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Case Report

# Repetitive intra-articular therapy in fungal arthritis: Adjunct to systemic therapy in a patient with pediatric acute lymphoblastic leukemia

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## ABSTRACT

Invasive fungal infections are important causes of mortality and morbidity in immunodeficiencies, hematological malignancies, and transplant recipients. There is scarce information in the literature about the diagnosis, treatment methods, and management. Herein, a unique involvement site of invasive fungal infection caused by *Aspergillus flavus* in the nadir of the induction chemotherapy of a 13-year-old boy with the diagnosis of acute lymphoblastic leukemia is presented. Despite prolonged intravenous antifungal therapy, the patient exhibited an inadequate response. As a result, intra-articular antifungal treatment was implemented alongside curettage and joint space irrigation. These additional interventions led to significantly improved clinical outcomes. Since fungal osteomyelitis can be an important cause of mortality and morbidity in immunosuppressed patients, prompt diagnosis and multidisciplinary treatment are crucial.

**Keywords:** Fungal osteomyelitis, immunocompromised patients, aspergillosis, amphotericin B-resistant, management of invasive aspergillosis

## INTRODUCTION

*Aspergillus* species are very common in nature, becoming increasingly important as an opportunistic agent in hematological malignancies, immunosuppressed patients, and transplant recipients, being the most common one. *Aspergillus fumigatus* is the major causative agent for invasive aspergillosis and also in osteomyelitis, identified in 80% of the cases, followed by *Aspergillus flavus (A. flavus)*. The most commonly affected sites are the lungs, sinuses, and brain.[1]

Herein, a case of *A. flavus* osteomyelitis in an adolescent with acute lymphoblastic leukemia (ALL) is presented.

## CASE PRESENTATION

A 13-year-old male diagnosed with ALL was being treated according to ALLIC BFM 2009 protocol. He became neutropenic on day 30th of induction. On the 12th day of nadir, swelling on the left knee joint was observed while he was under treatment with amikacin, meropenem, and prophylactic fluconazole. The

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whole blood count revealed pancytopenia, and the CRP level was 320 mg/dL, whereas the erythrocyte sedimentation rate (ESR) was 118 mm/h. A magnetic resonance imaging (MRI) was performed and disclosed multiple lesions, compatible with abscess and osteomyelitis in the distal metaphyseal area of the left femur, available in Figure 1a and 1b.

Intraarticular washing was performed, and the soft tissue and bone curettage materials were studied both microbiologically and pathologically. The fungi were isolated from the fungal culture of specimens and identified as *A. flavus* (Figure 2a). In pathological evaluation, few fungi associated with osteomyelitis by Gomorimethenamine silver stain were observed; pictures of the microscopic image are available in Figure 2b. Galactomannan index (GMI) was positive for the soft tissue and bone curettage specimens, >1.00 according to new European Organisation for Research and Treatment (EORT) 2019 criteria, but negative for blood with optical density index. The median GMI was 6.7 for specimens, and 0.3 for blood.

Liposomal amphotericin B was initiated with a 3 mg/kg/day dose. In the second week of the treatment, he had a fever with ongoing complaints like pain and swelling in the knee joint. He was still neutropenic with elevated acute phase reactants. Due to the lack of clinical response, an MRI was performed, and the progression of the osteomyelitis-related findings was disclosed. The amphotericin B dose was increased to 5 mg/kg/day. The drainage material of the abscess, joint fluid, and tissue samples were obtained surgically again. The pathology report revealed fungal osteomyelitis. A. flavus was also reproduced from the tissue samples.

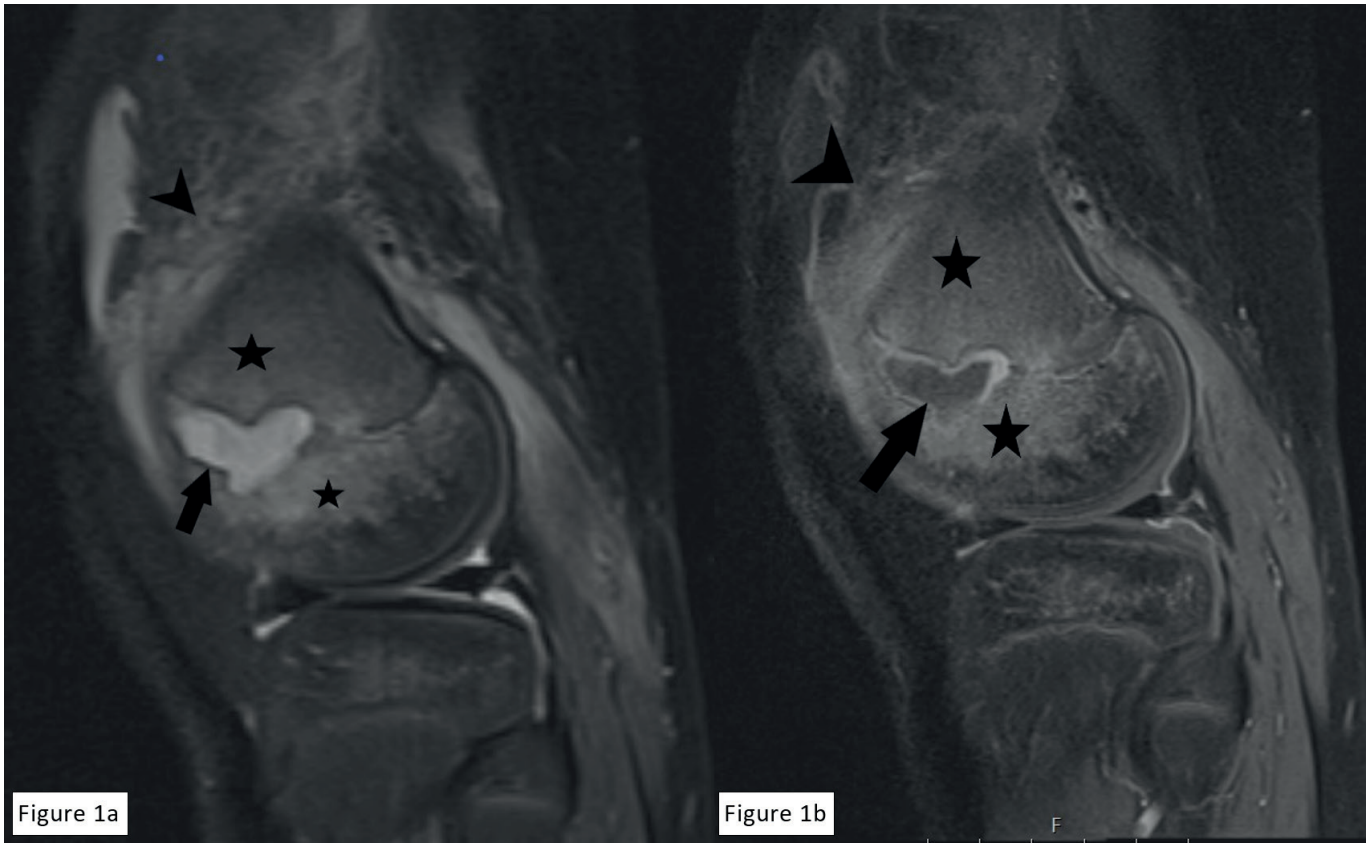


**Figure 1a.** Sagittal T2 weighted fat-suppressed image of the left femur shows a lesion with fluid signal in the physeal line (arrow). The bone marrow of the distal metaphysis and epiphysis has a diffuse high signal representing bone marrow edema (stars). Adjacent soft-tissue edema is also seen (arrowhead).

**Figure 1b.** Sagittal T1 weighted fat-suppressed image of the left femur after intravenous contrast administration shows that the lesion has a central low signal and peripheral enhancement (arrow). The central low signal represents pus, and the peripherally enhancing areas represent hypervascular granulation tissue. These findings confirm an intraosseous abscess. Contrast enhancement of bone marrow pointing out osteomyelitis is seen in distal metaphysis and epiphysis (stars). Also, contrast enhancement of soft tissue is seen (arrowhead).

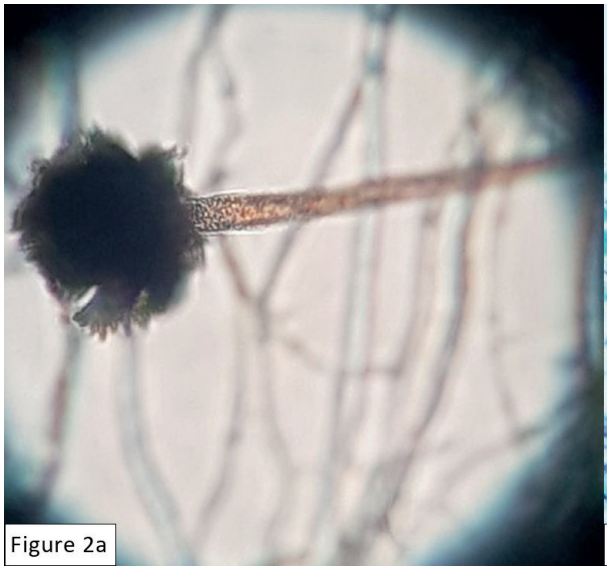
Figure 2a

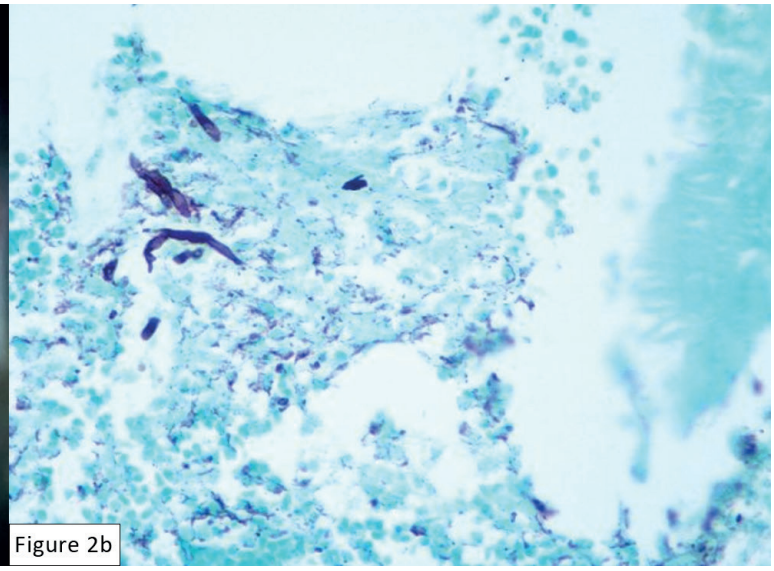
Figure 2b

**Figure 2a.** Image of Aspergillus flavus in slide culture.
**Figure 2b.** Fungal hyphae staining positively with Gomori Methenamine silver stain.

On account of the unresponsiveness, the minimum inhibitor concentration (MIC) values for amphotericin B, caspofungin, voriconazole, anidulafungin, itraconazole, and posaconazole were studied and resulted as; >2 µg/ml, 0.125 µg/ml, 0.064 µg/ml, 0.002 µg/ml, 0.25 µg/ml, and 0.125 µg/ml, respectively. Based on MIC results, since the fungus is resistant to amphotericin B, treatment was changed to solely voriconazole with a loading dose of 9 mg/kg/dose every 12 hours for two doses on day one and a maintenance dose of 8 mg/kg/dose every 12 hours.

On the second week of the voriconazole therapy, an MRI disclosed radiological progression. However, the whole blood count was improved, with ongoing elevation in acute phase reactants. He had gone through curettage for the third time and washing the joint space with voriconazole was performed. Intra-articular voriconazole treatment was administered as a single dose, utilizing 20 mL of the intravenous formulation at a concentration of 10 mg/mL. Specimens from the joint space were obtained revealing *Aspergillus*-like fungi. Also, the galactomannan (GM) antigen resulted positive in blood, with no reproduction in cultures. Caspofungin was added with a loading dose of 70 mg/m$^2$/dose on day 1, then 50 mg/m$^2$/dose once daily in maintenance. In the follow-up, the patient had the combination therapy of voriconazole and caspofungin for 16 weeks while he was being treated for ALL. He did not require surgical intervention again. After the treatment, he experienced sequelae related to walking and, therefore, received physical therapy. He completed his anticancer chemotherapy and is still in remission.

## DISCUSSION

Fungal osteomyelitis and arthritis are rare but debilitating sites of involvement for invasive aspergillosis. Considering the osteomyelitis caused by aspergillus species, the most often affected bones are vertebral bodies, cranium, and ribs. Long bone and articular spaces are less frequently involved; among them, the most common site is the tibia.[2] Our patient had knee, joint space, and synovial fluid involvement, which is rare in the literature.

Diagnostic procedures generally consist of culture and/or histological evaluation of the specimens achieved by biopsy, as in our patient. Also, the positivity of serum GM-antigen can be determined.[2,3] However, similar to our patient's diagnostic process, making the exact clinical diagnosis can be challenging. Because, as previously described in the literature, while the GM-antigen in serum is negative, local samples may culminate positively. When used alone, GM-antigen has insufficient sensitivity and specificity in diagnosing invasive aspergillosis and must be correlated with clinical practice.[4] The patient should be overall assessed with respect to clinical history, underlying disease, immunity status besides the cultures, histopathological assessments, and direct analysis of the specimens with a high index of suspicion.[2-5]

Imaging methods have an important impact on diagnosis. The most frequently observed patterns comprise osteolysis, bone destruction, and erosion.[6] In our case, MRI findings were similar

and contributed to surgical sampling and guiding treatment by revealing progression during periods of unresponsiveness.

In addition to its rarity, there is scarce knowledge about knee joint involvement in terms of evidence-based treatment modalities. As observed in our case, amphotericin B resistance can be detected, and evaluation of MIC concentrations can guide treatment. Surgical debridement is one of the treatment methods. Although there is scarce data on the timing and necessity of surgical intervention in invasive fungal osteomyelitis, recent literature supports the utilization of surgical debridement to reduce the infective burden and allow better drug penetration.[2,7]

The management of osteoarticular infections in immunosuppressed patients presents significant challenges due to the complex clinical course and the limited availability of evidence-based clinical guidelines. Long-term treatment with effective antifungal agents is crucial. In immunosuppressed patients, mean treatment time is reported within at least 6-12 weeks.[5] As well, our patient had the antifungal treatment for 16 weeks. In addition to systemic therapy, local interventions such as intra-articular irrigation, curettage, and antifungal administration have improved clinical outcomes.[8] This is particularly relevant in patients with hematological malignancies or those who have undergone bone marrow transplantation, where joint involvement is associated with a poor prognosis. Due to the limited penetration of systemic antifungal agents into soft tissues and osteoarticular spaces, combining systemic therapy with local treatments—such as curettage, joint space irrigation, and intra-articular antifungal administration—has been demonstrated to yield superior outcomes.[9] In the current case, it is obvious that clinical response was obtained after combining intraarticular treatment with extended systemic long-term therapy and also with the recovery from myelosuppression.

### Informed consent

The family of the patient signed the free and informed consent form. In addition, appropriate permissions have been obtained for reproduced images.

### Author contribution

Surgical and Medical Practices: ŞA, AÖ, İK, EÜ; Concept: ŞE, EÜ; Design: EÜ, ŞA; Data Collection or Processing: NAE, MAA,ZFK, ŞA, KD, ANK; Analysis or Interpretation: ŞA; NAE; Literature Search: ŞA, AÖ, EÜ; Writing: ŞA, AÖ, EÜ. All authors reviewed the results and approved the final version of the article.

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### Conflict of interest

The authors declare that there is no conflict of interest.

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