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Osteoarticular mucormycosis of the distal femur in a post COVID-19 patient

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ABSTRACT

A 38 year old man with no known comorbidities presented with pain and swelling over the knee joint a few days after recovery from severe COVID-19. Initial debridement and cultures revealed growth of Mucorales affecting a large segment of the distal femur with also positive cultures obtained from the maxillary sinus and the lower lobe of the right lung. Due to this involvement of a long segment of the femur, right lung and left maxillary sinus, a multidisciplinary approach of above knee amputation along with debridement of left maxillary sinus and lobectomy of right lung lower lobe was performed to decrease the fungal load and favour good prognosis. This report warrants the need for early imaging and surgical debridement of tissue for fungal cultures and biopsy in immunocompromised individuals.

1. Introduction

Mucorales which primarily inhabit soil and decomposing matter are rarely associated with human infections, and are seen mostly in immunocompromised leading to poor prognosis and mortality due to its angio-invasive nature [1]. Most cases of fungal osteomyelitis reported in the literature are caused by *Aspergillus* [2] and *Candida* species [3]. Possible routes to acquire fungal osteomyelitis include direct inoculation through open traumatic injuries contaminated with soil, or as an extension from a contiguous site of soft tissue infection or through iatrogenic contamination [4]. Osteomyelitis caused by Mucorales is rare. To date, all reported cases of mucormycosis causing osteomyelitis of long bones were due to direct inoculation or iatrogenic contamination5. Hematogenous dissemination of Mucorales is reported in severe immunocompromised patients [5]. COVID-19 associated mucormycosis has been observed as a severe complication of COVID-19 during the pandemic. Cases of rhino orbital mucormycosis with intracranial extension following COVID- 19 have been widely reported [6]. There are no cases of osteoarticular mucormycosis post COVID-19 reported in literature. We report the first case of an osteoarticular mucromycosis of the distal femur in a 38 year old man who recently recovered from a severe course of COVID–19.

2. Case report

A 38 year old man without any known comorbidities, was treated for severe COVID-19 during the pandemic with intravenous steroids (Methylprednisolone 2mg/Kg body weight, twice a day for ten days) and supplementary oxygen for ten days. Two weeks after symptomatic recovery, he developed pain and swelling in the medial aspect of right knee that gradually increased and was treated with intravenous antibiotics assuming a localized abscess by a physician. He was then referred to us, as there was no improvement. At presentation (day 0) his white blood cell counts and inflammatory markers (ESR, CRP) were normal. An MRI was performed which showed signs of osteomyelitis of the right distal femur [Fig. 1]. Knee joint arthrotomy and debridement was done by lateral approach (day 1). Intra-operatively, synovium was noted to be inflamed and hypertrophied and was sent for biopsy. Periosteum of the distal femur was noted to be peeling off easily like an orange peel and the distal femur was softened, dry, powdery and discoloured [Fig. 2]. All the tissues obtained, including synovium and bone, were sent for bacterial and mycobacterial cultures, gram staining, fungal staining, histopathology and fungal culture. Patient continued to have serous discharge through the wound site.

On day 5, the synovium tissue showed no growth of any organism

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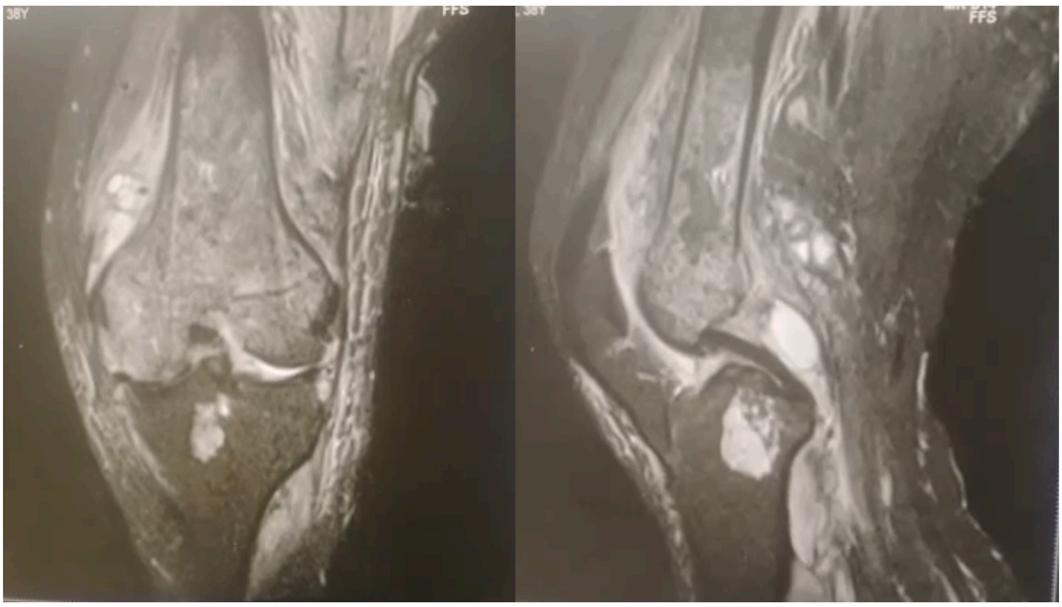

Fig. 1. PD Fat Sat sequence of MRI knee showing intracavitory lesion involving the distal third of femur with surrounding bone oedema, periosteal reaction and surrounding significant soft tissue oedema.

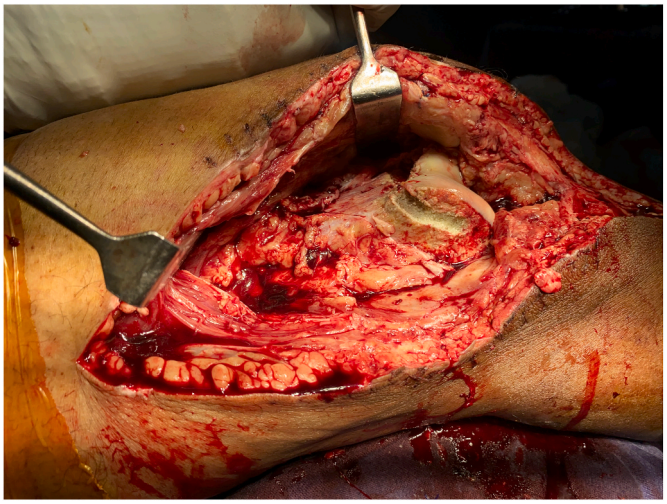

Fig. 2. Intra operative image at time of debridement showing peeling of periosteum along with discoloured bone which was dry, powdery and softened.

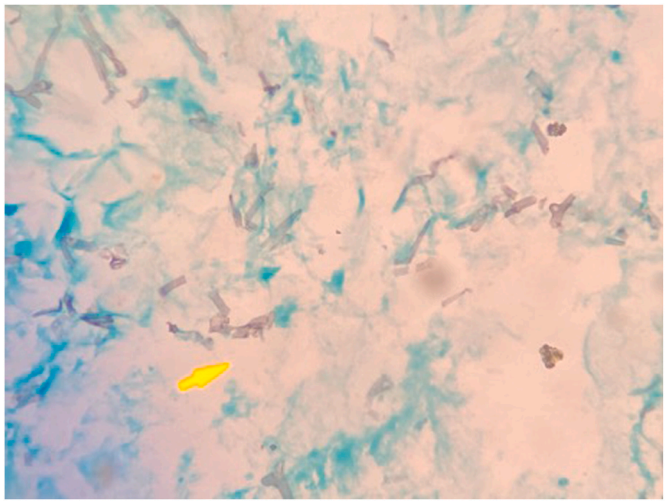

Fig. 3. Grocott Methenamine Silver staining (GMS stain) of the distal femur specimen showing scattered broad aseptate, wide angle branching fungal hyphal forms along with few narrow septate, branching hyphal forms.

upon culture, but showed inflamed and ulcerated synovial lining with fibrinous exudate and neutrophils and the underlying fibrovascular stroma showed dense chronic inflammation with scattered neutrophils on histopathological examination. The distal femur sample showed necrotic bone fragments along with stromal dense chronic inflammation and numerous foreign body giant cells. Grocott Methenamine Silver staining (GMS stain) highlighted scattered broad aseptate, wide angle branching fungal hyphal forms along with few narrow septate, branching hyphal forms [Fig. 3]. The bony specimen examined on KOH mount showed mucorales like fungi and the culture bottle was filled with white fluffy growth in 18 hours [Fig. 4]. Fludeoxyglucose F18 Positron Emission Tomography scan (FDG PET CT) was performed on day 7, and it showed hypermetabolic cortical irregularity involving the distal femur with surrounding hypermetabolic soft tissue component and heterogenous fluid collection along with hypermetabolic cavitary lesion in the lower lobe of the right lung and left maxillary sinus [Fig. 5]. CT brain showed left maxillary sinus infiltration without intracranial spread [Fig. 6A]. Considering disseminated mucormycosis involving a long segment of the femur, the right lung and the left maxillary sinus, a multidisciplinary approach was planned to control the infection (day 7). Above knee amputation and left maxillary sinus debridement [Fig. 6B] and lobectomy of right lung lower lobe [Fig. 7] was performed to decrease the fungal load and favour good prognosis (day 8). This was combined with medical management by Liposomal amphotericin B (10mg/Kg/day for 4 weeks), started on day 8 with regular monitoring of his renal function, followed by maintenance dose of posaconazole (300mg once a day for six months). The specimen of the bivalved femur showed complete destruction of the femoral condyles extending up to the meta-diaphysis junction [Fig. 8]. Lactophenol Cotton Blue staining of the distal femur specimen showed Mucorales like aseptate hyphae and sporangia with rhizoids [Fig. 9].

Patient was ambulatory with the help of prosthesis and he was followed up to 3 years after discharge and he did not develop any further complications including recurrence of infection and resumed his professional work.

Fig. 4. The culture bottle showing white frothy growth in 18 hours.

3. Discussion

Osteoarticular Mucormycosis is a devastating condition seldom seen in traumatic open injuries and post operative scenarios. Hematogenous spread of this disease is very rarely seen affecting the long bones. While Mucormycosis is highly aggressive and destructive in lungs, sinuses and brain, it is more indolent in bone thereby delaying the diagnosis. Taj-Aldeen SJ et al. in their systematic review of osteoarticular Mucormycosis noted a mean time of 73 days to diagnose Mucor fungal osteomyelitis [5]. The paucity of fever in such cases would add to delay in presentation of the patient. Costa-Paz et al. have reported a total of 21 cases of osteoarticular Mucormycosis following ACL reconstruction surgeries [7]. In their series they found that none of the patients had comorbid conditions and all the cases were a result of post operative inoculation. Direct inoculation of the organism in open injuries is commonly reported earlier. Cases of cutaneous Mucormycosis also had direct inoculation as a result of trauma and responded well to local debridement and antifungal agents [8]. Invasive aspergillosis and candidiasis represent the leading cause of invasive mold infections, whereas invasive Mucormycosis is less common [9]. Mucormycosis related osteoarticular infections as a result of hematogenous spread are reported in immunocompromised patients such as post bone marrow transplant [10], Sickle cell disease [11], uncontrolled Diabetes. However, so far there have been no reports of Mucormycosis affecting osteoarticular region or bone in a patient who has recovered from a COVID-19 infection.

A combination of factors including various medications such as high dose steroids, preexisting or steroid induced diabetes and systemic immune alteration in COVID-19 infection itself have led to an array of many secondary infections in patients affected by COVID-19. An alarming increase in Mucormycosis of rhino-orbital region including invasion in to intracranial space has been reported in recent past [12]. Such COVID-19 patients with intracranial mucormycosis invasion had a high mortality rate [6]. In the case reported by us, the patient had no pre-existing comorbidities and he has acquired COVID-19 moderate infection for which he was treated with intravenous steroids and oxygen therapy. As he recovered well, he noticed to have pain and swelling over knee joint without any fever. The time to presentation to an orthopaedic surgeon following the symptoms in knee was around 19 days. The time to diagnosis of Mucormycosis of distal femur was 26 days. The indolent nature of fungal osteomyelitis even with aggressive Mucormycosis and spectrum of clinical features and lack of awareness of fungal affection leads to delayed diagnosis which at times could be fatal.

Mucormycosis spreads hematogenously to other organs. The most common sites of origin are sinuses (39 %), lungs (24 %), and skin (19 %) [13]. Dissemination commonly affects lung and brain, whereas liver, heart, and kidneys are rarely colonized by Mucor species [14]. Our patient showed lesions in lung and sinus as demonstrated in PET-CT. There is no consensus on treatment protocol in osteoarticular diseases affected by Mucormycosis, although treatment with first line of antifungal drugs, Liposomal Amphoterecin B and maintenance antifungals like Posoconazole along with surgical debridement is effective. Treatment is always customised basing on other systematic involvement and clinical status of the affected patient and should always be multidisciplinary by discussing with microbiologists, pathologists and infectious disease specialists, Pulmonologists and Otorhinolaryngologists. In our case, the patient had a long segment of femur affected along with foci of colonization in lungs and maxillary sinuses, which warranted for amputation to avoid mortality. Treatment protocol cannot be standardised and should be individualized on a case-by-case basis, based on pressing clinical issues with close monitoring of patients clinical condition.

All osteoarticular infections should be screened ideally for fungal elements along with bacterial and mycobacterial foci, particularly in immunocompromised including post COVID-19 patients. Establishing the diagnosis of invasive fungal infections by conventional culture based mycological methods is often difficult, especially in early stages [15]. Routine blood investigations and inflammatory markers are not effective in diagnosing the osteo-articular fungal infections. Mucorales-specific antigens are not yet accepted for diagnostic purposes because of its low sensitivity [15]. Clinical suspicion along with early radiological evaluation by MRI particularly in post COVID-19 recovered patients would be helpful for early diagnosis and recovery. Early and aggressive surgical debridement's and tissue evaluations for fungal elements should not be hesitated to establish early diagnosis of osteoarticular Mucormycosis.

This aggressive case of osteoarticular Mucormycosis with hematogenous dissemination illustrates the diagnostic challenge particularly during COVID-19 pandemic. Due to potentially devastating complications, including mortality and amputation, high index of clinical suspicion to diagnose fungal musculoskeletal infections should always be considered. Successful treatment of mucormycosis infection requires a multidisciplinary approach, especially in systemic colonization. This report justifies the need for early imaging and surgical debridement of tissue for fungal cultures and biopsy to establish the diagnosis of fungal osteomyelitis and prevent devastating complications.

CRediT authorship contribution statement

Srinivas Kasha: Writing – review & editing, Visualization, Validation, Supervision, Software, Resources, Methodology, Project administration, Investigation, Formal analysis, Data curation, Conceptualization. **Venugopal Palakurthi:** Writing – review & editing, Visualization, Validation, Supervision, Software, Resources, Methodology, Investigation, Formal analysis, Conceptualization. **Ranjith Kumar Yalamanchili:** Writing – review & editing, Visualization, Validation, Software, Resources, Methodology, Investigation, Formal analysis, Data

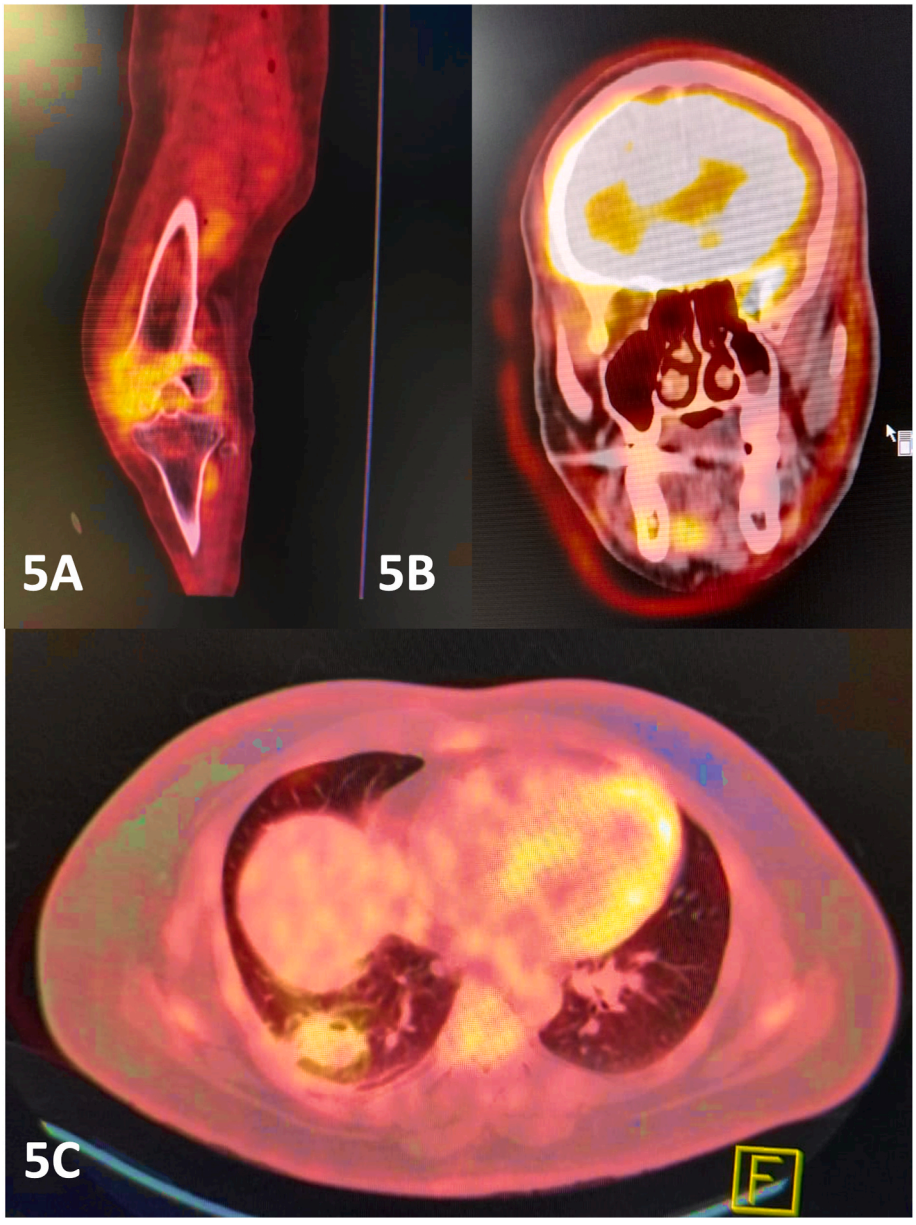

Fig. 5. Fludeoxyglucose F18 (FDG) Positron Emission Tomography scan (FDG PET CT) showing hypermetabolic activity in distal femur (4A), left maxillary sinus (4B) and lower lobe of right lung (4C).

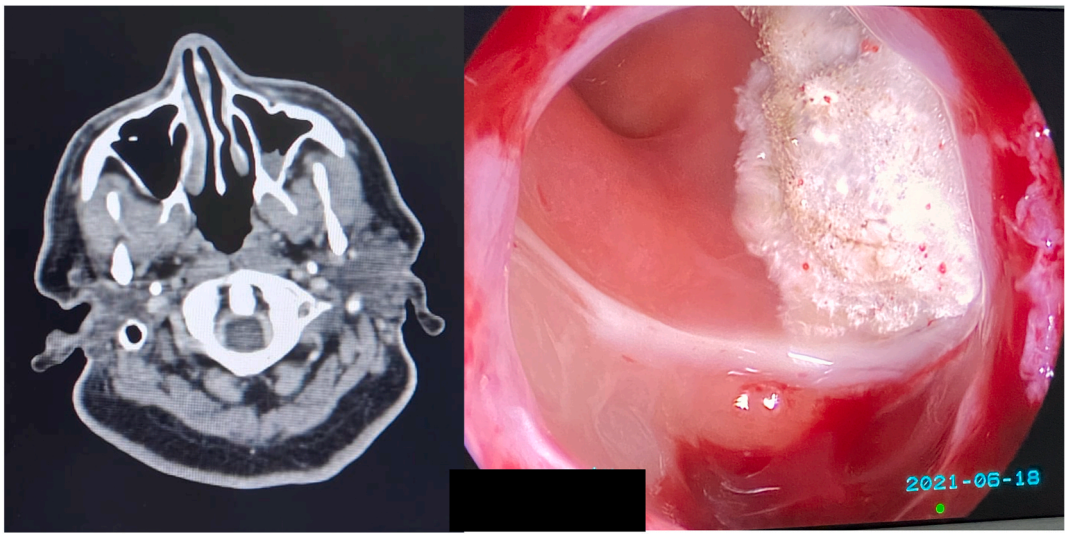

Fig. 6. Fig. 6A) CT Brain axial section showing left Maxillary sinus mucosal thickening due to mucormycosis. Fig. 6B) Nasoendoscopic picture of the same patient with a fungal ball in the left maxillary sinus.

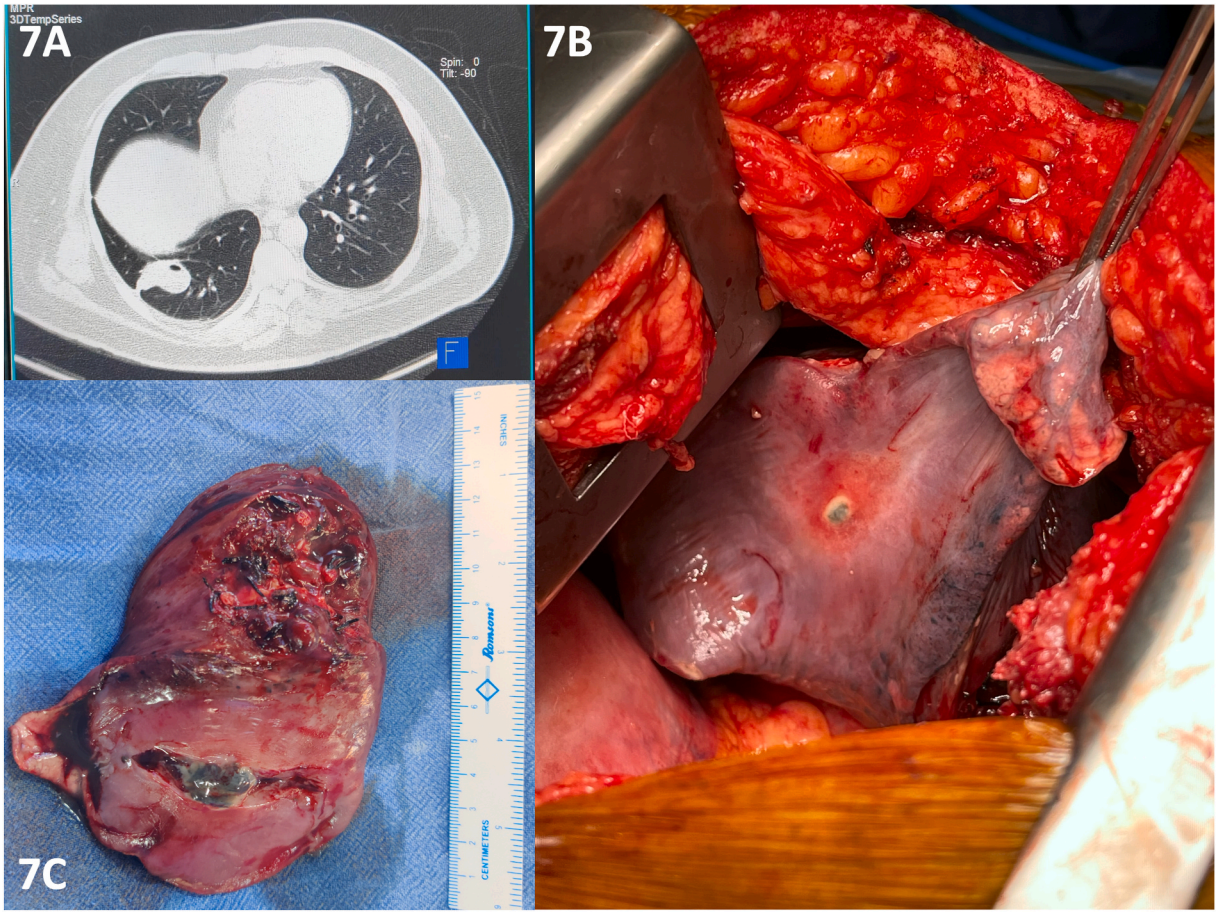

Fig. 7. Fig. 7A: CT chest showing the lesion in left lower lobe. Fig. 7B: Intra operative picture of lobectomy of the lesion. Fig. 7C) Specimen of resected right lung lower lobe affected with a Mucor cavitatory lesion.

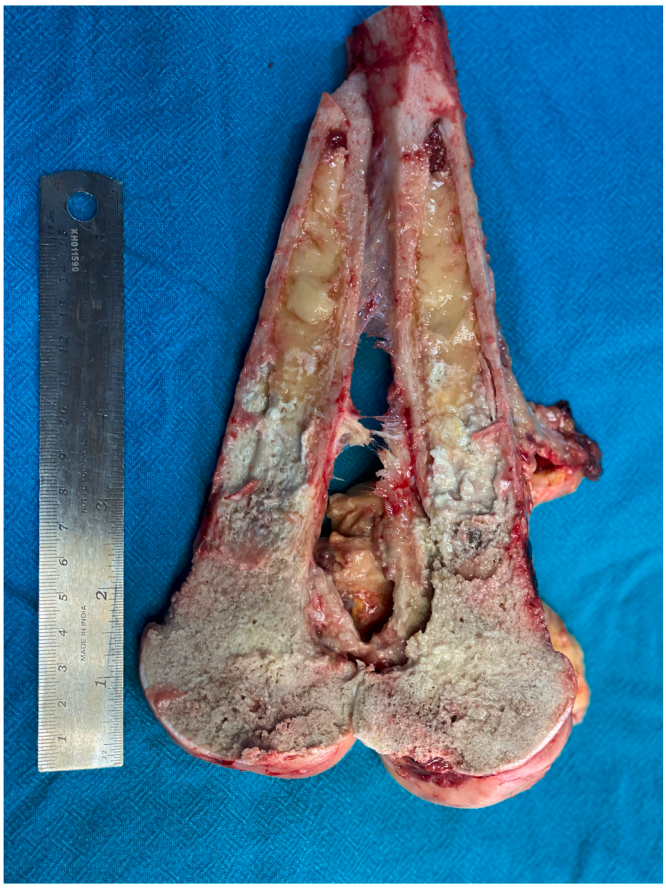

Fig. 8. Bivalved distal femur specimen showing destruction of large segment distal femur by Mucor osteomyelitis.

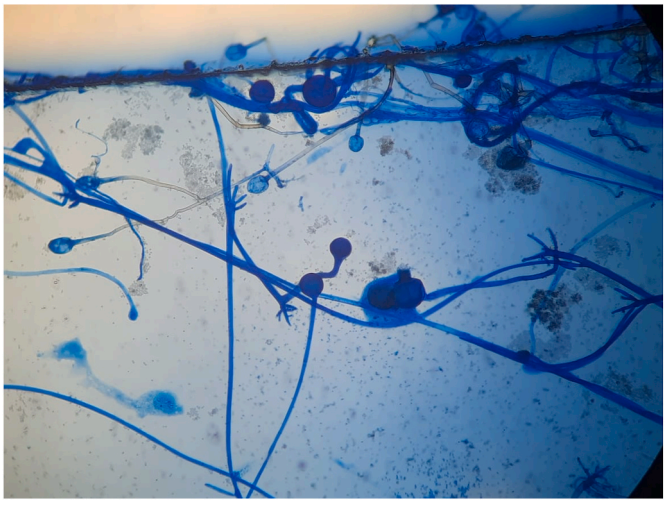

Fig. 9. Lactophenol Cotton Blue staining in a 10x view shows Mucormycosis eliciting aseptate hyphae, sporangium with rhizoids. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

curation, Conceptualization. **Patil Pratik Yashavant:** Writing – review & editing, Visualization, Validation, Supervision, Software, Resources, Methodology, Investigation, Formal analysis, Conceptualization. **Rohith GPRK:** Writing – review & editing, Visualization, Validation, Supervision, Software, Resources, Methodology, Investigation, Formal analysis, Conceptualization.

Declaration of competing interest

"The authors declare that they have no competing interests".

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References

[1] M.Z. Gomes, R.E. Lewis, D.P. Kontoyiannis, Mucormycosis caused by unusual mucormycetes, non-Rhizopus, -Mucor, and -Lichtheimia species, Clin. Microbiol. Rev. 24 (2011) 411–445.
[2] M.N. Gamaletsou, B. Rammaert, M.A. Bueno, et al., Aspergillus osteomyelitis: epidemiology, clinical manifestations, management, and outcome, J. Infect. 68 (2014) 478–493.
[3] A.K. Slenker, S.W. Keith, D.L. Horn, Two hundred and eleven cases of Candida osteomyelitis: 17 case reports and a review of the literature, Diagn. Microbiol. Infect. Dis. 73 (2012) 89–93.
[4] M.N. Gamaletsou, B. Rammaert, M.A. Bueno, B. Moriyama, N.V. Sipsas, D. P. Kontoyiannis, et al., Aspergillus osteomyelitis: epidemiology, clinical manifestations, management and outcome, J. Infect. 68 (5) (2014 May) 478–493.
[5] S.J. Taj-Aldeen, M.N. Gamaletsou, B. Rammaert, N.V. Sipsas, V. Zeller, E. Roilides, D.P. Kontoyiannis, M. Henry, V. Petraitis, B. Moriyama, D.W. Denning, O. Lortholary, T.J. Walsh, International Osteoarticular Mycoses Consortium, Bone and joint infections caused by mucormycetes: a challenging osteoarticular mycosis of the twenty-first century, Med. Mycol. 55 (7) (2017 Oct 1) 691–704, https://doi.org/10.1093/mmy/myw136.
[6] S.M. Revannavar, S.S. P, L. Samaga, et al., COVID-19 triggering Mucormycosis in a susceptible patient: a new phenomenon in the developing world? BMJ Case Reports CP 14 (2021) e241663.
[7] M. Costa-Paz, D.L. Muscolo, M.A. Ayerza, et al., Mucormycosis osteomyelitis after anterior cruciate ligament reconstruction: treatment and outcomes of 21 reported cases, Bone Jt Open 2 (1) (2021) 3–8, https://doi.org/10.1302/2633-1462.21.
[8] K.D. Lineberry, A.K. Boettcher, A.L. Blount, S.D. Burgess, Cutaneous Mucormycosis of the upper extremity in an immunocompetent host: case report, J Hand Surg Am 37 (4) (2012 Apr) 787–791, https://doi.org/10.1016/j.jhsa.2011.11.010. Epub 2012 Feb 2. PMID: 22305738.
[9] D.P. Kontoyiannis, R.E. Lewis, Invasive zygomycosis: update on pathogenesis, clinical manifestations, and management, Infect Dis Clin North Am 20 (3) (2006) 581–607, vi.
[10] N. Harrasser, I.J. Banke, M. Hauschild, U. Lenze, P.M. Prodinger, A. Toepfer, C. Peschel, R. von Eisenhart-Rothe, I. Ringshausen, M. Verbeek, Clinical challenge: fatal mucormycotic osteomyelitis caused by Rhizopus microsporus despite aggressive multimodal treatment, BMC Infect. Dis. 14 (2014 Sep 6) 488, https://doi.org/10.1186/1471-2334-14-488. PMID: 25195155; PMCID: PMC4164739.
[11] M. Fartoukh, H. Prigent, B. Thioliere, A. Enache-Angoulvant, A. Garbarg-Chenon, R. Girot, Fatal fungal superinfection complicating B19 virus-induced massive bone marrow necrosis in sickle-cell disease, Haematologica 91 (6 Suppl) (2006) ECR18.
[12] S. Mehta, A. Pandey, Rhino-orbital mucormycosis associated with COVID-19, Cureus 12 (9) (2020) e10726, https://doi.org/10.7759/cureus.10726. Published 2020 Sep. 30.
[13] B. Ye, D. Yu, X. Zhang, K. Shao, D. Chen, D. Wu, Y. Zhang, Y. Zhou, Y. Shen, Q. Yu, Disseminated Rhizopus microsporus infection following allogeneichematopoietic stem cell transplantation in a child with severe aplastic anemia, Transpl. Infect. Dis. 15 (6) (2013) E216–E223.
[14] O. Lebeau, C. Van Delden, J. Garbino, J. Robert, F. Lamoth, J. Passweg, Y. Chalandon, Disseminated Rhizopus microsporus infection cured by salvage allogeneic hematopoietic stem cell transplantation, antifungal combination therapy, and surgical resection, Transpl. Infect. Dis. 12 (3) (2010) 269–272.
[15] Z. Odabasi, V.L. Paetznick, J.R. Rodriguez, E. Chen, M.R. McGinnis, L. Ostrosky-Zeichner, Differences in beta-glucan levels in culture supernatants of a variety of fungi, Med. Mycol. 44 (3) (2006) 267–272.