General

Deep Fungal Infections of the Upper Extremity - A Review

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Deep fungal infections are rare in the upper extremity. Vessel and nerve infection, synovitis, tenosynovitis, myofasciitis, arthritis and osteomyelitis have been discovered in literature. Treatment in most cases includes surgical procedure and antifungal agent use. Amputation is the final, most devastating for patient's functionality, solution. Intravenous antifungal drugs, frequently followed by oral administration, are important ancillary agents both for the initial treatment and the prevention of recurrence. We therefore performed a review of the current literature, in order to assemble the dispersed results of different studies and clarify the various aspects of upper extremity fungal infections.

INTRODUCTION

Upper extremity infection is usually caused by bacteria, such as Staphylococcus and Streptococcus species.[1] Fungal infections are relatively rare, however there is an increasing incidence in recent years, due to the propagation of medical immunosuppression and the rise of the number of immunodeficient patients.[2]

Fungal infections of the upper extremity can be divided in three groups based on the depth of the infection, namely cutaneous, subcutaneous and deep. Cutaneous infections are located on nails and skin and are mainly caused by microorganisms that metabolize keratin. Subcutaneous infections affect the deep skin layers, subdermal fat, dermal nerves and blood and lymphatic vessels and bursae in the space overlying joints and are usually caused by low virulence organisms. Deep infections affect deep vessels and nerves, the synovium, tendons, muscles, bones and joints and are commonly caused by microorganisms that enter the body as spores and attack deep tissues of the upper limb in a different form.[3] The latter are related to significant morbidity and mortality, varied from stiffness and contracture to the need of amputation and even death. This is because of the relatively usual delay in the diagnosis, and it is important in cases of immunosuppressed patients or deep infections resistant to conventional treatment, a fungal causing factor to be considered.[4]

The aim of this review is to collect information about all deep fungal infections of the hand reported in literature and give an update with emphasis on their presentation, diagnosis and treatment.

ASPERGILLOSIS

Aspergillosis is an infection caused by the Aspergillus fungal genus. Fungi can affect deep tissues by two ways, either as a regional expansion of primary cutaneous aspergillosis, or as a secondary location of disseminated invasive aspergillosis of other organs.[2] Deep infection has been described in both pediatric and adult population. Predisposing factors include malignant hematological disease, immunodeficiency after organ transplant, intravenous catheter placement, chronic granulomatous disease, burns and puncture wounds. Cosgarea et al described a case of a 42-year-old farmer with invasive aspergillosis after a metal spike injury, without any other morbidity factor.[5] Clinical presentation varies from local swelling and restricted range of motion to deep necrotic ulcers and gangrene. In most cases empiric antibiotic therapy was given based on signs and symptoms, even though specific bacteria were not always isolated. Osteomyelitis, arthritis, myofasciitis, gangrene and deep diffused infections are the reported manifestations of deep aspergillosis. Four species have been isolated from biopsy specimen of involved tissue, A. flavus, A. fumigatu, A. niger and A. ustus. Co-infection with mucorales and phycomycetes species have been detected. Diagnosis is based on microscopic morphology, histopathological examination and culture result. Aspergillus reveals characteristic fungal hyphae on potassium hydroxide wet preparation.[1] X-rays are helpful in cases of arthritis, osteomyelitis and in lung infiltrate detection in disseminated invasive disease and magnetic resonance imaging (MRI) is used for the diagnosis of myofaciitis and osteomyelitis. Treatment strategies mainly include surgical debridement

and intravenous amphotericin B administration. Combination of amphotericin B with capsofungin and terbinafine, as well as switch of amphotericin B to oral fluconazole or itraconazole have been successfully tried. In advanced cases amputation may be inevitable. Klein et al. reported a case of a 52-year-old heart transplant recipient man with progressive gangrene of his fingers, caused by Aspergillus and mucorales species co-infection, who ended up in hand disarticulation.[6] The cases of aspergillosis are presented on **Table 1**.

BLASTOMYCOSIS

Blastomycosis is a fungal infection caused by Blastomyces dermatitides. In most cases it sets up as pulmonary disease and it disseminates secondarily to deep tissues.[14] Alternatively, deep infection is a result of regional spread of primary cutaneous blastomycosis, usually after contact with contaminated soil.[1,2] It has been described in pediatric and adult population, immunocompromised or not and it has been associated with history of pulmonary disease, diabetes mellitus, intravenous catheter insertion and local trauma. Banerjee et al. reported a 42-year-old diabetic man with hand blastomycotic osteomyelitis after an intravenous line infiltration.[15]Upper extremity deep infection may appear as verrucous ulcerative superficial lesion, subcutaneous nodules or articular swelling and restricted range of motion, while local x-rays demonstrate cortical defects and bone erosions. In addition, chest x-ray or computed tomography (CT) may show lung infiltrates. Osteomyelitis and septic arthritis are the deep demonstrations of systemic blastomycosis. Osteomyelitis of long bones is located at the epiphysis or subarticular region and from there it may spread to the joint and cause arthritis.[16] Diagnosis is based on clinical signs, imaging, histopathological studies and cultures. Microscopy after periodic acid-schif or silver stains illustrate characteristic double refractile cell wall and broad-based buds.[2] Blastomyces dermatitides antigens are available, but they do not have the desirable specificity.[16] Irrigation and debridement or lesion excision and antifungal therapy with amphotericin B or itraconazole were effective in most cases. Ketoconazole and fluconazole have also been used. Meier and Beekmann recommend itraconazole 200 to 400 mg/d or ketoconazole 400 to 800 mg/d for 6 months for mild infections and iv amphotericin B 0.4 to 0.6 mg/kg/d in total dose of 1.5 to 2 g for life threatening disease.[17] The cases of blastomycosis are presented on **Table 2**.

CANDIDIASIS

Candidiasis is an infection caused by Candida genus. Invasion of deep tissues is less common than cutaneous and subcutaneous forms and it usually happens in immunosuppressed population. Patients with history of HIV or HBV infection, diabetes mellitus, rheumatoid arthritis, steroidal use, autoimmune hepatitis and Buckley's immunodeficiency have been reported. In diabetic patients glycosylated proteins favor adhesion of Candida to epithelium.[23] However, deep candidiasis has appeared after trauma, burn injury, former surgical intervention and prolonged antibiotic therapy in immunodeficient patients. Clinical examination commonly reveals swelling and limited range of motion or a nontender mass, depending on the underlying infected tissue. Flexor and extensor tenosynovitis, pyomyositis, arthritis, periprosthetic infection and osteomyelitis have been reported. Dunkley and Leslie reported a rare case of candida prosthetic infection after silicone metacarpophalangeal arthroplasty in a patient with rheumatoid arthritis.[24] X-rays, MRI and technetium bone scan are used in the evaluation, but the final diagnosis is established by aspiration fluid or debrided tissue biopsy, histopathological examination and cultures.[2] C. albicans, C. glabrata, C. guilliermondii and C. parapsilosis have been isolated from fungal cultures. In direct microscopy Candida albicans has characteristic spherical budding yeastlike cells.[25] Treatment is corresponding to the infected tissue type and usually combines surgical intervention and antifungal agents. The former include surgical debridement, implant removal, synovectomy or amputation in advanced cases. Systemic antifungal therapy is based on fluconazole or amphotericin B administration.[2] However, other antifungal agents have also been used. Fichadiaa and Layman reported a case of flexor tenosynovitis from C. parapsilosis treated successfully with synovectomy, intravenous micafungin for 2 weeks and oral voriconazole for another 6 weeks.[26] Finally, Yang et al. recommend anidulafungin (a semisynthetic echinocandin) and fluconazole for 6 weeks for treatment of C. albicans pyomyositis.[27] The cases of candidiasis are presented on **Table 3**.

COCCIDIOMYCOSIS

Coccidiomycosis is an infection caused by coccidioides species, namely C. immitis and C. posadasii.[15] Fungals found in the soil of endemic areas, such as United States, Mexico and South America. Their evolution relates to animal hosts, however transmission from animals to humans is rare.[4] Disseminated coccidiomycosis affects both healthy and immunosuppressed hosts. In the later population it can be fatal in rare cases.[37] Acute lymphoblastic leukemia, Crohn's disease, organ transplant, lymphocytic lymphoma, rheumatoid arthritis, juvenile inflammatory arthritis and diabetes mellitus are reported predisposing factors. Typically, patients have a history of pulmonary infection, presented with flu-like symptoms, which spreads secondarily to other sites, like the synovium, tendons, bones and joints of the upper extremity.[3] Gropper et al. reported a case of coccidioidal flexor tenosynovitis in a 50-year-old man with acute lymphoblastic leukemia under immunossupressants and history of lung coccidiomycosis.[38] Upper extremity infection often presents as painful erythematous swelling or palpable mass with restricted rang of joint or finger motion. The most common manifestations are osteomyelitis, arthritis and tenosynovitis. The later can lead to tendon rupture. Also, Gavrin end Peterfy described a rare case of coccidioidal intramuscular cyst in the extensor muscles of his elbow.[39] Bone prominences at the insertion points of ten-

Table 1. Case reports of deep aspergillosis of the upper extremity

Author (year)	Age	Predisposing factors	Infected site	Clinical presentation	Diagnostic means	Microorganism	Diagnosis	Treatment	Outcome
Salisbury et al. (1974)[7]	22	Burn injury	Hand	N/A	Culture, histopath. exam	Aspergillus	Burn-wound fungal infection	Debridement	N/A
	20	Burn injury	Forearm, hand	N/A	Culture, histopath. exam	Aspergillus	Burn-wound fungal infection	Tournique and ice	Death
	20	Burn injury	Both arms and legs	N/A	Culture, histopath. exam	Aspergillus	Burn-wound fungal infection	Debridements	Death
Goldberg et al. (1982)[8]	6	Acute monomyelocytic leukemia, intravenous catheter insertion	Palm	Abscess	Histopath. exam, culture	Aspergillus niger, Aspergillus flavus	Invasive aspergillosis	I&D (hematoma with necrotic tissue in thenar space, midpalmar space, carpal tunnel and hypothenar muscles, amphotericin B, index, long and ring finger rays resection	Death
Jones et al. (1986)[9]	4	ALL, intravenous catheter insertion	Dorsal and palmar 4th hand web space	Necrotic ulcer	Punch biopsy, culture	Aspergillus flavus	Invasive aspergillosis	Debridement, amphotericin B	Ring finger ray amputation
Cosgarea et al. (1993)[5]	42	Metal spike trauma	Wrist	Pain, tenderness, swelling	X-ray (osteolysis), surgical exploration (soft tissue and bone destruction), culture	Aspergillus flavus	Fungal osteomyelitis	Debridements, subtotal carpectomy and wrist arthrodesis, iv amphotericin B	Cure
Klein et al. (2000)[6]	53	Heart transplant, peripheral vascular disease	Long, ring, small fingers	Gangrene, gradual extension to wrist	Histopath. exam, culture	Aspergillus and mucorales species	Fungal gangrene	Multiple ampuattion procedures until hand disarticulation, iv liposomal amphotericin	Cure
Everett et al. (2003)[10]	27	Burn injury	Arm	N/A	Culture, histopath. exam	Aspergillus, phycomycetes	Burn-wound fungal infection	Tourniquets	Death
Saba et al. (2004)[11]	57	AML, intravenous catheter	Elbow	Swelling, limitation of elbow	Elbow x-ray and MRI (arthritis, humerus	Aspergillus fumigatus	Fungal arthritis	Debridement, iv amphotericin B lipid complex (5 mg/kg/day), then oral itraconazole (400	Death

Author (year)	Age	Predisposing factors	Infected site	Clinical presentation	Diagnostic means	Microorganism	Diagnosis	Treatment	Outcome
				movement	osteomyelitis), aspiration, culture			mg/day)	
Olorunnipa et al. (2010)[12]	61	Cardiac transplant, lung aspergillosis	Volar forearm	Swelling, paresthesia in ulnar distribution, difficulty in flexing fingers	Punch biopsy, aspiration, surgical exploration (necrotic muscle, tendon involvement), histopath. exam, culture	Aspergillus ustus	Invasive aspergillosis	Debridements, caspofungin, terbinafine and lipid-complex amphotericin B	Cure, range of motion deficits
Camanni et al. (2017)[13]	14	Chronic granulomatous disease	Forearm	Swelling, warm, hyperemic skin, reduced flexion-extension of forearm and of middle and ring fingers	MRI (facia and muscle involvement), culture	Aspergillus fumigatus	Fungal myofasciitis	Surgical derbidement, iv liposomal amphotericin B (150 mg/day), then oral fluconazole (200 mg x2/day), then oral itraconazole (200 mg/day)	Cure

ALL: acute lymphoblastic leukemia, AML: acute myeloid leukemia, I&D: irrigation and debridement, MRI: magnetic resonance imaging, N/A: not available

Table 2. Case reports of deep blastomycosis of the upper extremity

Author (year)	Age	Predisposing factors	Infected site	Clinical presentation	Diagnostic means	Microorganism	Diagnosis	Treatment	Outcome
Gelman et al. (1973)[18]	17	None	Little finger	Tenderness, acute swelling	X-ray (bone erosion), FNA, open biopsy, histopath. exam, culture	Blastomyces dermatitidis	Fungal osteomyelitis	Amphotericin B and cloxacillin	Follow-up
Monsanto et al. 1986)[19]	26	Deep-sea and fresh water fisherman, ulceration at open biopsy wound	Thumb, distal radius	Fungating wounds, restricted motion	Wrist x-ray (lytic lesion of distal radius), chest x-ray (lung lesion), biopsy, histopath. exam, culture	Blastomyces dermatitidis	Fungal osteomyelitis	Iv amphotericin B (50mg x3/w)	Cure
Taxy et al. (2007)[20]	78	N/A	Ring finger	Mass	X-ray (destroed proximal phalanx), histopath. exam	Blastomyces dermatitidis	Blastomycosis	Debridement, excision (no information of antifungal agents)	Cure
Hankins et al. (2009)[21]	15	N/A	Ring finger	Multiple subcutaneous nodules of upper eyelid, both upper limbs and chest, finger swelling	Finger x-ray (lytic cortical defect), chest x-ray (infiltrate), brain CT (brain stem lytic areas), histopath. exam	Blastomyces dermatitides	Blastomycosis	I&D, iv liposomal amphotericin B, then oral fluconazole	Cure
	43	N/A	Middle finger	Verrucous and ulcerative lesions of the face, hands, trunk, and legs	Finger x-ray (lytic cortical defect), chest x-ray (infiltrate), histopath. exam	Blastomyces dermatitides	Blastomycosis	Amphotericin B, whirlpool bath	Cure
Banerjee et al. (2017)[15]	42	DM, intravenous catheter insertion	Dorsal hand	Swelling, inflamation, reduced grip strength	X-ray (cortical erosion), MRI (cortical destruction), histopath. exam, culture	Blastomyces dermatidis	Fungal osteomyelitis	I&D, itraconazole	Cure
Kaka et al. (2017)[22]	39	History of pulmonary disease	Ring finger	Erythematous, swollen, tender finger	X-ray (osteomyelitis), chest CT (infiltrate), microscopy, culture	Blastomyces dermatitidis	Fungal osteomyelitis	Itraconazole	Cure

CT: computed tomography, DM: diabetes mellitus, FNA: fine-niddle aspiration, N/A: not available

Table 3. Case reports of deep candidiasis of the upper extremity

Author (year)	Age	Predisposing factors	Infected site	Clinical presentation	Diagnostic means	Microorganism	Diagnosis	Treatment	Outcome
Murdock et al. (1983)[28]	49	Index, middle and ring finger and 3rd metacarpal amputation of contralateral hand due to bacterial infection	Ring finger, hand	Edema, induration, draining sinus	Technetium bone scan (4th PIP, MCP joints ostomyelitis), biopsy, histopath. exam	Candida glabrata (former Torulopsis holmii)	Fungal osteomyelitis	Iv amphotericin B (50mg x3/d), oral flucytosine (1,25gr x4/d)	Recurrence
Yuan et al. (1985)[29]	11	Buckley's immunodeficiency, chronic mucocutaneous candidiasis	Thenar, palm, thumb	Nontender spongy mass, painless restricted active motion	Surgical exploration, histopath. exam	Candida albicans	Fungal tenosynovitis	Extensive flexor and extensor tendon synovectomy, iv amphotericin B, ketoconazole	Cure
Townsend et al. (1994)[30]	36	HIV	Hand, wrist	Pain, swelling, fluctuant, non-tender mass at anterior wrist	Aspiration, culture	Candida albicans	Fungal flexor tenosynovitis	I&D (bulging flexor tendon sheath), debridement, oral fluconazole	Death due to Pneumocystis carinii pneumonia
Dunkley et al. (1997)[24]	76	RA, SSPR of 2nd to 5th MCP joints	Index finger	Increasing pain, swelling, erythema, painful restricted motion	Culture	Candida albicans	Fungal infection of silicone prothesis	Prothesis removal, derbidement	Cure
Tietz et al. (1999)[31]	57	DM, peripheral diabetic microangiopathy	Finger	Painfull inflammatory reddening of nail, serous-purulent secretion	X-ray (osteolysis), histopath. exam, culture	Candida guilliermondii	Fungal osteomyelitis	Partial amputation at DIP joint, fluconazole,	Cure
Imamura et al. (2014)[32]	45	Steroidal use for systemic lupus erythematosus	Elbow	Swelling, bulky mass	Aspiration, culture, microscopy, histopath. exam	Candida albicans	Fungal arthritis	Excision (mass intraarticular communication), fluconazole (100mg/d)	Cure
	16	Burn injury	Index finger	N/A	Culture	Candida albicans, Pseudomonas aeruginosa	Fungal osteomyelitis	Iv amphotericin B, oral fluconazole, iv piperacillin/ tazobactam, oral	Amputation

Author (year)	Age	Predisposing factors	Infected site	Clinical presentation	Diagnostic means	Microorganism	Diagnosis	Treatment	Outcome
								ciprofloxacin	
Lopez et al. (2014)[33]	51	Partial thumb amputation	Thumb	Pus discharging surgical trauma	Bone biopsy, histopath. exam, culture	Candida parapsilosis	Fungal osteomyelitis	Debridements, oral fluconazole	Cure
Fichadia et al. (2015)[26]	46	Crush injury	Middle finger	Swelling, reduced range of motion, finger tenderness	MRI (flexor tenosynovitis), histopath. exam, culture	Candida parapsilosis	Fungal flexor tenosynovitis	Flexor tenosynovectomy, iv micafungin, then oral voriconazole	Cure
Yamamoto et al. (2017)[34]	84	History of tenosynovectomy of trigger thumb	Wrist, little finger	Swelling	Culture, histopath. exam	Candida parapsilosis	Chronic fungal flexor tenosynovitis	Flexor synovectomy and irrigation (two times), clarithromycin ethambutol, fluconazole	Cure
Rosanova et al. (2018)[35]	13	Burn injury	Hand	N/A	Culture	Candida parapsilosis, Acinetobacter baumannii	Fungal osteomyelitis	Iv amphotericin B, oral fluconazole, iv colistin, oral ciprofloxacin	Hand retraction
Vulsteke et al. (2019)[36]	38	Autoimmune hepatitis	Dorsal hand	Swelling,	MRI (tenosynovitis of extensor tendons), biopsy, histopath. exam, culture	Candida albicans	Fungal extensor tenosynovitis	Limited synovectomy, fluconazole	Cure
Yang et al. (2020)[27]	54	HBV, DM	Shoulder	Warmness, erythematous lesion	CT, MRI (abscess of supraspinatus, infraspinatus and deltoid muscles), needle aspiration, culture	Candida albicans	Fungal pyomyositis	Surgical debridements, micafungin, ampicillin/ sulbactam	Cure after multiple debridements and different combos of antibiotic and antifungal therapy

CT: computed tomography, DIP: distal interphalangeal, DM: diabetes mellitus, HBV: hepatitis B virus, HIV: human immunodeficiency virus, MCP: metacarpophalangeal, MRI: magnetic resonance imaging, N/A: not available, PIP: proximal interphalangeal, RA: rheumatoid arthritis, SSPR: Swanson silastic prosthetic replacement

dons and ligaments frequently are affected by coccidioidal osteomyelitis. There is also a predilection for sites such as humeral condyles, olecranon and radial and ulnar styloid process, where higher volume of red marrow is observed.[17] Another interesting point is the rather frequent symmetric bilateral development.[37] X-rays demonstrate cystic and lytic lesions and in cases of articular involvement, loose bodies from subchondral bone can be seen.[17] Microscopic evaluation demonstrates characteristic hyphae and immature spherules with endospores after periodic acid–Schiff (PAS) and silver methenamine stains.[15] Cultures and coccidioidal complement fixation establish the diagnosis.[1] Tenosynovectomy is the treatment of choice for tenosynovitis; however, recurrence up to 50% has been reported.[40] Debridement and lesion excision are effective in other types of infection. Antifungals like amphotericin B, fluconazole and itraconazole are necessary and useful as additional therapy. Meier and Beekmann recommend itraconazole 400 mg/d or fluconazole 400 mg/d as first line treatment and ketoconazole 400 mg/d, secondarily, for 12 months or until 6 months after clinical improvement for mild infections and iv amphotericin B 0.5 to 0.7 mg/kg/d for 10 to 12 weeks followed by oral azole for more than a year for life threatening disease.[18] The cases of coccidiomycosis are presented on **Table 4**.

CRYPTOMYCOSIS

Cryptomycosis is a fungal infection caused by Cryptococcus genus. It is associated with pigeons and pigeon droppings and host's immunosuppression.[2] Deep infection has been described in patients with rheumatoid arthritis, diabetes mellitus, unicentric Castleman's disease, Waldenstrom macroglobulinemia and after local trauma. Amirtharajah and Lattanza point out the importance of cryptococcal hand infection diagnosis in patients under TNF-a antagonist drugs.[4] Superficial hand infections are a secondary manifestation of pulmonary involvement in most cases,[3] while deep infections present as primary lesions. Usual presentation includes swelling and a tender mass of wrist or fingers with restricted motion. Flexor or extensor tenosynovitis is the most common diagnosis. Braun et al. reported an uncommon case of cryptococcal fistula infection in a diabetic patient.[45] Additionally, Chen et al. described a case of middle finger osteomyelitis from C. neoformans.[46] Microscopy detects characteristic ovoid budding yeastlike cells and thick capsules with India ink preparation.[25] Cultures also demonstrate numerous budding yeasts, and high cryptococcal antigen titer is the evidence of cryptococcal infection.[37] X-rays of osteomyelitis illustrate discrete osteolytic lesions with dense surrounding bone.[16] C. neoformans is usually associated with deep upper extremity cryptomycosis. Hunter-Ellul et al. described a rare case of extensor cryprtococcal tenosynovitis caused by C. luteolus.[47] Debridement and synovectomy or excision is usually necessary followed by systemic antifungal therapy. Singh et al. reported the use of amphotericin B, fluconazole or itraconazole with concurrent flucytosine in organ transplant patients with C. neoformans infection.[48] Meier and Beekmann recommend fluconazole 200 to 400 mg/d as first line treatment and itraconazole 400 mg/d, secondarily, for 3 to 6 months and iv amphotericin B 0.3 mg/kg/d plus flucytosine 37.5 mg/kg/6h for 6 weeks or amphotericin B 0.5 to 0.7 mg/kg/d for a total dose of 1.5 to 2.5 g for life threatening disease.[17] The cases of cryptomycosis are presented on **Table 5**.

HISTOPLASMOSIS

Histoplasmosis is a fungal infection caused by Histoplasma genus. Two kinds have been described. Histoplasmosis is associated with cat and bat feces, it is endemic to some areas like Ohio and Mississippi river valleys and is caused by H. capsulatum.[2] African histoplasmosis is a result of H. duoboisii invasion and it is reported in some African countries.[51] Candida and bacterial co-infections have been detected. Immunocompromise states like organ transplant under immunosuppressants, diabetes mellitus and steroidal use for Crohn's disease, rheumatoid arthritis, Sjogren's syndrome and asthma predispose hosts to deep histoplasmosis infection. However, it has been described in immunodeficient patients, too. Onwuasoigwe et al. reported a case of forearm African histoplasmosis in a patient without any predisposing factor.[52] Deep hand infection may be primary or disseminated after pulmonary involvement.[37] Erythema and swelling with or without distal numbness is the usual presentation. Fungal tenosynovitis, carpal tunnel syndrome, myofasciitis, bone cyst and osteomyelitis are the reported manifestations. Care et al. reported an uncommon case of capitate's bone cyst in a patient with history of carpal tunnel syndrome from H. capsulotum.[53] Hypercalcemia and elevated serum angiotensin-converting enzyme may be found in blood serum test.[25] Diagnosis is established by fungal serologic test for Histoplasma-yeast forms, complement fixation test, culture and the discovery of large round single-celled spores by microscopy after Grocott's methenamine silver strain.[1] In cases of tenosynovitis or carpal tunnel syndrome the infected synovioum is red-brown and sometimes contains rice bodies.[2] X-rays may illustrate bone erosion or distruction in cases of osteomyelitis. Surgical debridement, excision or synovectomy is necessary, followed by systemic antifungal therapy, such as itraconazole, ketoconazole or iv amphotericin B. Meier and Beekmann recommend itraconazole 200 to400 mg/d as first line treatment and ketoconazole 400 mg/d or fluconazole 400 mg/d for 6 to 12 months for mild infections and iv amphotericin B 0.4 to 0.7 mg/kg/d in total dose of 1.5 to 2.5 g for life threatening disease.[17] The cases of histoplasmosis are presented on **Table 6**.

MUCORMYCOSIS

Mucormycosis is an infection caused by Mucorales order fungi. Mucor, Rhizipus and Absidia species are responsible for deep upper extremity mucormycosis infections.[1] Al-Qattan and al-Mazrou described the natural history of untreated upper extremity mucormycosis. First, dermal

Table 4. Case reports of deep coccidiomycosis of the upper extremity

Author (year)	Age	Predisposing factors	Infected site	Clinical presentation	Diagnostic means	Microorganism	Diagnosis	Treatment	Outcome
Danzig et al. (1977)[41]	59	History of flu-like illness	Wrist	Swelling, redness, pain, mass	Microscopy, culture	Coccidioides immitis	Fungal extensor tenosynovitis	Synovectomy, iv amphotericin B, then iv miconazole	Recurrence, restricted wrist motion
Gropper et al. (1983)[38]	50	ALL, history of pulmonary coccidioidomycosis	Palmar wrist	Diffuse erythematous swollen area, drainage sinus	Culture	Coccidioides immitis	Flexor fungal tenosynovitis	Flexor tenosynovectomy, amphotericin B	Cure
Garvin et al. (1995)[39]	21	N/A	Elbow	Palpable mass within extensor muscles	MRI (well-defined mass within proximal extensor muscles), histopath. exam, culture	Coccidioides immitus	Fungal intramuscular cyst	Excision	N/A
Blair et al. (2004)[42]	60	Renal transplant, history of lung coccidioidomycosis	Wrist	Pain	Culture	Coccidioides immitis	Fungal arthritis	I&D, synovectomy, fluconazole	Cure
Mitter et al. (2010)[43]	34	Crohn's disease	Elbow	Warm, swollen elbow joint, erythematous skin lesions on scalp, lip and torso, tachypnea	Elbow MRI and bone scan (bone involvement) , histopath. exam, culture	Coccidioides immitis	Fungal arthritis due to disseminated coccidioidomycosis	Elbow joint debridement, fluconazole, amphotericin B liposomal complex	Death
Campbell et al. (2015)[40]	26	N/A	Palmar middle and little fingers	Swelling, pain, limited ROM to flexion in fingers and wrist	Biopsy, culture, histopath. exam	Coccidioides species	Fungal flexor tenosynovitis	Flexor tenosynovectomy	Recurrent
	39	Lymphocytic lymphoma	Palmar hand and wrist	Swelling, pain, erythema, and limited ROM to	Biopsy, culture, histopath. exam	Coccidioides species	Fungal flexor tenosynovitis	Wrist flexor tenosynovectomy, amphotericin B	Cure

Author (year)	Age	Predisposing factors	Infected site	Clinical presentation	Diagnostic means	Microorganism	Diagnosis	Treatment	Outcome
				flexion in IP and MCP joints					
	59	N/A	Dorsal hand (4rd compartment)	Pain, swelling, erythema	Biopsy, culture, histopath. exam	Coccidioides species	Fungal extensor tenosynovitis	Wrist extensor synovectomy, iv amphotericin B, iv miconazole	Recurrent
	67	Insulin dependent DM	Dorsal wrist	Decreased ROM to extension of 2nd and 3rd digits; "mass" over dorsum of wrist	Biopsy, culture, histopath. exam	Coccidioides species	Fungal extensor tenosynovitis	Wrist extensor tenosynovectomy, oral ketoconazole (400 mg/d)	Cure
	52	ALL	Volar hand/ wrist	Pain, tenderness, swelling, erythema	Biopsy, culture, histopath. exam	Coccidioides species	Fungal flexor tenosynovitis	Wrist flexor tenosynovectomy, oral ketoconazole (400 mg/d)	N/A
	63	Insulin dependent DM	Dorsal wrist	Pain, tenderness, erythema; tendon rupture	Biopsy, culture, histopath. exam	Coccidioides species	Fungal extensor tenosynovitis	Extensor tenosynovectomy, oral fluconazole (400 mg/d)	Recurrent
	74	None	Palmar and volar hand and wrist	Pain, tenderness, swelling, ROM limitation	Biopsy, culture, histopath. exam	Coccidioides species	Fungal flexor tenosynovitis	I&D, forearm flexor tenosynovectomy, oral fluconazole (400 mg/d)	Recurrent
	45	Rrenal transplant	Dorsal hand, wrist	Pain, tenderness, swelling, erythema	Biopsy, culture, histopath. exam	Coccidioides species	Fungal extensor tenosynovitis	Wrist extensor tenosynovectomy, oral fluconazole (200 mg/d)	Recurrent
	55	Ankylosing spondylitis	Dorsal hand	Pain, swelling	Biopsy, culture, histopath. exam	Coccidioides species	Fungal extensor tenosynovitis	I&D, oral fluconazole (200 mg x3/d), then iv amphotericin B(400 mg x3/w), then posaconazole	Recurrent
	47	Liver transplant, RA,	Index finger	Pain, swelling,	Biopsy, culture,	Coccidioides	Fungal flexor	Flexor	Cure

Author (year)	Age	Predisposing factors	Infected site	Clinical presentation	Diagnostic means	Microorganism	Diagnosis	Treatment	Outcome
		DM		erythema, decreased ROM	histopath. exam	species	tenosynovitis	tenosynovectomy, oral fluconazole (400 mg/d)	
	74	RA, polymyalgia rheumatica	Dorsal hand	Pain, tenderness, swelling, ROM limitation	Biopsy, culture, histopath. exam	Coccidioides species	Fungal extensor tenosynovitis	Wrist fusion, open carpal tunnel release, extensor tenosynovectomy, oral fluconazole (400 mg/d)	Cure
	58	None	Dorsal hand (3rd compartment)	Pain, swelling, tenderness, erythema	Biopsy, culture, histopath. exam	Coccidioides species	Fungal extensor tenosynovitis	Extensor tenosynovectomy, oral fluconazole (400 mg/d)	Recurrence
	19	Juvenile inflammatory arthritis	Dorsal hand	Pain, tenderness, swelling, ROM limitation	Biopsy, culture, histopath. exam	Coccidioides species	Fungal extensor tenosynovitis	Radical dorsal wrist synovectomy/ capsulectomy, oral fluconazole (400 mg/d)	Cure
	69	None	Dorsal hand, wrist	Pain in wrist, considerable swelling and redness, mostly at base of thumb and dorsal aspect of hand	Biopsy, culture, histopath. exam	Coccidioides species	Fungal extensor tenosynovitis	Radical extensive wrist tenosynovectomy, fluconazole (600 mg/d)	Cure
O'Shaughnessy et al. (2017)[44]	58	Immunosuppression, DM	Dorsal hand, wrist	Dorsal erythema, swelling, pain with passive flexion	X-ray, MRI (tenosynovitis), culture	Coccidioides posadasii/ Immitis	Fungal extensor tenosynovitis	Wrist extensor tenosynovectomy, fluconazole	Recurrence
	74	Immunosuppression, history of pulmonary coccidioides infection	Dorsal wrist	Dorsal swelling, pain, crepitus	X-ray, culture	Coccidioides posadasii/ Immitis	Fungal extensor tenosynovitis	Wrist extensor tenosynovectomy, itraconazole	Recurrence

ALL: acute lymphoblastic leukemia, DM: diabetes mellitus, IP: interphalangeal, MCP: metacarpophalangeal, MRI: magnetic resonance imaging, N/A: not available, RA: rheumatoid arthritis, ROM: range of motion

Table 5. Case reports of deep cryptomycosis of the upper extremity

Author (year)	Age	Predisposing factors	Infected site	Clinical presentation	Diagnostic means	Microorganism	Diagnosis	Treatment	Outcome
Braun et al. (1994)[45]	66	DM, fistula	Dorsal hand, wrist, forearm	Swelling, erythema, pustules	Biopsy, culture	Cryptococcus neoformans	Fistula fungal infection	I&D, graft removal, amphotericin B, oral flucytosine and fluconazole	Recurrence
Horcajada et al. (2007)[49]	69	RA	Index finger	Finger edema and compartmental signs	Culture, microscopy, histopath. exam	Cryptococcus neoformans	Fungal flexor tenosynovitis	Surgical decompression (infiltration of vasculonervous bundles, flexor tendon synovitis), finger amputation, iv liposomal amphotericin B (300 mg/d), iv flucytosine (2,5grx3/d), then iv fluconazole (400mgx2/d), then oral fluconazole (400mg/d)	Cure
O'Shaughnessy et al. (2017)[44]	67	Thorn trauma	Volar long finger	Volar swelling, exquisite pain with palpation tendon sheath, pain with extension, flexed posture	None	Cryptococcus neoformans	Fungal flexor tenosynovitis	Digit flexor tenosynovectomy, fluconazole	Cure
Mason et al. (2011)[50]	48	Unicentric Castleman's disease	Dorsal hand	Irregular, tender mass, notable reduction in wrist dorsiflexion	MRI (mass arising from extensor tendon sheath), biopsy, culture, histopath. exam	Cryptococcus neoformans	Chronic fungal extensor tenosynovitis due to cryptococcosis	Excision, oral fluconazole	Cure
Hunter-Ellul et al. (2014)[47]	68	DM, minor trauma	Index finger	Tender nodule	Surgical exploration, histopath. exam, culture	Cryptococcus luteolus	Fungal extensor tenosynovitis	Synovectomy, fluconazole (800mg/d)	Cure
Chen et al. (2018)[46]	63	Waldenstrom macroglobulinemia	Dorsal middle phalanx	Tender, compressible erosive mass	X-ray (bone erosion), MRI	Cryptococcus neoformans	Fungal osteomyelitis due to	Mass excision and bone debridement, fluconazole	Cure

Author (year)	Age	Predisposing factors	Infected site	Clinical presentation	Diagnostic means	Microorganism	Diagnosis	Treatment	Outcome
			of middle finger	on finger, soft tissue mass on tibia	(osteolytic soft tissue mass), chest CT (multiple pulmonary nodules), FNA, microscopy		disseminated cryptococcosis		

CT: computerized tomography, DM: diabetes mellitus, FNA: fine-niddle aspiration, I&D: irrigation and debridement, MRI: magnetic resonance imaging, N/A: not available, RA: rheumatoid arthritis

Table 6. Case reports of deep histoplasmosis of the upper extremity

Author (year)	Age	Predisposing factors	Infected site	Clinical presentation	Diagnostic means	Microorganism	Diagnosis	Treatment	Outcome
Mascola et al. (1991)[54]	28	None	Wrist	Wrist and hand swelling and pain, numbness in the radial three fingers	Electromyographic and nerve conduction studies (median nerve compression at wrist), surgical exploration (synovium thickening), microscopy, culture	Histoplasma capsulatum	Carpal tunnel syndrome	Synovectomy, ketoconazole (400mg/d)	Cure
Wagner et al. (1996)[55]	17	Renal transplant, RA, dog claw scratch	Volar forearm (extension to arm)	Erythema, swelling	Diagnostic incision, CT (muscle attenuation), microscopy, culture	Histoplasma capsulatum, Mycobacterium avium-intracellulare	Necrotizing myofasciitis	Forearm compartements irrigation, extensive necrotic tissue excision, bipedical fasciocutaneous flap, amphotericin B, clarithromycin, ethambutol	Death
Care et al. (1998)[53]	35	N/A	Volar wrist	Night awakening, numbness, tingling in radial digits	X-ray (capitate's cystic lesion), electromyography, nerve conduction studies (median nerve compression), histopath. exam, culture	Histoplasma capsulatum	Fungal bone cyst due to disseminated histoplasmosis	Carpal tunnel release, flexor tenosynovectomy, capitates debridement, ketaconazole	Recurrence (after 10 years – extensive tenosynovectomy, capitates cyst cutterage, itraconazole)
Onwuasoigwe et al. (1998)[52]	30	None	Forearm	Tender firm tumor, axillar lymphadenopathy	X-ray (bone erosion), biopsy, histopath. exam, culture	Histoplasma. duoboisii	African histoplasmosis, osteomyelitis	Debridement, ketoconazole (400mg x2/d)	Cure
Schasfoort et al. (1999)[56]	71	Oral steroids for emphysema, steroid injection	Dorsal hand	Painfull swelling	Microscopy, culture, x-ray (scaphoid bone destruction)	Histoplasma capsulatum	Chronic fungal osteomyelitis	Synovectomy, wound debridement, proximal row carpectomy, iv amphotericin B	Cure
Smith et al. (2005)[57]	70	Insulin-dependent DM, use of oral steroids for asthma, history of pulmonary histoplasmosis	Wrist	Soft mass on palmar wrist, numbness and pain in middle, ring and little fingers, weakness of the hand	U/S (cystic masses in association with flexor tendon), culture, histopath. exam	Histoplasma capsulatum	Chronic fungal flexor tenosynovitis	Carpal tunnel release (synovium excision), itraconazole (few days)	Cure
Akinyoola et al. (2006)[51]	23	Minor trauma	Shoulder, elbow	Shoulder mass with discharging sinuses, elbow mass, muscle wasting, pain	X-ray (bone distruction), biopsy, histopath. exam	Histoplasma. duoboisii	African histoplasmosis	Ketoconazole	Cure
Young et al. (2011)[58]	45	History of bone debridement at shoulder	Shoulder	Deltopectoral healed incision, punctuate area that drained purulent fluid, restrictred motion	X-ray (resection of proximal humeral metaphysis), MRI (enhancement in the humeral head, sinus tract), histopath. exam	Histoplasma capsulatum	Chronic fungal osteomyelitis	Remainder humeral head excision, oral fluconazole	Cure
Vitale et al. (2015)[59]	48	Sjogren's syndrome, corticosteroid injection	Volar wrist, thumb	Swelling, numbness, paresthesias, hand grip weakness	MRI (flexor tenosynovitis, carpal tunnel stenosis), histopath. exam, culture	Histoplasma capsulatum	Fungal flexor tenosynovitis and carpal tunnel	Carpal tunnel release, flexor tenosynovectomy, iv liposomal amphotericin B (186 mg/d), then oral itraconazole	Cure

Author (year)	Age	Predisposing factors	Infected site	Clinical presentation	Diagnostic means	Microorganism	Diagnosis	Treatment	Outcome
							syndrome		
O'Shaughnessy et al. (2017)[44]	59	Immunosuppression	Dorsal and volar wrist, dorsal thumb	Volar and dorsal swelling, skin discoloration, pain with flexion/ extension, wheezing	X-ray, MRI (tenosynovitis)	Histoplasma capsulatum	Fungal tenosynovitis	Flexor and extensor tenosynovectomy, digit extensor tenosynovectomy, itraconazole	Cure
	76	RA	Volar hand, wrist, forearm	Volar forearm and hand, wrist erythema, swelling, skin ulcerations, severe pain, fevers chills	X-ray	Histoplasma capsulatum, bacterial and candida co-infection	Fungal flexor tenosynovitis	Flexor tenosynovectomy, itraconazole	Cure
	47	History of histoplasmosis	Volar wrist	Volar wrist and digit swelling, erythema, severe pain, fevers, chills	N/A	Histoplasma capsulatum	Fungal flexor tenosynovitis	Flexor tenosynovectomy, itraconazole	Cure
	50	Immunosuppression	Dorsal wrist	Dorsal wrist pain, swelling, wrist abscess	MRI (tenosynovitis)	Histoplasma capsulatum	Fungal extensor tenosynovitis	Extensor tenosynovectomy, abscess removal, itraconazole	Lung and disseminated infection
	66	Immunosuppression, DM	Dorsal and volar wrist	Volar and dorsal wrist pain, swelling, open wound at carpal tunnel	MRI (tenosynovitis)	Histoplasma capsulatum, bacterial co-infection	Fungal tenosynovitis	Flexor and extensor tenosynovectomies, amphotericin B, voriconazole	Cure
	49	Immunosuppression	Volar forearm, wrist, hand, thumb	Volar wrist, hand, thumb pain, swelling, carpal tunnel symptoms	MRI (tenosynovitis, carpal tunnel inflammation)	Histoplasma capsulatum	Fungal flexor tenosynovitis	Flexor tenosynovectomy, debridement of wrist and all digits amphotericin B, itraconazole	Cure
	53	Immunosuppression	Volar wrist, digits	Volar wrist and digit swelling, erythema, skin taught, pain with extension, night sweats	X-ray, MRI (tenosynovitis)	Histoplasma capsulatum	Fungal flexor tenosynovitis	Flexor tenosynovectomy itraconazole	Cure
Rieth et al. (2020)[60]	42	Crohn's disease	Palm	Erythema, tenderness	MRI (flexor tenosynovial enhancement with surrounding inflammation), histopath. exam, culture	Histoplasma capsulatum	Fungal flexor tenosynovitis	Flexor tenosynovectomy, carpal tunnel release, itraconazole	Cure

CT: computerized tomography, DM: diabetes mellitus, FNA: fine-niddle aspiration, MRI: magnetic resonance imaging, N/A: not available, RA: rheumatoid arthritis, U/S: ultrasonography

plexuses are invaded resulting in superficial enlarging black eschars. Subsequently, the infection spreads to subcutaneous vessels, manifesting as bleeding from the ulcerated skin. Finally, major arteries appear thrombosis causing distal gangrene.[61] Cutaneous infection usually develops at sites of trauma or peripheral vessel catheter insertion.[2] Immunocompromised patients may have history of organ transplant, diabetes mellitus, HIV, intravenous drug abuse or systemic steroid use. In diabetic patients ketone reductases result in high-glucose conditions more favorable for Rhizopus.[23] Scheffler et al. reported a case of hand mucormycosis in a premature neonatal under corticosteroid use for respiratory distress syndrome.[62] In immunocompetent patients it appears after severe injuries or burns. Moran et al. reported a series of mucor species upper limb infection after motor vehicle and conveyor belt injuries.[63] Clinical presentation varies from edema and black skin discoloration to deep ulcers and extensive necrosis. In most cases, gangrene requiring amputation is the devastating outcome. Early diagnosis and intervention are of upmost importance. Computed tomography and magnetic resonance imaging scans are rarely used to reveal the depth of invasion[3] and routine fungal cultures seldom grow the causing species.[4] Diagnosis is based on histopathological examination. Microscopy, after potassium hydroxide strain of biopsy specimens, reveals characteristic 90° hyphae.[1] Histological examination after a hematoxylin-eosin or periodic acide Schiff staining may demonstrate invasive thrombosis of minor or major vessels, leading to necrosis.[64] Aggressive debridement of necrotic tissue in early stages followed by systematic antifungal medication is necessary to prevent further dissemination. Liposomal amphotericin B at dose of 5 to 10 mg/kg/d with or without posaconazole is used in aggressive cases.[63] Bohac et al. successfully treated a man who had hand mucormycosis and Staphylococcus coinfection, after a conveyor belt injury, with Maggot therapy.[65] Amputation in healthy borders is inevitable in advanced cases. Cases of mucormycosis infections are presented on **Table 7**.

MYCETOMA

Eumycetoma is a fungal infection of skin and subcutaneous tissues, which can extent to deep structures. Actinomycetoma is a different type of mycetoma, caused by bacteria.[25] The most common causative agent of eumycetoma is Madurella mycetomatis, while Pseudallescheria, Acremonium, and Leptosphaeria have also been identified.[14] Often, fungus invades the skin and subcutaneous tissues through minor traumas and may remain inactive for many years. Deep infection is a result of local spread and may result in functional deficit, bone erosion and even death.[75] Clinical presentation typically reveals regional swelling with sinus tracts and x-rays, CT scans and MRI demonstrate bone destruction.[14] Except for these illustrative techniques, ultrasonography, cytological, histopathological examination and cultures are usually used for the diagnosis.[75] Recommended treatment is a combination of debridement, excision or amputation and antifungal agents, such as ketoconazole 400 to 800 mg per day or itraconazole 200 to 400 mg per day for 6 months to 3 years.[76] Fluconazole, voriconazole and posaconazole have also been tested. The high recurrence rate is noteworthy.[14] Three cases of deep upper extremity eumycetoma were found in database research. Altman et al. described a case of hand eumycetoma from C. albicans after prolonged antibiotic therapy for a multibacterial infection at the same site. Subcutaneous lesion with draining sinus was extended to third metacarpal bone and bone excision followed by oral fluconazole for 6 months led to complete cure.[75] Tomimori-Yamashita et al. also reported a case of hand mycetoma caused by Fusarium solani treated with oral ketoconazole, without any follow-up.[77] Finally, Cartwright et al. reported a case of hand mycetoma from Leptosphaeria tompkinsii.[78] It developed in the palm of a clothing manufacturer with no significant past medical history. It presented as palm swelling with multiple sinus tracts. X-rays, MRI and surgical exploration revealed no bone involvement. Treatment with oral itraconazole followed by oral voriconazole at dose of 200 mg twice daily at first and consequently 300 mg twice daily was unsuccessful, as symptoms insisted, and MRI illustrated carpal and metacarpal bone involvement at 12 months' time.[78] Cases of mycetoma infections are presented on **Table 8**.

SPOROTRICHOSIS

Sporotrichosis is a chronic or subacute granulomatous infection considered to be caused by Sporothrix schenkii, a fungus found in tropical and temperate areas, growing in decaying vegetation, rose thorns, soil and hay. Main target infection group are people spending considerable time working outdoors, such as florists, farmers, laborers, carpenters, beekeepers and fishermen. Infection is initiated with either direct abrasion - penetration of patient dermis from contaminated materials and subcutaneous inoculation of the fungus or by fungus spores inhalation. Direct inoculation is the common way of infection. Sites involved are usually uncovered by clothes body parts, such as distal extremities, chest and fascial head. Four types of sporotrichosis have been described, lymphocutaneous, fixed cutaneous, extracutaneous (involving mucocutaneous) and disseminated, with the first being the most common.[79] Disseminated form usually occurs in patients with altered immunity such as chronic alcoholism, diabetes mellitus, myeloproliferative disorders or patients under immunosuppression medication such as transplant recipients and HIV infection. Deep tissue sporotrichosis occurs because of direct inoculation, spreading from upper tissue layers or hematogenous/lymphogenous spreading. Joints, bone, muscles, tendons, synovium and peripheral nerves have been reported to be involved. Usual findings of joint infection are pain and swelling over the joint, with decrease in range of motion and progressive destructive arthritis. Reduction of joint space, abnormality of articular margins, joint effusions and soft tissue swelling are often seen. Regarding the upper limbs, hand small joints, wrist and elbow are more likely to be infected and shoulders are usually

Table 7. Case reports of deep mucormycosis of the upper extremity

Author (year)	Age	Predisposing factors	Infected site	Clinical presentation	Diagnostic means	Microorganism	Diagnosis	Treatment	Outcome
Palmer et al. (1970)[66]	41	DM, crush injury	Index and middle fingers	Gangrene	Microscopy, culture, histopath. exam	Rhizopus species, staphylococcus aureus	Fungal gangrene	Second and third metacarpal rays amputation, amphotericin B, penicillin	Cure
Salisbury et al. (1974)[7]	20	Burn injury	Hand	N/A	Culture, histopath. exam	Mucor species	Burn-wound fungal infection	Hand disarticulation	N/A
	20	Burn injury	Arm, chest wall	N/A	Culture, histopath. exam	Mucor species, Phycomycetes	Burn-wound fungal infection	Transfumeral arm amputation	Death
	21	Burn injury	Shoulder, back, chest wall	N/A	Culture, histopath. exam	Mucor species	Burn-wound fungal infection	Forequarter amputation, chest wall debridement	Death
	23	Burn injury	Hand	N/A	Culture, histopath. exam	Mucor species	Burn-wound fungal infection	Debridement, wrist disarticulation	N/A
	37	Burn injury	Shoulder	N/A	Culture, histopath. exam	Mucor species	Burn-wound fungal infection	Glenohumeral disarticulation	N/A
	28	Burn injury	Hand	N/A	Culture, histopath. exam	Mucor species	Burn-wound fungal infection	All finger amputation	N/A
Kraut et al. (1993)[67]	42	Burn injury	Forearm	Edematous forearm, decrease in capillary refill	Culture, histopath. exam	Mucor species	Intravascular mucormycosis	Arm amputation, contralateral hand amputation, debridement, amphotericin B	Death
al-Qattan et al. (1996)[61]	15	HIV, intravenous catheter insertion	Dorsal forearm	Large ulcer after eschar separation, thumb, middle and ring fingers gangrene	Biopsy	Mucor species	Mucormycosis	Amphotericin B	Through elbow amputation
Lidor et al. (1997)[68]	28	DM, burn injury	Forearm, hand	Necrosis	Histopath. exam	Rhizopus oryzae	Burn-wound fungal infection	Above elbow amputation	Cure
Klein et al. (2000)[6]	53	Heart transplant, peripheral	Long, ring, small fingers	Gangrene, gradual extension to wrist	Histopath. exam, culture	Mucorales and aspergillus species	Fungal gangrene	Multiple ampuattion procedures until hand disarticulation, iv	Cure

Author (year)	Age	Predisposing factors	Infected site	Clinical presentation	Diagnostic means	Microorganism	Diagnosis	Treatment	Outcome
		vascular disease						liposomal amphotericin	
Scheffler et al. (2003)[62]	15d	Premature, systemic corticosteroid use for respiratory distress syndrome, intravenous catheter insertion	Dorsal hand	Bluish-black skin discoloration, necrosis	Histopath. exam	Mucorales order	Necrotizing soft tissue fungal infection	Debridement, amphotercin B	Through elbow amputation
Moran et al. (2006)[63]	12	Motor vehicle collision	Arm, forearm	Humerus, open radius and ulna fractures	Culture, histopath. exam	Mucor species	Mucormycosis	Local flap, STSG, iv amphotericin B	Limb salvage
	26	Conveyor belt injury	N/A	N/A	Culture, histopath. exam	Mucor species	Mucormycosis	STSG, iv amphotericin B	Limb salvage
	28	Motor vehicle collision	Arm	Open humeral fracture	Culture, histopath. exam	Mucor species	Mucormycosis	Above-elbow amputation, iv amphotericin B	Cure
	46	Motor vehicle collision	Arm, elbow	Open humeral, radial neck, olecranon and ulnar fracture	Culture, histopath. exam	Mucor species	Mucormycosis	Glenohumeral disarticulation, iv amphotericin B	Cure
	56	Conveyor belt injury	Forearm	Radial and ulnar fracture	Culture, histopath. exam	Mucor species	Mucormycosis	Free latissimus flap, STSG, iv amphotericin B	Limb salvage
	52	Conveyor belt injury	Elbow	Elbow dislocation	Culture, histopath. exam	Mucor species	Mucormycosis	Anterior lateral thigh free flap, STSG, iv amphotericin B	Amputation of ring and small fingers
	70	Corn auger injury	Wrist, fingers	Radius fracture, index finger amputation, open thumb dislocation	Culture, histopath. exam	Mucor species	Mucormycosis	Below-elbow amputation, iv amphotericin B	Cure
Rajakannu et al. (2006)[69]	55	DM, cut injury	Hand fingers, palm	Blackish discoloration, dry gangrene	Histopath. exam	Mucorales order	Fungal gangrene	Transcarpal amputation, iv amphotericin B	Cure
Raizman et al.	38	Alcoholic cirrhosis, fungal	Forearm	Ulcer with dark, necrotic borders	Microscopy, histopath.	Rhizopus arrhizus	Fungal gangrene	Midforearm amputation,	Death, due to septic shock

Author (year)	Age	Predisposing factors	Infected site	Clinical presentation	Diagnostic means	Microorganism	Diagnosis	Treatment	Outcome
(2007)[70]		urinary tract infection, arterial catheter		around the site of the arterial line, line of demarcation on forearm, ulcer on contralateral forearm	exam			contralateral forearm debridement	
Chew et al. (2008)[71]	17	ORIF Smith's fracture, hydrocortisone for ARDS	Forearm	Blister at incision, necrotic area with overlying dark eschar after it bursted	Culture, microscopy, histopath. exam (first bacterial infection)	Mucor species	Fungal thrombosis due to mucormycosis	Surgical debridement, iv amphotericin B (0.5 mg/kg/d)	Forearm amputation (ulnar and radial artery thrombosis)
Sochaj et al. (2009)[72]	59	Myelodysplasia, steroidal use due to asthma and polymyalgia rheumatica	Brachial artery	Ischemic hand, loss of brachial, radial and ulnar pulses, progressive ischemia of lower extremity	Angiogram, brain CT (multiple infractions), histopath. exam, post mortem examination	Mucor species	Intravascular mucormycosis	Embolectomies, angioplasty, carotid brachial bypass	Death
Bohac et al. (2015)[65]	21	Conveyor belt injury	Dorsal forearm, wrist, hand, fingers	Limited vitality of soft tissue and extensor tendons	Culture	Absidia corymbifera and Staphylococcus haemolyticus	Necrotizing soft tissue fungal infection	Debridement, itraconazole and antibiotics, Maggot therapy, negative pressure therapy, pedicle groin flap and split-thickness skin graft	Cure, rehabilitation
Jevalikar et al. (2018)[73]	4	DM, intravenous catheter	Middle finger, interdigital space and palm between middle and ring fingers	Erythema, black discoloration, gangrene	Arterial Doppler (interdigital artery thrombosis between middle and ring fingers), microscopy, culture	Mucor species	Fungal gangrene	Middle and ring fingers amputation, iv liposomal amphotericin B	Cure, motor dysfunction little finger
Kelpin et al. (2019)[74]	25	Intravenous drug abuse, trauma	Dorsal hand	Ulcerated wound (skin, subcutaneous tissues, extensor tendons,	X-ray (absence of four ulnar metacarpal bones), culture	Mucormycotina subgroup, Staphylococcus aureus	Fungal osteomyelitis	Debridements, hand disarticulation, iv amphotericin B and antibiotics	No follow-up

Author (year)	Age	Predisposing factors	Infected site	Clinical presentation	Diagnostic means	Microorganism	Diagnosis	Treatment	Outcome
				metacarpals)					

ARDS: adult respiratory distress syndrome, CT: computerized tomography, DM: diabetes mellitus, HIV: human immunodeficiency virus, N/A: not available, ORIF: open reduction-internal fixation, STSG: split-thickness skin graft

Table 8. Case reports of deep mycetoma of the upper extremity

Author (year)	Age	Predisposing factors	Infected site	Clinical presentation	Diagnostic means	Microorganism	Diagnosis	Treatment	Outcome
Altman et al. (1994)[76]	62	Minor trauma, history of bacterial hand infection with prolonged antibiotic therapy	Palmar hand	Small palmar lesion, draining sinuses, necrotic lesion	Histopath. exam, culture	Candida species	Hand mycetoma	Debridement, 3rd metacarpal excision, oral fluconazole	Cure
Tomimori-Yamashita et al. (2002)[77]	71	History of hallux amputation due to similar lesions	Dorsal hand	Multiple crusted, cicatricial lesions	X-ray (osteolytic lesions), U/S (pseudocysts, fistulae) culture, histopath. exam	Fusarium solani	Hand mycetoma	Oral ketoconazole (400mg/d)	No follow-up
Cartwright et al. (2011)[78]	51	None	Palmar hand	Multiple sinus tracts on palmer aspect of hand	Surgical exploration, culture, histopath. exam, fungal PCR	Leptosphaeria tompkinsii	Hand mycetoma	Debridement, oral itraconazole, then oral voriconazole (300 mg x2/d)	Unsuccessfull treatment (MRI: carpal and metacarpal bones erosion)

MRI: magnetic resonance imaging, PCR: Polymerase Chain Reaction, U/S: ultrasonography

spared. Periarticular bone infection is thought to be secondary to joint infection. Radiographic features of chronic joint sporotrichosis are calcifications within the joint (rather caused by periarticular bone fragmentation), periarticular osteoporosis and erosions and rarely bursa calcification. Differential diagnosis of an unspecified granulomatous tenosynovitis should include sporotrichosis as stated by Stratton et al.[80] and it may be introduced even with a tendon rupture following tenosynovitis.[81] Sporotrichosis may be present with single peripheral mononeuropathy due to nerve compression such as carpal tunnel syndrome[80] as well as multiple peripheral mononeuropathies following reasons such as nerve compression, nerve direct infection and bystander effect of immune response to the infection after immunosuppression medication withdrawal.[82] Diagnosis of deep tissue sporotrichosis includes plain radiographs, CT and MRI scans, fine needle aspiration or surgical discharge with histopathological examination (granulomatous disease with asteroid bodies present at approximately 40% of patients) and cultures of material obtained. Multiple cultures may be needed to reach the diagnosis. Additionally, Moeller et al. reported the use of ultrasonography for the evaluation of periarticular sporotrichosis.[83] Treatment options for sporotrichosis include local measures such as hyperthermia, azoles (ketoconazole, itraconazole and fluconazole), polyenes (amphotericin B) and allylamines (terbinafine). Deep tissue infection is best treated with systematic amphotericin B, alone or with surgical debridement, followed by long-standing suppressive therapy with itraconazole as stated by da Rosa et al.[84] Engle et al. also reported an over 90% response rate of mild osteoarticular sporotrichosis treated with oral itraconazole 100 to 200 mg daily for 3 to 6 months.[85] Cases of sporotrichosis infections are presented on **Table 9**.

UNUSUAL DEEP INFECTIONS

A case of shoulder basidiomycosis was reported by Kothari et al. presented as fungal myositis after a thorn pick injury in an 11-year-old girl. Ultrasonography and MRI were used for the evaluation of the diffuse non-tender shoulder swelling and microscopy of aseptate hyphae and smooth-walled zygospores with characteristic conjugation beaks after lactophenol cotton blue wet mount established the infection by Basidiobolus ranarum. Itraconazole 100 mg/d for 6 weeks led to symptom resolution with no recurrence.[88]

Phaeohyphomycosis is an infection caused by dematiaceous fungi.[3] Patients present with papules, nodules, ulcers or swelling with or without motion limitation.[14] Biopsy reveals characteristic brown hyphae from yeast-like cells, hyphae, or pseudohyphae produced in diseased tissue.[25] Treatment includes surgical debridement with antifungal therapy, itraconazole or fluconazole for mild cases and amphotericin B for more severe.[14] Two cases of phaeohyphomycosis were discovered. Li et al. reported a case of hand arthritis and osteomyelitis from Alternaria tenuissima after a rose thorn injury. Debridement followed by oral itraconazole 200 mg twice daily led to resolvement of symptoms.[89] Sorkin et al. described a case of hand extensor tenosynovitis from Phialophora verrucosa in a 77-year-old woman with autoimmune hepatitis after a wood splinter trauma, resulted in extensor digitorum communis tendon rupture. After surgical synovectomy, extensor carpi radialis longus tendon transfer and a course of itraconazole followed by voriconazole led to satisfactory outcome.[90]

Three cases of deep upper extremity infection from Fusarium species were found, except for one described in mycetoma category. Two of them, reported by Rosanova et al., referred to children with extensive burn injuries and led to finger osteomyelitis. Both were treated by intravenous and oral voriconazole, but one of them required amputation.[35] Furthermore, a case of a 55-year-old also burned man infected by Fusarium solani at his forearm, reported by Goussous et al., needed below amputation, too.[91]

Keshtkar-Jahromi et al. described a case of synovial infection from Paecilomyces lilacinus. The patient presented with swelling at the third metacarpophalangeal joint of his hand. Diagnostic synovectomy and microbiological examination revealed the causing factor. Three-month course of voriconazole, which stopped due to side effects, finally led to treatment.[92]

A case of hand extensor tenosynovitis in a renal transplant patient caused by Phoma species was reported by Everett et al. Synovectomy followed by histopathological examination and cultures revealed the unusual causative fungi. Treatment with iv amphotericin B followed by oral fluconazole was insufficient at first, leading to recurrence. However, debridement and higher dose of iv amphotericin B eventually resulted in resolution of symptoms.[10]

Phycomycetes, a polyphyletic fungal taxon, have been isolated from sites of deep burn-wound infections of upper extremities. Both Foley and Shuck[93] and Salisbury et al.[7] reported such cases of phycomycosis, most of them requiring amputation as an ultimate solution.

Three cases of deep infection of the upper extremity by Scedosporium apiospermum were found out in literature. Schaenman et al. reported a case of necrotizing deep soft tissue infection on the dorsal aspect of the wrist and forearm of a woman with history of Behcet's disease. Surgical debridement followed by voriconazole therapy successfully treated the infection.[94] Abrams et al. described a case of wrist fungal extensor and flexor tenosynovitis of a woman with rheumatoid arthritis treated with tumor necrosis factor inhibitor. Radical tenosynovectomy and voriconazole administration were not completely effective, leading to loss of hand function.[95] Finally, Kim et al reported a case of hand extensor tenosynovitis of a woman with history of diabetes mellitus. They highlight that the diagnosis was confirmed by DNA sequencing of Scedosporium apiospermum. Debridement and fluconazole therapy were successful in this case.[96] Cases of other unusual fungal infections are presented on **Table 10**.

CONCLUSION

In this review we summarized the basic characteristics of all deep fungal infections of the upper extremity found in

Table 9. Case reports of deep sporotrichosis of the upper extremity

Author (year)	Age	Predisposing factors	Infected site	Clinical presentation	Diagnostic means	Microorganism	Diagnosis	Treatment	Outcome
Winter et al. (1972)[86]	56	N/A	Elbow	Progressive swelling and soreness	Elbow x-ray (bone erosions), aspiration, culture	Sporothrix schenckii	Fungal arthritis due to systemic sporotrichosis	Articular surface excision, multiple antifungal agents (nonspecific)	Cure
	64	N/A	Both wrists, shoulders, elbow, knee	Destructive arthritis	Elbow x-ray (bone erosions), culture	Sporothrix schenckii	Fungal arthritis due to systemic sporotrichosis	Amphotericin B	Partial cure
Stratton et al. (1981)[80]	43	Wood splinter trauma	Wrist, thumb, little finger	Swelling, restricted motion	Surgical exploration (flexor tenosynovitis, rice bodies), microscopy, culture, mice inoculation and histopath. exam	Sporothrix schenckii	Fungal granulomatous tenosynovitis	Debridements, iv amphotericin B	Cure
	49	None	Wrist	Moderate synovial swelling, restricted motion	Surgical explorations (flexor and extensor tenosynovitis, rice bodies, ruptured extensor pollicis longus tendon), microscopy, culture	Sporothrix schenckii	Fungal granulomatous tenosynovitis	Carpal tunnel release, amphotericin B, repair of extensor pollicis longus tendon	Cure
Moeller et al. (1982)[83]	68	History of sporotrichosis, minor trauma	Forearm, distal arm	Fluctuant masses	U/S (solid and cystic components), elbow x-ray (displaced fat pads, periarticular erosions of all	Sporothrix schenckii	Chronic sporotrichosis	I&D, iv amphotericin B	N/A

Author (year)	Age	Predisposing factors	Infected site	Clinical presentation	Diagnostic means	Microorganism	Diagnosis	Treatment	Outcome
					bones), culture				
Hay et al. (1986)[81]	73	N/A	Dorsal hand	Boggy mass, loss of extension of ring finger	Chest x-ray (irregular nodular density), surgical exploration (tenosynovitis, ruptured ring finger's tendon), histopath. exam, culture	Sporothrix schenckii	Fungal extensor tenosynovitis	Ring finger's extensor tendon repair, oral ketoconazole (400 mg/d)	Cure
Janes et al. (1987)[87]	45	DM	Wrist	Tenderness, erythema, warmth, restricted motion	Aspiration, x-ray (bone destruction), histopath. exam, culture	Sporothrix schenckii	Fungal arthritis	Dorsal synovectomies, debridements, amphotericin B	Cure, wrist arthrodesis
Mauerman et al. (2007)[82]	61	None	Wrists, hands	Pain, hand grip weakness, wrist swelling and erythema, paresthesias, ulcrations of wrist and contralateral thumb, multiple muscle weakness of upper and lower extremities	Culture, nerve conduction studies (focal conduction blocks of many nerves)	Sporothrix schenckii	Multiple fungal mononeuropathies due to disseminated sporotrichosis	Carpal tunnel release, forearm and hand debridements, iv itraconazole amphotericin B	Improvement

DM: diabetes mellitus, I&D: irrigation and debridement, N/A: not available, U/S: ultrasonography

Table 10. Case reports of other deep fungal infections of the upper extremity

Author (year)	Age	Predisposing factors	Infected site	Clinical presentation	Diagnostic means	Microorganism	Diagnosis	Treatment	Outcome
Li et al. (2016)[89]	49	Rose thorn injury	Dorsal hand	Swelling and erythema of second metacarpophalangeal joint	X-ray, MRI (bone involvement), surgical exploration, biopsy, culture, direct microscopy, histopath. exam	Alternaria tenuissima	Fungal arthritis and osteomyelitis	Debridement, oral itraconazole (200 mg x2/d)	Cure
Kothari et al. (2019)[88]	11	Thorn prick injury	Shoulder	Diffuse, non-tender, indurated swelling, discoloured and adherent skin, painful restricted motion, axillary lymphadenopathy	U/S and MRI (mass in deltoid muscle), FNA, biopsy, histopath. exam	Basidiobolus ranarum	Fungal myositis	Oral itraconazole (100 mgx2/d)	Cure
Goussous et al. (2019)[91]	55	Burn injury	Forearm, hand	35% total body surface area full thickness burn, blackish discoloration of deep tissues, yellowish discharge of muscles	Wound exploration, culture	Fusarium solani	Burn-wound fungal infection	Voriconazole, below elbow amputation and skin graft	Cure
Rosanova et al. (2018)[35]	3	Burn injury	Index finger	N/A	Culture	Fusarium species	Fungal osteomyelitis	Iv and oral voriconazole	Retraction
	11	Burn injury	Little finger	N/A	Culture	Fusarium species	Fungal osteomyelitis	Iv and oral voriconazole	Amputation
Keshtkar-Jahromi et al. (2012)[92]	60	None	Third MCP joint	Swelling, slight redness that blanched to pressure, no limitation of motion	Diagnostic synovectomy, microscopy, culture, histopath. exam	Paecilomyces lilacinus	Fungal synovial infection	Voriconazole	Cure
Sorkin et al. (2014)[90]	77	Autoimmune hepatitis, wood splinter trauma	Dorsal hand	Recurrent dorsal hand mass, loss of extension of middle, ring and small fingers	Biopsy, culture, histopath.. exam	Phialophora verrucosa	Fungal extensor tenosynovitis	Synovectomy, transfer of extensor carpi radialis longus tendon to the EDC of the middle, ring and small fingers, itraconazole,	Cure

Author (year)	Age	Predisposing factors	Infected site	Clinical presentation	Diagnostic means	Microorganism	Diagnosis	Treatment	Outcome
								then voriconazole	
Everett et al. (2003)[10]	50	Renal transplant, splenectomy	Wrist	Diffuse painfull swelling over extensor tendons, decreased range of motion	Biopsy, microscopy, histopath. exam	Phoma species	Fungal extensor tenosynovitis	Debridements, amphotericin B	Cure
Foley et al. (1968)[93]	20	Burn injury	Thenar, thumb, index finger	Swelling, tenderness, ischemia	Surgical exploration (necrotic muscle and soft tissue), histopath. exam	Phycomycetes	Burn-wound fungal infection	Hand disarticulation	Cure
Salisbury et al. (1974)[7]	19	Burn injury	Arm	N/A	Culture, histopath. exam	Phycomycetes	Burn-wound fungal infection	Wide wound excision	N/A
	20	Burn injury	Phalanx of thumb and little finger	N/A	Culture, histopath. exam	Phycomycetes	Burn-wound fungal infection	Amputation of proximal phalanx of thumb and little finger	N/A
	20	Burn injury	Both forearms	N/A	Culture, histopath. exam	Phycomycetes	Burn-wound fungal infection	Bilateral elbow disarticulation	Death
	21	Burn injury	Arm, contralateral hand, lip, head	N/A	Culture, histopath. exam	Phycomycetes	Burn-wound fungal infection	Wrist and shoulder disarticulation	N/A
	16	Burn injury	Hand, forearm	N/A	Culture, histopath. exam	Phycomycetes	Burn-wound fungal infection	Elbow disarticulation	Death
	27	Burn injury	Arm	N/A	Culture, histopath. exam	Phycomycetes, aspergillus	Burn-wound fungal infection	Tourniquets	Death
	20	Burn injury	Arm, chest wall	N/A	Culture, histopath. exam	Phycomycetes, mucor species	Burn-wound fungal infection	Transfumeral arm amputation	Death
Schaenman et al. (2005)[94]	58	Behcet's disease, history of bacterial infection	Dorsal wrist, forearm, elbow	Pain, swelling, erythema	Surgical exploration (necrosis of extensor tendons),	Scedosporium apiospermum	Necrotizing soft tissue fungal infection	Debridement, iv voriconazole (4mg/kg x2/d), then oral voriconazole (300mg x2/d)	Cure

Author (year)	Age	Predisposing factors	Infected site	Clinical presentation	Diagnostic means	Microorganism	Diagnosis	Treatment	Outcome
					culture, microscopy				
Abrams et al. (2010)[95]	77	RA	Wrist	Hand and wrist tightness with grasp, increasing finger numbness	Culture, histopath. exam	Scedosporium apiospermum	Fungal tenosynovitis	Carpal tunnel release, radical dorsal and palmar tenosynovectomy, debridements, voriconazole	Recurrence (no compli-ance to antifungal therapy), finally cured with loss of hand funcion
Kim et al. (2017)[96]	73	DM	Dorsal wrist, hand	Poorly defined, erythematous fluctuant papule with pustules and crusts, restricted movements	Aspiration, biopsy, MRI (extensor tenosynovitis), culture, microscopy, histopath. exam, DNA sequencing	Scedosporium apiospermum	Fungal extensor tenosynovitis	Debridement, iv fluconazole (400mf/d), then oral fluconazole (200mg/d)	Cure

DM: diabetes mellitus, EDC: extensor digitorum communis, FNA: fine-needle aspiration, MRI: magnetic resonance imaging, N/A: not available, RA: rheumatoid arthritis, U/S: ultrasonography

literature. Information about the clinical presentation, diagnosis and treatment of each main category were separately analyzed. It is proved that these infections are causes of high morbidity and mortality, especially in immunosuppressed patients. Proper evaluation and high level of suspicion are needed to treat them without delay and prevent further expansion and functional deficiency.

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