chapter 31

Fungal Infections of the Upper Limb in Immunocompetent Patients

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Fungal infections of the hand are being reported with increasing frequency. Most fungal infections are superficial and relatively benign. There are general signs and symptoms suggesting the presence of a fungal infection. The early symptoms include atypical, nonspecific signs, such as low-grade fever, night sweats, weight loss, lassitude, easy fatigability, cough and chest pain. Cutaneous mycoses are caused by fungi (dermatophytes) that infect superficial keratinized structures suchas as skin, hair, and nails. These are spread from infected persons by direct contact. The most common subcutaneous mycoses are sporotrichosis and phaeomycotic cysts. Sporotrichoses are the only fungal infections which involve predominantly the upper limb. They are caused by the dimorphic fungus Sporothrix Schenckii, which is a ubiquitous organism found in soil in temperate and tropical climates. Deep and systemic fungal infections are rare, but quite serious. Clinical problems from deep and system fungal infections often result in significant morbidity, and even mortality.

Keywords: mycoses; dermatophyte infection; immunocompetence; sporotrichosis; systemic fungal disease.

1. Mycology: Generalities

Fungi, which include both yeasts and molds, are eukaryotic organisms [1]. Most fungi recognized today are obligate aerobes. Few are facultative anaerobes, while there are no recognized obligate anaerobic fungi. With the exception of *Candida albican,* the environment provides the natural habitat for most fungi. Candida albicans is part of the normal human flora. *Conidia,* consisting of asexual spores, are the most medically interesting fungi. Conidia, which are of the greatest significance, include the arthrospores, the chlamdospores, blastospores and the sporangiospores. The arthrospores comprise the mode of transmission of Coccidioides immitis. The chlamydospores (Candida albicans) are a quite resistant fungal category, and the blastospores and sporangiospores, such as *Rhizopus* and *Mucor,* are formed within a sac (sporangium) [1].

Despite the plethora of fungal species, fungal diseases can be readily diagnosed in laboratory. Diagnostic modes include: 1) direct microscopic examination, 2) culture of the organism, 3) DNA probe tests, and 4) serologic tests [1]. Systemic mycosis can be diagnosed with tests of presence of antibodies in patient's serum or spinal fluid. In cases where there is a suspicion of coccidioidomycosis, histoplasmosis or blastomycosis, the most frequently used diagnostic modality is the complement fixation test [1].

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2. Fungal Infections

2.1. Patients at risk for Mycoses

Various patient populations are at risk for fungal infections. One groups includes various categories

of immunosuppressed patients, including: a) patients with reduced number or compromised function of polymorphonuclear leucocytes, b) organ transplant recipients, c) patients with malignant neoplasms during periods of chemotherapy, d) patients with immunologic and metabolic disorders (SLE, collagen vascular diseases), e) diabetes mellitus, f) dysgammaglobulinemia, and g) patients who have previously received treatment with corticosteroids or cytotoxic agents. In addition, it is now will recognized that various categories of immunocompetent patients are also at risk. These include: a) travelers or inhabitants of regions known to be endemic for fungal infections and b) participants in activities or occupations that bring them in direct skin contact with infected animals or contaminated materials or ingestion or inhalation of aerosols or dust contaminated with fungal spores, and c) recipients of prolonged antibiotic therapy [2].

2.2. Signs and symptoms in Mycoses

There are general signs and symptoms suggesting fungal infection. The early signs are atypical and nonspecific symptoms, such as low-grade fever, night sweats, weight loss, lassitude, easy fatigability, cough, and chest pain. Systemic fungal diseases may mimic other infections, such as tuberculosis, brucellosis, syphilis, sarcoidosis and disseminated carcinomatosis. Often they present with mucocutaneous lesions. Initial clues to the presence of a fungal infection may be provided with non specific laboratory findings, including accelerated erythrocyte sedimentation rate, increase in C-reactive protein, elevations in γ -globulin or low-grade and persistent elevations in peripheral blood neutrophils and/or monocytes.

2.3. Categorization of fungal infections

Fungal infections may be categorized as superficial or systemic. Systemic infections may have been caused by dimorphic fungi (forms of mold in the environment), or other fungal agents formerly considered as saprobes or contaminants in immunosuppressed individuals. Opportunistic mycoses comprise the nonpathogenic fungi that can cause subcutaneous and disseminated infections in intravenous drug users or immunosuppressed individuals. Some of these nonpathogenic fungi include Aspergillus species, Candida species, and Zygomyces species [2]. Cutaneous and subcutaneous mycoses are also medical mycoses.

Cutaneous fungal diseases are caused by dermatophytes that infect only superficial keratinized structures, such as skin, hair, and nails. This is usually attributed to *Tinea versicolor* (pityriasis versicolor). A superficial skin infection of cosmetic importance is attributed to *Malassezia furfur,* while *Tinea Nigra* is an infection of the keratinized layers of the skin by the organism *Gladosporium werneckii* which is normally found in the soil.

Subcutaneous mycoses, including sporotrichosis, chromomycosis and mycetoma, are caused by fungi that grow in the soil and on vegetation. These are usually introduced in subcutaneous tissue through trauma [1].

Systemic mycosis result from inhalation of the spores of dimorphic fungi that have their saprophytic mold forms in the soil. Within the lungs, their spores differentiate into yeasts or other specialized forms. Most of these infections are asymptomatic and self-limited. Examples of these types of systemic mycosis include coccidioidomycosis, histoplasmosis and blastomycosis.

Opportunistic fungi as *Candida, Cryptococcus, Aspergillus, Mucor* and *Rhizopus* do not induce disease in most immunocompetent individuals. However, they are quite effective in inducing disease in patients with impaired defense mechanisms [1].

3. FUNGAL INFECTIONS OF THE UPPER LIMB

3.1. Generalities in upper limb mycoses

Fungal infections of the hand are being reported with increasing frequency. Clinically, these can be usefully classified into four categories: cutaneous fungal infections, subcutaneous, deep and systemic fungal infections. Most fungal infections are superficial and relatively benign. On the other hand, deep and systemic result in serious clinical problems, which if not managed effectively, can often result in significant morbidity and even mortality [3].

3.2. Cutaneous mycoses of the hand

Cutaneous mycoses are caused by fungi that infect superficial keratinized structures, such as the skin, hair, and nails. These are referred to as dermatophytes and they are transmitted from an infected person by direct contact. Dermatophytosis, including "tinea" and "ringworm", are chronic infections favored by heat and humidity. They are characterized by pruritic papules and vesicles, broken hair and thickened broken nails. Treatment involves local antifungal creams (undecylenic acid, myconazole, etc), or oral griseofulvin. Prevention centers on keeping skin dry and cool [1].

A rare type of mycosis of the hand is referred to in the literature as *tinea manuum bullosa.* The causative organism is a zoophylic mycete, T.verrucosum. In a case report, the patient was a 36-year-old male, a crop and livestock farmer by trade, complaining of an erythematous-squamous lesion on the palm of his right hand. Mycological culture produced a profuse growth of *Trichophyton verrucosum.* Blood chemistry and immunology test results were normal. Treatment with terbinafine 250 mg per day led to clinical and mycological healing [4,5].

Generalized dermatophyte infection is referred to as *Trichophyton rubrum* infection syndrome. Prerequisites for this diagnosis include skin lesions at the following

four sites: 1) feet, often involving soles, 2) hands, often involving palms, 3) nails, and 4) at least one lesion in other location than the feet, hands or nails with the exception of the groin. In addition, diagnosis requires positive microscopic findings with potassium hydroxide preparations of skin scrapings in all four locations. Finally, identification of *T. rubrum* by culture of scrapings at three of the four locations, at least, is also necessary [5].

3.3. Subcutaneous mycoses of the hand

The most common subcutaneous mycoses are sporotrichosis and phaeomycotic cysts. Sporotrichoses are the only fungal infections which involve predominantly the upper limb. They are caused by the dimorphic fungus, *Sporothrix Schenckii,* which is a ubiquitous organism in soil in temperate and tropical climates. Sporothrix spores produce by subcutaneous implantation, a chronic granulomatous infection, with ulcers primarily and secondarily with regional adenopathy. The most common manifestation is lymphocutaneous involvement with characteristic violatious ulcerations and drain seropurulent fluid.

Patients at great risk for Sporothrix infections are home gardeners who handle soil and sharp objects. Definitive diagnosis of Sporotrichosis requires fungal cultures with the isolation of *Sporothrix Schenckii.* The standard medium for culturing is modified Sabouraud's agar. Because of the delay of clinical diagnosis that is usually related to incorrect diagnosis and treatment (usually for a presumed bacterial infection), culture of all ulcerated skin lesions for both bacteria and fungi and separate cultures grown at room temperature are mandatory. Because of the risk for atypical mycobacterial infections which have the same pattern as granulomatous infections, appropriate cultures for the isolation of these organisms should also be performed.

The drug of choice for lymphocutaneous sporotrichosis is itraconazole. Complete resolution in most patients occurs with treatment of 100 to 200mg/day for 3 to 6 months. Longer treatment periods are required for deep or disseminated infections [6]. A case of an unusual clinical course of sporotrichosis has been reported involving a 79-year-old female, employed as farmer, where sporotrichosis occurred on the patient's face at the first infection. After three recurrences of the infection near the original lesion and because medical treatment with potassium iodide and itraconazole had not been successful the facial lesion has been excised. This therapeutic experience indicates the possibility that *Sporothrix Schenckii* gradually develops resistance to potassium iodide and itraconazole. After an interval of four years unexpectedly cutaneous lesions developed on the left upper limb, a previously unaffected area. She developed nodules on her left hand and forearm. The primary lesion was crusted and granulomatous, but the lesions on the hand and forearm were nodular. Lymph nodes were not palpable. Biopsy material revealed *Sporothrix Schenckii.* The patient responded to treatment with potassium iodide (600mg/day).The cutaneous lesions completely resolved after 26 weeks of treatment [7].

A rare subcutaneous infection is the phaeomycotic cyst attributed to a darkly pigmented fungus *Exophiala, Phialophora,* or *Bantalis.* The infection occurs by traumatic implantation of wood or by intravenous catheter in an immunocompromised patient. Surgical removal is the standard treatment for this infection. Antifungal therapy alone is not clearly successful.

3.4. Deep and systemic mycoses of the hand

Deep and systemic fungal infections are rare, but very serious clinical problems that often result in significant morbidity and even mortality. These infections of the upper limb have three common clinical presentations: septic tenosynovitis (Fig. 1), septic arthritis and osteomyelitis [8] (Fig. 2). Infectious disease consultation is recommended for diagnosis and treatment in both immunocompetent and immunocompromised patients to avoid recurrence of infection. Sporotrichotic septic arthritis after direct joint inoculation may be confused with inflammatory arthritis of pyogenic infection. Sporotrichosis can also produce osteomyelitis (multifocal) or tenosynovial infection (dorsal wrist tendons). Extensor tenosynovitis may cause rupture of an extensor. Flexor tenosynovitis may result in carpal tunnel syndrome or ulnar nerve entrapment.

Bursal sporotrichosis has been reported in the olecranon and also sporotrichal myositis of the biceps muscle. The basic principles of successful treatment are surgical debulking of the infecting area, combined with systemic antifungal therapy (intravenous amphotericin B or oral itraconazole) [9].

Another deep hand infection, fungal mycetoma, is particularly resistant to medical therapy and often re-

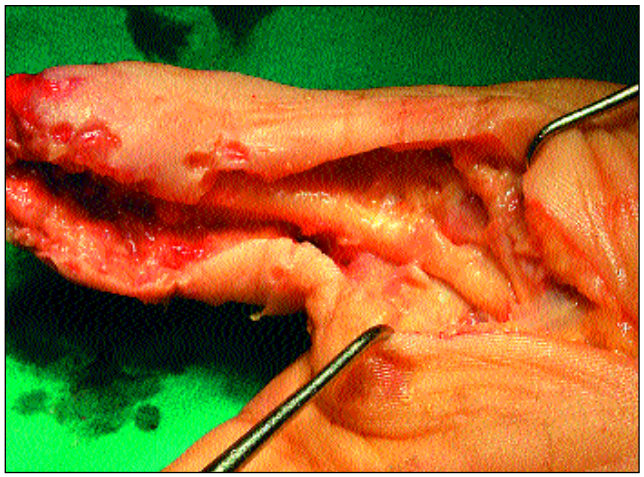

FIGURE 1. Iatrogenic Mycotic tenosynovitis in immunocompetent patients' deep infection.

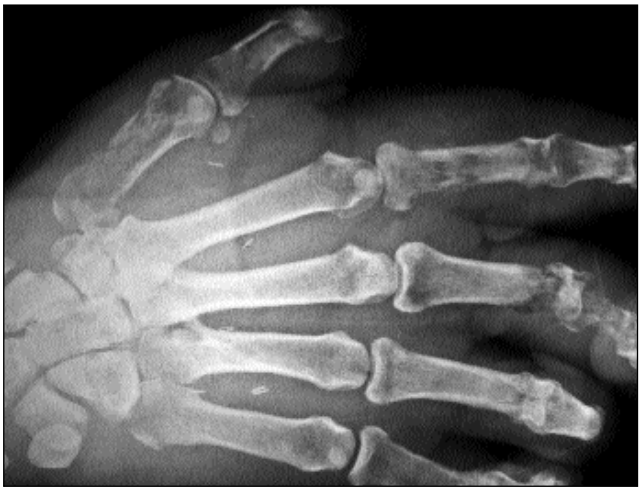

FIGURE 2. Mycotic Osteomyelitis confirmed by microscopy and culture investigation.

quires amputation. Mycetomas are subdivided into two groups: those caused by aerobic bacteria (actinomycetomas) and those caused by fungi (eumycetomas). Actinomycetomas have usually successful antimicrobial treatment and surgery is almost never needed. Eumycetoma is caused by saprophytic soil fungi that are usually inoculated through minor injuries. The most affected countries are India, Sudan, Senegal, Somalia, Venezuela, Mexico, Yemen, and Zaire. Sporadic cases also occur in temperate regions [9]. They are usually localized on the lower extremities (70%), and the hand (12%). Eumycetomas are usually caused by maduromycete fungi, especially *Madurella mycetomatis* and *M. grisea.* The prevalence of the different fungi varies from country to country and seems to be influenced by rainfall conditions. *A. kalrae* has occasionally been reported as an opportunistic human pathogen [10].

Antifungal treatment of Eumycetoma remains unsatisfactory. Intravenous amphotericin B, oral thiabendazole, topical and intravenous myconazole, oral griseofulvin, and ketoconazole have been tried. These medications are most often used in association with surgery. They limit the size of the excision, when used before surgery, and they reduce the risk of recurrence, when used after it, for at least 6 to 12 months. Itraconazole is more potent *in vitro* against some fungi than ketoconazole, it has better tissue diffusion and a better safety profile without hepatotoxicity, even with prolonged administration.

There have been a few reports concerning itraconazole treatment of eumycetoma. Of the six cases caused by *M. mycetomatis* that have been reported, one case showed a good initial response to treatment (300 mg daily for 1 year), but recurred when treatment was stopped. Three cases of eumycetoma caused by *M. grisea* were resistant to therapy. Two cases caused by *Pseudallescheria* sp. have been described: one caused by *P. larensae,* with no success and one caused by *P. boydii,* was treated with success. Two cases caused by *Acremonium* sp, have also been reported, one caused by *A. kilience* and one caused by *A. falciforme* were treated with success. One case caused by *Fusarium* sp. was reported, with improvement. These results suggest that the efficacy of itraconazole is variable, inconstant, and often partial.

Eumycetoma generally occurs in immunocompetent hosts, which differs from other opportunistic infections, such as cutaneous Alternaria infection. However, despite the presence of saprophyte mycetoma agents in soil and the high frequency of trauma, cases of mycetoma are uncommon. In a study on the immunologic status of patients with mycetoma, it was found that these patients were partially deficient in cell-mediated immunity [11].

Systemic fungal diseases occur in healthy individuals and in immunocompromised patients. They include histoplasmosis, blastomycosis, coccidioidomycosis, paracoccidiomycosis and mucormycosis. All of these diseases are endemic to certain geographic areas.

Histoplasmosis is caused by Histoplasma capsulatum and is endemic in Mississippi and Ohio river valleys. Typical pulmonary calcifications on a chest radiograph in association with positive skin or serologic testing confirm the diagnosis.

In disseminated rare cases tenosynovial infections are present or carpal tunnel syndrome, arthritis, or fatal necrotizing myofascitis in the upper extremity. A case of recurrent osteomyelitis of capitate bone was also reported. Diagnosis of *H. Capsulatum* is confirmed by measuring complement fixing (CF) antibodies and precipitin bands. A titer more than 1:32 is suggestive of active infection. A polysaccharide antigen test is available commercially and can help in diagnosis.

Critical treatment to prevent recurrence is a combination of complete tenosynovectomy, bone debridement and prolonged systemic antifungal therapy as oral ketoconazole or itraconazole or intravenous amphotericin B is utilized. San Joaquin Valley in California and the deserts of southwest of United States are the endemic regions of a highly infectious fungus Coccidioides immitis. This fungus has a predilection for synovium and 10% of coccidioidal infections occur in the wrist and hand. Tenosynovitis, joint infection and osteomyelitis of the hand have been reported. Osteomyelitis of a metacarpal may mimic an enchondroma. Tenosynovitis is present with chronic diffuse swelling over the dorsal or volar side of the wrist or palm. Untreated cases may lead to extensor tendon rupture and mimic rheumatoid arthritis [8]. Diagnosis may be confirmed by culture or serologic testing. Coccidioidomycosis also responds favorably to synovectomy and systemic antifungal therapy [3].

Mucormycosis is an acute and chronic fungal infection caused by fungi of the order Mucorales. The most commonly isolated agents are Rhisopus and Rhizomucor. These infections are aggressive and destructive, but fortunately rare [8]. Rapid diagnosis and radical debride-

ment are essential to preserve tissue devastation. The most common predisposing condition is diabetic ketoacidosis, but other such conditions include chronic renal failure, hematological malignancies, connective-tissue disorders and organ transplantation [4].

Rhisopus and Mucor infection of the hand is usually cutaneous and subcutaneous. (24% of all cutaneous cases) [8]. Fifty percent of primary cutaneous mucormycosis cases, occur in patients with severe trauma contaminated by soil or water. The other fifty percent involves patients with diabetes (20%), leukemia (9%), and chronic kidney failure (5%), or organ transplantation (4%). These cutaneous and subcutaneous infections are presented with progressive gangrenous cellulitis and necrosis of the wound margin. Advanced disease is indicated with black eschars and pus especially in an immunocompromised host.

In an unpublished case of a deep antebrachial and hand zygomatosis with flexor synovitis, we observed median nerve and bone involvement. An immunocompetent patient was admitted to our clinic with a recurrent flexor tenosynovitis and history of a recent superficial cutaneous infection of the ipsilateral hand related to catheter insertion and involving the middle and ring fingers, and the thumb. The mycosis had been misdiagnosed and previously treated by classical antibiotics for two months. With the exception of the thumb, a subungual purulent collection was present (Fig. 3). ESR and CRP were elevated. WBC count and differential was normal. Hand X-rays revealed osteolysis of the 1st ray and the phalanges of 2nd and 3rd finger. Surgical exploration revealed brownish purulent fluid in all spaces and tendon sheaths. There were fibro-purulent bands and the median nerve was necrotic (Fig. 4). Opening of all the hand septa, synovectomy and extensive debridement, including the median nerve, were performed. The trauma was packed with surgical gauze, so as it could heal secondarily. Specimens were sent for cultures and biopsy. The cultures revealed a zycomycete, *R. orysae,* and treatment with amphotericin B was initiated. The patient underwent surgical debridement weekly and hyperbaric oxygen therapy daily for four weeks. Although two months after the initial debridement healing of the wound was satisfactory, resection of the first ray and the phalangeal bones of the index and middle finger was performed because osteomyelitis still persisted. A few weeks later, a wrist-bone subtotal carpectomy which excluded the pissiform and trapezium, was performed. Six months after the last bone resection, the patient was found free of infection and the mycosis eradicated.

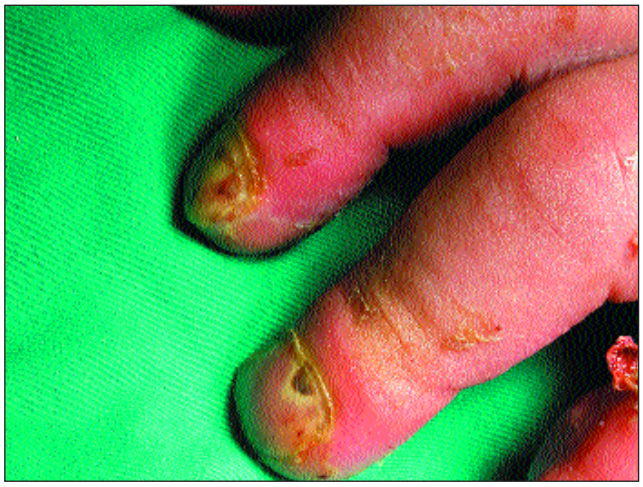

FIGURE 3. Subungual purulent collection caused by upper limb zygomatosis.

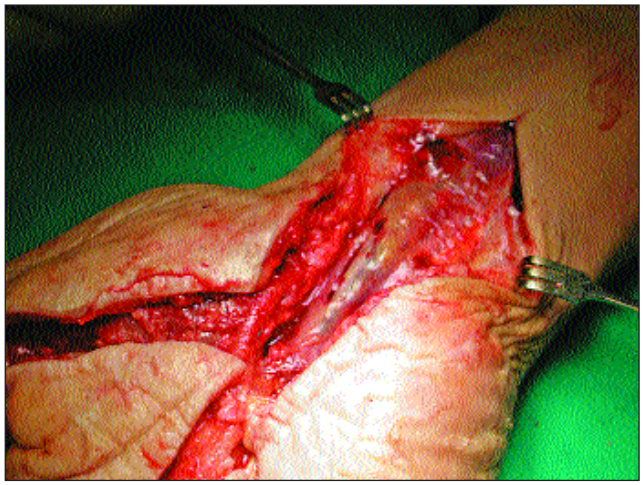

FIGURE 4. Median nerve necrosis caused by *Rhizopus oryzae* in an immunocompetent male young patient.

Timely and accurate diagnosis of zygomycosis can be difficult because these infections often present in an indolent and chronic manner. As a result, hand surgeons should have general awareness of the possibility, particularly since most patients are initially wrongly treated for an inflammatory condition. Definitive diagnosis can be made with a surgical biopsy and appropriate culture. Because these organisms are fastidious, good collaboration with the microbiologist is essential.

Successful treatment of deep zygomycosis of the hand requires surgical debridement and appropriate chemotherapy with amphotericin B. The surgical principles are similar to those for the treatment of common hand infections. The anatomic location of the infectious disease dictates the extent of debridement. The underlying risk factors for developing zygomycosis should be addressed, if possible. Because long-term antimicrobial therapy is usually necessary, consultation with an infectious disease specialist is recommended. With this multimodal approach a functional, disease-free hand can be obtained. Despite al these, deep zygomycosis of the hand due to *R oryzae* is not always curable, and at least bone excision or partial amputation is needed when osteomyelitis coexists.

Mucormycosis can result after a forearm infection at an intravenous infusion site, an intramuscular injection in an immunocompromised patient, or a contamination of devitalized tissue after major or minor trauma [7]. Burn wounds dressed with contaminated elasticized tape have been reported with this disease [11]. *Mucor hiemalis,* a common soil inhabitant, was recovered from a diabetic gardener with a localized subcutaneous infection of a finger.

Mucormycosis has a tendency to invade deep tissues, although osteomyelitis in the hand is rare. The diagnosis is typically made histologically. It requires that tissue is examined for presence of characteristic irregular, broad, nonseptate, right-angle branching hyphae. Biopsy and smears often reveal the organisms when cultures are negative. Cultures from an excised ulcer may grow *Rhisopus, Mucor,* or *Absidia,* as well as other *Mucorales,* such as *Cunninghamella* and *Apophysomyces.*

The standard therapy for mucormycosis is prompt and aggressive surgical debridement of necrotic tissue, skin grafting and amphotericin B. Predisposing systemic factors and diabetes should be aggressively managed. Intravenous amphotericin B remains the drug of choice and should be given in full dose without the delay of increasing dose titration. The lipid formulations of amphotericin B such as Abelcet and Ambisome can be used. High doses of these agents are necessary in patients who are at risk of dying of this infection, despite their known toxicity.

CONCLUSION

The most clinically interesting fungi in hand surgery are conidia which include arthrospores, chlamydospores, blastospores and sporangiospores (Rhisopus and Mucor). Mycoses occur in immunosuppressed patients usually and in certain groups of immunocompetent patients. They can be superficial or systemic and deep.

Although deep mycoses are rare they often result in significant morbidity and long term both operative and conservative treatment. When extensor or flexor tenosynovitis and fasciitis of the hand are present care must be taken with radical surgical debridement and opening of the fascia and rapid culture or serologic testing to prevent recurrence and tissue devastation.

REFERENCES

[1] Hitchcock TF, Amadio PC. Fungal infections. Hand Clin 1989;5: 599-611.
[2] Dressler F. Infectious diseases affecting the musculoskeletal system in children and adolescents. Curr Opin Rheumatol 1993;5: 651-7.
[3] Amadio P. Fungal infections of the hand. Hand Clinics 1998; 14(4):605-12.
[4] Aste N, Pau M, Aste N. Tinea manuum bullosa. Mycoses 2003; 48:80-81.
[5] Kick G, Korting HC. The definition of Trichophyton rubrum syndrome, Mycoses 2001;44:167-171.
[6] Goodman NL. Sporotrichosis. In: AF Di Salvo, editor, Occupational Mycoses. Philadelphia: Lea & Febiger, 1989.
[7] Shinogi T, Misago N, Narisawa Y. Cutaneous Sporotrichosis with Refractory and Reinfectious Lesions in a Healthy Female. J Dermatol 2004;31:492-496.
[8] Patel MR, Malaviya GN, Sugar AM. Chronic Infections: Fungal Infections. In: DP Green (ed.), Hand Operative Hand Surgery, 5th Edition, Philadelphia, PA: Elsevier-Churchill Livingstone, 2005; 106-116.
[9] Welsh O. Mycetoma: Current concepts in treatment. Int J Dermatology 1991;30:387-98.
[10] Mahgoub ES. Mycetoma. Semin Dermatology 1985;4:230-9.
[11] Degavre B, Joujoux JM, Dandurand M, Guillot B. First report of mycetoma caused by Arthrographis. Kalrae: Successful treatment with itraconazole. Am Acad Dermatology 1997;37:318-20.