

Chapter 2

**BONE AND JOINT INFECTIONS
BY MUCORMYCETES**

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ABSTRACT

Fungal osteomyelitis and arthritis are uncommon diseases that generally present in an indolent manner. Being one of the most challenging complications in orthopedic and trauma surgery, fungal bone and joint infections often require complex treatments in specialized centers. Mucormycosis is a disease caused by fungi of the order Mucorales. The Mucorales are the second most common cause of mould infections of the bone after *Aspergillus* spp. The organisms are characterized by broad, non-septate or sparsely septate hyphae with non-dichotomous branching in tissue. The most common species causing infection are *Rhizopus rhizopodoformis*, *Rhizopus microsporus*, *Lichtheimia corymbifera* (*Absidia corymbifera*), *Apophysomyces elegans*, *Mucor circinelloides*, and *Cunninghamella bertholletiae*. The organisms are ubiquitously found in soil and decaying matter, as well as on the surfaces of plants. Although these fungi show minimal intrinsic pathogenicity to normal persons, they can initiate aggressive and fulminant infections under certain clinical conditions. The patient populations at risk for bone and joint mucormycosis are those with diabetes mellitus, hematological malignancies,

transplantation, corticosteroid therapy, and trauma or burns. Infections of bone by the Mucorales in immunocompromised patients are usually hematogenously disseminated. Bone and joint mucormycosis constitutes a serious diagnostic and therapeutic challenge. The treatment of choice is amphotericin B, but some patients had an unfavorable outcome. Bone and joint mucormycosis is a highly destructive infection with poor prognosis if not diagnosed early. Control of underlying conditions and surgical debridement of infected tissue is critical.

INTRODUCTION TO THE MUCORALES

This chapter reviews the epidemiology, pathogenesis, clinical manifestations, diagnosis, and treatment of mucormycetes as causative pathogens of osteomyelitis. Fungi belonging to the order Mucorales are predominantly naturally occurring saprotrophs inhabiting soil and decomposing matter [1]. Fungi of the Mucorales are also known to be rarely involved in human infections mucormycosis (previously known as zygomycosis). However, the incidence of mucormycosis is increasing in hosts with severe immune or metabolic impairment, hematological malignancy, hematopoietic stem cell transplantation, and uncontrolled ketoacidotic diabetes mellitus [2-4]. The names that have been given to these fungi in the medical literature include the currently accepted subphylum Mucoromycotina has two orders, the Mucorales and the Entomophthorales.

Fungi classified as Entomophthorales were originally identified as parasites or pathogens of insects that occasionally cause mucocutaneous disease in immunocompetent human hosts. Conversely, the order Mucorales comprises a vast variety of genera cause a spectrum of predominantly angioinvasive disease in immunosuppressed patients [5]. The Mucorales species have been recently reclassified according to DNA barcoding and internal transcribed spacer (ITS) ribosomal sequencing [6]. Mucormycosis may take a dramatic course with unfavorable prognosis and mortality due to disseminated disease in patients with immune deficiency is extremely high, but varies depending on the associated risk factor and clinical presentation [7]. Little is known, however, about osteoarticular mucormycosis.

ETIOLOGY

The most common causes of mucormycosis are *Rhizopus* species [8-19], followed by *Mucor* species [20-22], *Apophysomyces elegans* [23-26], *Cunninghamella bertholletiae* [27, 28], *Lichtheimia* (formerly *Absidia*) species [29], and *Saksenaea vasiformis*[30]. Infections caused by unidentified mucormycetes were also reported [31-38]. Cases may be classified as proven with hyphae in histopathology tissue sections and probable in which histopathology was not performed.

TERMINOLOGY

There are different classification systems by which to categorize osteomyelitis [39]. Descriptive terms have been applied to infections and pathologic characteristics that are

encountered during the course of osteomyelitis, mechanism of bone infection, criteria for diagnostic probability, and onset of infection. All definitions used throughout this chapter are previously published definitions [40-47]. Direct inoculation indicates local bone or joint infection following a skin breakdown, Hematogenous denotes seeding to bone or joint by dissemination from a distant site of inoculation/infection. Contiguous implies to seeding to bone or joint from an adjacent infection site. Proven fungal osteomyelitis is the evidence of a positive culture, and/or histology from bone tissue, joint fluid, or metal hardware. Probable fungal osteomyelitis means compatible clinical and radiological features of osteomyelitis with evidence of positive histology and/or fungal culture from an extra-osteoarticular site. Overall response is the complete or partial resolution of clinical and radiological findings of osteomyelitis. Children are defined as being ≤ 15 years.

OSTEOARTICULAR MYCOSES

Fungal osteomyelitis and arthritis are uncommon diseases. Most reports are limited to individual case descriptions and small case series. Data on the epidemiology of osteoarticular mycoses were reviewed recently [48]. As with other fungal diseases, currently an increasing trend of fungal bone infections was reported due to a growing number of patients at risk [49, 50]. A series of important comprehensive analyses of osteoarticular mycoses were recently published to address the epidemiological, clinical, diagnostic, and therapeutic aspects of these infections [40-47]. Fungal osteomyelitis and arthritis generally present in an indolent manner. Being one of the most challenging complications in orthopedic and trauma surgery, fungal osteoarticular infections often require complex treatments in specialized centers. The majority of these infections are caused by *Candida* species [40, 43, 49] and *Aspergillus* [41, 44, 46]. Other osteoarticular infections are reported with dimorphic fungi, which demonstrate distinctive clinical presentations, occur predominantly in immunocompetent patients, and develop from hematogenous dissemination [42].

Opportunistic infections due to other groups of fungi are increasingly reported as potential emerging pathogens but with limited description and relatively few reports of osteoarticular mycoses. A comprehensive literature analysis addresses the clinical aspects, microbiology, therapy, and outcome of osteoarticular infections caused by non-*Aspergillus* moulds [45, 47].

PATHOGENESIS OF MUCORMYCOSIS

Mucormycetes usually invade the body via inhalation or via damaged skin as a portal of entry. The hyphae invade the vascular endothelium, producing thrombosis and infarctions resulting in gradual tissue ischaemia and necrosis of the affected tissue or organ. The fungal infection may disseminate further to cause osteomyelitis particularly in hematological malignancy [31] and renal transplant patients [27]. The infection is relentlessly progressive with aggressive soft tissue compromise and bone destruction and may result in extremity amputation [20, 10].

HOST DEFENSES

Host defenses against the sporangiospores of pathogenic Mucorales is primarily through macrophages that phagocytose, inhibit their germination, and destroy them through non-oxidative mechanisms. Host defenses against proliferating mucromycetous hyphae are mediated through the oxidative metabolism of neutrophils. Thus, patients who have diseases affecting the function of these two cell types will be at risk for infection [1]. Increased susceptibility to infection also is mediated by enhanced availability of iron in tissue or serum, which promotes aggressive invasive growth of infecting sporangiospores [51]. Diabetic ketoacidosis causes dysfunction of macrophages and is the frequent underlying disease for bone infection. As expected, chemotherapy and stem cell transplantation have emerged in the past 2 decades as major risk factors for invasive bone mucormycosis. In addition, the Mucormycetes thrive when excess iron is present in the host, as well as in those patients receiving iron-chelating agents such as deferoxamine to reduce iron overload [12, 20, 27].

POSSIBLE RISK FACTORS AND MECHANISM OF INFECTION

Among the patients with mucormycetous bone and joint infection, male subjects tend to predominate. The disease is more prevalent in adults than in children. The main mechanism of infection appears to be direct inoculation, especially in patients subjected to prior trauma or previous surgery. Hematogenous dissemination appears to occur less frequently and is more likely to occur particularly in immunocompromised hosts and patients with hematological malignancy.

Among the underlying conditions in immunocompetent patients are surgery, trauma, and road accidents with compound fractures, and penetrating wounds. Corticosteroid therapy and diabetes mellitus also a putative risk factors. Severe immunocompromised patients including hematological malignancies, bone marrow transplantation, solid organ transplantation, and HIV/AIDS, account for other cases at risk for osteoarticular mucormycosis.

HISTOPATHOLOGY

Morphological characteristics of Mucorales genera can be seen in clinical specimens. Tissue identification of these molds is a very important diagnostic tool, as it distinguishes the presence of the fungus as a pathogen in the specimen from a culture contaminant and is indispensable to define whether there is blood vessel invasion. Mucorales genera produce non-pigmented, broad (5- to 20- μ m), thin-walled, ribbon-like hyphae with right angle branching and sparse septa in tissue (Figure 1). The hyphae may vary in width and appear folded, crinkled, or fragmented.



Figure 1. Mucormycetes hyphae are seen in bone biopsy specimen of Figure 2. Typical hyphae are broad, thin walled, and pleomorphic (arrow). They vary in caliber and produce irregular branches that often arise from parent hyphae at right angles. Stain hematoxylin and eosin, magnification x400. From reference # 8 by license number 3738671462265 from Springer publishers.

In lesions exposed to air, thick-walled spherical structures (sporangia) can form along hyphae [19]. Routine H and E stains may show only the cell wall with no structure inside. It is important to mention that hyphal elements are observed in the specimen, since this identifies the source where the fungus is found and will rule out contamination if there are questions about contamination in the culture. Stains that can help highlight the fungal wall include GMS and PAS stains; however, fragmentation and necrosis of the fungal elements may cause these stains, in particular GMS, to be either faintly positive or negative.

The major morphological differentiation between genera of the Mucorales and other filamentous fungi is with other fungi that produce non-pigmented hyphae in tissue, including *Aspergillus* spp., other hyaline septated fungi such as *Fusarium* spp. and *Scedosporium* spp. and *Candida* spp. [1, 52]. The presence of abundant septation and acute-angle branching should suggest the diagnosis of *Aspergillus*, *Scedosporium*, or *Fusarium* spp., while yeasts with pseudohyphae should suggest *Candida* spp. Whereas, poor staining of hyphae with GMS stain should suggest mucormycosis.

DIAGNOSTIC IMAGING

The manifestations of bone and joint infection by Mucormycetes are heterogeneous, depending on several factors, the specific causative fungus involved, anatomic area of involvement, segment of affected bone, route or type of infection, host factors, and the

presence of underlying comorbidities. Imaging techniques play a key role in the early diagnosis and follow up of osteoarticular mucormycosis [53].

Osteoarticular abnormalities are detectable by different imaging techniques. Magnetic resonance imaging may show low signal intensity on T1weighted and patches of high signal intensity on T2 weighted images in [11, 27, 37]. Conventional radiographs may reveal osteolytic lesions [17, 24, 31, 32], lucencies [12, 21], or multiple small erosions of the vertebral bodies [36]. Bone destruction may be reported on CT scan in tibial osteomyelitis infection (Figure 2). Bone destruction due to mucormycosis developed in the tibia after anterior cruciate ligament reconstruction of the affected tibia with allograft after radical debridement (Figure 3). Increased Tm_{99} pyrophosphate scan of radionuclide activity also is observed in these infections [12, 17, 18].



Figure 2. Tibial fungal osteomyelitis, a coronal view CT scan of the knee before radical debridement shows cortical and cancellous bone destruction. From reference # 8 by license number 3738671462265 from Springer publishers.

TREATMENT GUIDELINES AND OUTCOME

Patients with osteoarticular mucormycosis are usually managed with combined medical and surgical intervention. Amphotericin B is the primary agent for treatment of mucormycetous infections of bone and joint tissue. There are no controlled studies to support combinations of antifungal therapy of osteoarticular mucormycosis.

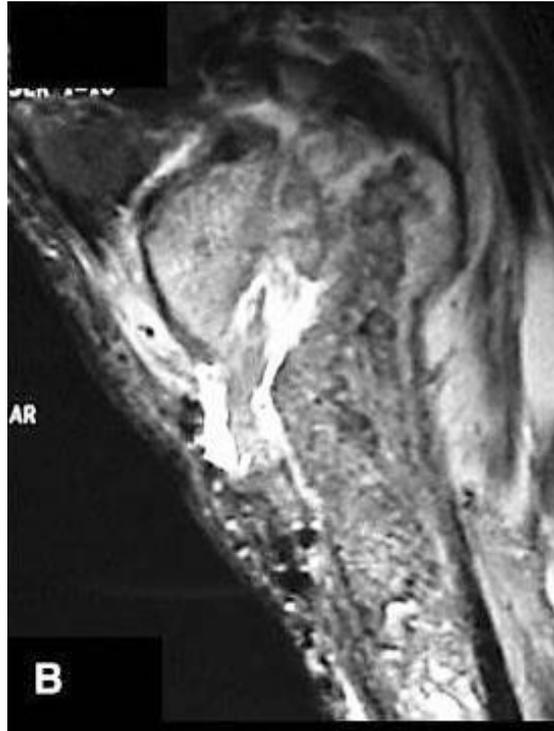


Figure 3. A 29 year old male with a fungal infection after ACL reconstruction of the affected tibia with allograft. A sagittal T2 –weighted MR image shows the preoperative extent of the tibial fungal infection, including the tunnel and the craft. From reference # 8 by license number 3738671462265 from Springer publishers.

Debridement is the most common surgical intervention followed by bone grafting/fixation procedures, excision, and amputation. Reversal of primary immune impairments, including recovery from neutropenia, withdrawal of corticosteroids, and reversal of diabetes mellitus is essential to successful management of osteoarticular mucormycosis, which may be a fatal process due to infection elsewhere, advanced bone infection, and treatment failure with amphotericin B.

CONCLUSION

Bone infections with mucormycetes are characterized by high morbidity and mortality. Guidelines for the treatment of mucormycetes bone infection require antifungal therapy with

amphotericin B and surgical intervention in most cases. The role for isavuconazole in treatment of osteoarticular mucormycosis remains to be defined.

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