Sternal osteomyelitis secondary to *Aspergillus fumigatus* after cardiothoracic surgery

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**ABSTRACT**

Sternal Osteomyelitis from *Aspergillus fumigatus* in immunocompetent patients is extremely rare with limited number of cases reported so far. Here we discuss the case of a 65-year-old female with osteomyelitis of the sternum caused by *Aspergillus fumigatus* after undergoing coronary artery bypass graft surgery. Patient was treated with surgical debridement and prolonged antifungal therapy; however, the course was complicated due to poor adherence to antifungal therapy.

1. Introduction

*Aspergillus* species are one of the most ubiquitous saprophytic fungi known to us [1]. The most common mode of transmission of *Aspergillus* is by inhalation of conidia by their human hosts from the environment and therefore pulmonary manifestations are the most prevalent among its victims. Invasive aspergillosis can involve multiple organs, lung being the most commonly affected especially in patients with immunocompromised status such as HIV or chronic granulomatous diseases (CGD) [2]. *Aspergillus* osteomyelitis (OM), a debilitating and severe form of the diseases; however, is very rare in immunocompetent individuals. Considering the pool of patients with bone involvement, sternal osteomyelitis is extremely rare [3]. Based on our search on PubMed there have been only 11 cases of *Aspergillus fumigatus* OM in immunocompetent patients reported in the literature to date. Here we report a case of *Aspergillus fumigatus* infection of the sternum in a patient, six months after undergoing coronary artery bypass graft surgery.

2. Case

Our patient is a 65-year-old female with a history of poorly controlled type 2 diabetes and three vessel coronary artery disease, who underwent a coronary artery bypass graft in January 2018 (Day-0). Her surgical sternotomy wound appeared to be healing well during her postoperative clinic follow up visit but had an exuberant scar and a necrotic appearing eschar. There was no purulent drainage, tenderness or fluctuance. During the post hospital visit (Day-198), patient presented with one week of anterior chest wall pain over the sternum and some skin blisters over the lower end of the incision. There was no fever, chills or any other systemic signs of infection. There was no purulent drainage, erythema or induration of the skin. The sternum was tender, with a palpable sternal wire under the skin. Chest x-ray was unremarkable. At baseline erythrocyte sedimentation rate (ESR) was 22 mm/hr. (Ref. < 30 mm/hr.) and C-reactive protein (CRP) was 4.1 mg/dl (Ref. < 0.5 mg/dl). Non-contrast CT of the chest was obtained which revealed partial sternal union, but showed a large area of lucency in the manubrium and the body of the sternum (Fig. 1A & B). This was alarming for an infectious process and patient was taken to the operating room (Day-213). She had multiple noncontiguous abscess pockets at the sternomamubrial junction. She underwent incision and drainage of the abscesses, partial sternectomy, removal of six sternal wires and excision and debridement with wound-vac application. She was started on ceftriaxone and vancomycin as an empiric therapy while awaiting tissue culture results. Gram stain was negative. The intraoperative cultures which included both swab from the wound and tissue specimens were negative at 5 days, but after 7 days of incubation, a slow growing organism was identified triggering a prolonged incubation and PCR studies. The culture from both wound swab and all tissue specimens grew a fungus, which was later identified as *Aspergillus fumigatus*, which was susceptible to Micafungin (MIC < 0.015 mcg/ml), voriconazole (MIC < = 1 mcg/ml), amphotericin B (MIC < 0.5 mcg/ml), Caspofungin (MIC < 0.125 mcg/ml) and Posaconazole (MIC < 0.06 mcg/ml). She was started on intravenous micafungin (100 mg intravenous, daily) and voriconazole (200 mg per oral twice daily) after initial intravenous loading doses. She underwent a delayed wound closure and discharged to home with home health on intravenous...
micafungin for six weeks and oral voriconazole for six months at a dose mentioned above (Day-224). During the 4-week clinic follow up, she had undetected voriconazole levels and so, the dose was increased from 200mg to 400mg twice daily. At 8-weeks follow up, she again had undetected voriconazole level. Patient was confronted about the sub-therapeutic drug levels. She then confirmed that she was not taking the medication due to intractable nausea and poor appetite. ESR was 68 mm/hr, CRP was 2.6 mg/dl. Therefore, her antifungal therapy was switched to oral Isavuconazole (372 mg orally, every 8 hours for six doses and then 372 mg daily). However, again the patient was not compliant with it due to drug-induced alopecia. Our patient reported that she started having progressive hair loss after she started taking Isavuconazole and that the hair loss subsided after she stopped taking the drug. Although, alopecia is not a common adverse reaction of Isavuconazole, it has been reported in less than five percent of the subjects taking the drug (Reference: Cresemb Prescribing Information, Astellas Pharma US Inc, Northbrook, IL; December 2019). She stopped following up in the infectious diseases clinic and stopped responding to the phone calls by clinic staff.

Six months later, (Day-430) she presented to the emergency room with worsening sternal pain, erythema and drainage from wound. ESR was 50 mm/hr, CRP was 12.6 mg/dl. CT scan showed worsened osteomyelitis and mediastinitis (Fig. 2A & B). She was readmitted to the hospital and started on triple antifungal regimen with liposomal amphotericin (400 mg IV daily), voriconazole (400 mg IV twice daily) and micafungin (100 mg IV daily). After 2 weeks, amphotericin was discontinued due to worsening renal function. She underwent multiple surgical debridement during this admission and had an open sternal wound. Pathology showed chronic inflammation with fungal hyphae. She had a complicated hospital course with acute renal failure, metabolic encephalopathy, anorexia and malnutrition. She recovered and after six weeks of antifungal therapy, she underwent a plastic surgery reconstruction and flap closure of her open sternal wound (Fig. 3). She was discharged to a skilled nursing home on Micafungin 100 mg IV daily for 6 weeks and oral voriconazole 200 mg twice daily for six months with close follow up. ESR was 36 mm/hr, and CRP was 3.7 mg/dl at the time of discharge.

3. Discussion

Invasive aspergillosis is most prevalent in immunocompromised hosts such as patients with hematological malignancy, neutropenia, solid organ or stem cell transplants, HIV/AIDS and CGD [2]. Chronic steroid therapy and poorly controlled diabetes increases the risk of these infections as well. Bone infections in immunocompetent host is extremely rare. Most of the cases of *Aspergillus OM* are contracted either by hematogenous dissemination or from contiguous spread from a preexisting invasive pulmonary aspergillosis. Postoperative infections resulting from direct inoculation such as after orthopedic procedures can also lead to osteomyelitis [4]. There have been several reported cases of nosocomial infections due to unfiltered air, dirty air conditioning filters and during hospital construction and renovation activities [5,6]. Among the cases of *Aspergillus OM*, vertebral osteomyelitis is most prevalent [4]. Sternal OM is a rare condition and usually

![Figure-1A](image1.png) ![Figure-1B](image2.png)

**Fig. 1.** A and B (Day-198), Non-contrast CT of chest depicts a lucency in the body of sternum showing an osteolytic process.

![Figure-2A](image3.png) ![Figure-2B](image4.png)

**Fig. 2.** A and B (Day-430), Contrast CT of the chest depicts the post-operative status after sternectomy and worsening of infection and sternal defect.
seen either after chest trauma or surgery. According to the three most robust reviews available on PubMed [3,4,7], there are about 26 cases of sternal OM secondary to *Aspergillus* species reported so far in immunocompetent patients. Among these, *Aspergillus flavus* followed by *A. fumigatus* were responsible for the most infections. Our patient had OM due to *A. fumigatus* and we could find only 11 cases of *A. fumigatus* sternal OM in immunocompetent patients after a thorough review of literature which is summarized in Table 1. It is also interesting to note that, a large proportion of these reported cases were part of major *Aspergillus* outbreaks in healthcare settings [5–7].

The reported cases do suggest that the interval between surgery and clinical presentation with sternal osteomyelitis by *A. fumigatus* is highly variable. The incubation period can vary from one to twelve months: average six months. In one case the interval was six years [8]. It is not clear what accounts for this variable latency but the host immunity and the size of the inoculum may play a role. Our patient presented six months after surgery and the only risk factor she had was type 2 diabetes. She did not have any other immunocompromising condition. Her HIV serology was negative and Oxidative Burst Assay for chronic granulomatous diseases was normal.

It is important to remember that fever, leukocytosis and other constitutional symptoms may not be very evident in such fungal infections and therefore a high degree of suspicion is key to begin further investigation in post-operative patients suspected of having *Aspergillus* infection. Bone biopsy and tissue culture can only provide the definitive diagnosis and is always required to better target antimicrobial therapy. Negative bacterial cultures should trigger the clinician to consider fungal infections such as aspergillosis as in this case and consider prolonged incubation of the sample to identify the organism.

The best clinical outcome for *Aspergillus* sternal OM is seen with a combination of extensive surgical debridement and prolonged antifungal therapy [9,10]. Among the antifungal agents available, amphotericin remains the mainstay of therapy, however given the need of prolonged therapy, over 6 weeks to 6 months; many clinicians avoid using this agent due to the risk of nephrotoxicity. Infectious Diseases Society of America (IDSA) recommends use of voriconazole due to its

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**Table 1**

| Citation | Age | Risk factors | Presentation after sternotomy | Diagnosis | Treatment | Outcome |
|----------|-----|--------------|-------------------------------|-----------|-----------|---------|
| This report | 53 Y | Type 2 diabetes | 6 months | *A. fumigatus* (wound culture, bone biopsy) | Surgery, MICA x 6 weeks, VOR x 6 months | Cured at 2 years |
| Barzaghi et al. | 60 Y | None | 10 months | *A. fumigatus* (wound culture) | Surgery, AMB x 3 weeks, ITRA x 2 months | Presumed cured during 8-year follow-up |
| Barzaghi et al. | 70 Y | None | 8 days | *A. fumigatus* (bone biopsy, wound culture) | Surgery, ITRA x 30 days | Death from another cause during treatment |
| Asare et al. | 69 Y | None | 9 months | *A. fumigatus* (bone biopsy) | Surgery, VOR x 6 months | Case recurrence, further treated with ITRA x 10 months |
| Elahi et al. | 62 Y | Type 2 diabetes | 6 months | *A. fumigatus* (wound, bone biopsy) | Multiple surgical debridement, ITRA x 30 days | Cure |
| Richet et al. (Six cases) | 55–78 Y | Unknown | 22–110 days | *A. fumigatus* (wound culture) | Surgery, prolonged therapy with AMB | Cure |
| Sachs et al. | 69 Y | Diabetes, Rheumatoid arthritis | 6 months | *A. fumigatus* (tissue culture) | AMB x 6 weeks | No recurrence at 12 months follow-up |

**Abbreviations:** MICA: Micafungin; VOR: Voriconazole; AMB: Amphotericin B; LAMB: Liposomal Amphotericin B. * Individual patient data was not available, four patients had Chronic obstructive lung diseases and emphysema and two patients had Hypothyroidism.

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**Fig. 3.** (Day-512), Contrast CT of the chest depicts the post-operative status after sternectomy and resolution of infection followed by plastic reconstruction.
extensive clinical experience and controlled trial studies supporting its efficacy for treatment of invasive Aspergillus infections [9]. While gastrointestinal intolerance and solar sensitivity could be a barrier in some patients to adherence to therapy with voriconazole, other agents like posaconazole, itraconazole and isavuconazole are reasonable alternatives with a number of studies supporting their use [9,11,12].

In conclusion, postoperative sternal osteomyelitis caused by Aspergillus fumigatus is an extremely rare but debilitating infection that requires extensive surgical debridement and prolonged antifungal therapy and yet associated with high morbidity and mortality. These infections are indolent and often present months and even years after the original exposure. Diagnosis requires a high index of clinical suspicion especially when cultures from apparently infected wounds are sterile.

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**Consent**

Written informed consent was obtained from the patient or legal guardian(s) for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

**Declaration of competing interest**

No conflicts of interest to report.

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