Subcutaneous zygomycosis caused by *Mucor hiemalis* in an immunocompetent patient

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CASE REPORT

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Abstract

Zygomycosis is an opportunistic fungal infection with a high mortality rate. It is known to cause invasive disease in immunocompromised hosts but it may produce only cutaneous/ subcutaneous infections in immunocompetent hosts. Treatment is difficult due to its fulminant course and lack of effective anti-fungal drugs. Here, we report a rare case of subcutaneous zygomycosis caused by *Mucor hiemalis* in an immunocompetent patient without any debilitating illness. The patient was successfully treated by aggressive surgical debridement and anti-fungal therapy.

Key Words
Immunocompetent, *Mucor hiemalis*, subcutaneous zygomycosis

Implications for Practice:

1. What is known about this subject?
Subcutaneous zygomycosis is usually caused by *Basidiobolus ranarum* and *Conidiobolus coronatus*, while *Mucorales* are a rare cause.

2. What is the key finding in this case report?
An adult male patient presented with diffuse swelling in the thigh. There was no history of immuno-suppression, malignancy or steroid therapy. On histopathological examination, granulomas were seen, based on which he was treated with anti-tubercular drugs. KOH examination revealed broad fungal hyphae with few septations, suggestive of subcutaneous zygomycosis. *Mucor hiemalis* was repeatedly isolated from tissue biopsies. The patient responded well to aggressive debridement and itraconazole.

3. What are the implications for future practice?
Although a rare cause of subcutaneous mycosis, infection by *Mucorales* should be suspected in patients with granulomatous lesions not responding to anti-tubercular treatment. KOH examination and repeated isolation of the fungus may be useful in diagnosing this condition.

Background

Zygomycosis is a rare, devastating and life threatening fungal infection, involving cutaneous, sub-cutaneous tissue and systemic infection.[1] Mortality is high because of misdiagnosis, lack of appropriate treatment and the fulminant course of disease. Although, *Entomophthorales* which includes *Basidiobolus* and *Conidiobolus* species are the common causes of subcutaneous zygomycosis, *Mucorales* have also been rarely implicated in causation of subcutaneous zygomycosis.[1,2] Here, we report a rare case of subcutaneous zygomycosis caused by *Mucor hiemalis* in an immunocompetent patient without any debilitating illness.

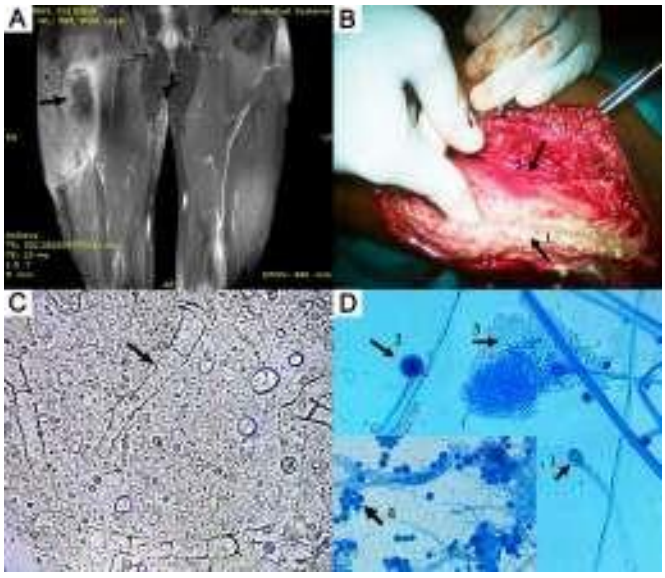
Case details

A 44-year-old male, a resident of Thiruvannamalai, South India was admitted for complaints of a painless, diffuse swelling, with a linear scar in the middle of the swelling, over the lateral aspect of right upper thigh for four months with low grade fever for three days. There was a past history of an incision and drainage done for a suspected

abscess at another institute two months ago which had resulted in the scar. There was no history of immuno-suppression, malignancy or steroid therapy. The man was a lorry driver by occupation.

On local examination, an indurated woody, hard swelling of approximately 15 x 12 cm with well defined margins was present over the lateral aspect of the right upper thigh. The swelling was bosselated, of uniform consistency and mobile over the underlying structures. The patient was sero-negative for HIV. A MRI of the right thigh was done on a clinical suspicion of soft tissue tumor. The MRI showed an abnormal signal intensity and heterogenous enhancement with areas of necrosis involving the muscles of the lateral and posterolateral aspects of the right thigh and edema of adjacent subcutaneous fat. The imaging studies were more suggestive of an infective etiology (myositis) rather than a sarcoma (Figure 1A).

Figure 1: (A) Post contrast T1 fatsat image showing heterogeneous enhancement of the lesion with central necrosis; (B) Intraoperative picture showing the plane between devitalised tissue (1) and viable tissue (2); (C) KOH mount showing broad, infrequently septate fungal hyphae suggestive of subcutaneous zygomycosis; (D) Lactophenol cotton blue showing hyaline, unbranched sporangiophores with ellipsoidal columella (1) bearing globose sporangia (2) filled with numerous hyaline, smooth walled, ellipsoidal sporangiospores (3); oidia are seen in substrate hyphae (4)



Since the diagnosis remained uncertain, an open biopsy was done to confirm the etiology and to drain the suspected abscess. On exploration, greying white tissue quite distinct from the normal muscle was seen. There was no gross necrosis or abscess cavity. Multiple biopsies were done. On histopathological examination, numerous granulomas composed of epithelioid cells and Langhans type of multinucleated giant cells with focal areas of caseous necrosis and lymphocytic infiltration were observed. No fungal elements were seen on H & E stain. Hence, a diagnosis of tuberculous inflammation was offered. The patient was started on an anti-tubercular regimen consisting of Rifampicin, isonicotinic acid hydrazide, pyrazinamide and ethambutol.

However, on follow up after two weeks, the patient had high grade fever with an increase in the size of swelling associated with severe tenderness, multiple discharging sinuses and focal areas of cutaneous gangrene. Debridement of the devitalised tissue was performed (Figure 1B) and sent for histopathological examination and culture. Gram staining of the tissue showed many thick Gram-negative bacilli and KOH examination revealed broad fungal hyphae with few septations, suggestive of subcutaneous zygomycosis (Figure 1C). The bacterial culture grew *Klebsiella pneumoniae*. On Sabouraud's dextrose agar (SDA) culture, rapidly growing, woolly colonies were seen. Lactophenol cotton blue examination of the growth on SDA revealed hyaline, unbranched sporangiophores with ellipsoidal columella bearing globose sporangia filled with numerous hyaline, smooth walled, ellipsoidal sporangiospores; oidia in substrate hyphae and absence of rhizoids (Figure 1D). Based on these features, the fungus was identified as *Mucor hiemalis*. Re-examination of the original histo-pathological block with special stains (PAS) revealed fungal hyphae characteristic of *Mucor* species. The patient was started on itraconazole and appropriate antibiotics for the secondary bacterial infection according to sensitivity reports and the anti-tubercular drugs were stopped. On follow up after a week, the patient showed a favorable response to the treatment and the wound appeared clean. Repeat cultures were sterile. The patient was advised to take itraconazole 200 mg BD for four weeks and is awaiting skin grafting.

Discussion

The agents causing human zygomycosis belong to the class *Zygomycetes*, which is subdivided into two orders, *Mucorales* and *Entomophthorales*.[1] Members of the order *Entomophthorales*, such as *Basidiobolus ranarum* and *Conidiobolus coronatus* are associated with chronic cutaneous and subcutaneous infections and usually do not disseminate to internal organs.[1,3] The order *Mucorales* are usually involved in rhinocerebral, pulmonary, cutaneous/subcutaneous and gastrointestinal infections in immunocompetent and immunocompromised individuals, and is characterised by a tendency to disseminate.[1,3]

Rhizopus and *Absidia* species are the most common pathogens in the order *Mucorales*, while *Mucor* species are only rarely implicated in causation of zygomycosis.[1] Our patient presented with a chronic subcutaneous infection of the thigh without dissemination to internal organs, suggestive of zygomycosis caused by *Basidiobolus ranarum*. However, *Mucor hiemalis*, a member of the order Mucorales was repeatedly isolated from this patient. This is an unusual presentation, as the infections caused by the *Mucorales* are usually rapidly spreading and tend to disseminate. Moreover, this patient was apparently immunocompetent with no risk factors such as diabetes, haematological malignancy, deferoxamine or steroid therapy. Although *Mucor* species tend to cause invasive disease in immunocompromised hosts, it produces only cutaneous/ subcutaneous infections in immunocompetent hosts.[1] Traumatic implantation is the common mode of transmission of mucormycosis.[1] Although he denies a history of injury prior to the appearance of the swelling, it is likely that he had a trivial injury with a vegetable matter, following which he would have developed the lesion. The organism may have been implanted at the time of previous surgery.

As the clinical presentation of zygomycosis can be varied, with a tendency to spread rapidly, early and accurate diagnosis of zygomycosis is very important.[1,4] Although the morphology and growth characteristics of the fungus in culture can aid in accurate identification of the fungus, there are several impediments in diagnosing this condition. Superficial swabs are not reliable for diagnosis of this condition and tissue biopsy is the ideal specimen.[4] It is often difficult to grow this fungus in culture even from a biopsy specimen, as the zygomycetes due to their coenocytic (aseptate) hyphae, will often be damaged and become nonviable during the biopsy procedure or tissue grinding processes in the laboratory. This emphasises the importance of direct microscopy or histopathological examination in diagnosing this condition as they may often be missed in culture. The presence of broad, infrequently septate, thin-walled hyphae, with focal bulbous dilatations and irregular branching in KOH mount is diagnostic of zygomycosis.[4] Similarly, tissue sections stained with hematoxylin and eosin stain may clearly reveal the hyphae.

Presence of an eosinophilic sheath (Splendore-Hoeppli phenomenon) surrounding the hyphae in histopathological examination is characteristic of *Entomophthorales*, while it is absent in *Mucorales* and therefore it may be useful in differentiating entomophthoromycosis from mucormycosis.[1,4] KOH examination of the biopsy samples from our patient repeatedly showed the broad, sparsely septate hyphae characteristic of zygomycosis. In addition, the Splendore-Hoeppli phenomenon was absent in histopathological examination, which suggested that the patient is having mucormycosis rather than entomophthoromycosis. Although histopathological examination is useful in diagnosing mucormycosis, it can at times lead to misdiagnosis. For instance, our patient was initially misdiagnosed as having cutaneous tuberculosis based on the presence of numerous granulomas composed of epithelioid cells and Langhans multinucleated giant cells with focal areas of caseous necrosis. Although well formed granulomas are rare in zygomycosis, in a report of subcutaneous zygomycosis caused by *M. hiemalis*, focal collections of epithelioid and Langhans multinucleated giant cells have been observed similar to our report.[5] This emphasises the importance of being aware of such unusual findings in histopathological examination.

It is of utmost importance to clearly distinguish the infections caused by *Mucorales* and *Entomophthorales* as the treatment and prognosis differ.[1,4] The culture on SDA is very useful for identification of the fungus. However, the isolation of a zygomycete on a single occasion from a non-sterile site, such as skin or sputum, must be interpreted with caution.[4] However, in this patient, the *M. hiemalis* was isolated repeatedly and it was also detected in direct microscopy. Further, histopathological examination also suggested that a member of the *Mucorales* is the likely agent of zygomycosis in this case. Sabouraud's dextrose agar (SDA) containing antibiotic is the widely used medium for primary isolation of zygomycetes. Our isolate also grew rapidly on this medium and pushed the lid off the petridish in a few days. The lactophenol cotton blue examination of the growth on SDA helped in identifying the fungus as *Mucor hiemalis*. *M. hiemalis* has been earlier reported from a few cases of human cutaneous infection.[1,4] Although its pathogenicity for deep invasive disease is being challenged as its optimum growth temperature is only 32˚C, *M. hiemalis* has been definitely linked to chronic cutaneous infections and rarely subcutaneous infection.[1,5-7] Its relatively lesser optimum growth temperature is a probable explanation for this fungus being limited to the subcutaneous tissue in our patient without dissemination, as the temperature at this site may be cooler than core body temperature.[1]

The successful management of infections caused by mucoraceous zygomycetes depends on early diagnosis, control or reversal of any underlying disease, repeated aggressive surgical debridement and antifungal therapy.[1,4,8] Although, amphotericin B is the only approved agent for treatment of this condition, *Mucorales* are either relatively

or highly resistant to amphotericin B.[1,8,9] Itraconazole is the only azole antifungal agent which has demonstrated in vitro activity against *Mucorales*. However, its role in treatment of this condition is not known.[9] In a report from China, a case of fungal myositis caused by Candida was successfully treated with itraconazole.[10] The favourable outcome in our patient is largely attributable to the aggressive surgical debridement and anti-fungal therapy with itraconazole.[8]

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PEER REVIEW

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CONFLICTS OF INTEREST

The authors declare that they have no competing interests. We also declare that all the authors have approved the final version of this manuscript.

PATIENT CONSENT

The authors, Desai RP, Joseph NM, Ananthakrishnan N, Ambujam S, declare that:

1. They have obtained written, informed consent for the publication of the details relating to the patient(s) in this report.
2. All possible steps have been taken to safeguard the identity of the patient(s).
3. This submission is compliant with the requirements of local research ethics committees.