

Osteomyelitis Due to *Aspergillus flavus* in an Immunocompetent Child with Fatco Syndrome: A Case Report and Literature Review

*Fatco Sendromlu Immün Sağlıklı Bir Çocukta *Aspergillus flavus* Nedenli Osteomyelit Due to *Aspergillus flavus* in an: Bir Olgu Sunumu ve Literatürün Gözden Geçirilmesi*

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Abstract

An 8-year-old boy, with fibular agenesis, tibial camptomelia, and oligosyndactyly (FATCO syndrome), had been operated on for reconstruction 3 weeks prior at another hospital. He was admitted to our hospital because of right leg pain and purulent exudates from the surgical wound site for one week. Physical examination revealed purulent material at the surgical wound on the right leg. Radiological examination confirmed the clinical diagnosis as osteomyelitis. Clinical findings did not improve with empirical antibacterial therapy. A microbiological examination yielded a filamentous fungus from three different specimens that was identified as *Aspergillus flavus*. The patient was treated successfully with oral itraconazole for 6 weeks. In conclusion, invasive *Aspergillus* infections can affect immunocompetent adults and children. Trauma and surgical intervention can also be a risk factor for immunocompetent individuals. In addition to surgery, itraconazole can be a good choice in the treatment of *Aspergillus* osteomyelitis, especially in children.

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Key words: *Aspergillus flavus*, osteomyelitis, immunocompetent, itraconazole

Özet

Fibula yokluğu, tibiada kampomeli ve oligosindaktilisi olan (FATCO sendromu) 8 yaşındaki bir erkek çocuk, üç hafta önce başka bir hastanede rekonstrüksiyon amacıyla opere olmuştu. Bir haftadır devam eden sağ bacak ağrısı ve cerrahi yara bölgesinden pürülan akıntı şikayeti ile hastanemize başvurdu. Fizik muayenede sağ bacakta cerrahi yarada pürülan materyal gözlemlendi. Radyolojik incelemeler klinik osteomyelit tanısı ile uyumlu bulundu. Ampirik olarak başlanan antibakteriyel tedavi klinik bulgularda iyileşme sağlamadı. Mikrobiyolojik incelemelerde üç farklı klinik örnekten filamanöz bir mantar izole edildi ve bu mantar *Aspergillus flavus* olarak tanımlandı. Hastaya oral itraconazol ile 6 haftalık başarılı bir tedavi uygulandı. Sonuç olarak, invaziv *Aspergillus* enfeksiyonları immün sağlıklı erişkin ve çocukları etkileyebilir. Travma ve cerrahi müdahaleler immün sağlıklı bireyler için risk faktörü olarak ortaya çıkabilir. Cerrahiye ilave olarak itraconazol, özellikle çocuklardaki *Aspergillus* osteomyelitinin tedavisinde iyi bir seçenek olabilir.

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Anahtar kelimeler: *Aspergillus flavus*, osteomyelit, immün sağlıklı, itraconazol

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Introduction

Invasive aspergillosis usually affects the lungs, and osteomyelitis due to *Aspergillus* spp. is a rare manifestation of invasive aspergillosis. Generally, there are underlying immunosuppressive conditions such as prolonged granulo-

cytopenia, immunosuppressive therapy, and chronic granulomatous disease. Although amphotericin B is one of the most preferred agents for invasive aspergillosis management, its poor bone penetration and renal toxicity limit its use for the treatment of osteomyelitis, especially in pediatric ages.

Case Report

An 8-year-old boy was admitted to our clinic with right leg pain and purulent exudates at a surgical site without fever for one week. He had fibular agenesis, tibial cam-pomelia, and oligosyndactyly (FATCO syndrome). Surgical interventions (two times) for reconstruction were performed at 5 years of his age and 3 weeks prior of his admission in another hospital. He had no history of recurrent local or systemic infections and no family history for underlying chronic conditions. Physical examination revealed short stature and an incision scar with yellow-greenish purulent material at a recent surgical site on the right leg, pes equinovagis, right foot oligodactyly, syndactyly between the third and fourth fingers, and oligodactyly as a bifid digit on the left foot. Laboratory findings included hemoglobin 12.2 g/dL, leukocyte count 8700/mm³ with 66% neutrophils, C-reactive protein 1.66 mg/dL and erythrocyte sedimentation rate 22 mm/h. X-ray examination revealed an expansive, osteolytic lesion in the metaphysis of the proximal tibia. Nuclear scintigraphic examination showed increased radionuclide enhancement at three stages and confirmed the clinical diagnosis as osteomyelitis.

Empirically, cefazolin sodium and amikacin were started for bacterial soft tissue and bone infection. In spite of this treatment, clinical findings did not improve. Two consecutive purulent materials from the surgical site and necrotic bone tissue after surgical debridement on day 10 were submitted for microbiological examination. By the microscopic examination of this tissue material, fungal structures with septate hyphae were observed and the mold was isolated from purulent materials and necrotic bone tissue (three different specimens in all) on Sabouraud dextrose agar. The resulting colonies were yellowish-green, velvety and goldish. Microscopic examination revealed conidial heads, radiate, conidiogenous cells, uni- and biserial conidiophore stipes, rough walls, as well as hyaline and spherical vesicles. The isolate was identified as *Aspergillus flavus* on the basis of macroscopic and microscopic characteristics. Final identification was made as *A. flavus* by PCR amplification of the D1-D2 region of the 28S rRNA gene and sequencing of the resulting amplicons. PCR amplification of fungal genomic DNA was achieved using the primers and conditions as described previously (1). The resulting sequences shared 100% identity with *Aspergillus flavus* isolate V5F-13 28S ribosomal RNA gene present in the publicly available GenBank sequence database of the NCBI. No bacterial agent was isolated from any specimens. We evaluated the in vitro susceptibility of this strain against amphotericin B (AMB), voriconazole (VOR) and itracon-

azole (IT) by the Etest method; MICs were >32, 0.19 and 0.38 µg/mL, respectively. Antifungal therapy was added as IT at a dose of 6 mg/kg/day per oral. One week later, the purulent exudate diminished. Fungal cultures were negative after the second week of treatment. The patient has been advised to continue treatment for a total of 6 weeks and his clinical findings completely disappeared at the end of this treatment. During the follow-up period of three years, clinical or radiological recurrent osteomyelitis was not observed.

Discussion

Fungal infection of the bones due to *Aspergillus* spp. is unusual and usually affects immunocompromised patients. Osteomyelitis is the fourth most common form of infection for aspergillosis following pulmonary, sinus and cerebral infections; primary *Aspergillus* osteomyelitis involving the extremities is rare (2). *A. flavus* is the second most common cause of invasive and non-invasive aspergillosis.

Osteomyelitis due to *A. flavus* reported in the literature is commonly associated with underlying immunosuppression (Table 1) (3-11). Our patient had no predisposing factors such as an immunocompromised condition or diabetes mellitus for *Aspergillus* osteomyelitis; however, he had a history of surgical interventions due to his congenital lower limb anomalies (FATCO syndrome). We could not demonstrate a relationship between osteomyelitis and other infections with FATCO syndrome, due to limited information about this condition. Surgical interventions described as a major predisposing factor in 42 immunocompetent patients with *Aspergillus* osteomyelitis between 1996 and 2001 (12). We think that the predisposing factor for *Aspergillus* osteomyelitis in our patient was multiple surgical interventions. To our knowledge, he is the first pediatric *A. flavus* osteomyelitis case without immunosuppression.

Aspergillus spp. may occasionally infect bone; the most commonly reported site is the spine and it rarely affects the tibia, ribs, wrist, sternum, pelvis, and knee (13, 14). Many studies have associated the occurrence of post-operative aspergillosis with the dissemination of *Aspergillus* spores in the operating room, but contamination from paranasal sinuses, bronchopulmonary lesions, hematogenous dissemination, and contaminated grafts are also possible (15). Our patient was admitted to our clinic three weeks after his last surgery. We suppose that the primary source was inoculation through a local injection for diagnostic procedures or from the air during surgery.

Recently reported osteomyelitis cases of *A. flavus* are reviewed in Table 1. Most of cases were found in men,

Table 1. Recently reported osteomyelitis cases of *A. flavus*

Reference	Age & Sex	Risk factor(s)	Site	Treatment	Result
Present case	Pediatric (8 y) ♂	Multiple surgeries	Tibia	IT and surgery	Recovered
Zhu et al. (3)	Adult (46 y) ♂	Liver transplantation	Vertebral	IT	Recovered
Vergheze et al. (4)	Adult (70 y) ♂	DM and CABP surgery	Rib	VOR and surgery	Recovered
Garazzino et al. (5)	Adult (69 y) ♂	DM and multiple surgeries after trauma	Tibia	VOR and surgery	Recovered
Beluffi et al. (6)	Pediatric (18 m) ♂	AML and HSCT	Spinal	AMB and surgery	Died of AML
Stodulski et al. (7)	Adult (65 y) ♂	DM and chronic alcohol abuse	Skull base	AMB and IT	Died
Chi et al. (8)	Adult (63 y) ♂	DM	Spinal	IT following AMB and surgery	Died
Tang et al. (9)	Adult (43 y) ♂	Liver transplantation	Hip	AMB following IT and surgery	Recovered
Cimerman et al. (10)	Adult (22 y) ♂	Fracture of the femur subsequent surgery	Femur	AMB and surgery	Recovered
Hovi et al. (11)	Pediatric (5 y) ♂	DM, aplastic anemia and bone marrow transplant	Maxilla	AMB, IT and surgery	Recovered
	Pediatric (5 y) ♀	AML	Mandible	AMB and surgery	Died of AML

DM: Diabetes mellitus, CABG: Coronary artery bypass graft, AML: Acute myeloid leukemia, HSCT: Hematopoietic stem cell transplantation, VOR: Voriconazole, AMB: Amphotericin B, IT: Itraconazole.

and only three cases and our patient were of pediatric age. Only one adult case did not have a described risk factor other than trauma and surgical intervention, similar to our patient; other patients had underlying risk factors.

Treatment of *Aspergillus* osteomyelitis can be difficult and generally requires prolonged antifungal therapy combined with surgical intervention. Although AMB is one of the most preferred agents for invasive aspergillosis management, its poor bone penetration and renal toxicity can require the choice of alternative antifungal agents for osteomyelitis, especially in pediatric patients. However, IT has good anti-*Aspergillus* activity and achieves good bone penetration. It has mainly been used as monotherapy with good clinical outcomes (16). Our patient was treated successfully with oral itraconazole for 6 weeks. It is likely that the immunocompetent status of this child was also a factor in this response. VOR was not officially licensed in Turkey during the hospitalization of this case.

Conclusion

Trauma or surgical intervention can be a risk factor for *Aspergillus* osteomyelitis in immunocompetent individuals. For the prevention of these infections, application of infection control procedures, adequate sterilization techniques, and special care regarding the ventilation system in the operating room should be provided. We think that, in addition to surgery, itraconazole can be a good alternative for treatment of *Aspergillus* osteomyelitis especially in children.

Conflict of Interest

No conflict of interest is declared by the authors.

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