)	226 (97.42)
Panniculitis			
1.Present	5 (3.09)	9 (12.86)	14 (6.03)
2.Absent	150 (92.60)	57 (81.43)	207 (89.23)
3.Cannot be assessed	7 (4. 31)	4 (5.71)	11 (4.74)

Dermal & subcutaneous changes	Immuno competent patients (n=162) (n/%)	Immuno compromsied patients (n=70) (n/%)	Total patients (n=232) (n/%)
Type of panniculitis			
1.Lobular	2 (1.23)	5 (7.15)	7 (3.02)
2.Septal	3 (1.86)	4 (5.71)	7 (3.02)
3. Absent/ Cannot be assessed	157 (96.91)	61 (87.14)	218 (93.96)
Splendor-Hoeppli phenomenon			
1.Present	4 (2.46)	3 (4.29)	7 (3.02)
2.Absent	158 (97.54)	67 (95.71)	225 (96.98)
Vascular invasion			
1.Present	0	5 (7.14)	5 (2.16)
2.Absent	162 (100)	65 (92.86)	227 (97.84)
Necrosis/Infarction			
1.Present	2 (1.24)	5 (7.14)	7 (3)
2.Absent	160 (96.76)	65 (92.86)	225 (97)

The most commonly observed dermal change in our study was chronic dermal inflammation (71.12%). The inflammation was predominantly mild (47.41%) in immunocompetent patients and severe in immunocompromised individuals.

Dermal edema and more severe inflammation was found to be more in immunocompromised patients which was statistically significant with a p value of <0.05

According to our study presence of chronic dermal inflammation, associated with inflammatory cells like lymphocytes and histiocytes and dermal edema gives us the

clue to look for fungal organisms. Similarly absence of histological features like perifollicular inflammation, dermal telangiectasia, abscess formation, panniculitis and necrosis could not exclude cutaneous fungal infection.

Granulomas: Granulomas was seen in 37 cases (15.95%). 25 of these patients were immunocompetent and 12 were immunocompromised. 4 cases had necrotizing granulomas, 2 cases had suppurative granulomas and the remaining 31 cases had non-necrotizing granulomas. Twenty two cases had granulomas in the dermis, 11 cases had granulomas in the subcutis and 4 cases had granulomas involving both the dermis and subcutis. Fungal organisms within the multinucleate giant cells were seen in 13 cases. There was no statistically significant difference between the different types of granulomas seen.

Associated neoplasm of skin: There was associated neoplasm of skin observed in 7 cases (3.01%). Two of these patients had seborrheic keratosis, 2 cases had adnexal tumours, 1 case had squamous cell carcinoma, 1 case had basal cell carcinoma and 1 case had lymphoma.

Culture/skin scraping results: Among the 232 cases, culture/skin scraping was done for 128 cases and it was found to be positive in 60 cases (46.87%) and negative in 68 cases (53.13%). For the remaining 104 cases neither culture nor skin scrapping was done. So biopsy was found to be more sensitive than culture in diagnosing cutaneous mycoses. (Figure 23)

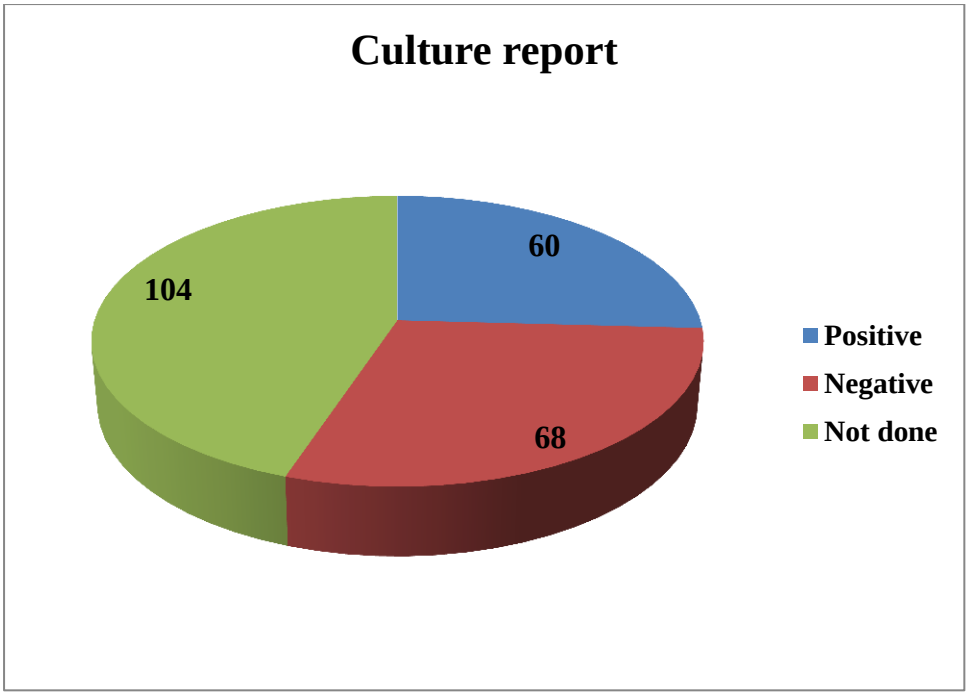


Figure 23: Culture/skin scrappings results of all cases

Blood sugar: Random blood sugar level was done in 118 cases, of which 23 cases (19.5%) were found to have abnormal blood sugar levels and 95 cases (80.5%) were found to have normal blood sugar.

CD-4 counts:

CD-4 counts were available only for 11 immunocompromised patients of which 7 cases had CD-4 count <50 cubic mm, 2 cases 51-90 cubic mm and 2 cases had 91-200 cubic mm.

Dermatophytoses:

In our study 114 patients were found to have dermatophytic infections. The most common age of presentation was between 21-40 years (36%). There was a male preponderance. (60% were males and 40% were females). House wives (25%) were the most commonly affected group followed by agricultural workers (15%).

Among 114 patients, 86 cases (75%) were immunocompetent and 28 cases (25%) were immunocompromised. Diabetes (43%) was the most commonly observed immunocompromised condition.

The most common site involved was scalp (18%) and upper extremity (18%). The most common symptom was skin lesions (31%). The most common duration of symptom was <6months (14%) followed by >5 years (13%). The most commonly observed skin lesion in immunocompetent cases was macule/papule (16%), whereas the commonly observed skin lesion in immunocompromised patients was plaque (13%).

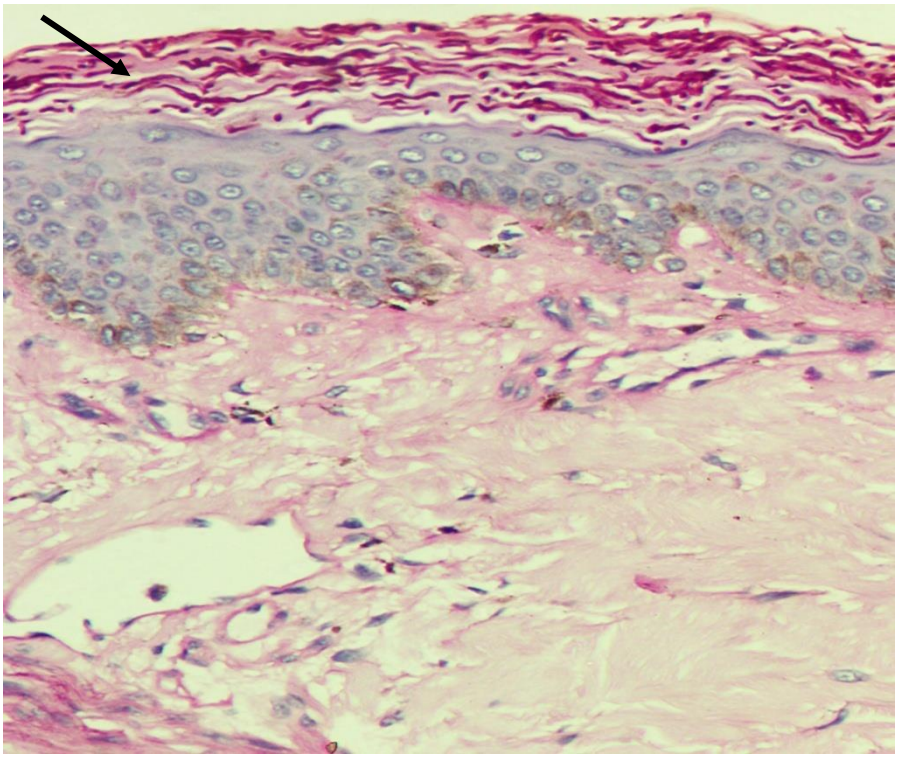
In 86 immunocompetent cases, 78 cases had fungi confined to the epidermis and 8 cases had both epidermal and dermal involvement. Among 28 immunocompromised patients 26 cases had fungi confined to the epidermis and 2 cases had both epidermal and dermal involvement. Fungal morphology was similar in both the groups.

Associated histological features:

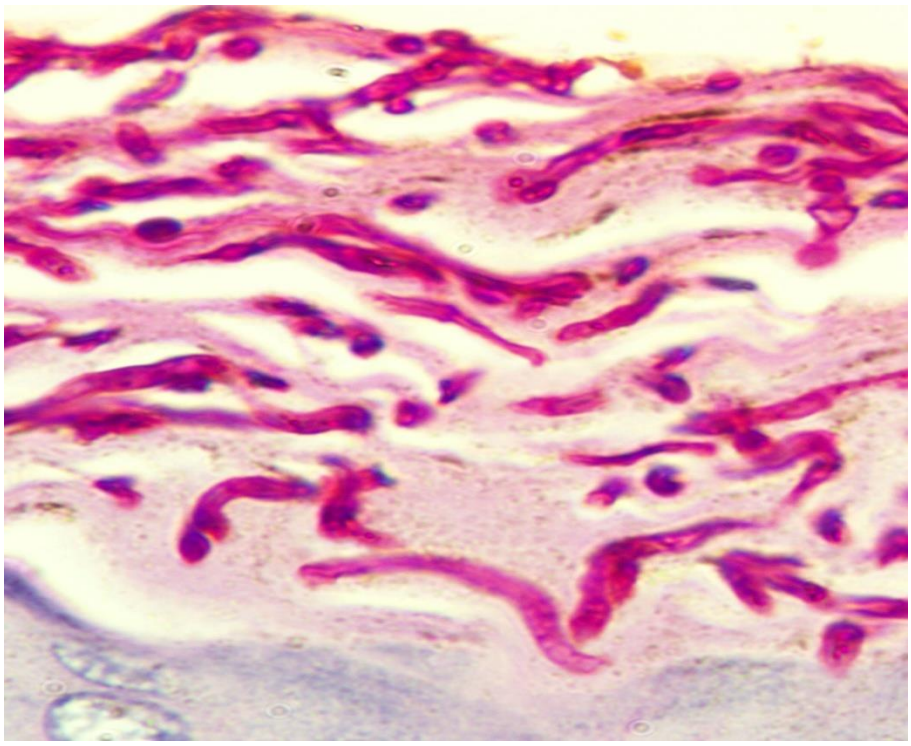
The commonly observed histological features in both the groups were hyperkeratosis (78.9%), hyperplasia (64.9%), parakeratosis (50%), mild chronic dermal inflammation

with lymphocytes and histiocytes being the predominant inflammatory cells (79.8%). Spongiosis and dermal edema and was seen more in immunocompromised patients as compared to immunocompetent patients with a significant p value of <0.05. There were no other significant differences in histological features between the two groups. Sandwich sign was noted only in 4 cases (3.5%). Similarly other histological features like neutrophilic crusting (17%), surface ulceration (8.8%), perifollicular inflammation (7.9%), periadnexal inflammation (3.5%) and intraepidermal neutrophilic microabscess (3.5%) were seen only in few cases.

Culture/skin scraping was done in 13 immunocompetent patients, of which 6 cases (46%) showed positivity, 4 cases were found to be positive for dermatophytes and 1 case was positive for Pityrosprum ovale and 1 case showed non-dermatophytic molds. Among immunocompromised patients, 9 had culture/skin scraping done, of which 5 cases (55%) showed positivity for dermatophytes and 4 cases were negative for culture. In immunocompromsied patients random blood sugar was found to be normal in 22%, elevated in 22% and for 56% cases the blood sugar report was not available.



Photomicrograph 1: Dermatophytes displaying sandwich sign (PAS at 200x)



Photomicrograph 2: Dermatophytes displaying sandwich sign (PAS at 400x)

Pityrosporum

43 patients were found to have Pityrosporum folliculitis, 33 (77%) were immunocompetent and 10 (23%) were immunocompromised. Malignancy (30%) and transplants (30%) were the common immunocompromised condition observed. The most common age of presentation was 21-40 years (39%). Most commonly affected group of patients were housewives (21%) followed by agricultural workers. (18%) Face and neck region (30%) was the most commonly involved site. The most common clinical symptom in both the groups were skin lesion (67%) with macule/papule (53%) being the most common type of lesion observed. In both the groups duration of symptoms was (<6 months, 17 cases).

In 33 immunocompetent patients, 28 cases with pityrosporum were confined to the hair follicle, 5 cases had perifollicular dermal involvement with granulomatous inflammation. Of the 10 immunocompromised patients 9 cases had pityrosporum confined to the hair follicle, and one case had perifollicular dermal involvement without granuloma formation. Immunocompetent patients were more likely to have granulomas compared to immunocompromised patients though this is not statistically significant. Fungal morphology was similar in both the groups.

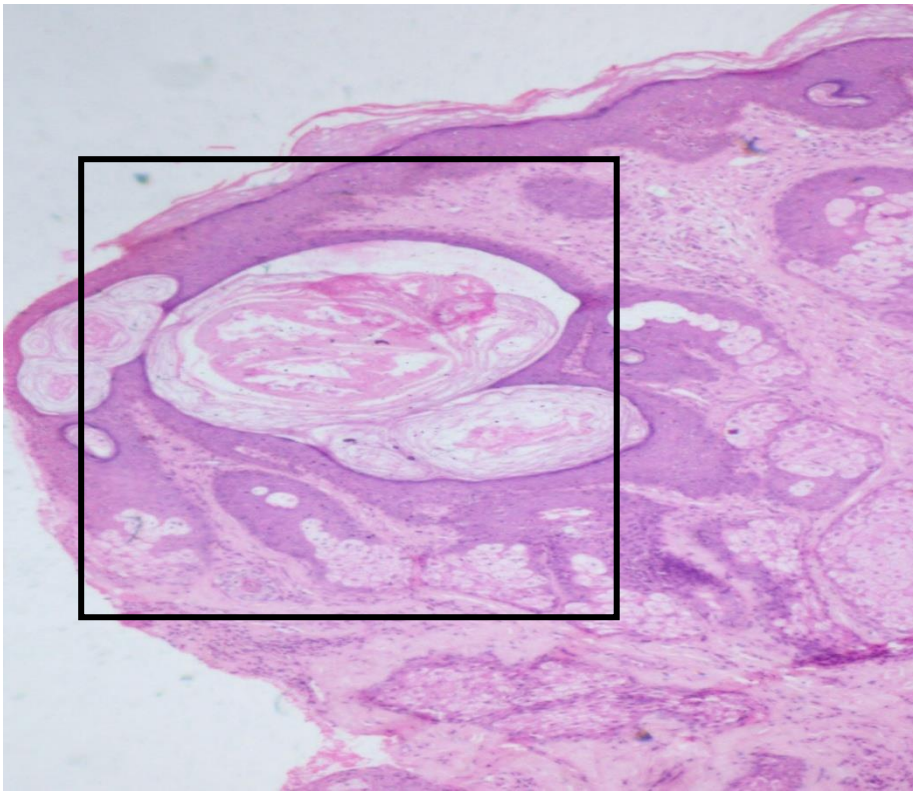
Associated histological features:

The commonly observed histological changes in both the groups were follicular plugging (89%), hyperkeratosis (63.5%) and hyperplasia (54%). Perifollicular inflammation and intensity of dermal inflammation were found to be more in immunocompromised patients (50% & 90%) as compared to immunocompetent

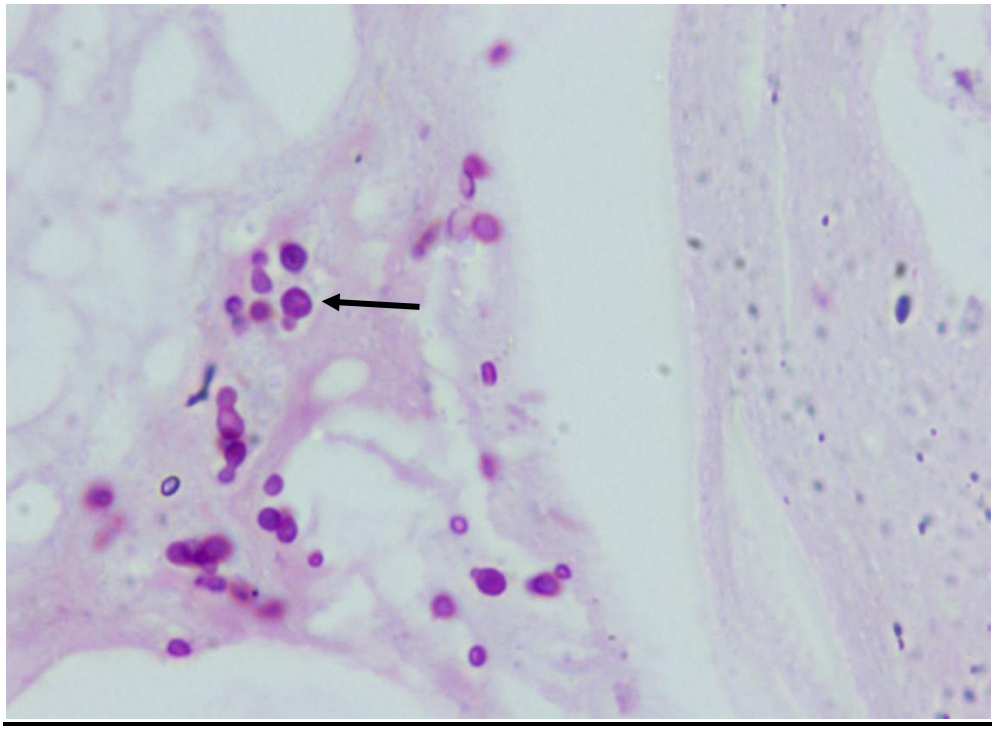
individuals (39% & 81%). There were no other significant differences in histological features among both the groups. A minority of the cases showed other features like parakeratosis (19%), dermal telangiectasia (17.5%) and non-necrotising granuloma (15%).

Culture/skin scraping was done for 6 (18%) immunocompetent patients and 3 (9%) were positive for pityrosporum ovale and 1 was positive for dermatophytes. In immunocompromised group, culture/skin scraping was done for 3 cases (30%), 2 cases (20%) were positive for pityrosporum and 1 case was negative.

In immunocompromised group 1 case (10%) was found to have normal blood sugar level, 6 cases(60%) were found to have elevated blood sugar levels and for 3 cases (30%) blood sugar was not available.



Photomicrograph 4: Pityrosporum folliculitis with dilated follicle plugged with keratinous material (H&E at 200x)



Photomicrograph 5: Yeast and budding yeast forms of Pityrosporum (PAS at 400x)

Candidiasis:

In our study 16 patients (7%) were found to have candidiasis, 10 were immunocompetent (63%) and 6 (37%) were immunocompromised (8%). The most commonly observed immunocompromised condition were transplant (33%) (2 bone marrow transplant) and patients on immunosuppressant (33%). The most commonly affected age group was 21-40 years with 8 cases (50%). The most commonly affected group of patients were students (50%).

In immunocompetent patients lower extremity (30%) was the most common site, whereas in immunocompromised individuals upper extremity (50%) was the most commonly affected site. Most common symptoms among both the groups were skin lesions (62%) with plaque (50%) being the most common type of lesion. The duration of symptoms were mostly <6 months, 9 cases (56%).

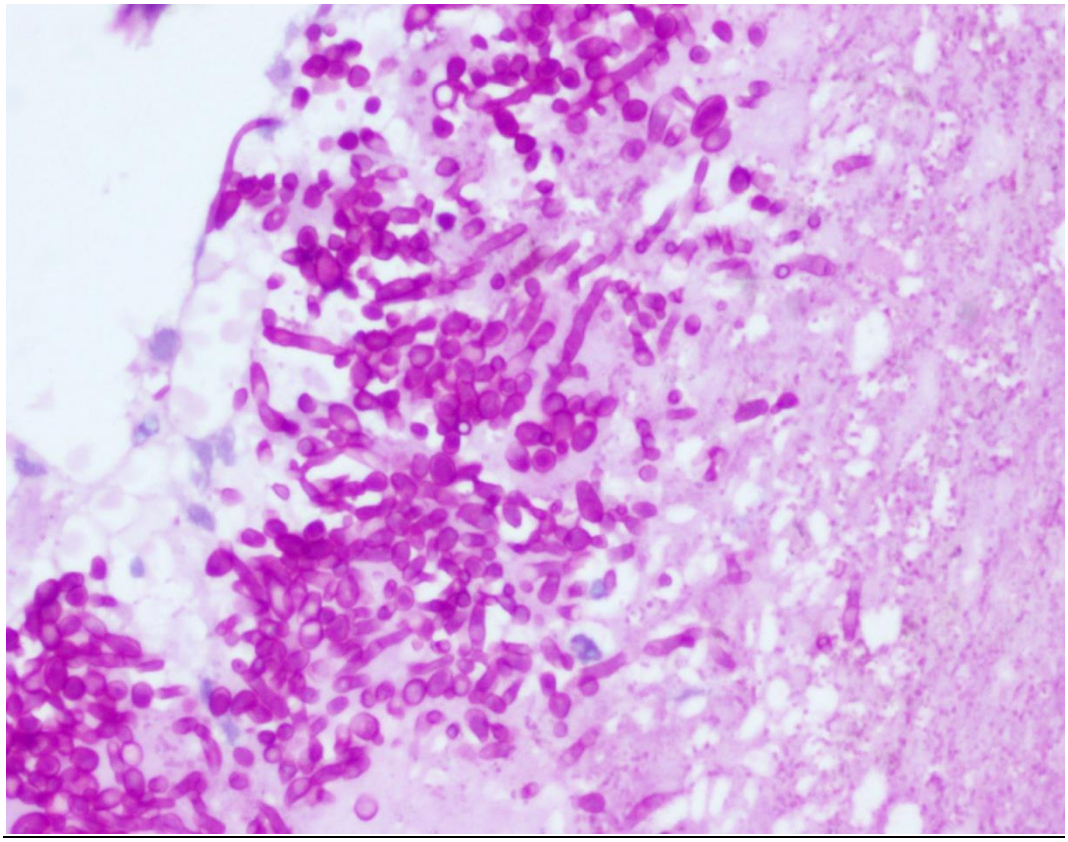
In immunocompetent patients 8 cases (50%) were found to have superficial candidiasis confined to the epidermis. Dermal involvement was seen only in 1 case which did not have granulomas and subcutaneous candidial infection was seen in 1 case (6%). In immunocompromised patients 3 cases (50%) were found to be superficial candidial infection confined to epidermis, 2 cases (33%) had dermal involvement with granulomas, and 1 case (17%) was in subcutis without granulomas. Fungal morphology was similar in both the groups.

Associated histological features:

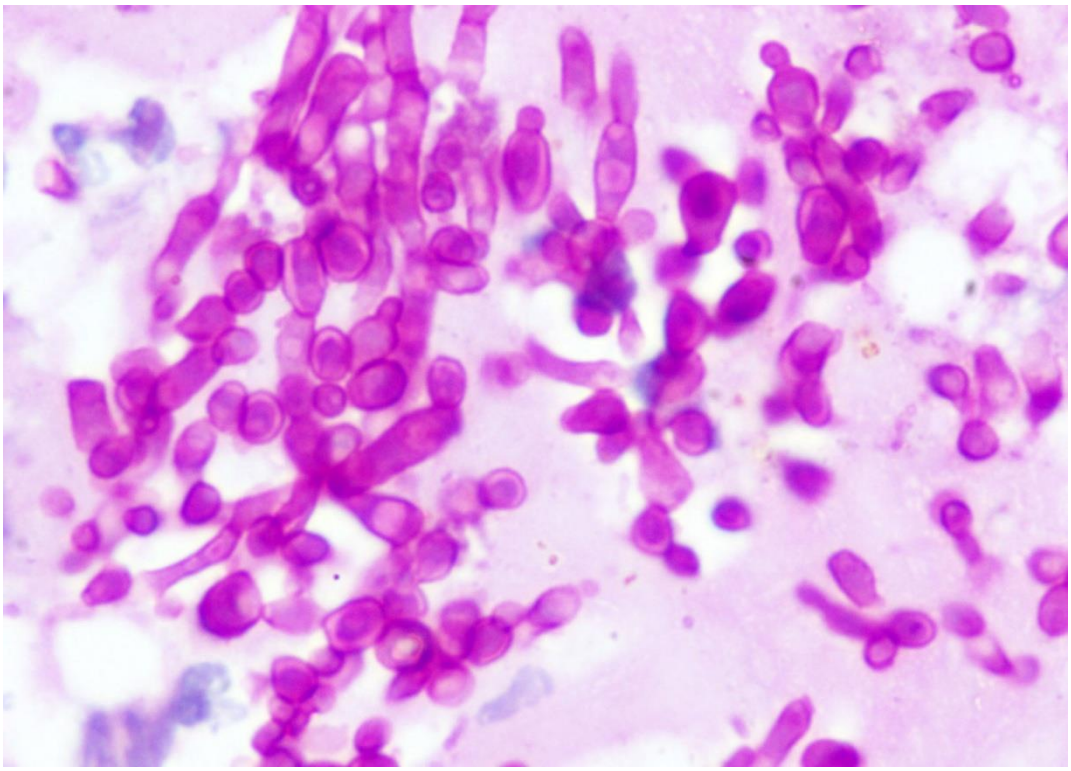
The commonly observed histological features in both the groups were hyperplasia (63.5%), hyperkeratosis (58.5%), parakeratosis (40%) moderate acute on chronic inflammation with lymphocytes, histiocytes and neutrophils being the predominant inflammatory cells (50%). Neutrophilic exocytosis (50%), non-necrotising granulomas (50%), lobular panniculitis (67%), vascular invasion (16%) and infarction (16%) were found to be more commonly seen in immunocompromised patients as compared to immunocompetent individuals though they were not statistically significant. There were no other significant differences in histological features among both the groups. Few of the cases showed other features like intraepidermal neutrophilic abscess (16%) and surface ulceration (13%).

Associated bacterial colonies were seen in 2 (20%) immunocompetent cases and 1 (16%) immunocompromised patient. Recurrence was seen in one immunocompetent case (16%).

In immunocompetent group culture was found to be positive in 3 cases, 2 showed Candida and one showed dematiaceous fungi (10%) and culture was negative in 7 cases (70%).In 6 immunocompromised patients, 2 cases (33%) were found to be positive for Candida and 1 case (16%) was positive for filamentous fungi and 3 cases (50%) were found to be culture negative. In immunocompromised group, 3 cases(50%) were found have normal blood sugar level 1 (16%) case was found to have elevated blood sugar level and for 2 cases(33%) blood sugar level were not available.



Photomicrograph 5: Yeast, budding yeast & pseudohyphal forms of Candida (PAS at 400x)



Photomicrograph 6: Yeasts, budding yeasts & pseudohyphal forms of Candida (PAS at 1000x)

Histoplasmosis:

Thirteen cases (6%) were found to have histoplasmosis. Two of these cases (15%) were immunocompetent and 11 cases (85%) were immunocompromised. HIV-AIDS (91%) was found to be the most commonly associated immunocompromised condition. Housewives (38%) were found to be most the commonly affected group. The most common age of presentation was found to be 21-40 years (69%).

In immunocompetent (100%) and immunocompromised (73%) patients face and neck region was the most commonly involved site. Skin lesion and ulcer was the common clinical presentation in both immunocompetent (50%&50%) and immuncompromised patients (72%&18). The commonly observed duration of symptoms was less than 6 months in both the groups (77%).

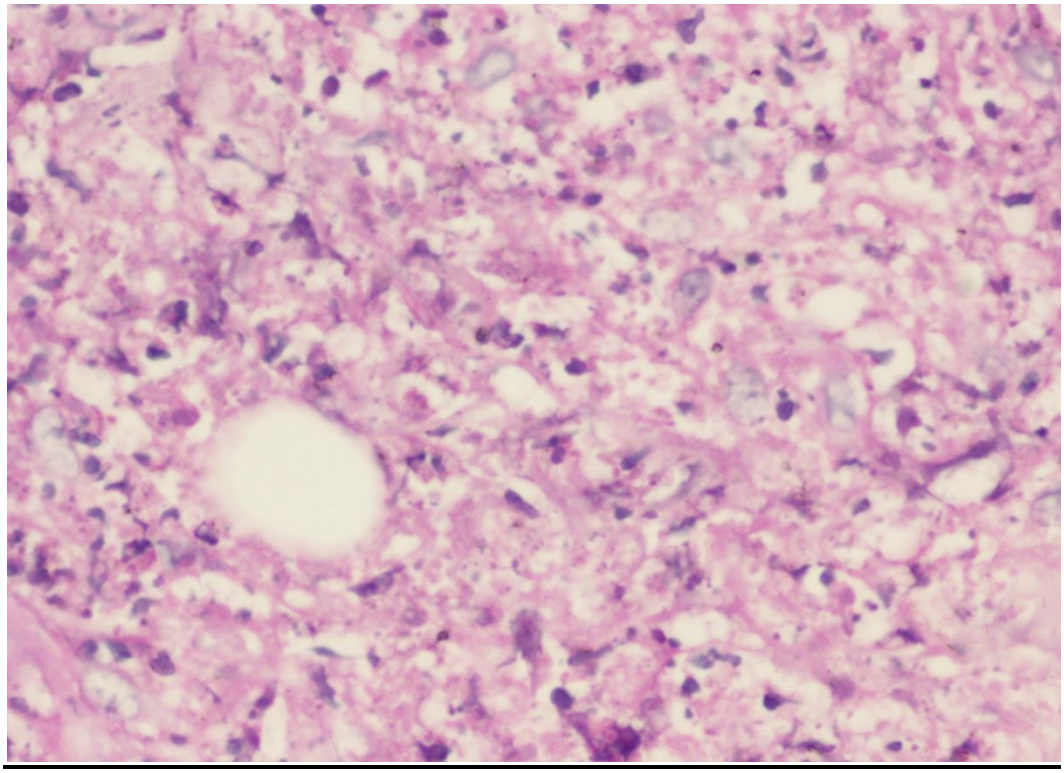
In immunocompetent patients the type of skin lesion observed was plaque (50%) and ulcer (50%), whereas in immunocompromised patients the commonly observed type of skin lesion was macule/papule (72%). In immuocompetent patients, 50% was seen in dermis with associated granuloma and 50% case was seen in dermis without granulomas. In immunocompromised patients 36% of the cases had dermal involvement with associated granulomas, 64% of the cases had dermal involvement with associated inflammation but no granulomas. Fungal morphology was found to be similar in both the groups.

Associated histological features:

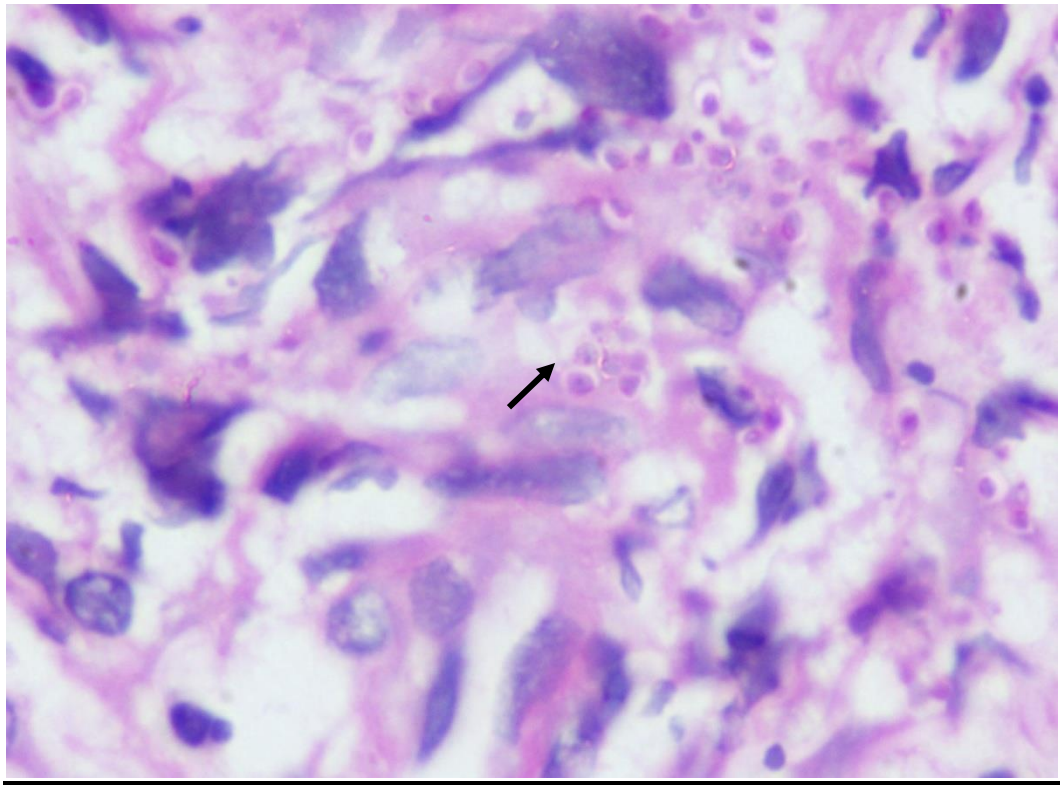
The commonly observed histological features in both the groups were hyperkeratosis (52.3%) and moderate chronic inflammation with lymphocytes, histiocytes and plasma cells being the predominant inflammatory cells (56.8%). Surface ulceration and dermal granulomas were found to be more commonly seen in immunocompetent patients (50% & 50%) when compared to immunocompromised individuals (9%&36%). Few of the cases showed other features like parakeratosis (17%), spongiosis (6%), intraepidermal neutrophilic abscess (6%) and lobular panniculitis (9%).

In immunocompetent patients culture was found to be positive in 1(50%) of the 2 cases and in immunocompromised patients culture was found to be positive in 7 (64%) out of 11 cases.

In immunocompromised patients blood sugar level was found to be normal in 3 cases (27%) and for 8 cases (73%) blood sugar level was not available. In immunocompromised patients CD-4 count was under <50 cubic mm for 7 cases(64%), for 2 cases(18%) it was 51-200cubic mm and for 2 cases CD-4 count (18%) was not available.



Photomicrograph 7: Histoplasmosis (H&E at 400x)



Photomicrograph 8: Histoplasmosis (PAS at 1000x)

Sporotrichosis:

In our study 1 case (0.43%) was found to have sporotrichosis, who was a known diabetic. The affected site was lower extremity, with swelling as the presenting complaint, the type of lesion was nodule and the duration of symptom was for <6 months. The fungi were seen in dermis associated with granulomatous inflammation and neutrophilic microabscess.

Fungal organism was seen as described. Characteristic "Sporothrix asteroid body was not found.

Associated histological findings:

The observed histological features was hyperkeratosis, parakeratosis, pseudoepitheliomatous hyperplasia, spongiosis, neutrophilic exocytosis, dermal neutrophilic microabscess with inflammatory infiltrates of lymphocytes, plasma cells and neutrophils, dermal telangiectasia and suppurative granulomas.

Culture was found to be positive for Sporothrix schenckii. Random blood sugar was found to be elevated >220.

Subcutaneous phycomycosis

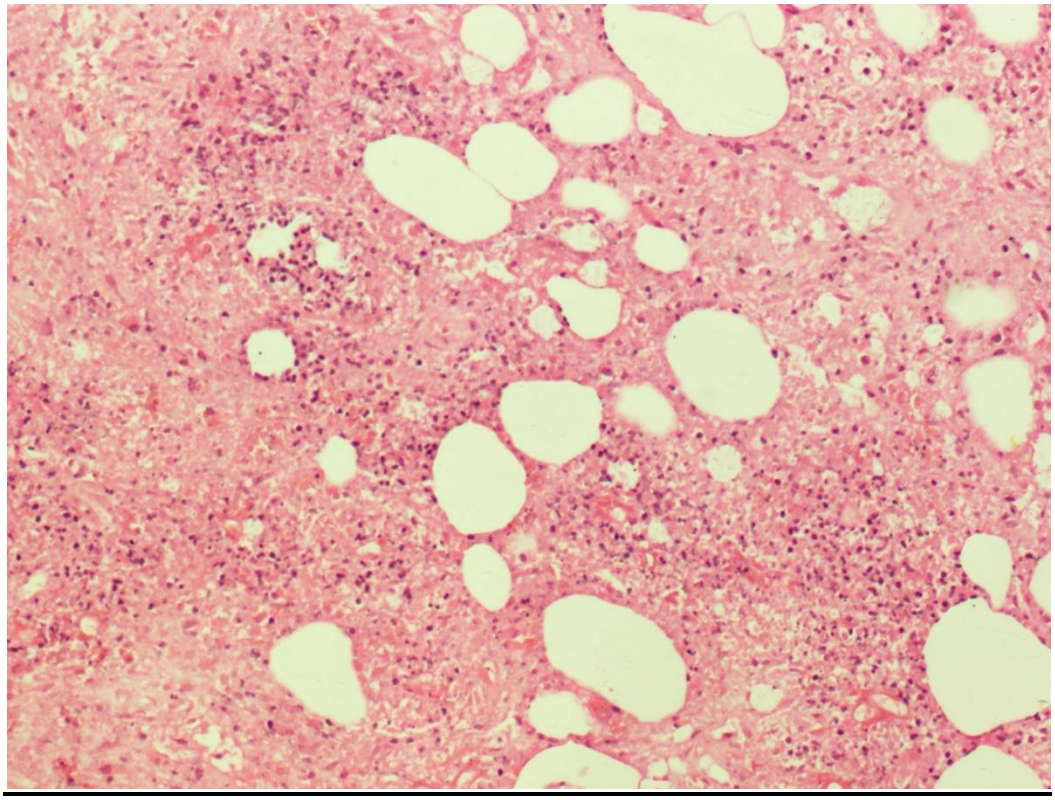
In our study 3 cases (1.3%) were found to have subcutaneous phycomycosis and all the three were immunocompetent. Housewives were the most common affected groups (66.7%). The most commonly affected age group was 21-40 years (50%).

The most commonly involved site was lower extremity 2 cases (67%). The common clinical symptom was skin lesion (100%). All the 3 cases fungi were seen in subcutis. Fungal organism was seen as described

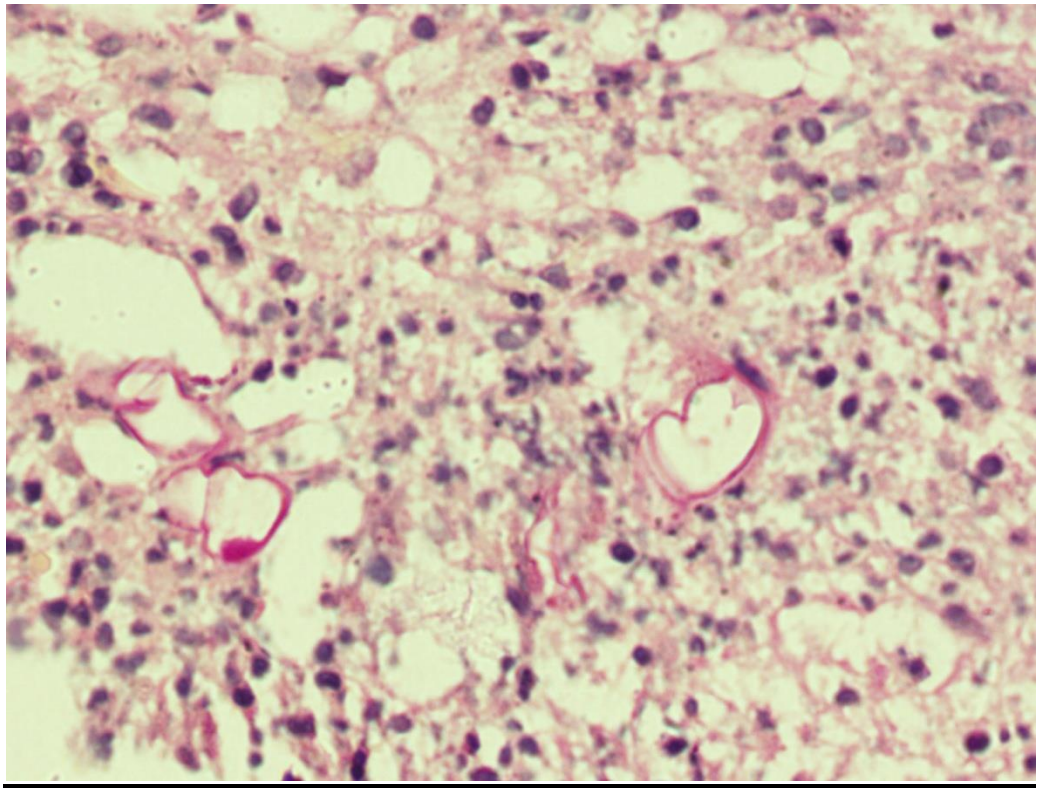
Associated histological features

The commonly observed histological features were epidermal hyperplasia (67%), moderate chronic dermal inflammation with lymphocytes, histiocytes and eosinophils being the predominant inflammatory cells (50%), granulomas (67%), lobular panniculitis (67%) and Splendore-Hoeppli phenomenon (67%).

All the 3 cases (100%) were found to be culture positive for Basiodiobolus. Recurrence was seen in one case (33%).



Photomicrograph 9: Subcutaneous phycomycosis (H&E at 200x)



Photomicrograph 10: Subcutaneous phycomycosis (PAS at 400x)

Zygomycosis:

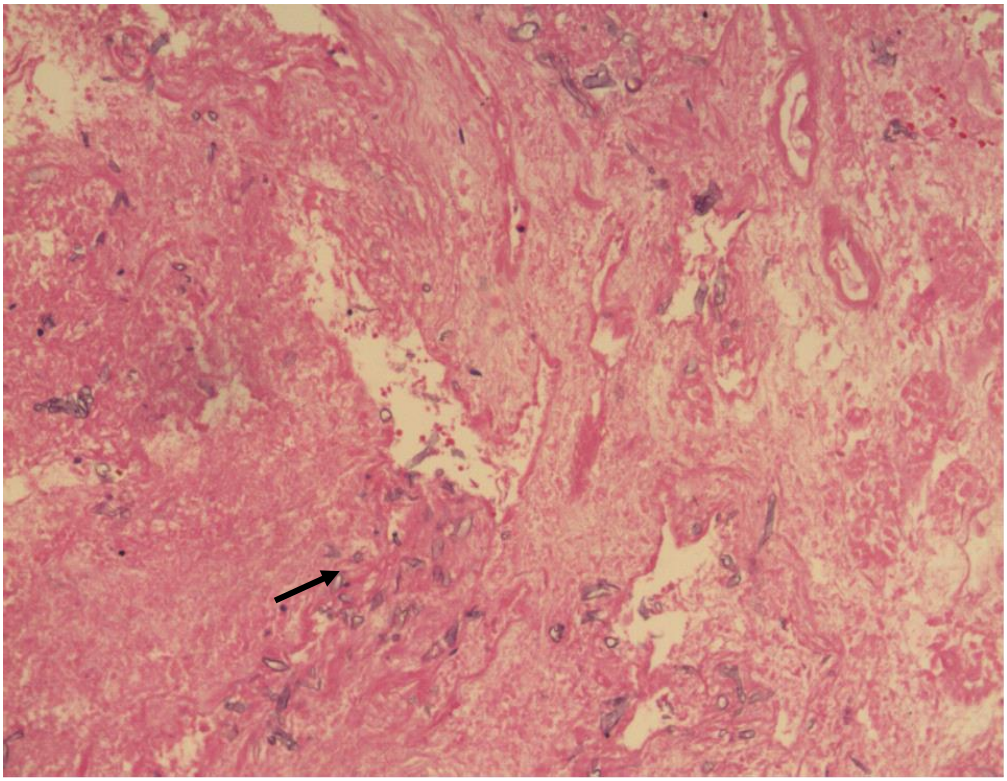
In our study 3 cases (1.3%) were found to have zygomycosis and all the three were immunocompromised. There was a male preponderance (67%). The most commonly affected age group was 41-60 years (67%).

The most common symptom was skin lesion (100%), with common duration of symptom being <6 months. All the three cases fungi were seen in dermis without associated granulomas. Fungal organism was seen as described

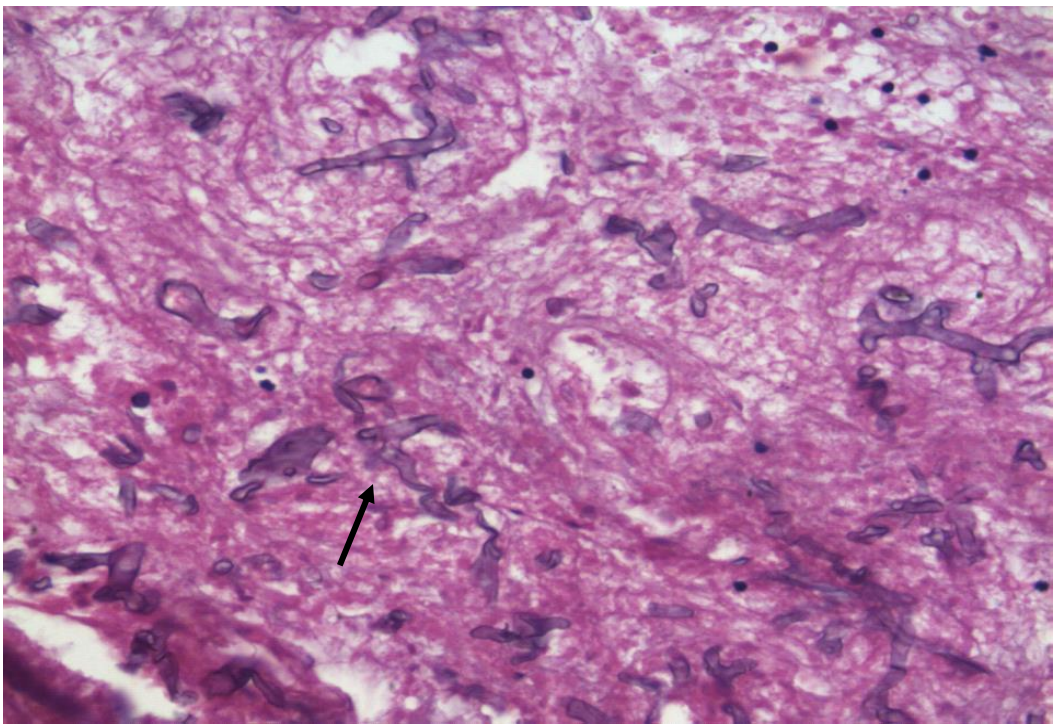
Associated histological features:

The most commonly associated histological features were hyperkeratosis (100%), hyperplasia (100%), moderate chronic dermal inflammation with lymphocytes, histiocytes and eoisnophils being the predominant inflammatory cells (100%) and vascular invasion (67%).

Two cases (67%) were culture positive of which 1 case was positive for Mucor (33%) and 1 case (33%) was positive for Fusarium. Recurrence was seen in one case (33%).



Photomicrograph 11: Zygomycosis with infarction and vascular invasion (H&E at 200x)



Photomicrograph 12: Zygomycosis (H&E at 400x)

Chromomycosis:

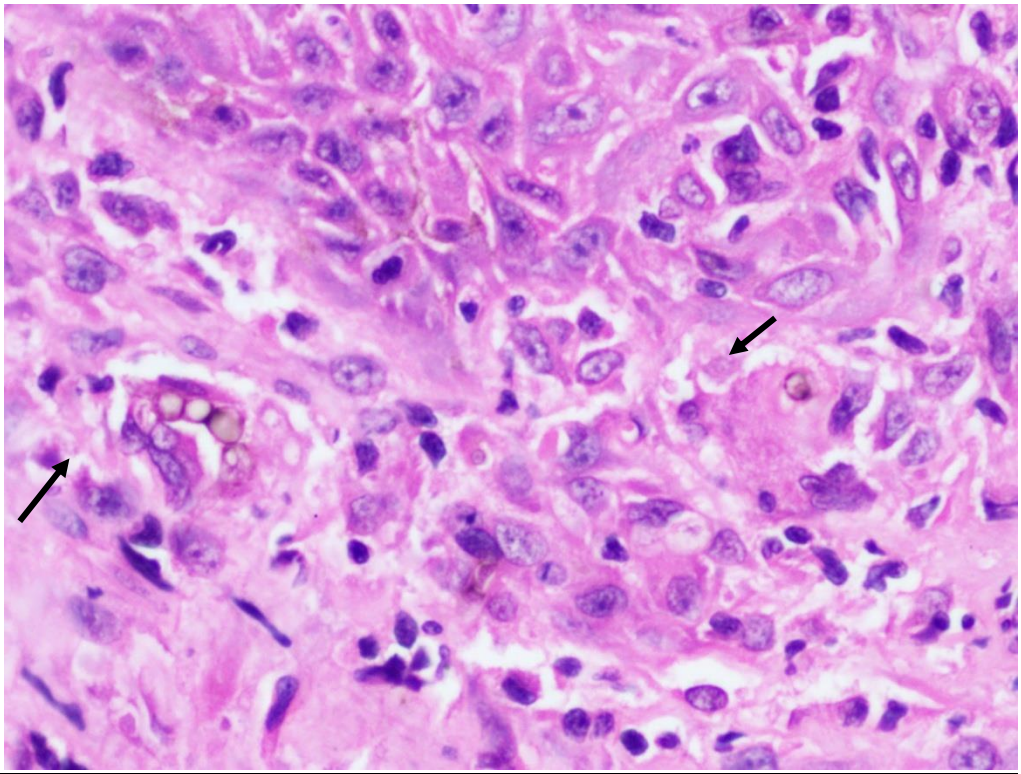
All 8 cases (3.4%) of chromomycosis observed in our study were seen in immunocompetent patients with a male preponderance (100%).

The common site involved was upper extremity (37.5%) and lower extremity (37.5%), common symptom was skin lesions 6 cases (75%), with macule/papule (37.5%) being the common type of lesion and common duration of symptom was > 5years (37.5%). All our cases (100%) fungi were seen in dermis with associated granulomatous inflammation. Fungal organism was seen as described.

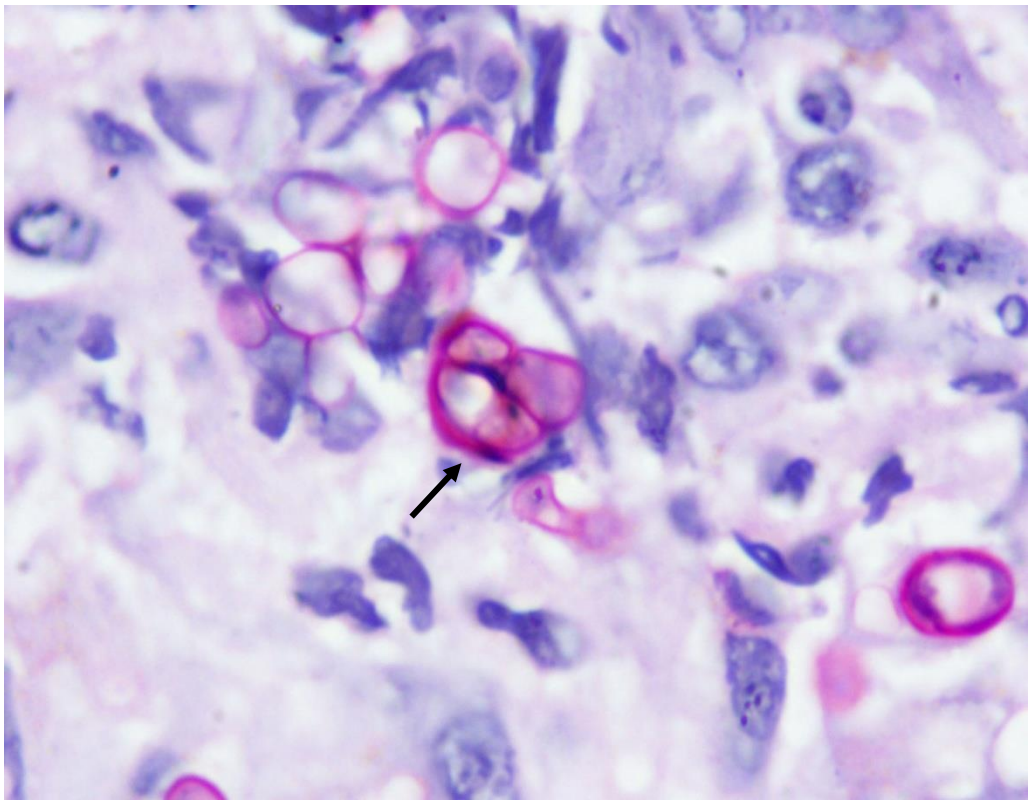
Associated histological features:

The commonly observed histological changes were pseudoepitheliomatous hyperplasia (90%), parakeratosis (63.5%), hyperkeratosis (50%), moderate acute on chronic dermal inflammation with lymphocytes, histiocytes, plasma cells and neutrophils being the predominant inflammatory cells (73.5%), dermal granulomas (100%) (2 non-necrotising and 1 suppurative granuloma), dermal abscess (60%) and fungal organisms seen within the multinucleate giant cells (53.5%). Few cases had other features like surface ulceration (12.5%) and transepidermal elimination of fungi (12.5%). Recurrence was observed in 1 case (12.5%).

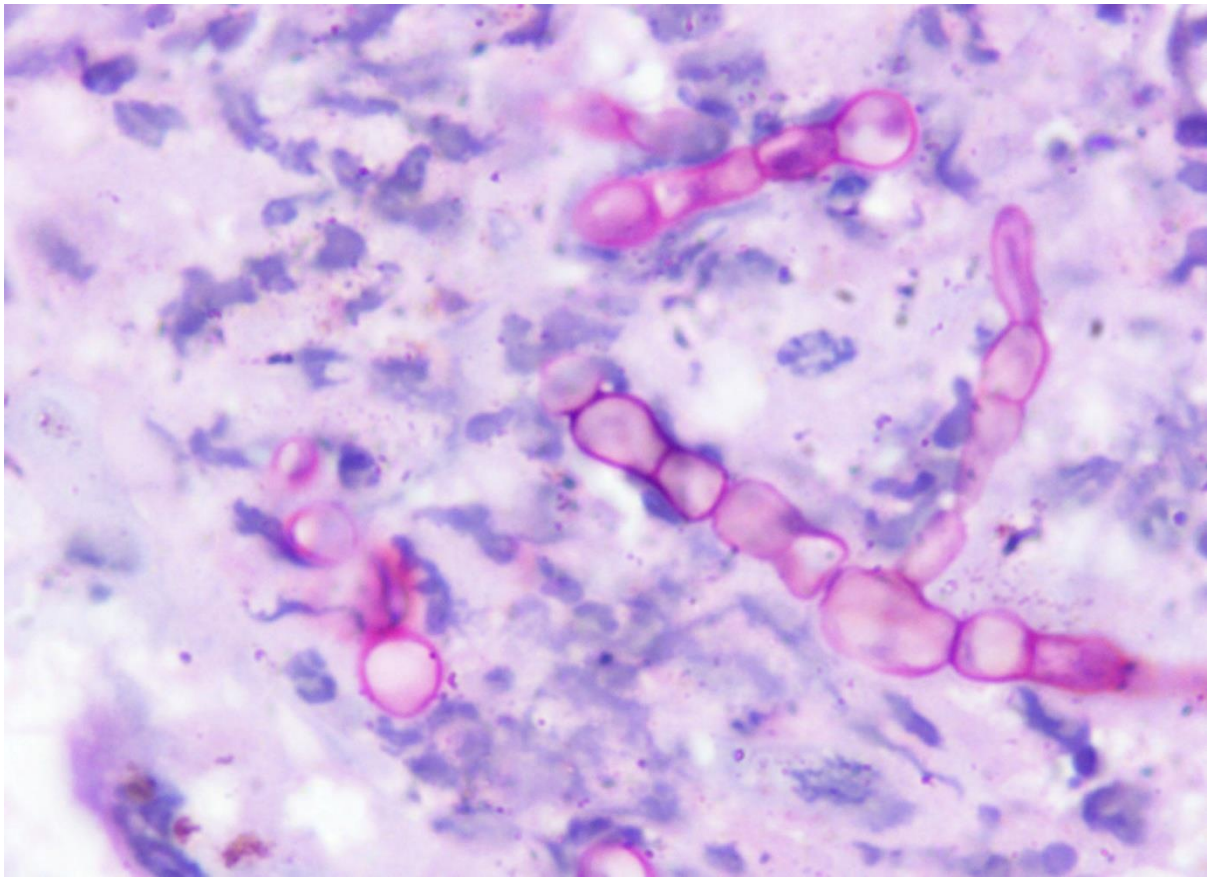
Seven cases (87.5%) were positive for culture, 3 cases were positive for Fonsacea pedrosoi (37.5%), 3 cases were positive for dematiaceous fungi (37.5%) and 1 case was positive for Philophora (12.5%).



Photomicrograph 13: Chromomycosis (H&E at 400x)



Photomicrograph 14: Chromomycosis with sclerotic bodies (PAS at 1000x)



Photomicrograph 15: Chromomycosis with hyphal forms (PAS at 400x)

Aspergillosis:

In our study 4 cases (1.7%) were found to have Aspergillosis, of which 3 were (75%) immunocompromised patients. The most commonly associated immunocompromised condition was HIV-AIDS (67%). There was a male preponderance (100%). Agricultural workers (50%) and clerical workers (50%) were commonly affected group, with the commonly affected age group being 21-40years (50%) and 41-60 years (50%).

In immuocompetent patients the site involved was upper extremity whereas in immunocompromised patients face & neck, abdomen and lower extremity was involved. Ulcer (67%) was the common symptom observed in both the groups. The duration of symptoms was >5 years in the immunocompetent patient, whereas in immunocompromised patients most common duration of symptoms was <6 months (100%). In the immunocompetent patient the fungus was seen in dermis with associated granuloma. In immunocompromised patients 2 cases were seen in dermis with associated granulomas and 1 case was seen in subcutis. Fungal morphology was similar in both the groups.

Associated histological findings:

The commonly observed histological changes in both the groups were hyperkeratosis (50%), hyperplasia (50%), parakeratosis (50%), and moderate chronic dermal inflammation with lymphocytes, histiocytes and plasma cells being the predominant inflammatory cells (58.5%). Few histological features like vascular invasion (33%),

necrosis (33%) and panniculitis (33%) were seen more commonly in immunocompromised patients, though they were not statistically significant.

In immunocompetent patient culture was found to be positive for filamentous fungi, and in immunocompromised patients 1 case was found to be positive for Aspergillus (33%) and 2 cases (67%) showed no growth.

In immunocompromised patients random blood sugar level was not available for 3 cases.

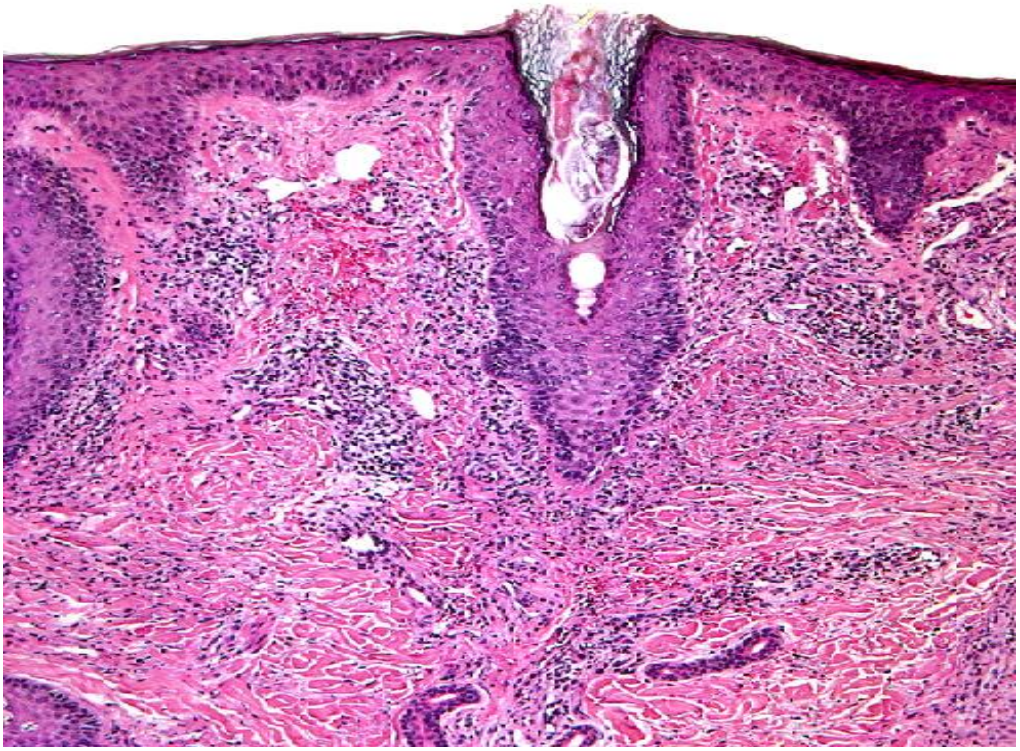
Cryptococcosis

In our study 1 immunocompetent patient was found to have cryptococcosis (12.5%) and lower extremity was the involved site. The presenting symptom was nodular lesion with the duration symptom being <6 months. Fungal morphology was observed as described.

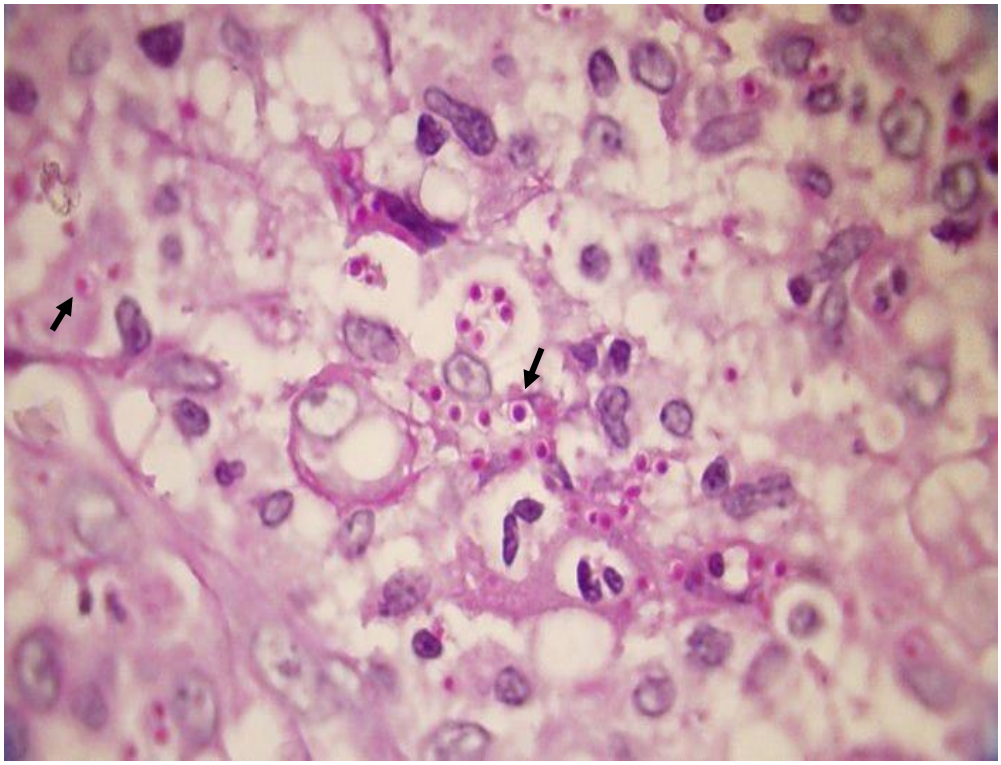
Associated histological features:

The observed histological features included hyperkeratosis, follicular plugging, perifollicular inflammation, chronic moderate dermal inflammation, granulomas in subcutis and lobular panniculitis.

Culture was found to be positive for Cryptococcus and CD-4 count was not available.



Photomicrograph 16: Cryptococcosis (H&E at 200x)



Photomicrograph 17: Cryptococcosis (PAS at 400x)

Eumycetoma

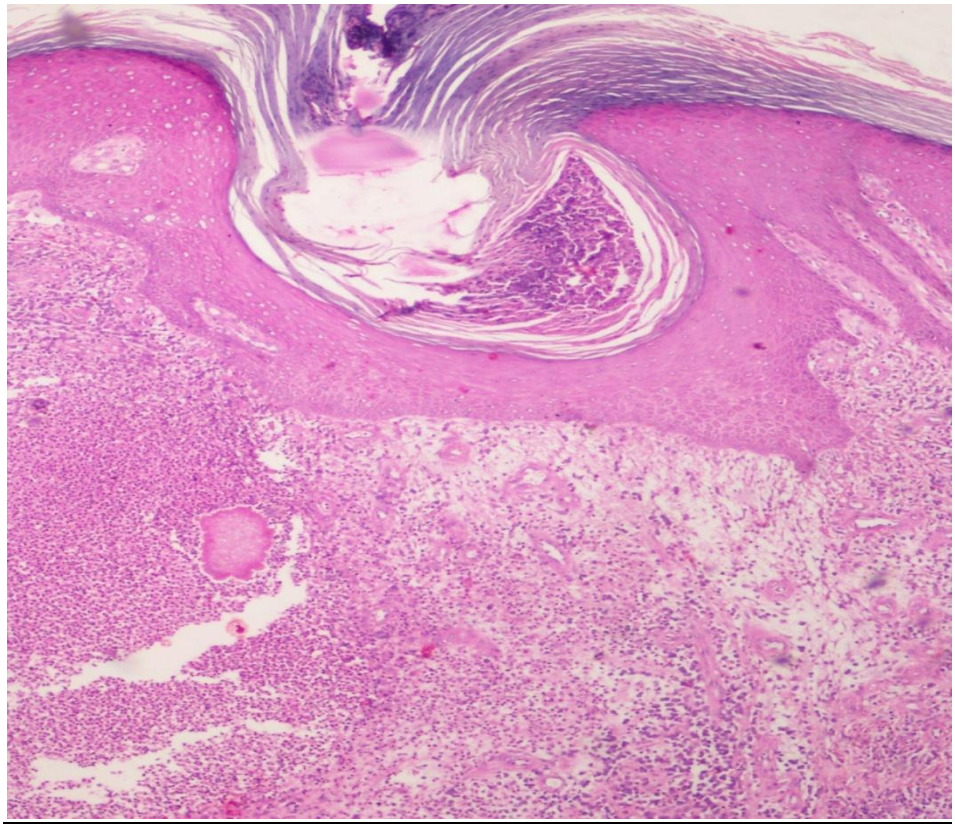
In our study 8 cases (3%) were found to have eumycetoma, 6 cases were in immunocompetent (75%) and 2 cases (25%) were in immunocompromsied patients, with chronic disease associated immune dysfunction as the most common immunocompromised condition (100%).

In both the groups lower extremity (87%) was the commonest site involved, common symptoms was ulcer 3 cases (37%) and common type of lesion was ulcer (50%). In immunocompetent patients for 5 cases (83%) the grains were seen in the dermis and 1 case (17%) was seen in subcutis. In immunocompromised patients 2 cases (100%) were seen in subcutis. There were no granulomas. Fungal morphology was similar in both the groups.

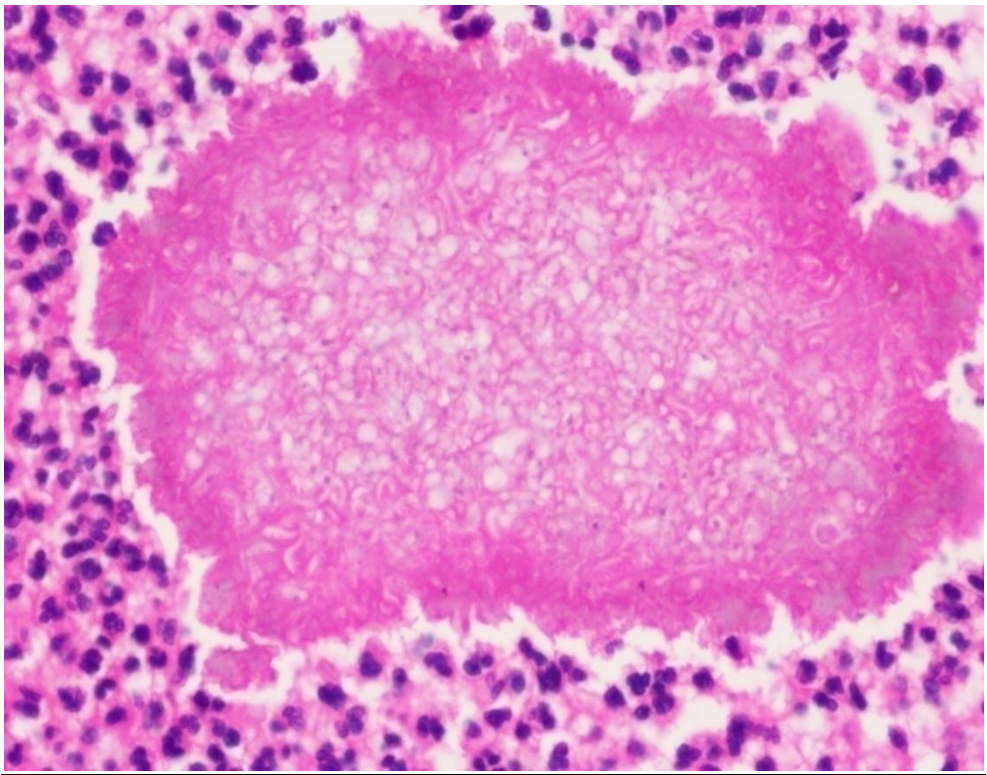
Associated histological features: The commonly observed histological changes in both the groups were hyperplasia (58.5%), hyperkeratosis (50%), surface ulceration (55%), moderate chronic dermal inflammation with lymphocytes, histiocytes and neutrophils being the predominant inflammatory cells (75%) and Splendore-Hoeppli phenomenon (75%). There were no other significant differences in histological features among both the groups. Few cases showed other histological features like dermal edema (16%) and dermal telangiectasia (16%). Recurrence was seen in 2 cases (25%).

In immunocompetent patients culture was found to be positive in 2 cases (33%) for dematiaceous fungi (1 case) & filamentous fungi (1 case). In immunocompromised patients, 2 cases (100%) were culture negative.

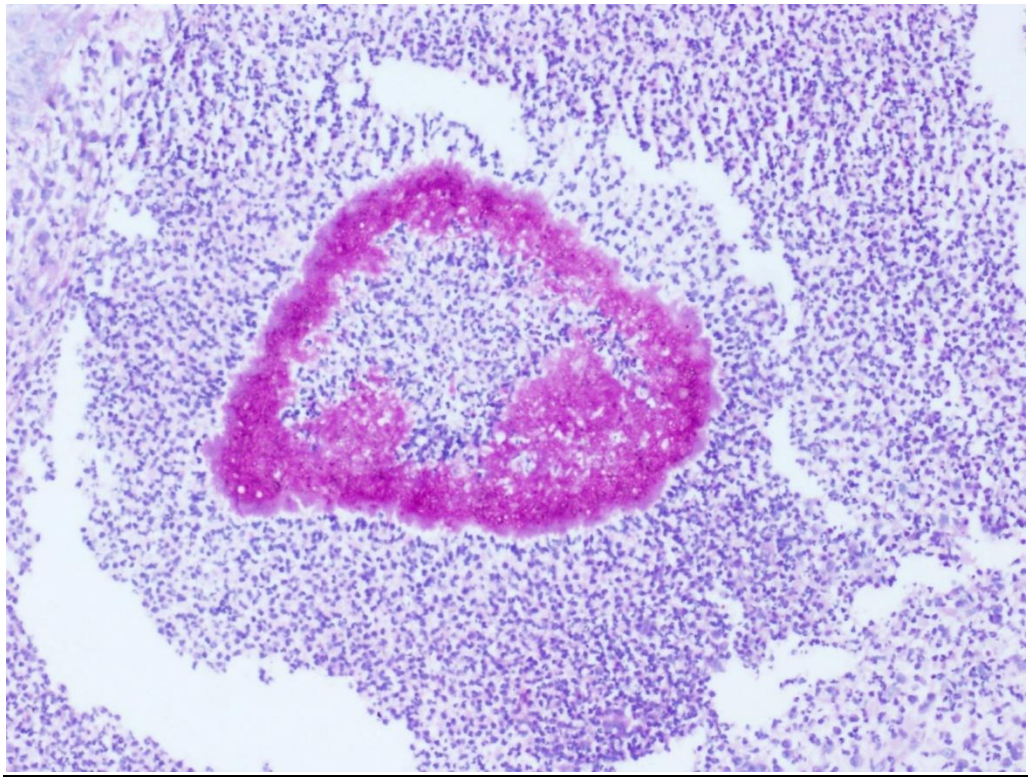
In immunocompromised patientsrandom blood sugar was normal for 1 case and for 1 case blood sugar level was not available.



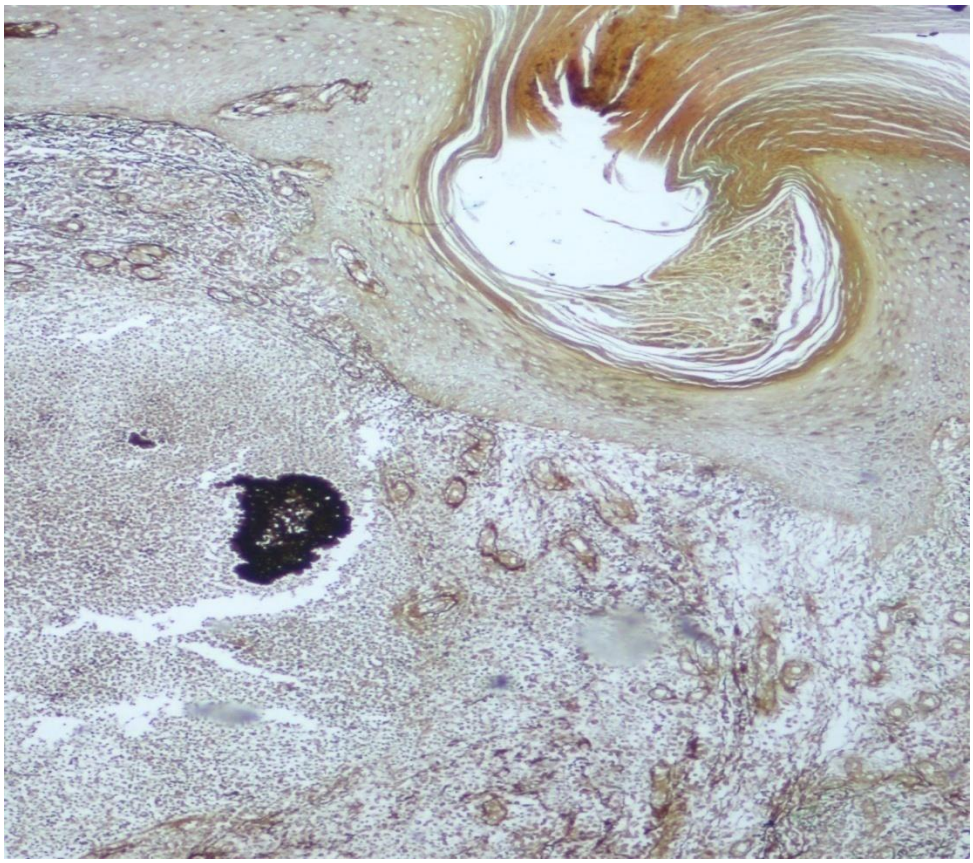
Photomicrograph 17: Eumycetoma (H&E at 200x)



Photomicrograph 18: Eumycetoma (H&E at 400x)



Photomicrograph 19: Eumycetoma (PAS at 200x)



Photomicrograph 20: Eumycetoma (GMS at 200x)

DISCUSSION

Discussion:

Fungal infections amount to a major health problem all over the world. Among fungal infections, dermatomycoses are an important category of cutaneous disease. Fungal infections of skin cause cosmetic defacements. The existing literature points to a varying trend in prevalence of cutaneous fungal infection depending on different geographic locations, ethnicity and socioeconomic status of the population studied. Ours is one of the study on cutaneous fungal infections in a tertiary care centre in south India catering to patient care across different parts of India and also one among few studies to compare the clinical and histomorphological features of of cutaneous fungal infections among immunocompetent and immunocompromised individuals. (76) Our total cases were 232, of which 70 (30.2%) cases was found to have varying degrees of immunocompromised state.

Clinical and epidemiological parameters:

Age of patients: In this study, the cutaneous fungal infections occurred in age group ranging from 0 years to 83 years. The mean age at diagnosis was 38 years. The most common age at presentation was 21-40 years (40%), which is explained by the fact that this group is active and take part in more outdoor activity. Similar to this study increased prevalence was found between the age group 21-40 years in an another study done on 315 patients at New Delhi in 2015 (77). In another study done in north India the commonest age group involved was found to be 21-40 years (39.5%) (78). In a study done in Brazil by Costa-Orlandi et al, the predominant age at presentation

was found to be 41-70 years (68.29%) which was found to be slightly higher than that in ours (79). The mean age of immunocompromsied patients was 43 years with an age range of 9-77 years.

Table3:. Comparison between the distribution of study populations according to the age groups in our study and a similar study.

Age groups (in years)	Alina Jankowaska- Konsur et al, Poland (N=2468)	CMC (India), present study (N=232)
<15	6.37%	8.62%
15-55	60.69%	77.15%
>55	32.94%	14.23%

Table 4:. Comparison between the distribution of study populations according to the age groups in our study and a similar study.

Age groups (in years)	Muhammad Hasibur Rahman, Bangladesh et al (N=601)	CMC (India), present study (N=232)
<15	29.95%	8.62%
15-65	59.5%	**85.64%**
>65	10.64%	6.04%

Gender: In our study there was a male predominance with a male:female ratio of 1.72:1. The available literature also suggests a male preponderance in these cases similar to our study, with male: female ratio ranging from 1.05:1 to 3.76:1(80–83)(84). Increase incidence in males may be because of relatively increased exposure

to outdoor activity and more prone to trauma. Lower extremity was the most common site involved in male, whereas in female it was face & neck region.

Demographic: Ours is a tertiary care super-speciality hospital, which caters to a large part of the population from Eastern and Southern India, and this has been reflected in outpatient demographic. About 35.8% of the patients were from West Bengal. We did not observe any specific or significant geographic variation among immunocompromised patients.

Occupation

In our study higher incidence of cutnaeous mycoses was noted in agricultural workers (58 cases) which may be explained by the working environment and more exposure to sunlight which further increases sweating and facilitate the infection. The second most common population to be affected was home makers. This was similarly observed in few other studies done in India. (85,86).

Two groups of patients

In this study we classified our total study population (n=232) into two groups namely immunocompetent (69.8%) and immunocompromised (30.2%) population. The most common immunocompromised condition observed in our study was diabetes (30%). There are several studies documenting an increased risk of skin and mucous

membrane mycotic infections in patients with diabetes (87–89) (90) which supported our study. HIV-AIDS (22%) was found to be the next common immunocompromised condition in our study with increased cutaneous fungal infection. Similarly there are studies on HIV-AIDS patients which had demonstrated increased prevalence of cutaneous fungal infections(91) (13). Post-bone marrow transplant(7) and Post-renal transplants(4) were the transplants observed in our cohort, among which post-renal transplant patients tend to have more superficial fungal infection and post-bone marrow transplant patients were found to have more invasive fungal infections. Similar findings were observed in the literature. (47)

Clinical Presentation:

Skin lesions (64.5%) were the most common clinical presentation observed in our study followed by itching (11.2%). Our findings were similar to the reported studies which observed inflammatory skin lesions and pruritus to be the dominant symptom of cutnaeous fungal infections (92). The most common skin lesions observed in both the groups of our study was macule/papule (33.19%), and the most common site involved was lower extremity (22.41%). This was similar to the findings of few other studies done in India by Das S et al and R kaur et al. (93, 94) . Nail involvement was seen only in 2 cases (0.86%). Lakshmanan et al in 2015 had found skin as the commonest site of superficial infection, followed by nail and hair. In discordance with ours, studies done by Veer et al in Aurangabad, India & Ravinder Kaur et al in New Delhi, India found dermatomycoses of nail seen in 48.86% and 55.8% respectively

(95). In our study head & neck region was the most commonly affected site in 20 cases (28.75%) of the immunocompromised population followed by lower extremity in18 cases (25.71%). In discordance to this, a study done on cancer patients receiving chemotherapy by Quatresooz et al in Belgium, revealed skin lesions were most commonly seen on the trunk and proximal extremities and rarely on the head or neck region (96).

Most of the immunocompromised patients (68.57%) presented with duration of symptoms within 6 months, whereas most of the immunocompetent cases (29.62%), presented with duration of symptoms for >5 years.

Histomorphologic analysis

Classification of fungi: We classified cutaneous fungi into four categories namely 1) Superficial fungi 2) Dermal/cutaneous fungi 3) Subcutaneous fungi and 4) Disseminated fungi.

A majority of the cases of cutaneous mycoses in our study are superficial fungi confined to the epidermis i.e. 120 of 162 cases (74.07%) of immunocompetent patients and 43 0f 70 cases (61.43%) of immunocompromised patients. Dermal/cutaneous fungi involving the dermis was evident in 34 case of immunocompetent and 22 cases of immunocompromised patients (20.99% and 31.43% respectively). Subcutaeous fungi involving the subcutaneous tissue with or without dermal involvement was evident in 7 cases of immunocompetent patients and 3 cases of immunocompromised patients (4.3% and 4.3% respectively). Disseminated

fungi with cutaneous manifestation were evident in 1 immunocompetent patient and 2 immunocompromised patients (0.8% and 2.9% respectively).

Superficial fungi:

163 (70.26%) of the total 232 cases had superficial fungal infection confined to the epidermis. Dermatophytes were the fugal organisms most commonly evident in 84 ca immunocompetent patients and 28 immunocompromised patients (51.855 & 40% respectively). We were not able to categorize 1.3% of fungal organisms as dermatophytes or Candida as the organisms were very few and their yeast forms ranged in size from 1-5 microns. The following table depicts comparison of various studies done in India. (Table 5)

Table 5: Comparison of various studies on superficial fungal infection in India

Year/study	1995/ Hudd MM et al	2003/ Singh S et al	2007/Das et al	Present study
Place	Assam	Baroda	New Delhi	CMC Vellore
Number of patients	100	260	1975	232
Site	1.Extremities 2.Groin region 3. Scalp	1.Extremities 2.Groins 3.Scalp	1.Nails 2.Extremities 3.Scalp	1.Lower extremity 2.Head & neck 3Upper extremity 4. Scalp
Organisms	Dermatophytes 94.6% Candida 5.4%	Dermatophyes (100%)	Dermatophytes (78.9%) Candida 16.7% Aspergillus 2.2% Penicillium 1.4% Scopuloropsis0.6%.	Dermatophytes (48.27%) Pityriasis 15.95% Candida 4.74% Unclassifiable1.3

.

Fifty six of the 232 patients in our study were observed to have dermal/cutaneous fungal infection, of which 34 patients (20.9%) were immunocompetent and 22 (31.4%) patients were immunocompromised. Dermal/cutaneous fungal infection was found to be more commonly seen in immunocompromised patients. The available literature also suggests increased susceptibility of immunocompromised patients for dermal/cutaneous and subcutaneous fungal infection similar to our study. (97) Of these 56 cases further categorization based on adequate morphological features were possible for 51 cases. Among the 51 cases 24 were associated with granulomas and 37 cases with an inflammatory infiltrate but no granulomas.

Chromomycosis (8) dermatophytes (8), eumycetoma (6), Pityrosporum folliculitis (5), Histoplasmosis (2), Aspergillosis(1) , Candidiasis (1) were the fungal infections observed in immunocompetent patients and was confined to the dermis.

Histoplasmosis (10), Zygomycosis (3), Aspergillosis (2), Dermatophytes (2), Candidiasis (2), Pityrosporum folliculitis (1) and Sporotrichosis (1) were the fungal infections observed in immunocompromised patients and was confined to the dermis.

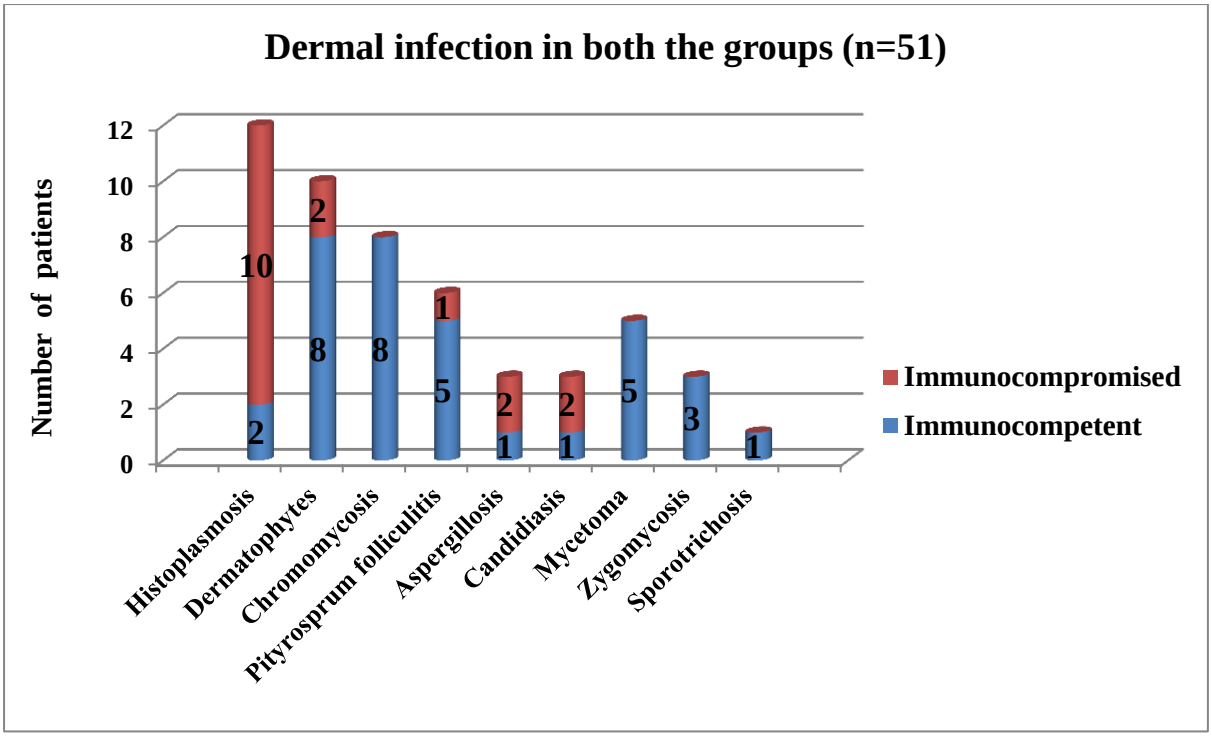


Figure 24: Dermal infections in both the groups.

Subcutaneous/deep fungi:

In our study totally 10 cases(4.3%) showed subcutaneous/deep fungal infection, out of which for 9 cases categorization was possible with adequate histomorphological features, however 1 case had an occasional yeast forms ranging in size from 2-4 microns within the inflammatory infiltrates of subcutaneous tissue. Phycomycosis(3), eumycetoma (3), candidiasis (2) and aspergillosis (1) were the subcutaneous fungal infections observed in our study. This was in discordance to what was observed in a study done in Karnataka, south India with most common clinical type being chromoblastomycosis, (64%) followed by mycetoma (16%), sporotrichosis (16%) and zygomycosis (4%) (98). (Table 6).

Table 6: Comparison of studies on subcutaneous fungal infection in India

Study	Bordolai et al, 2015 Assam, India.	Bhat et al, 2015 Karnataka, India	Present study CMC vellore, India
Number of cases	15 cases	25 cases	10 cases
Clinical presentation	Nodule and ulcer	Nodule, verrucous plaque & ulcers	Nodule (5), ulcer (3) and plaque(2)
Organisms	Chromoblastomycosis (40%) Hyalohypomycosis (20%) Sporotrichosis (13.3) Mycetoma (13.3)	Chromoblastomycosis(64%) Mycetoma (16%) Sporotrichosis(16%) Zygomycosis(4%)	Phycomycosis (30%) Eumycetoma (30%) Candidiasis(20%) Aspergillosis(10%)

Disseminated fungi:

Disseminated fungi were seen in 3 patients, 1 in an immunocompetent patient which was found to be cryptococcosis and 2 in immunocompromised patients, one of who had candidiasis and for the other one further categorization based on histomorphology was not possible since only occasional septate hyphal forms was seen ranging in size from 3-5 microns, however blood culture of that case revealed Fusarium species. This was similar to the study done by Mays et al in immunosuppressed patients, which revealed Candida, Fusarium spp and Aspergillus as the common disseminated fungal pathogens with cutaneous manifestation.(99) Similarly in another study done in immunocompromised patients, Cryptococcus and Aspergillus were the common systemic fungi with cutnaeous manifestation. (100)

Clinical & histological features of each fungi among both the groups

Dermatophytoses:

In our study 114 patients (49%) were found to have dermatophytic infections. 86 patients (75.4%) were immunocompetent and 28 patients (24.6%) were immunocompromised. Of the 28 immunocompromised patients, 12 patients had diabetes, 9 patients were on immunosuppressive therapy, 4 patients had malignancy, 2 patients were post-transplants, (1 post- renal transplant and 1 bone marrow transplant) and 1 patient had HIV-AIDS. There was increase in prevalence of dermatophytoses among diabetic patients when compared to non-diabetic patients. This finding was in discordance to a study done by Romano et al (101). In concordance with ours, a study done by Lugo Somolinos et al, showed higher prevalence of dermatophytoses in diabetic patients and they also found a correlation between the incidence of fungal invasion and blood sugar levels. (102).

The most common site involved was scalp (18%) and upper extremity (18%). The most common symptom was skin lesions (31%). The most common duration of symptom was <6months (14%) followed by >5 years (13%). The most commonly observed skin lesion in immunocompetent cases was macule/papule (16%), whereas the commonly observed skin lesion in immunocompromised patients was plaque (13%). The study done by Sentamil selvi et al on immunocompromised patients reported similar findings (103)

In 86 immunocompetent cases, 78 cases had fungi confined to the epidermis and 8 cases had both epidermal and dermal involvement. Among 28 immunocompromised patients 26 cases had fungi confined to the epidermis and 2 cases had both epidermal and dermal involvement.

Associated histological features:

The commonly observed histological features in both the groups were hyperkeratosis (78.9%), hyperplasia (64.9%), parakeratosis (50%), mild chronic dermal inflammation with lymphocytes and histiocytes being the predominant inflammatory cells (79.8%). Spongiosis and dermal edema and was seen more in immunocompromised patients as compared to immunocompetent patients with a significant P value of <0.05. Most of the histological features were in concordance to the other studies in literature. (104) There were no other significant difference in histological features among both the groups. Sandwich sign was noted only in 4 cases (3.5%). This was in discordance to the studies in the literature. (44)

Pityrosporum folliculitis:

In our study 43 patients (18.5%) were found to have Pityrosporum folliculitis, 33 cases (20.37%) were immunocompetent and 10 cases (14.28%) were immunocompromised. Of the 10 immunocompromised patients, 3 cases had malignancy, 3 cases were post transplant (2 were post renal transplant and 1 was post bone marrow transplant), 2 cases were on immunosuppressive therapy, and 2 cases were diabetic. There was no increase in prevalence of Pityrosporum folliculitis

among diabetic patients when compared with non-diabetic patients. Similar findings was observed in a study done by Back et al. (105)

In immunocompetent patients face and neck region (10 cases) are most commonly involved followed by scalp (7 cases). In immunocompromised patients 3 cases involved scalp and 3 cases involved face & neck region. This was in discordance to a study done by Back et al, wherein Pityrosporum folliculitis was more commonly noted in upper back, shoulder and chest. (105)The most common clinical symptom in both the groups were skin lesion followed by itching. Itching was the most common symptom according to the study done by Back et al. (105) In immunocompetent the common duration of symptoms was (<6 months, 12 cases) followed by and >5 years(8 cases), while in immunocompromised patients most cases presented with shorter duration of symptoms (<6 months , 5 cases). The common types of skin lesion in both the groups were macule/papule (16 cases & 7 cases). Similar findings was observed in a study done by Back et al (105).

Associated histological features:

The commonly observed histological features in both the groups were were hyperkeratosis (65%), follicular plugging (88%), dilated follicles (67%), mild chronic and acute on chronic dermal inflammation (76.7%), perifollicular inflammation (41.8%) and with lymphocytes & histiocytes (76.7%) being the predominant inflammatory cells. There was no significant difference in the histological features among both the groups. The histological findings were in concordance with the study

done by Back et al (105). Associated bacterial colonies are seen in very few (6.9%) cases.

Candidiasis:

In our study 16 patients (7%) were found to have candidiasis, 10 were immunocompetent (63%) and 6 (37%) were immunocompromised (8%). The most commonly observed immunocompromised condition was transplants (33%) (2 bone marrow transplant) and patients on immunosuppression (33%). The most commonly affected age group was 21-40 years with 8 cases (50%). The most commonly affected group of patients were students (50%). There was a female preponderance (20%) in our study for cutaneous candidiasis as compared to male (4%). This finding was similar to a study done by D Heidrich et al, in Brazil. (106)

In immunocompetent patients lower extremity (30%) was the most common site, whereas in immunocompromised patients upper extremity (50%) was the most commonly affected site. The type of skin lesion was predominantly plaques (50%). The duration of symptoms were mostly <6 months, 9 cases (56%).

Associated histological features:

The commonly observed histological features in both the groups were hyperplasia (63.5%), hyperkeratosis (58.5%), parakeratosis (40%) moderate acute on chronic inflammation with lymphocytes, histiocytes and neutrophils being the predominant inflammatory cells (50%). Neutrophilic exocytosis (50%), non-necrotising

granulomas (50%), lobular panniculitis (67%), vascular invasion (16%) and infarction (16%) were found to be more commonly seen in immunocompromised patients as compared to immunocompetent individuals though they were not statistically significant. Similar findings were observed in literature. (44) There were no other significant differences in histological features among both the groups. Few of the cases showed other features like intraepidermal neutrophilic abscess (16%) and surface ulceration (13%).

Histoplasmosis:

In our study 13 cases (5.6%) were found to have histoplasmosis. Of these 2 patients were immunocompetent and 11 patients were immunocompromised. Out of 11 immunocompromised patients, 10 cases were found to have HIV-AIDS and 1 case had diabetes. Histoplasmosis was found to be seen most commonly associated with HIV-AIDS. Similar finding was in literature.(107) (108)

In immunocompetent patients face and neck region was the commonest site involved (2 cases). The duration of symptoms was less than 6 months. The common type of lesion observed was ulcer (1) and plaque (1 case). Of the 2 cases, 1 case was seen in dermis with associated granuloma and 1 case was seen in dermis without granulomas.

In immunocompromised patients face and neck was the most common site affected (8 cases) followed by upper extremity (2 cases). The most common symptom was skin lesion (10) followed by ulcer (1 case). Duration of symptom was <6 months (10

cases). Most common presentation was macular/papule lesion (8 cases). Similar finding was observed in literature. (107) Of the 11 cases, 4 cases were seen in dermis associated with granulomas, 6 cases were seen in dermis without granulomas and 1 case was found to be disseminated. This was similar to the finding in literature. (109)

Associated histological features:

The commonly observed histological features in both the groups were hyperkeratosis (52.3%) and moderate chronic inflammation with lymphocytes, histiocytes and plasma cells being the predominant inflammatory cells (56.8%). Surface ulceration and dermal granulomas were found to be more commonly seen in immunocompetent patients (50% & 50%) when compared to immunocompromised individuals (9%&36%). hyperkeratosis (50%), hyperplasia (42%), neutrophilic exocytosis (42%), neutrophilic crusting (33%). Few of the cases showed other features like parakeratosis (17%), spongiosis (6%), intraepidermal neutrophilic abscess (6%) and lobular panniculitis (9%). The dermal inflammation was found to moderate to severe in immunocompromised patients which was in discordance to study done by Eidbo et al. (109)

In immunocompetent patients culture was found to be positive in 1 out of 2 cases and in immunocompromised patients culture was found to be positive in 7 out of 11 cases. Hence biopsy was found to be as sensitive and specific as culture in immuocompromised individuals.

Diabetes was not associated with histoplasmosis. However HIV-AIDS with CD-4 counts less than 200 was found to be strikingly associated with cutaneous histoplasmosis.

Sporotrichosis:

In our study 1 case (0.43%) was found to have sporotrichosis, who was a known diabetic. The affected site was lower extremity, with swelling as the presenting complaint, the type of lesion was nodule and the duration of symptom was for <6 months. The fungi were seen in dermis associated with granuloma formation. Similar finding was observed in literature (110). The frequency of sporotrichosis in our cohort was found to be very less (0.43%) unlike north Indian states which are endemic for these infections. (111)

Associated histological findings:

The observed histological features was hyperkeratosis, parakeratosis, pseudoepitheliomatous hyperplasia, spongiosis, neutrophilic exocytosis, intraepidermal neutrophilic microabscess, dense acute on chronic inflammation, with inflammatory infiltrates of lymphocytes, plasma cells and neutrophils, dermal telangiectasia and suppurative granulomas. Similar findings were observed in literature.(44)

Subcutaneous phycomycosis:

In our study 3 immunocompetent patients were found to have subcutaneous phycomycosis.

The most common site was lower extremity (2 cases) (67%), and the common symptom was skin lesion with plaque, nodule, and swelling. All the 3 cases were seen in subcutis. Similar finding was observed in a study done by Chandrasekar et al ((112)

Associated histological features:

The commonly observed histological features were hyperkeratosis 33%, hyperplasia 33%, moderate dermal acute on chronic inflammation with lymphocytes, histiocytes and eosinophils being the predominant inflammatory cells (100%) and dermal granulomas 67%. Similar finding was observed in literature.(44)

All the 3 cases were found to be positive for Basiodiobolus.

Zygomycosis:

In our study 3 immunocompromised patients had zygomycosis. Of which 1 had malignancy, 1 had HIV-AIDS and 1 case was on immunosuppressive therapy. There was increased in prevalence among immunocompromised patients. This finding was in concordance with the study done by Kaushik et al. (64)

In immunocompromised patients the site involved was face & neck, upper extremity and genitalia, the most common presentation was skin lesion with macule/papule,

ulcer and plaque. The duration of symptoms was <6 months. All the 3 cases were seen in dermis without associated granulomas.This finding was similar to the study done by Rodent et al. (111)

Associated histological features:

The commonly observed histological features hyperkertosis 100%,hyperplasia 100%, , intraepidermal neutrophilic microabscess (33%), with moderate acute on chronic inflammation with lymphocytes, histicytes and eosinophils being the predominant inflammatory cells (67%) , dermal abscess formation (33%) vascular invasion (67%) and necrosis/infarction (33%). Similar finding was observed in literature. (105)

Chromomycosis:

All 8 cases (3.4%) of chromomycosis observed in our study were seen in immunocompetent patients with a male predominance. The common site involved was upper extremity (2 cases) and lower extremity (2 cases), common symptom was skin lesion (3), with macule/papule being the common type of lesion and all cases presented with duration of symptoms >5 years (3 cases). This was slightly in discordance to another study done in Brazil, which revealed verrucous lesion being the most common presentation. (111). All our cases were seen in dermis with associated granulomatous inflammation. .

Associated histological features:

The most commonly associated histological features were pseudoepitheliomatous hyperplasia(87.5%), parakeratosis (62.5%), hyperkeratosis (37.5%), surface ulceration (37.5%), intraepidermal neutrophilic microabscess (25%), moderate acute on chronic inflammation with lymphocytes, histiocytes and neutrophils being the predominant inflammatory cells (75%), dermal granulomas (100%), abscess formation (50%) and fungal organisms within the multinucleate giant cells (50%). These findings were in concordance with those observed in few other studies (112). Recurrence was observed in 1 case (12.5%)

7 cases (87.5%) were positive for culture; the result showed Fonsacea pedrosoi as the common etiological agent in 5 cases (71.4%), Philophora in 1 case (12.5%) and dematiaceous fungi in 1 case (12.5%). This was in concordance to a study where Forsake pedrosoi, was found to be the common cause (77.8% of cases) (111). Dematiaceous fungi were found to be positive in 40% of cases.

Aspergillosis:

In our study totally 4 cases (1.7%) were found to have Aspergillosis, of which 3 were immunocompromised patients, 1 case had malignancy and 2 cases had HIV-AIDS.

In immuocompetent patients most common site involved was lower extremity, ulcer was the common symptom and common duration of symptoms was >5 years. This

was similar to the finding observed in literature (59). It was seen in dermis with associated granulomas.

In immunocompromised patients , sites affected were face & neck, abdomen and lower extremity with ulcer & nodule being the clinical presentation and common duration of symptoms was <6 months,. Two cases were seen in dermis with associated granulomas and 1 case was seen in subcutis.

Associate histological findings:

The commonly observed histological features were surface ulceration (50%), hyperkeratosis (25%), parakeratosis (25%), hyperplasia (25%), neutrophilic crusting (25%), moderate chronic inflammation with lymphocytes and histiocytes being the predominant inflammatory cells (50%), vascular invasion (25%), necrosis (25%) and panniculitis (25%). Similar finding was observed in literature. (105)

In immunocompetent patient culture was found to be positive for filamentous fungi, and in immunocompromised patients 1 case was found to be positive for Aspergillus and 2 cases showed no growth. Hence biopsy was found to be more sensitive to identify the fungus as compared to culture.

Cryptococcosis

In our study 1 immunocompetent patient was found to have Cryptococcosis and lower extremity was the involved site. This was in discordance to literature. (44). The

presenting symptom was nodular lesion, with the duration of symptom being <6 months.

Associated histological features:

The observed histological features were hyperkeratosis, follicular plugging, perifollicular inflammation, chronic moderate dermal inflammation, granulomas in subcutis and lobular panniculitis. Similar finding was observed in literature.(44)

Eumycetoma

In our study totally 8 cases (3.4%) were found to have eumycetoma, 6 cases were immunocompetent and 2 cases were immunocompromsied with chronic disease associated immune dysfunction.

In immunocompetent patients the most common site of involvement was lower extremity (87.5%), common symptoms was ulcer (37.5%), common duration of symptom was >5 years (25%) and 6 months – 1 year (25%). 5 cases were seen in dermis without granulomas and 1 case was seen in subcutis.

In Immunocompromised patients lower extremity was the commonest site involved (2), sinus discharge being the common symptom (2), duration of symptom was (>5 years), common type of skin lesion was ulcer & nodule. 2 cases were seen in subcutis. Similar finding was observed in a study done by Mt et al. (68)

Associated histological features:

The commonly observed histological features were hyperplasia (62.5%), hyperkeratosis (50%), surface ulceration (50%), parakeratosis (25%), moderate acute on chronic dermal inflammation , with lymphocytes, histiocytes & neutrophils being the predominant inflammatory cells (75%) and dermal abscess (25%). Recurrence was seen in 2 cases (25%). Similar finding was observed in literature. (105)

CONCLUSIONS

Conclusion.

- There was a male preponderance for cutaneous mycoses. The most common age of presentation in our cohort was found to be 20-40 years. Most of the patients presented with skin lesion with macule/papule as the common presenting complaints.
- In our cohort 70 patients (30.17%) were found be immunocompromised with diabetes (29%) as the most common cause for immunosuppression followed by HIV-AIDS (21%).
- In immunocompromised patients the duration of symptoms was mostly <6 months (65.71%) when compared to immunocompetent patients who generally had a chronic course. There was no other significant difference in clinical features among both the groups.
- Fungal infections were categorized into superficial, dermal/cutaneous, subcutaneous and disseminated types.
- Superficial mycoses (70.25%) was the predominant category observed in our cohort with dermatophytes (48.27%) being the most common fungal organisms identified in all age groups and both the genders.
- Dermal/cutaneous and disseminated fungal infection was found to be more common in immunocompromised patients (31.4%&2.9%) as compared to immunocompetent patients (20.9%&0.8%).
- Increases in prevalence of dermatophytoses were observed in diabetics (63.33%) as compared to non-diabetic individuals (47.6%).

- Histoplasmosis was seen to be more commonly associated with HIV-AIDS while, post-bone marrow transplant showed invasive candidiasis and post-renal transplants showed dermatophytoses as the most common cutaneous mycoses unlike other studies which showed increased frequency of invasive fungal infection in solid organ transplants.
- The frequency of sporotrichosis in our cohort was found to be very low (0.43%) unlike north Indian states which were found to be endemic for these infections, whereas mycetomas were more commonly seen in our study compared to other studies in India.
- Chromomycosis, sporotrichosis and aspergillosis were associated with granulomas.
- Eumycetoma were not associated with granulomatous inflammation.
- In histoplasmosis immunocompetent individuals tend to have granulomas, while immunocompromised patients did not have granulomas.
- The most common histological features in all the four different types of cuatneous mycoese were hyperkeratosis and hyperplasia.
- Parakeratosis was associated with superficial fungi but not significantly.
- Dermal edema and spongiosis were found to be significantly associated with superficial fungal infection especially in immunocompromised individuals, whereas eosinophils were not significantly associated in both the groups.
- Subcutaneous phycomycosis showed many eosinophils with Splendore-Hoeppli phenomenon. Splendore-Hoeppli phenomenon was also seen in mycetoma which were predominantly non-pigmented.

- In our study culture was found to be specific but not as sensitive as biopsy in all the four categories of fungal infection.

LIMITATIONS

Limitations.

- There were few cases for which exact categorization of fungus by histology were not possible in those cases we did not do other ancillary studies to arrive at a diagnosis.
- Culture report was not available for all cases hence correlation with histopathology report could not be carried out accurately
- There were few cases which was discordant with the culture report, review of histological sections of those cases were not done.
- The accuracy of the diagnostic modality was not carried out based on assessment of response to antifungal therapy

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APPENDIX

Appendix 1

Location of the fungal organsisms: The location of fungus, whether it is in epidermis, dermis or subcutis was assessed.

Structural forms of the fungus: The presence of yeasts, pseudohyphae, hyphae, spherules, sclerotic bodies and grains was assessed .

Morphology of the fungus: The size of the fungi and the other characteristic features like, shape of the fungi, colour of fungi whether they are hyaline or dematiaceous, cell wall nature, presence of grains, nature of the capsule if present, etc was assessed.

Splendor-hoeppli phenomenon: The presence or absence was noted.

Epidermis: The epidermis was assessed for features like epithelial hyperplasia, pseudoepitheliomatous hyperplasia, hyperkeratosis, parakeratosis, spongiosis, vesicle/bullous formation, neutrophilic crusting, intraepidermal microabscess formation, lymphocytic/neutrophilic exocytosis and papillomatosis with or without interface change.

Dermis: The dermis was assessed for features like type of inflammation, degree of inflammation, predominant inflammatory cells, granulomas, abscess formation, necrosis/infarction, vascular invasion, periadnexal and perifollicular inflammation.

Subcutis: Presence of inflammation, whether septal or lobular panniculitis, presence or absence of haemorrhage, granulomas and necrosis/infarction and vasculitis was assessed

Dermatophytes: Yeast forms or hyphal forms ranging in size from 1-3 microns are seen in the stratum corneum and may also be seen within the hair follicle. The stratum corneum may show hyperkeratosis, parkeratosis, spongiosis, neutrophilic microabscess and sandwich sign. It refers to the presence of hypahe ‘sandwiched in’ between an upper but normal basket-weave stratum corneum and a lower layer of recently produced stratum corneum which is abnormal in being compact orthokeratotic or parkeratotic in type. The dermis may show mild perivascular chronic inflammation and mild dermal edema may also be seen.

Pityrosporum: Spherical or oval yeast forms ranging in size from 2-4 microns in size may be seen. There may be budding yeast forms too. Involved follicles are dilated and usually plugged with keratinous material. There is mild chronic inflammatory infiltrate around the hair follicle.

Candida:They are seen as yeasts measuring 3-5 microns in size admixed with hyphal and pseudohyphal forms. The pseudohypahl forms may show periodic constrictions.

Cryptococcus: Cryptococci are encapsulated, spherical to oval yeasts that measures 5-10 microns in size. A thick polysaccharide capsule gives these organisms the distinctive appearance of having a clear halo around them that can be seen in tissue sections with H&E stains and Alcian blue stain.

Histoplasma: Histoplasma in tissue is seen as an oval 2-4 microns yeasts that may show narrow based buds. With H&E stain, the basophilic cytoplasm is seen separated from the surrounding tissue by a clear zone corresponding to the cell wall.

Chromomycosis: Round, thick walled, golden brown cells ranging in size from 5-12 microns in size (sclerotic bodies) may be seen lying free in the intraepidermal microabscess or within the multinucleate giant cells. Septate hyphal forms may also be seen.

Pheohyphomycosis: The pigmented hyphae are seen measuring 2-6 microns in size but are irregularly swollen with prominent septa may also be seen that show constrictions. Pigmented yeast like cells can also be seen and may show septation or budding.

Aspergillosis: Aspergillus spp are seen as thin septate acute angled branched hyphae ranging in size from 3-12 microns.

Zygomycosis:The hyphae are broad, non-pigmented wide and usually non-septate and ranges in size from 5-20 microns. The branching is usually seen at right angles. The hyphae are ribbon like in appearance and vary in width.

Eumycetoma: The segmented mycelial filaments ranging in size from 2-4 microns in size may be seen. Large granules (upto 5mm or more) with interlacing hyphae embedded in interstital brownish matrix may also be seen.

Appendix-2

PAS staining procedure:

1. The slide is deparaffinised in 15ml of xylene.

2. Then it is washed in graded absolute alcohol 90%, 80%, in each for 2 dips.

3. Then it is washed in distilled water for 5 minutes.

4. Then it is placed in 1% periodic acid solution for 5 minutes.

5. Then it is washed in distilled water for 5 minutes.

6.Then it is placed in Schiffs reagent for 15 minutes.

7. Then it is washed in water for 10 minutes.

8. Then it is stained in haematoxylin for 3 minutes.

9. Then it is washed in water for 2 minutes.

10.Then it is differentiated with 1% acid alcohol for 3 dips.

11.Then it is washed in water for 2 minutes.

12. Then it is dehydrated with absolute alcohol (80%, 90%) and then cleared and mounted.

Gomori's Methenamine- Silver Nitrate (GMS):

Procedure:

1. The slide is deparaffinised in xylene for 15 minutes.

2. Then it is washed in graded alcohol.

3. Then it is washed in water.

4. Then it is kept in 5%chromic acid for 1 hour.

5. Then it is washed in water.

6. Then it is kept in 1% sodium bisulfite for 1 minute.

7. Then it is washed in water.

8. Then it is kept in working silver methenamine solution for 30 minutes (until the section turn to yellowish)

9.Then it is washed in water.

10.Then it is kept in 2% sodium thiosulfate for 2 minutes.

11.Then it is washed in water.

12.Then it is counter stained with working light green for 30 seconds.

13. Then it is blotted and dried.

14. Then it is dehydrated and mounted.

Evaluation of special stains:

The positivity of the fungal organisms for PAS and GMS stains was assessed. PAS stains the fungal organisms magenta/pink in colour. GMS stains the fungal organisms black in colour.

PROFORMA

Serial no:

Hospital no:

Biopsy no:

Name:

Age:

Gender: Male/ Female

Occupation:

Place:

Site of the biopsy: Face & neck/Chest/Abdomen/Back/Upper extremity/ Lower extremity/Genitalia/Nails/Scalp

Immunocompromised condition: Yes/No

Which immunocompromised condition:

Associated comorbidity:

Prior anti-fungal treatment: Yes/No

Symptoms: 1. Itching/2. Ulcer/3. Skin lesions/4.Swelling/5. Nail discolouration/6. Hyperpigmentation/7. Hypopigmentation/8. Sinus/9. Alopecia

Duration of symptoms: <6 months/6 months-1 year/1-2 year/2- 5 years/> 5 years.
Nature of lesion: Macule/papule/Ulcer/Plaque/Nodule/ Pustule/Vesicle/bulla
Pigmentary lesions/Scales/ Scarring/Non scarring alopecia

Classification of fungi:1.Superficial 2.Dermal 3.Subcutaneous 4.Disseminated

Superficial fungi:1.Dermatophytes.2.Pityriasis 3.Candida

Dermal with granuloma: 1.Histoplasmosis 2.Zygomycosis 3.Pityrosporumfolliculitis 4.Chromoblastomycosis 5.Sporotrichosis 6.Aspergillosis 7.Cryptococcosis 8.Candida

Dermal infection without granuloma:1.Dermatophytes 2.Mycetoma 3.Candida 4.Zygomycosis. 5.Histoplasmosis 6.Pityrosporum

Deep/Subcutaneous 1.Zygomycosis/Phycomycosis 2.Aspergillus 3.Histoplasma 4.Sporotrichosis 5.Eumycetoma 6.Chroomblastomycosis 7.Candida 8.Phaeohypomycosis

Disseminated infection:1.Candida2.Histoplasma3.Penicillium marneffi 4.Mucor 5.Aspergillus 6.Pheohypomycosis 7.Cryptococcus

Structural form of fungi:1.Yeast 2.Hyphae 3.Spherules 4.Sclerotic bodies 5.Granules 6.Pseudohyphae/yeasts 7.Yeast/hyphae 8.Arthrospores

Morphology of fungi-dimensions:.1-5 microns/ 6-10 microns/ 11-15 microns/16-20 microns/21-25 microns/26-30 microns

Fungal organisms-yeast forms:Dermatophytes/.Pityriasis/ Candida/Histoplasmosis Cryptococcosis/Chromoblastomycosis/Pheohypomycosis

Fungal hyphal forms:1.Septate/Aseptate/Dematiaceous/Hylaine/Both septate and aseptate.

Fungal hyphal morphology:Septate forms/Aseptate forms/Septate form with acute angled branching/Aseptate form with irregular branching/collapsed walls

Fungal organisms-hyphal forms:Aspergillus/Mucor/zygomycosis/Dermatophytes. Chromoblastomycosis/Pheohypomycosis/Penicillium marneffi/Pityriasis/Fusarium species/Eumycotic mycetoma

Fungal organisms-Grains: Madurella/Actinomadura/Curvularia/Aspergillus

Fungal organisms-grains colour:Black/White/Yellow/Red/Not available
Histological features:
Hyperkeratosis: 1. Present 2. Absent

Papillomaosis: 1. Present 2. Absent

Parakeratosis: 1. Present 2. Absent

Hyperplasia: 1.Present 2.Absent

Pseudoepitheliomatous hyperplasia: 1.Present 2.Absent

Spongiosis: 1. Present. 2. Absent
Vesicle/bullous formation: 1. Present 2. Absent

Exocytosis: 1. Lymphocytic 2. Neutrophilic 3.Nil

Intraepidermal neutrophilic microabscsess 1.Present 2.Absent

Neutrophilic crusting: 1.Present 2. Absent

Eosinophilic microabscess: 1.Present 2.Absent

Surface ulceration: 1. Present 2. Absent
Sandwich sign: 1.Present 2.Absent

Follicular plugging: 1.Present 2.Absent

Inflammation surrounding the follicles 1.Presentn2.Absent

Dermal inflammation1.Acute 2.Chronic 3.Combined.

Periadnexal inflammation: 1. Present 2.Absent

Types of inflammatory cells:
1.Lymphocytes/histiocytes 2.Lymphocytes/histiocytes/neutrophils
3.Neutrophils/Lymphocytes/histiocytes
4.Lymphocytes/plasma cells/eosinophils
5.Lymphocytes/neutrophils/plasma cells
6.Plasma cells/lymphocytes/histicytes

Degree of inflammation:1.Mild 2.Moderate 3.Severe

Dermal edema:1. Present 2. Absent

Dermal telangiectasia: 1. Present 2. Absent

Location of abscess:1.Dermis 2.Subcutis3.Dermis& subcutis

Dermal abscess formation:1.Present 2.Absent

Fibrosis: 1. Present 2.Absent

Granulomas; 1.Present 2. Absent

Location of granulomas:1.Dermis2.Subcutis 3.Dermis& subcutis

New: Type of granulomas:1.Necrotising 2.Non necrotizing 3.Suppurative

Type of panniculitis:1.Lobular 2.Septal

Fungal organisms within multinucleate giant cells: 1. Present2.Absent

Panniculitis: 1. Present 2. Absent

Splendor-hoeppli phenomenon:1. Present 2. Absent

Vascular invasion; 1. Present 2. Absent

Necrosis/infarction: 1. Present 2. Absent

PAS stain: 1. Positive. 2. Negative

GMS stain:1. Positive 2. Negative

Associated bacterial colonies:1. Present 2. Absent

Recurrence: 1.Present 2.Absent

Associated malignancy of skin 1.Present 2. Absent

Type of malignancy of skin:

1. Squamous cell carcinoma
2. Basal cell carcinoma
3. Adnexal tumours
4. Lymphoma
5. Melanoma
6. Others
7. Nil

Culture report growth:

1. Present 2. Absent

Skin scrapping/nail clipping:1.Growth seen2. No growth3. Not done

Culture grown organisms:

Random blood sugar:
1.70-100
2.101-140
3.141-180
4.181-220
5.>221
6. Nil

V80- CD-4 count:
1. 501-1200 cubic/mm
2. 201-500 cubic/mm
3. 91- 200 cubic/mm
4. 51-90 cubic/mm
5. <50 cubic/mm
6. Not available

OFFICE OF RESEARCH
INSTITUTIONAL REVIEW BOARD (IRB)
CHRISTIAN MEDICAL COLLEGE, VELLORE, INDIA

Dr. B.J. Prashantham, M.A., M.A., Dr. Min (Clinical)
Director, Christian Counseling Center,
Chairperson, Ethics Committee.

Dr. Alfred Job Daniel, D Ortho MS Ortho DNB Ortho
Chairperson, Research Committee & Principal

Dr. Nihal Thomas,
MD, MNAMS, DNB (Endo), FIACP (Endo), FRCP (Edin), FRCP (Glasg)
Deputy Chairperson,
Secretary, Ethics Committee, IRB
Additional Vice-Principal (Research)

January 27, 2016

Dr. S. Rushni,
PG Registrar,
Department of Pathology,
Christian Medical College,
Vellore 632 004.

Sub: **Fluid Research grant project NEW PROPOSAL:**
Clinicomorphological study of mycotic infections of skin in immunocompetent and immunocompromised individuals and correlation with culture - A 7 year retrospective study.
Dr. S. Rushni, Emp. No: 20843, PG registrar, Pathology Dr. Meera Thomas, Emp. No: 20116, Professor, Department of General Pathology., Mr. Bijesh Yadav, Emp. No: 33244, Department of Biostatistics

Ref: IRB Min No: 9736 [OBSERVE] dated 10.11.2015

Dear Dr. S. Rushni
The Institutional Review Board (Blue, Research and Ethics Committee) of the Christian Medical College, Vellore, reviewed and discussed your project titled "Clinicomorphological study of mycotic infections of skin in immunocompetent and immunocompromised individuals and correlation with culture - A 7 year retrospective study" on November 10th 2015.

I enclose the following documents:-
1. Institutional Review Board approval 2. Agreement

Could you please sign the agreement and send it to Dr. Nihal Thomas, Addl. Vice Principal (Research), so that the grant money can be released.

With best wishes,

Dr. Nihal Thomas
Secretary (Ethics Committee)
Institutional Review Board

Dr. NIHAL THOMAS
MD, MNAMS, DNB (Endo), FIACP(Endo), FRCP(Edin), FRCP(Glasg)
SECRETARY - (ETHICS COMMITTEE)
Institutional Review Board,
Christian Medical College, Vellore, 632 002.

Cc: Dr. Meera Thomas, Dept. of General Pathology, CMC

Ethics Committee Blue, Office of Research, 1st Floor, Carman Block, Christian Medical College, Vellore, Tamil Nadu 632 002
Tel: 0416 – 2284294, 2284202 Fax: 0416 – 2262788, 2284481 E-mail: research@cmcvellore.ac.in

OFFICE OF RESEARCH
INSTITUTIONAL REVIEW BOARD (IRB)
CHRISTIAN MEDICAL COLLEGE, VELLORE, INDIA

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Secretary, Ethics Committee, IRB
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The Committee reviewed the following documents:

1. IRB Application format
2. Proforma
3. Request for waiver of informed consent
4. Document for sample size calculation.
5. Cvs of Drs. Rushni, Meera Thomas, Mr. Bijesh Yadav
6. No. of documents 1 - 5

The following Institutional Review Board (Blue, Research & Ethics Committee) members were present at the meeting held on November 10th 2015 in the CREST/SACN Conference Room, Christian Medical College, Bagayam, Vellore 632002.

Ethics Committee Blue, Office of Research, 1st Floor, Carman Block, Christian Medical College, Vellore, Tamil Nadu 632 002
Tel: 0416 – 2284294, 2284202 Fax: 0416 – 2262788, 2284481 E-mail: research@cmcvellore.ac.in

Serial number	Occupation	Age	Place	Sex	Year	Patient management	Immunocompromised	Which immunocompromised state	Associated comorbidity	Diabetes on control	Prior antifungal therapy	Site	Symptoms	Duration of symptoms	Nature of lesion
1	1	65	Andhra pradesh	1	2008	1	2	7	5	2	2	5	3	2	4
2	1	15	West bengal	1	2008	1	2	7	5	3	1	6	2	4	2
3	1	46	Kolkata	1	2008	2	1	6	2	3	2	1	3	1	2
4	9	6	West Bengal	2	2008	1	2	7	5	3	2	2	7	2	1
5	10	54	Nepal	1	2008	1	2	3	1	2	2	1	6	3	1
6	2	45	West Begal	1	2008	1	2	7	5	3	2	6	4	2	4
7	9	22	West Bengal	1	2008	2	2	7	5	3	2	9	1	5	8
8	1	32	Andhra pradesh	1	2008	1	1	6	5	3	2	1	3	1	3
9	1	45	Meghalaya	1	2008	2	1	6	5	3	2	1	2	1	2
10	3	36	Tamil Nadu	1	2008	2	1	6	5	3	2	3	2	1	9
11	4	65	West Bengal	2	2008	1	2	7	5	3	2	9	9	3	9
12	4	61	Uttar Pradesh	2	2008	1	2	3	1	1	2	5	1	4	1
13	9	11	West Bengal	2	2008	1	2	7	5	3	2	4	3	2	1
14	10	30	Vellore/ Tamil Nadu	2	2008	2	2	7	5	3	2	6	3	1	1
15	9	16	Thiruvarur/ Tamil Nadu	1	2008	2	1	1	5	3	2	4	1	2	1
16	7	63	Jharkhand/ India	1	2008	1	2	7	2	3	2	6	3	4	3
17	3	38	West Bengal	1	2008	2	2	7	5	3	2	4	3	1	5
18	9	16	Vellore/ Tamil Nadu	2	2008	1	2	7	5	3	2	9	9	1	9
19	7	53	Cachar/ Assam	1	2008	1	2	7	5	3	2	5	3	5	8
20	1	34	Jajpur/ Orissa	1	2008	1	2	7	5	3	2	9	2	1	2
21	9	13	Mizoram	1	2008	2	1	1	5	3	2	6	3	1	1
22	4	50	Lazmipur/Bangladesh	2	2008	2	2	3	1	1	2	4	3	4	1
23	1	83	Vellore/ Tamil Nadu	1	2008	1	2	7	5	2	2	8	3	3	3
24	4	28	Burdwan/ West Bengal	2	2008	1	2	7	5	3	2	1	3	5	1
25	10	77	Hooghly/West Bengal	1	2008	2	1	1	1	2	2	1	3	5	3
26	5	32	West Bengal	1	2008	1	2	7	5	2	2	1	1	2	1
27	3	58	Jharkhand	1	2008	2	1	2	1	2	2	2	3	1	5
28	6	53	Kolkata/ West Bengal	1	2008	1	2	3	1	2	2	2	3	1	1
29	9	29	West Bengal	2	2015	2	2	7	4	3	2	6	3	4	3
30	4	44	West Bengal	2	2015	1	2	7	5	2	2	5	3	5	3
31	9	21	West Bengal	1	2015	1	2	7	5	2	2	1	3	1	5
33	4	13	Jharkand	2	2015	1	2	7	5	3	2	1	3	5	1
33	8	49	Jharkand	1	2015	1	1	2	5	3	1	1	3	1	1
34	6	38	Chennai/Tamil Nadu	1	2015	2	1	2	5	2	1	9	3	1	4
35	10	43	Chittor/Andhra pradesh	1	2015	2	1	6	5	2	2	1	3	1	4
36	4	55	kottayam/kerala	2	2015	2	1	1	5	3	2	6	2	2	2
37	10	68	Malapuram/ Kerala	1	2015	1	2	7	5	2	2	4	1	2	8
38	1	56	Dindigal/ Tamil Nadu	1	2015	2	2	7	2	3	2	2	1	5	1
39	9	24	Tamil Nadu	1	2015	1	2	7	5	2	2	5	3	2	3
40	9	24	Vellore/ Tamil Nadu	1	2015	2	2	7	5	3	2	5	3	2	3
41	4	60	Assam	2	2015	2	1	3	1	1	2	1	3	1	1
42	3	48	Bangladesh	1	2015	1	2	7	5	2	2	6	3	1	1
43	4	52	West Bengal	2	2015	1	1	4	4	2	2	9	3	1	3
44	5	38	Ranchi/Jharkand	1	2015	1	2	7	5	3	2	4	3	1	1
45	1	53	West Bengal	1	2008	1	1	3	1	2	2	2	3	2	1
46	1	24	West Bengal	1	2015	1	2	7	5	3	2	4	3	1	7
47	9	29	West Bengal	2	2015	2	1	4	4	3	2	6	3	1	3
48	4	45	Tamil Nadu	1	2011	2	2	7	5	2	2	1	1	4	3
49	4	30	West Bengal	2	2011	2	1	6	5	3	2	5	3	1	1
50	10	73	Tamil Nadu	1	2011	2	1	3	1	2	2	9	3	2	8
51	3	40	Jharkand	1	2011	1	2	7	5	3	2	5	7	5	1
52	1	32	West Bengal	1	2011	1	2	7	5	3	1	6	8	5	2
53	1	41	Vellore	1	2011	2	2	7	5	3	2	9	1	1	3
54	9	31	Orissa	1	2011	1	2	7	5	3	2	9	3	5	3
55	4	64	Kerala	2	2011	2	1	3	1	1	2	5	3	2	3
56	1	52	Dharmapuri/ Tamil Nadu	1	2011	1	1	3	1	2	2	5	8	2	3
57	9	22	Jharkand	1	2011	2	2	7	5	2	2	6	3	4	7
58	3	36	West Bengal	1	2011	1	2	7	5	2	2	5	3	4	1
59	4	48	Assam	2	2011	1	2	7	5	3	2	1	3	1	1
60	4	72	Tamil nadu	2	2011	1	1	1	4	2	2	1	3	2	3
61	5	20	Bangladesh	2	2011	1	2	7	5	3	1	2	3	2	7
62	3	31	Bihar	1	2011	2	2	7	5	2	1	2	2	4	2
63	8	25	Tamil Nadu	2	2011	1	2	7	5	2	2	1	5	3	7
64	9	29	West Bengal	1	2011	1	2	7	5	2	2	1	3	4	1
65	4	64	Kerala	2	2011	2	1	3	1	2	2	5	3	2	3
66	1	51	Tamil Nadu	2	2011	2	2	7	5	2	2	5	3	5	7
67	11	5	West Bengal	1	2011	2	2	7	5	2	2	1	3	2	7
68	1	50	Tripura	1	2011	1	2	7	5	3	2	4	3	5	4
69	4	50	Vellore/Tamil Nadu	2	2011	1	2	7	5	2	2	6	3	5	3
70	5	41	West Bengal	1	2011	2	1	4	4	3	2	9	3	3	1
71	3	48	Kerala	2	2011	1	2	7	5	2	2	2	3	4	7
72	4	52	Bangladesh	2	2011	2	1	4	2	3	2	2	3	1	6
73	1	36	Andhra Pradesh	1	2011	1	2	7	5	3	2	4	3	5	7
74	1	19	Andhra pradesh	1	2011	1	2	7	5	2	2	4	1	1	8
75	4	52	Meghalaya	2	2011	1	2	7	5	2	2	7	3	4	7
76	4	34	West Bengal	2	2011	2	1	6	5	2	2	1	3	1	1
77	7	47	West Bengal	1	2011	2	2	7	2	3	2	5	1	5	8
78	3	41	West Bengal	1	2011	2	1	1	5	3	2	6	3	1	4

79	1	29	Tamil Nadu	2	2011	1	2	7	5	2	2	5	3	1	1
80	11	1	Meghalaya	2	2011	1	2	7	5	3	2	9	3	2	6
81	1	46	West Bengal	1	2011	2	2	7	5	2	2	1	3	1	1
82	3	49	West Bengal	1	2011	2	2	7	5	2	2	6	2	1	2
83	4	43	Tamil Nadu	2	2012	1	2	7	5	2	2	1	3	2	1
84	9	26	West Bengal	1	2012	2	1	1	5	3	2	5	3	1	1
85	9	25	Bangladesh	1	2012	1	2	7	5	3	2	6	3	5	7
86	4	34	Trissur/Kerala	2	2012	1	2	7	5	3	2	7	3	5	2
87	1	18	West Bengal	1	2012	2	2	7	5	3	1	5	3	5	1
88	4	47	West Bengal	2	2012	1	1	3	1	2	2	9	3	2	2
89	4	38	Tamil Nadu	2	2012	2	1	1	5	2	2	6	3	1	4
90	4	53	West Bengal	2	2012	1	1	3	1	2	2	6	1	5	3
91	7	53	Bangladesh	1	2012	1	2	7	5	3	2	5	1	5	7
92	4	37	Tamil Nadu	2	2012	2	1	4	2	3	2	6	3	5	7
93	4	55	Jharkand	2	2012	2	2	8	5	3	2	6	2	1	1
94	9	26	West Bengal	2	2012	2	2	7	5	3	2	6	3	4	3
95	10	51	West Bengal	1	2012	2	2	7	5	3	2	9	1	4	3
96	8	42	West Bengal	1	2012	1	2	2	5	3	2	4	3	1	1
97	9	37	Chitoor/Andhra pradesh	1	2012	1	2	7	5	3	2	9	3	2	3
98	9	21	Rajasthan	2	2011	2	2	7	5	3	2	1	3	4	3
99	3	27	West Bengal	2	2012	2	1	6	5	3	2	1	3	1	3
100	7	43	West Bengal	1	2012	2	1	4	4	3	2	6	3	1	1
101	3	29	West Bengal	1	2011	1	2	7	5	3	2	4	3	1	1
102	6	28	Tamil Nadu	1	2011	2	1	4	5	3	2	3	3	1	3
103	4	37	Andhra pradesh	2	2012	2	1	6	5	3	2	1	2	1	1
104	3	26	West Bengal	1	2012	1	2	7	5	3	2	2	3	5	7
105	1	44	Nepal	2	2012	1	2	7	5	3	2	6	2	2	2
106	5	26	Tamil Nadu	1	2011	2	2	7	5	3	2	2	3	1	7
107	4	40	Orissa	2	2013	1	2	7	5	3	2	1	3	1	3
108	10	69	Jharkand	1	2013	2	2	7	3	3	2	6	2	5	2
109	9	28	Bangladesh	1	2013	2	2	7	5	3	2	1	3	1	3
110	4	52	Bangladesh	2	2011	2	1	4	2	3	2	2	3	1	2
111	9	9	Andhra pradesh	2	2013	1	2	7	5	3	2	1	3	1	8
112	9	28	Jharkand	2	2013	1	2	7	5	3	2	6	3	5	3
113	9	13	Assam	1	2013	2	2	7	5	3	2	6	3	1	4
114	11	1	Jharkand	1	2013	2	2	7	5	3	2	6	6	1	7
115	1	25	Nellore	1	2013	1	2	7	5	3	2	8	5	1	7
116	11	4	West Bengal	2	2013	1	2	7	5	3	2	5	3	3	3
117	9	9	West Bengal	1	2013	2	1	2	5	3	2	5	3	1	1
118	9	16	Tamil Nadu	1	2013	2	1	1	5	3	2	4	3	1	5
119	9	15	Tail Nadu	2	2012	2	2	7	5	3	1	9	9	2	8
120	4	63	Jharkand	2	2012	1	1	3	1	2	2	5	1	1	3
121	4	29	Tamil Nadu	2	2012	1	2	7	5	3	2	6	4	4	3
122	9	12	Kerala	1	2012	1	2	7	5	3	2	5	3	4	1
123	11	3	West Bengal	1	2013	1	2	7	5	3	2	6	4	3	4
124	6	37	Tamil Nadu	1	2013	1	2	7	5	3	2	6	7	1	1
125	5	44	Jharkand	1	2013	2	1	2	5	3	2	1	3	1	5
126	4	34	Rajasthan	2	2013	1	2	7	5	3	2	2	1	2	1
127	1	47	Andhra pradesh	1	2013	1	1	3	1	2	2	6	1	5	3
128	11	1	Chattisgarh	1	2013	2	2	7	5	3	2	9	3	1	8
129	4	33	Andhra pradesh	2	2013	2	1	5	5	3	2	7	2	1	2
130	4	53	Uttar Pradesh	2	2013	2	2	7	5	3	2	5	4	5	4
131	1	50	Andhra Pradesh	1	2013	2	2	7	5	3	2	5	8	2	5
132	9	25	Kerala	2	2013	2	1	4	2	3	2	4	3	2	1
133	9	6	West Bengal	1	2014	1	2	7	5	3	2	1	6	5	7
134	9	16	Jharkand	1	2012	2	2	7	5	3	2	6	3	5	2
135	4	49	Tamil Nadu	2	2013	2	1	2	5	3	2	1	4	1	4
136	3	41	West Bengal	1	2014	1	2	7	5	3	2	6	8	2	5
137	10	72	Tamil Nadu	1	2014	1	1	3	1	2	2	1	3	1	3
138	1	67	Tamil Nadu	1	2014	2	2	6	5	2	2	7	3	1	6
139	5	34	West Bengal	1	2014	1	2	7	5	3	2		3	4	1
140	4	72	Kerala	1	2014	1	1	3	2	2	2	6	3	3	1
141	9	19	Nepal	1	2013	2	1	1	5	3	2	6	3	1	3
142	1	35	Tamil Nadu	2	2014	2	2	7	5	3	1	6	8	4	2
143	9	17	West Bengal	1	2009	1	2	7	5	3	2	6	3	4	4
144	4	55	West Bengal	2	2009	1	2	7	5	3	2	4	3	4	4
145	4	37	Chattishgarh	2	2009	1	2	7	5	3	2	9	3	5	5
146	4	59	West Bengal	2	2009	1	2	7	5	3	2	9	9	5	9
147	1	28	West Bengal	1	2009	1	2	7	5	3	2	4	3	1	6
148	10	53	Kerala	1	2009	2	1	8	5	3	2	7	2	1	2
149	10	55	Tamil Nadu	1	2009	2	1	2	1	1	2	5	3	1	4
150	10	49	West Bengal	1	2009	2	2	7	5	3	2	7	1	5	3
151	4	45	Tamil Nadu	2	2009	1	1	4	4	1	2	7	3	1	3
152	9	17	Chitoor	1	2009	1	2	7	5	3	2	9	3	4	3
153	4	45	Assam	2	2009	1	2	7	5	3	2	9	3	2	1
154	10	43	West Bengal	1	2009	1	2	7	5	3	2	6	3	3	1
155	1	46	Tamil Nadu	1	2009	1	2	7	5	3	2	6	3	5	1
156	1	58	West Bengal	1	2009	1	2	7	5	3	2	6	1	1	1
157	9	27	Chitoor	1	2009	1	2	7	5	3	2	1	6	1	7

158	1	34	Chitoor	1	2009	2	1	8	5	3	1	6	8	5	2	
159	10	52	Chitoor	1	2009	1	2	7	5	3	2	1	9	2	9	
160	4	39	Erode	2	2009	1	2	7	5	3	2	5	4	5	4	
161	10	58	Andhra pradesh	1	2009	1	1	3	2	2	2	7	3	1	2	
162	9	20	tamil Nadu	2	2009	2	2	7	5	3	2	5	3	5	3	
163	10	60	Chitoor	1	2009	1	1	3	1	1	2	6	2	1	2	
164	5	41	West Bengal	1	2009	1	2	7	5	3	2	7	3	1	2	
165	6	33	Karur	1	2009	2	1	6	5	3	2	1	3	4	1	
166	9	22	West Bengal	1	2009	1	2	7	5	3	2	4	1	5	1	
167	3	48	Bihar	1	2009	1	2	7	5	3	2	7	1	5	3	
168	10	70	West Bengal	1	2009	1	2	7	5	3	2	5	3	5	3	
169	9	10	Delhi	1	2009	1	1	2	5	3	2	4	3	3	1	
170	9	28	Chattisgarh	1	2009	1	2	7	5	3	2	3	3	2	3	
171	1	40	Andhra Pradesh	1	2009	1	2	7	5	3	2	2	3	3	3	
172	4	51	West Bengal	2	2009	1	2	7	5	3	2	9	9	5	9	
173	2	27	Meghalaya	2	2009	1	2	7	5	3	2	9	9	5	5	
174	5	33	West Bengal	1	2009	2	2	7	5	3	2	7	3	5	3	
175	1	47	Gujarat	1	2009	2	2	2	5	3	2	3	4	1	4	
176	6	27	West Bengal	1	2009	1	2	7	5	3	2	9	9	4	9	
177	10	60	Bangladesh	1	2009	1	2	7	5	3	2	6	1	5	1	
178	9	24	Trivandrum	2	2009	2	1	4	4	3	2	5	3	2	3	
179	9	24	West Bengal	2	2009	2	2	7	5	3	2	2	3	4	3	
180	10	57	West Bengal	1	2009	1	2	7	5	3	2	9	1	5	1	
181	1	38	West Bengal	1	2009	1	2	7	5	3	2	1	3	1	1	
182	4	57	West Bengal	1	2009	1	1	3	1	2	2	6	3	1	1	
183	1	34	Andhra praesh	1	2009	2	1	8	5	3	2	6	8	5	4	
184	3	44	Jharkand	1	2009	1	1	6	5	3	2	1	3	1	1	
185	9	25	Kerala	2	2009	1	2	7	5	3	2	4	6	2	7	
186	1	49	Orissa	1	2009	1	2	7	5	3	2	1	6	3	7	
187	4	37	Orissa	2	2009	2	2	7	5	3	2	6	3	2	3	
188	6	28	West Bengal	1	2009	1	1	6	5	3	2	5	3	1	1	
189	1	45	West Bengal	1	2009	1	2	7	5	3	2	6	3	2	7	
190	10	64	West Bengal	1	2009	1	2	7	5	3	2	6	3	2	4	
191	9	12	Andhra pradesh	2	2009	2	2	7	5	3	2	3	3	5	1	
192	4	77	Kerala	1	2009	2	1	1	1	2	2	1	6	5	1	
193	9	20	Tamil Nadu	1	2009	1	2	7	5	3	2	3	3	1	1	
194	9	17	Chitoor	1	2009	1	2	7	5	3	2	9	3	4	7	
195	10	54	West Bengal	1	2009	1	2	7	5	3	2	5	3	5	1	
196	3	55	Tail Nadu	1	2009	2	1	6	5	3	2	6	8	1	2	
197	5	31	Kerala	1	2009	1	2	7	5	3	2	1	6	4	7	
198	1	36	Jharkand	1	2009	1	2	7	5	2	2	4	3	1	7	
199	1	30	Bihar	1	2009	2	2	7	5	3	2	5	3	5	2	
200	1	36	West Bengal	1	2009	2	1	6	5	3	2	4	3	3	1	
201	9	12	West Bengal	1	2009	2	2	7	5	3	2	1	3	5	3	
202	9	15	West Bengal	2	2009	1	2	7	5	3	2	9	9	2	9	
203	1	39	West Bengal	2	2009	2	1	4	4	3	2	1	6	1	7	
204	9	11	Kerala	1	2009	1	2	7	5	3	2		3	2	1	
205	10	54	West Bengal	1	2009	1	2	7	5	3	2	1	3	4	1	
206	1	27	Andhra Pradesh	1	2009	1	2	7	5	3	2	1	3	1	3	
207	9	17	Tamil Nadu	2	2009	2	1	2	5	3	2	5	3	1	1	
208	9	19	Andhra Pradesh	1	2009	1	2	7	5	3	2	1	3	1	1	
209	1	19	West Bengal	1	2009	1	2	7	5	3	2	4	3	4	1	
210	4	48	West Bengal	2	2009	1	2	7	5	3	2	1	3	5	1	
211	4	39	Tamil Nadu	2	2009	2	1	4	4	3	2	1	3	1	1	
212	4	39	Jharkand	2	2009	2	1	3	5	2	2	6	3	5	5	
213	10	63	West Bengal	1	2015	1	2	7	5	3	2	5	6	4	7	
214	3	38	West Bengal	1	2011	1	2	7	5	3	2	1	7	5	7	
215	1	34	Tamil Nadu	1	2009	2	2	7	5	3	2	2	1	1	1	
216	9	21	West Bengal	1	2011	1	2	7	5	3	2	4	3	5	1	
217	9	22	Jharkand	2	2012	2	1	4	4	3	2	1	3	1	3	
218	9	6	Tamil Nadu	1	2012	1	2	7	5	3	2	6	7	1	1	
219	8	54	West Bengal	1	2015	2	2	7	5	3	2	1	2	1	2	
220	9	22	Bangladesh	1	2015	1	2	7	5	3	2	4	1	2	1	
221	9	36	Chhatisgary	1	2015	1	2	7	5	3	2	3	3	1	1	
222	4	28	Madhya pradesh	2	2015	1	2	7	5	3	2	2	3	1	1	
223	4	60	Bihar	2	2015	1	1	3	1	2	2	3	1	1	1	
224	9	22	Tripura	2	2015	2	2	4	4	3	2	3	2	1	2	
225	9	26	West Bengal	2	2015	1	2	7	5	3	2	1	1	5	1	
226	4	29	Chattisgarh	2	2015	1	2	7	5	3	2	5	3	3	4	
227	9	22	Jharkand	2	2015	2	1	2	5	3	2	6	3	1	1	
228	3	47	West Bengal	1	2015	1	2	7	5	3	2	2	3	4	1	
229	10	65	Tamil Nadu	1	2015	2	2	7	5	3	2	9	3	2	2	
230	9	24	Bihar	1	2015	1	2	7	5	3	2	5	3	2	7	
231	1	52	West Bengal	1	2015	1	2	7	5	3	2	6		1	7	
232	10	63	West Bengal	1	2015	1	2	7	5	3	2	5	6	4	7	

Site of fungi	Classification of fungi	Superficial fungi	Dermal infection with granulomas	Dermal infection without granulomas	Subcutaneous infection	Disseminated infection	Structural form of fungi	Fungal dimensions	Fungal organisms- yeast forms	Hyphal forms	Hyphal nature
1	1	1	9	4	7	7	8	1	1	5	3
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Fungal pseudohyphal forms	Fungal organisms- hyphal forms	Fungal organisms- grains	Fungal organisms- grains colour	Hyperkeratosis	Papillomatosis	Parakeratosis	Hyperplasia	Pseudoepitheliomatous hyperplasia	Spongiosis	Vesicle/bullous formation	Exocytosis	Intraepidermal neutrophilic microabscess
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Neutrophilic crusting	Eosinophilic microabscess	Surface ulceration	Sandwich sign	Follicular plugging	Perifollicular inflammation	Follicular infection pattern	Dermal inflamamtion	Periadnexal inflamamtion	Types of inflamamtory cells	Degree of inflammation	Dermal edema	Dermal telangiectasia	Abscess location	Dermal abscess formation	Fibrosis
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