Other Fungal Arthritis

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Introduction

There are around 100,000 species of known fungi, and about 150 are pathogenic to humans and animals; they can be challenging to identify and to define an appropriate therapy. Fungal arthritis and osteomyelitis are rare, and the causative agent often depends on the geographical location, occupation, sex, and social stratum, although today, with human mobility, these conditions can vary [1–3].

Osteoarticular infection can affect the joint cavity, bone, capsule, ligaments, tendons, and muscles, and its location is usually due to hematogenous spread but also by direct inoculation or contiguity from neighboring structures. It can affect primarily immunocompromised but sometimes immunocompetent patients; the most affected are those undergoing transplantation, chemotherapy for neoplasms, chronic granulomatous disease, AIDS, and autoimmune diseases such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) associated with debilitating conditions, disease activity, or the use of corticosteroids or immunosuppressants [4–6].

This topic is important since the diagnosis of fungal infections by health personnel is a challenge due to a low index of suspicion of fungal origin of osteoarticular infection, thus leading to late diagnosis with high morbidity and frequently devastating results. Herein, some other species are described.

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Aspergillus Species

Aspergillus is a ubiquitous, saprophytic but invasive fungus that can affect the lung. Pathogenic species include *A. fumigatus*, *A. niger*, *A. nidulans*, and *A. tubingensis* [7, 8]. *Aspergillus* species has a worldwide distribution, and its infection is frequently associated with debilitating conditions such as chronic granulomatous disease, solid organ or bone marrow transplantation, chemotherapy, intravenous drug use, diabetes mellitus, or malnutrition [7–9]. It has also been described in patients undergoing surgical interventions [8, 10, 11], immunocompetent individuals [12], and also in coinfection with tuberculosis [13, 14].

Aspergillus infection occurs through hematogenous spread, contiguous of a pulmonary foci in vertebral involvement, from chronic otitis in skull-base osteomyelitis, and lastly by inoculation in the case of surgeries or trauma [7, 8, 11–13].

Aspergillosis involves more males than females, with a median age of 50 years as demonstrated by Gameletsou et al. in 31 patients compiled by the International Consortium of Osteoarticular Mycosis, affecting both adults and children [8]. The most common clinical findings are pain and tenderness at the site of location, yet fever, edema, erythema, and decreased ranges of motion are rare. Most of the time the infection is monoarticular, predominately in knees and intervertebral joints and hips, among others. In the case of osteomyelitis, the tibia is the most compromised bone and juxta-articular osteomyelitis is common [8, 13]. Axial involvement is more frequent from a pulmonary foci; it often occurs with spondylodiscitis and can cause neurological deficit [2] (Figs. 24.1 and 24.2). Leukocytosis and neutrophilia may be present along with an elevation of acute-phase reactants. In synovial fluid, variable cell counts are described, mostly with a predominance of neutrophils [8].

Localized osteoporosis, joint space narrowing, lytic lesions, and adjacent periostitis can be observed [8, 10] with conventional radiography. Joint effusion, extension to neighboring soft tissues, increase in intensity signal in T2 and with

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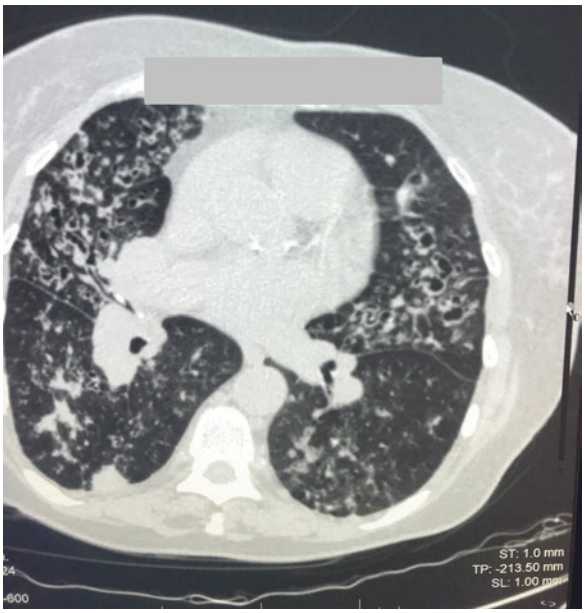

Fig. 24.1 Irregular thickening of interlobular septa, multiple micronodules, and irregular centrilobular distribution nodules with a ground-glass halo. Diffuse alteration of airway caliber conforming varicose bronchiectasis with some of them containing soft tissue due to aspergillosis. (Courtesy of Amalia Patiño MD, Radiologist. Clinica Las Americas)

contrast in T1, plus bone marrow edema can be demonstrated with magnetic resonance imaging [8, 9, 11, 12]. PET-CT can allow early diagnosis as well as treatment follow-up [7]. Arthrocentesis and open biopsy are the most commonly used methods for a definitive diagnosis of *Aspergillus* arthritis since fluid culture detects 100% of the cases; adjacent bone tissue culture is also highly sensitive [8]. In the histological study, about 50% of the cases are detected. With hematoxylin phloxine saffron stain, multinucleated giant cells with vacuolated cytoplasm are demonstrated [7]. Biomarkers such as galactomannan and β-D glucan and polymerase chain reaction are useful to establish a probable diagnosis [7, 15].

Cryptococcus Species

There are 19 cryptococcal species, but only two are pathogenic, *C. neoformans* and *C. gattii*; its life cycle is sexual and asexual. It has a worldwide distribution and is found in soil, in the feces of pigeons, and on trees such as eucalyptus [1, 3, 16]. *Cryptococcus gattii* is an emerging pathogen in the northwestern region of the United States and in western Canada [1].

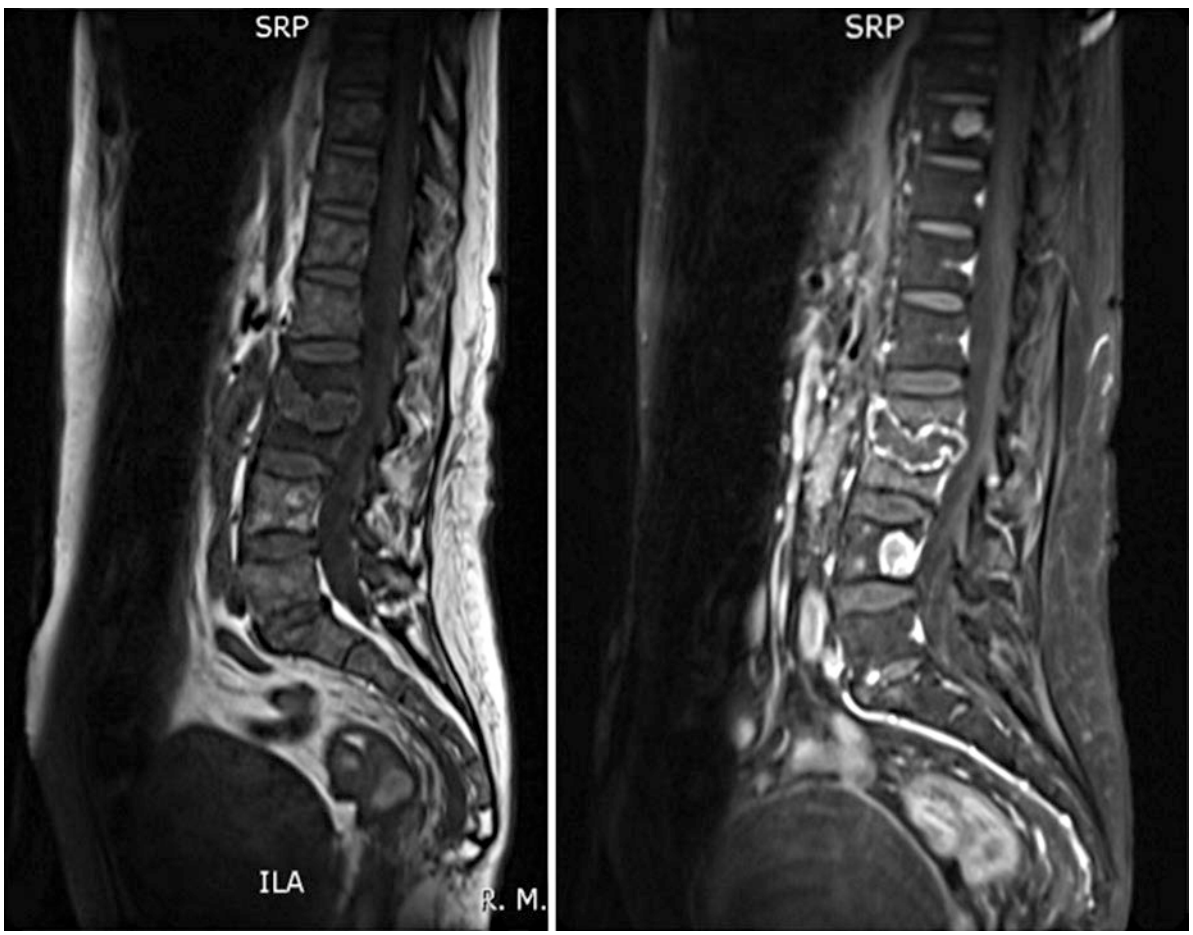

Fig. 24.2 L3 and L4 decreased height, hypointense in T1 that intensifies with contrast in SPIR. There is also an increase of the L3-L4 disc, enhancing due to spondylodiscitis. In the L4 vertebral body, there is another round image that magnifies and could have an infectious origin, by *Aspergillus*. (Courtesy of Isabel Ramirez MD, Infectious Disease. Hospital Pablo Tobon Uribe)

Cryptococcus is usually acquired by means of inhalation and occasionally secondary to trauma or inoculation through the gastrointestinal tract [1]. Three factors determine its pathogenicity: host defense, virulence of the strain, and inoculum size, but generally cryptococcosis is considered a relapsing disease [1, 14, 16]. It has a hematogenous dissemination in immunosuppressed patients, such as recipients of solid organ or bone marrow transplantation, with neoplasms undergoing chemotherapy, sarcoidosis, AIDS, or in autoimmune diseases such as SLE with high disease activity, corticosteroid use, and in RA with employment of biological agents against tumor necrosis factor [4, 6, 14–21], but it has also been described in immunocompetent subjects [22].

Cryptococcus, after *Candida* and *Aspergillus*, is the most common fungal infection, and its spread generally causes meningoencephalitis, pneumonia, pulmonary nodules, and kidney and skin involvement which can manifest as papules, nodules, acneiform lesions, ulcers, and cellulitis [22, 23] (Fig. 24.3). Osteoarticular infection is very rare since the number of reported cases is very low [16, 17, 20, 22, 24], and osteoarticular infection by *C. gattii* has not been described [2]. Osteoarticular infection can be subacute/chronic and produces evident inflammatory symptoms such as warmth, redness, edema, functional impairment, and joint effusion. In only 10–20% of cases, it is associated with osteomyelitis, the ribs, skull, pelvis, epiphysis of long bones, and vertebrae being the most affected. Tenosynovitis and myositis have also been reported [18, 19, 21, 25] (Table 24.1).

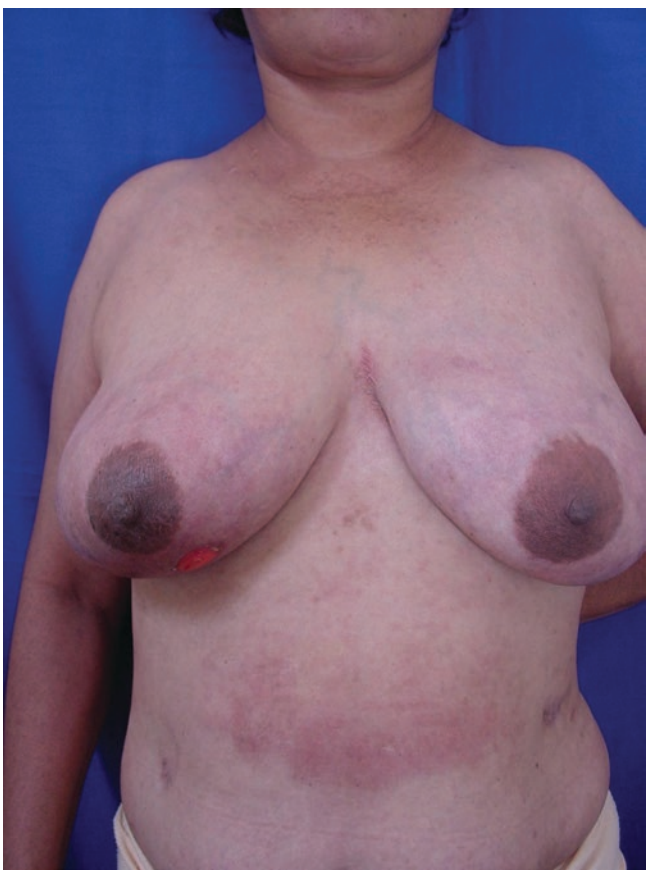

Fig. 24.3 Lupus patient with skin lesions: ulcers and papules due to cryptococcosis

Laboratory findings include both C-reactive protein and erythrocyte sedimentation rate elevation. The joint fluid may be turbid or purulent in appearance with variable cellularity but predominantly mononuclear, and the culture should always be searched for the germ on Sabouraud glucose agar with chloramphenicol. Blood and cerebrospinal fluid cultures should also be taken, as well as cultures of urine and other compromised tissues [18, 19, 21, 23, 25]. When *Cryptococcus* isolation is performed, lumbar puncture is necessary to rule out central nervous system involvement [21].

Another important aid is the detection of the blood antigen that can be done by latex agglutination or ELISA, being almost as sensitive as the isolation of the fungus, which does not happen with the detection of the antibody [21]. Another diagnostic aid is a biopsy in which stains are used, such as hematoxylin and eosin, methenamine silver, or PAS that enable yeast identification and also reveal acute and chronic inflammation with giant cell granulomas without caseification [18, 26] (Fig. 24.4).

Conventional radiological images can be normal or show osteopenia and erosive and frankly lytic lesions with diminution or loss of joint space and periosteal elevation, depending on the time of evolution [19, 23, 25, 26]. Magnetic resonance imaging can demonstrate soft tissue masses in T1 with gadolinium and fat suppression, bone edema with a focal replacement of the bone marrow, and increased intensity in tendons and muscle, with tendon thickening [19, 21].

Finally, it is necessary to draw attention to the importance of thinking about fungi as responsible for osteoarticu-

Table 24.1 Clinical characteristics in 25 patients with cryptococcal arthritis

Average age	42.16 years	
Sex	Female	9
	Male	15
	ND	1
Underlying disease	None	3
	Present	21
	ND	1
Immunosuppressants	Yes	10
	No	14
	ND	1
Involved joint	Knee	12
	Ankle	4
	Elbow	3
	Polyarthritis	3
	Other	5
	ND	2
Osteomyelitis		10
Joint Isolation		22

ND No data
Data from Refs. [18–21, 24, 25]

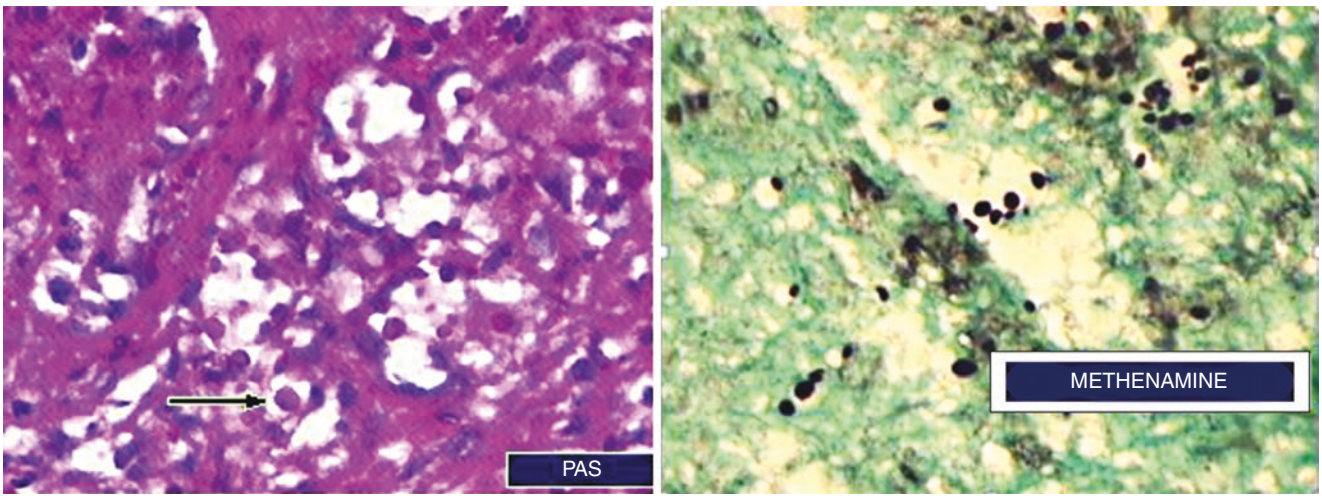

Fig. 24.4 Cryptococcus tissue demonstration with different stains. 400×

lar infection in predisposed patients as described earlier, in order to achieve a timely diagnosis, improving joint prognosis and survival.

Sporotrichosis Arthritis

It is a subacute/chronic mycosis caused by *Sporothrix schenckii*, of which five species capable of producing infection in humans have been described: *S. schenckii* sensu stricto, *S. brasiliensis*, *S. globosa*, *S. mexicana*, and *S. luriel*. It has a worldwide distribution and is found on soil and plants. It is a dimorphic fungus, which mostly involves men working in gardening, construction, mining, or peasants [27–30]. The first cases were reported in the USA, and later in France [29, 30].

Acquisition has not been totally elucidated, yet it is thought to be by inoculation secondary to trauma (even minimal), by cat scratch, contamination of soil or organic material, and even rose thorns [30–32]. It is assumed that the inhalation route is possible, when there is no evidence of trauma [33]. Sporotrichosis generally presents in alcoholic patients, diabetics, immunosuppressed by AIDS, use of corticosteroids or biological agents, myelodysplasia, neoplasia, organ transplantation [30, 34–41], and even in immunocompetent subjects [29, 31, 32, 39, 42–44].

Patients who undergo osteoarticular involvement do not regularly present significant systemic symptoms and have an indolent course [28, 31, 32, 35, 38]. The most frequent clinical affection is determined by the findings in the skin that can appear as painful nodules, sometimes with erythema or ulceration with or without exudate, or late with fistulous trajectories [34, 35, 39, 41]. More rarely, erythema nodosum has been described [41]. A finding that has been described as characteristic is a lymphangitic spread [29, 31] (Fig. 24.5). Another type of compromise is given by cervical or axillary satellite lymph nodes [28, 41]. Pneumonitis and meningitis have also been described.

Osteoarticular compromise is a late diagnosis, because clinicians rarely think *Sporothrix schenckii* as a cause of chronic arthritis that manifests with pain, erythema, functional impairment, with joint effusion and destruction, localized osteoporosis, and lytic lesions causing great morbidity [27, 29, 37, 44]. There is also bursal, tenosynovial, and muscle involvement [27, 40, 43, 44] (Figs. 24.6 and 24.7). This osteoarticular affection is rare, comprising 2–4% of all cases of sporotrichosis, and even more exceptional as an isolated clinical manifestation [30]; therefore, it is postulated that *Sporothrix schenckii* may have a hematogenous spread after inhalation, and it has also been isolated in the blood [37, 45]. Arthritis is more frequently monoarticular, although, as can be seen in a compilation of 19 cases, 10 were monoarticular and 8 were polyarticular; the most affected joints were knee (13), wrist (9), elbow (5), and ankle (2), among others, and there was concomitant osteomyelitis in 4 patients and only in one case, it was isolated (Table 24.2). The delay in diagnosis ranges from 3 to 96 months [33].

Laboratory studies are not very specific; the most striking feature is a high erythrocyte sedimentation rate, as well as C-reactive protein elevation. Synovial fluid is usually inflammatory or serohematic, with a predominance of neutrophils or lymphocytes. In this case, as well in the biopsies, the presence of the fungus is scarce, which also makes the diagnosis

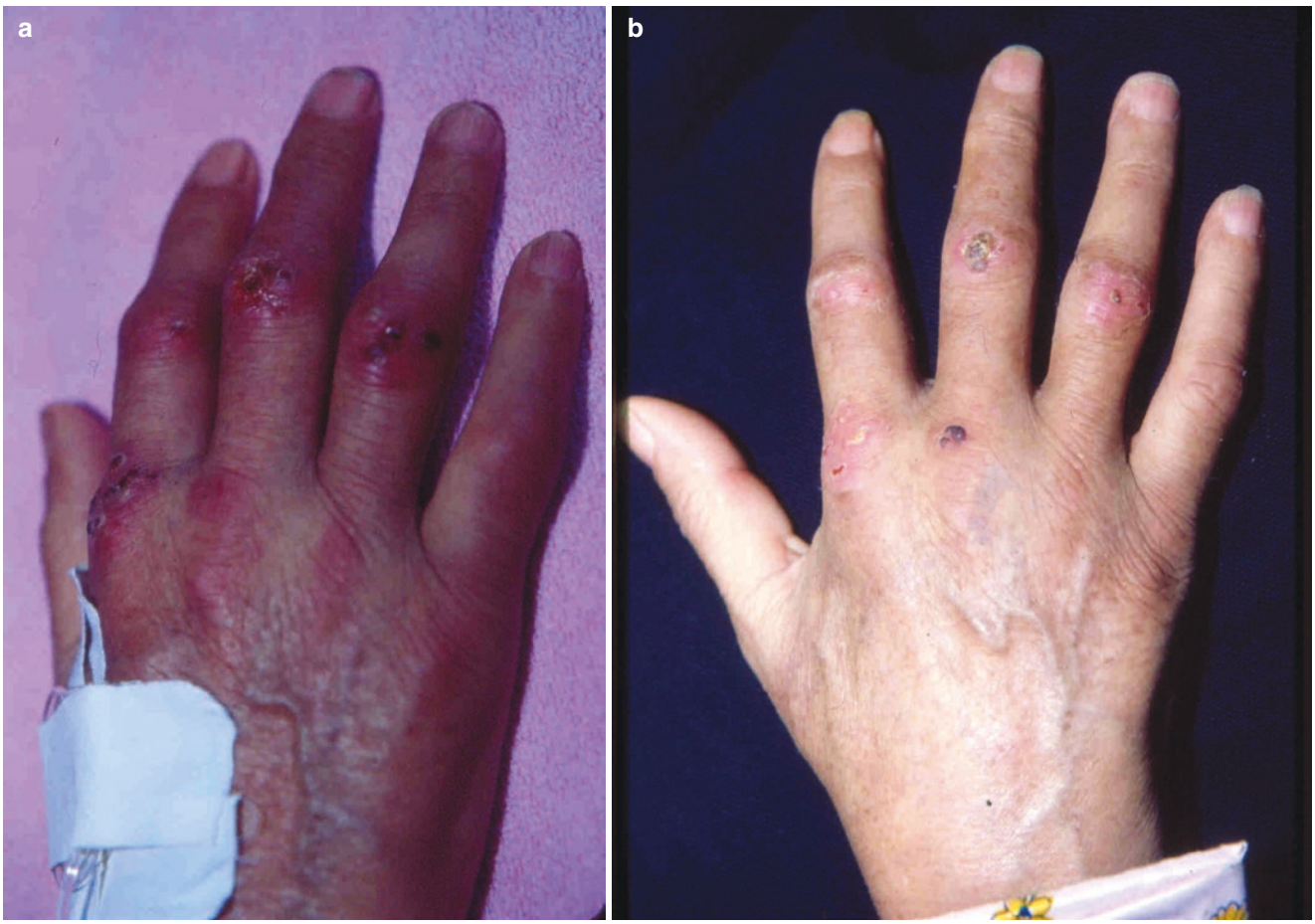

Fig. 24.5 (**a**) Papulovesiculosis lesions in early sporotrichosis; note the proximal interphalangeal arthritis. (**b**) Scarring lesions after treatment with itraconazole. (Courtesy of Oscar Uribe MD. Rheumatologist)

difficult [27, 40]. Serology for sporotrichosis has been used, employing ELISA with a fraction of SsCBF antigen, which is recognized by IgG antibodies and has shown a sensitivity of 90% and a specificity of 80% [42].

The gold standard for diagnosis is the culture, whether in synovial fluid, tissue samples, exudates of ulcers, and, occasionally, blood (see Table 24.2). The culture is done in Sabouraud dextrose agar [28, 30]. The biopsy shows granulomas with a central area of necrosis surrounded by multinucleated giant cells and palisaded histiocytes, but sometimes it does not have central necrosis which makes it indistinguishable from sarcoidosis. Although nonspecific and infrequent, oval bodies with a cigar shape and occasionally yeasts can be observed. The employed stains are glycol methacrylate, silver methenamine, or hematoxylin-eosin; asteroid bodies can also be observed [30, 40, 43, 44].

Conventional radiography is the most useful technique due to the chronic disease progression, demonstrating juxta-articular osteoporosis, soft tissue edema, diminution or loss of joint space, erosions, lytic bone lesions, periostitis, and great joint destruction [35, 38, 39]. Occasionally ultrasound, computed tomography, or magnetic resonance is used [29, 30, 40].

Paracoccidioidomycosis

Paracoccidioidomycosis is a disease that can be acute/subacute or chronic which is caused by *Paracoccidioides brasiliensis* and *P. lutzii*. It is a dimorphic fungus identified by multiple yeasts in what has become known as " pilot's wheel" [47]. Its study began in Brazil in 1908, when Lutz reported the first two patients, isolating the germ, and later described by Splendore, but it was not until 1930 when Almeida determined that it was a fungus and gave it its current name [48].

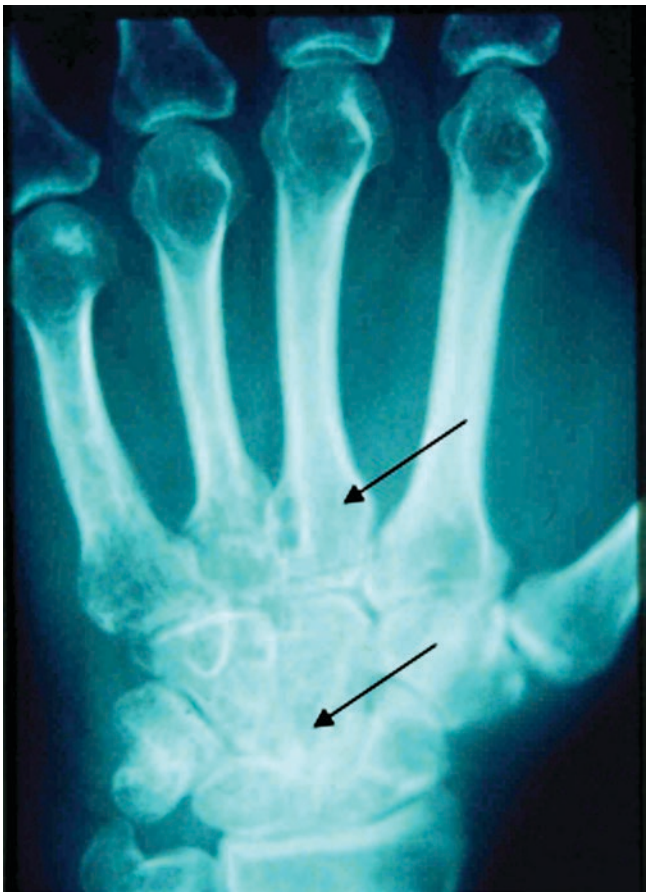

Fig. 24.6 Approach showing radiolucent lesions at the base of the third metacarpal and loss of intracarpal spaces with multiple radiolucent lesions by sporotrichosis. (Courtesy of Oscar Uribe MD. Rheumatologist)

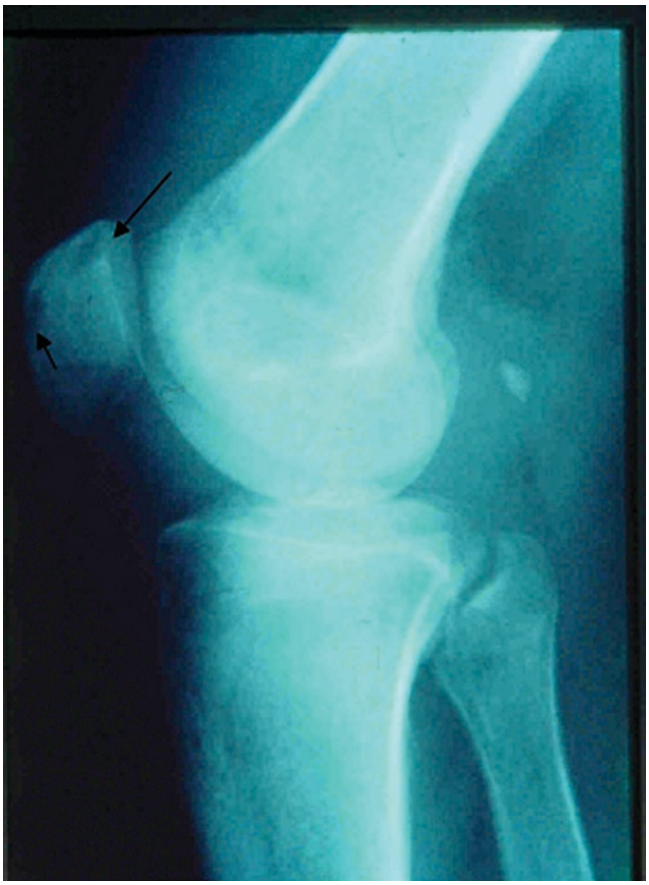

Fig. 24.7 Lateral knee X-ray demonstrating radiolucent lesions in the patella by sporotrichosis. (Courtesy of Oscar Uribe MD. Rheumatologist)

Paracoccidioidomycosis is the most frequent systemic mycosis in Latin America from Mexico to Argentina, with a high endemicity in Brazil, so that the cases described in other countries are imported due to the current high mobility [48, 49]. Approximately half of the described cases occur in rural areas, including landowners and agricultural workers; however, they have also been described in construction workers and generally occur in humid tropical and subtropical forest areas [48, 49].

The infection occurs through inhalation of the saprophytic fungus that is found in soil and plants and can be located in the lung where the human tissue can surround it or produce clinical involvement and disseminate hematogenously, affecting the skin, mucous membranes, reticuloendothelial system, gastrointestinal tract, central nervous system, osteoarticular system, genitals, and suprarenal glands [50–52]. This fungus' behavior has been associated with smoking, alcoholism, tuberculosis, chronic obstructive pulmonary disease, AIDS, and neoplasms [49].

The most common form of clinical presentation is chronic (75%), predominantly in males in a 6:1 ratio with respect to females; the average age is 40.8 years and is characterized by pulmonary involvement [49]. The acute/subacute form has no predilection for gender and is more common in children and adolescents with multisystemic manifestations: adenopathies, hepatosplenomegaly, skin lesions (papules, nodules, or ulcers), lung and osteoarticular involvement, as well as severe conditions of the general state with fever and anemia [50, 51].

Osteoarticular compromise is more predominant in the acute/subacute type and is occasionally observed in the chronic form. Most of the lesions are seen in long bones, involving metaphyses, clavicles, ribs, scapula, skull, and vertebrae [50–52]. Arthritis has been described affecting the hip, knee, shoulder, wrist, and small hand joints as acute or, very rarely, chronic manifestations [52–54]. It may cause myositis and has been described to be associated with rheumatoid arthritis [54, 55].

Table 24.2 Clinical characteristics of 19 patients with osteoarticular infection by *Sporothrix schenckii*

Reference	Age	Sex	Background	Joint pattern	Joint	Osteomyelitis	Fungus isolation
[27]	34	Male	Alcoholism	Poly	Wrist, elbow, knee	Yes	Bone
[28]	53	Female	Diabetes	Mono	Knee	No	Skin and joint fluid
[29]	74	Male	None	Mono	Wrist	Yes	Skin
[30]	33	Male	Alcoholism	Mono	Knee	No	Synovium, joint fluid
[31]	31	Female	None	Poly	Ankles, elbows	No	Skin
[32]	47	Male	None	Mono	Knee	No	Joint fluid
[32]	35	Male	None	Mono	Knee	Yes	Joint fluid
[34]	48	Female	Diabetes	–	None	Yes	Bone, skin
[35]	55	Male	Alcoholism	Poly	Wrist, elbow	No	Joint fluid
[36]	59	Male	Alcoholism	Mono	Knee	No	Joint fluid
[37]	60	Male	Alcoholism	Poly	Wrist, knee	Yes	Joint fluid, blood, skin
[38]	49	Male	Alcoholism	Poly	Wrist, elbow, knee, ankle	No	Joint fluid
[42]	88	Female	None	Mono	Knee	No	Joint fluid, synovium
[40]	72	Male	Ulcerative colitis and corticosteroids	Mono	Wrist	No	Synovium
[41]	51	Male	Diabetes	Mono	Knee	No	Joint fluid
[46]	49	Male	Immunosuppressants and alcoholism	Mono	Knee	No	Skin
[45]	78	Male	Immunosuppressants	Poly	Wrist, knee, shoulder, MCP, PIP	No	Blood
[43]	49	Female	None	Poly	Wrist, elbow	No	Synovium
[44]	50	Male	None	Poly	Wrist, knee	Yes	Joint fluid

MCP Metacarpophalangeal joint, *PIP* proximal interphalangeal joint

Laboratory studies can reveal anemia, leukocytosis (sometimes with eosinophilia), and elevation of erythrocyte sedimentation rate and C-reactive protein. In conventional radiography, lytic lesions without or minimal sclerosis are observed, single or multiple, and typically without periostitis [50–52]. Ultrasound has been used when there is soft tissue involvement, with the demonstration of tenosynovitis and intense signal in power Doppler [53]. Magnetic resonance imaging is described as a high-intensity signal that enhances with gadolinium, bone edema, and the penumbra sign in T1, similarly to other conditions that cause abscesses, findings that can be useful to differentiate it from neoplasms; none of these are characteristic of the entity [54].

Diagnosis is based on the identification of the fungus, either by direct microscopic examination or histopathology [47]. IgM and IgG antibody detection (serological study) has also been used, applying different techniques such as gel immunodiffusion, complement fixation, ELISA, or counter-immunoelectrophoresis. Complement fixation and ELISA have the limitation of cross-reacting with histoplasmosis [56]. Bellissimo-Rodrigues et al., in 1000 patients, found that counterimmunoelectrophoresis was positive in 97.2% and histopathology in 64.7%, while the culture of the fungus was only positive in 25.3% of the subjects [49]. Pathological anatomy reveals a granulomatous reaction with epithelioid and giant cells using silver methenamine or hematoxylin-eosin stains, allowing yeast identification [55, 57] (Figs. 24.8 and 24.9).

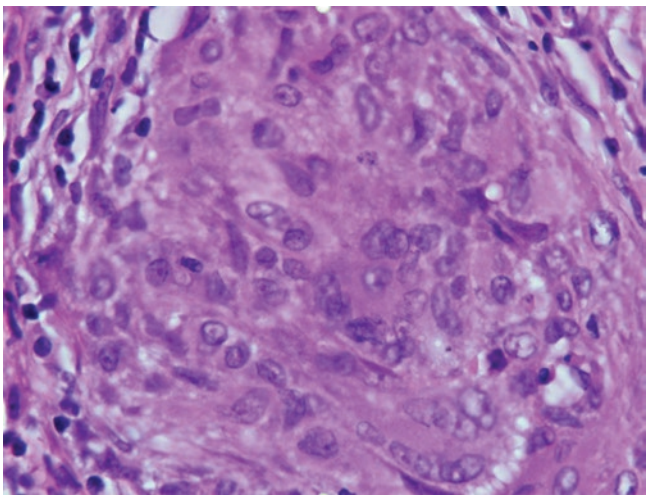

Fig. 24.8 Granulomatous inflammation with multinucleated giant cells due to paracoccidioidomycosis. Hematoxylin stain, 400×

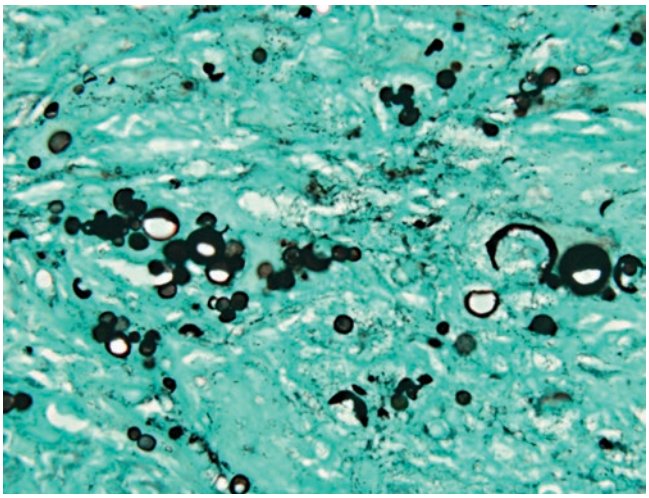

Fig. 24.9 Large, round yeast cell with multiple narrow-based budding yeast (paracoccidioidomycosis). Silver methenamine, 400×

Bone and Joint Infections Caused by Mucormycetes

Mucormycosis is a rare infection caused by filamentous fungi of the *Mucorales* order, previously called zygomycosis. The *Mucorales* are fungi of worldwide distribution, whose predominant pathogenic genera include *Rhizopus* species, followed by *Mucor*, *Rhizomucor*, and *Lichtheimia*, among others [58–60]. They are saprophytic and can be found in soil, decomposing materials, wastewater, decomposed plants, bread mold, and garbage. They are acquired by inoculation after trauma (even minimal), penetrating injuries, surgical procedures, and arthrocentesis [59, 60].

This infection is more commonly found in immunocompromised patients, such as diabetics, neutropenic, neoplasms in chemotherapy, solid organ or bone marrow transplantation, use of corticosteroids, systemic lupus erythematosus, rheumatoid arthritis treated with TNF blockers, and AIDS [2, 60–64]; however, it has also been described in immunocompetent individuals [65]. Diabetic patients, especially with ketoacidosis, have a greater predisposition since metabolic acidosis increases the pathogenic potential of the fungus by altering iron clearance [58].

This bone and joint infection predominates in men, corresponding to 71% in a series of 34 patients. It affects adults and children, and the average time for diagnosis was 73 days, being more indolent than other types of affection [60]. Skin involvement is more common on the face, cheeks, and periorbital region but can affect other body areas. It can present as papules, painful subcutaneous nodules, necrotic crusts, ulcers, fistulas, and abscesses. It is locally very invasive and can spread by contiguity or hematogenously to affect the central nervous system (rhinocerebral mucormycosis), lungs, gastrointestinal tract, or osteoarticular system

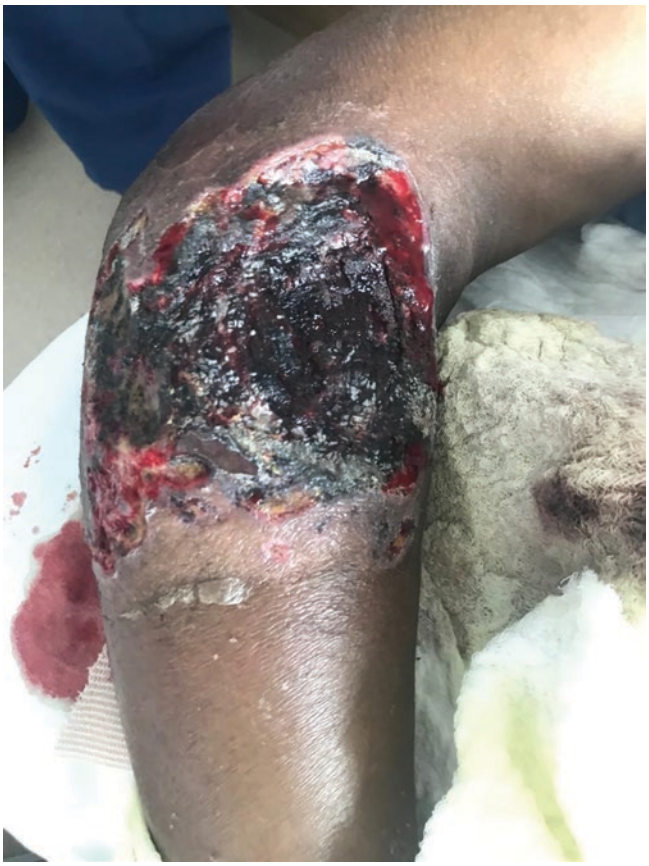

Fig. 24.10 Great ulceration with necrotic crust on the forearm due to mucormycosis

[59–62] (Fig. 24.10). Joint involvement manifests with pain, decreased range of motion, and edema which are predominant findings. The most involved joints are the hip, knee, and ankle, while osteomyelitis affects the tibia, femur, maxilla, vertebrae, skull, and humerus, among others [58–60].

Leukocytosis can be found, as well as elevation of acute-phase reactants, but the most important diagnostic aid is a skin biopsy with hematoxylin-eosin, methenamine silver, and/or PAS stains, showing suppurative granulomas suggestive of infectious panniculitis in the deep dermis and subcutaneous fat. Angioinvasive hyphae are also demonstrated in the light or wall of vessels, causing thrombosis and necrosis responsible for the aggressiveness of the affection. Such hyphae are large, broad, and not-septated and branch at right angles, unlike those of *Aspergillus* that do so at an acute angle, which is sufficient to prove the presence of the fungus [58, 62, 63]. Calcofluor white stain reveals up to 80% the presence of hyphae and allows their differentiation between septate and non-septate with 5% of false positives [66]. Culture in a non- selective medium allows identification of the germ with rapid growth [58]. There are still no biomarkers available for the diagnosis of mucormycosis [63, 66].

Imaging studies are important since multiple types of injuries can be observed, including lytic, erosive, and destructive with conventional radiography. Magnetic resonance imaging shows low-intensity signal in T1 and high-intensity patches in T2, enabling detection of invasion of neighboring tissues, which is why it is preferred over CT. Ultrasound and CT are used to take guided samples [58, 66].

Finally, it can be noted that joint and bone infections caused by *Mucorales* have been increasing in frequency since the number of patients at risk is rising. It is important to highlight the aggressiveness of this infection due to its capacity to cause angioinvasion with extensive tissue damage which makes early diagnosis mandatory, along with aggressive medical and surgical treatment to reduce its high morbidity and mortality.

Treatment

There are no controlled studies for the treatment of these bone and joint infections, given their low frequency. The management applied is based on the results of case series presentations although more recently there are recommendations from international societies for mucormycosis [66], sporotrichosis [67], and cryptococcosis [68], but are not centered in osteoarticular infection. Therefore, this management is extrapolated and adapted to individual conditions of the patient.

Treatment, in general, involves prolonged medical management with antifungal agents. In the surgical aspect, debridement of soft tissues, arthrotomy, bone curettage, removal of osteosynthesis material or joint prosthesis, and even amputation in some cases must be performed. Medical and surgical management results in better survival [1, 7, 8, 19, 21, 26, 39, 54, 58, 61, 63].

The drug most commonly used as a first option is amphotericin B with liposomal formulation (4–6 mg/kg IV) which has fewer side effects, such as renal failure and hypokalemia, compared to deoxycholate (0.5–1.0 mg/kg/day IV), the use of which should be discouraged [66, 67]. It should be noted that all treatments initiated with amphotericin B, after obtaining a good response, are continued with other medications such as itraconazole 200 mg bid PO. In the case of sporotrichosis, treatment is continued for up to 12 months, during which it is recommended to determine serum levels after two weeks of use to ensure adequate exposure to the medication [67] (Table 24.3).

For cryptococcosis, the recommendation is amphotericin B plus 5-flucytosine for 3–6 weeks as consolidation therapy, followed by fluconazole 400 mg/day for 10 weeks and then 200 mg/day for 12 months. The alternative is itraconazole 200 mg bid PO for individuals intolerant to fluconazole [21, 68].

For aspergillosis, the recommendation is voriconazole, which may be superior to amphotericin B initiated with an IV loading dose of 6 mg/kg bid for the first day and continued with 4 mg/kg/day bid for 3 more days. Afterward, it is switched to 100–150 mg bid PO 1 hour after or before a meal, achieving suitable concentrations both in synovial fluid and blood, yet monitoring of blood drug concentrations is required. The duration of treatment should be 6–12 weeks; however, it should always be individualized according to the

Table 24.3 Antifungal treatment in osteoarticular infection

Fungus	Medicine	Dose	Adverse effects
Aspergillosis	Voriconazole Ampho B lipo Anfo B DHC	4 mg/kg/d 4–5 mg/Kg/d 0.5–1 mg/Kg/d	Fever, AST and ALT elevation, cholestasis, rash, hypokalemia, anaphylaxis, chills
Cryptococcosis	Ampho B plus 5-flucytosine; then fluconazole	*Idem*	*Idem*
		50–150 mg/Kg/d 400 mg; then 200 mg/d PO	Rash, pruritus, elevated creatinine
		Children: 6–12 mg/kg/d	Nausea, vomiting, rash, AST and ALT elevation
Sporotrichosis	Ampho B; then itraconazole	*Idem*	*Idem*
		200 mg bid PO	Nausea, vomiting, AST and ALT elevation, myalgias, anxiety
Mucormycosis	Ampho B plus caspofungin or posaconazole	*Idem*	*Idem*
		50 mg IV/d > 13 years: 300 mg/d PO	Fever, diarrhea, AST and ALT elevation, fever, chills, vomiting, diarrhea, fatigue, myalgias, AST and ALT elevation
Paracoccidioidomycosis	Itraconazole	600 mg/ d for 3 days; then 200 mg/d	*Idem*
		Children: 5 mg/Kg/d	Leukopenia, anemia, rash
	TMP-SMX	TMP: 160–240 mg/d; children: 8–10 mg/Kg/d SMX: 800–1200 mg/d Children: 40–50 mg/Kg/d	

Ampho B lipo Liposomal amphotericin B, *Ampho DHC* deoxycholate amphotericin B, *ARF* acute renal failure, *PO* oral route, *TMP-SMX* trimethoprim-sulfamethoxazole
Data from Refs. [8, 21, 47, 54, 58, 63, 67, 68]

severity of involvement and the degree of immunosuppression of the patient as with any fungal treatment [21]. Amphotericin B followed by itraconazole has also been used [8].

In mucormycosis, the drug of choice is amphotericin B in the liposomal formulation, and, in some cases, it has been recommended to combine it with caspofungin [58]. Posaconazole with delayed release has also been employed [58, 63].

The treatment of choice for paracoccidioidomycosis is itraconazole 600 mg/day for 3 days followed by 200 mg/day for 6–9 months. Amphotericin B, voriconazole, or trimethoprim/sulfamethoxazole has also been used [47, 54].

Conclusion

In conclusion, the cornerstone for proper treatment of these bone and joint infections is that clinicians keep in mind to facilitate early diagnosis, which is not easy due to the scarcity of their occurrence, in addition to their torpid evolution (except for mucormycosis), and the necessary installation of aggressive diagnostic and therapeutic procedures to reduce morbidity and mortality.

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