

Osteomyelitis of the Hip secondary to *Aspergillus fumigatus* - A Case Report and Comprehensive Review of the Literature

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Introduction

Aspergillus infection in an immunocompetent human host is a rare entity. In most cases it presents as an opportunistic pathogen in immunocompromised patients. The portal of entry is usually the respiratory tract or direct inoculation of the organism to the site. *Aspergillus* osteomyelitis is a debilitating and severe form of Invasive Aspergillosis.

This paper presents a case of osteomyelitis of the hip without a recent obvious source of entry and reviews the literature of osteomyelitis and bone infections caused by *Aspergillus*.

Case Report

This is a 70 year-old male with past medical history of Chronic Obstructive Pulmonary Disease (COPD), Hypothyroidism, Bilateral Inguinal Hernia (repaired in 2006) and Benign Prostate Hypertrophy. His home medication prior to this event were Synthroid 100 mcg daily and Montelukast 10 mg daily.

The patient was evaluated for a persistent mild cough without fever, chills, chest pain or any muscular or musculoskeletal pain. During the process of this particular illness, he complained of pain to the right hip. Further work up three months later revealed increasing pain localized to the right hip, non-radiating, severe in nature, aggravated with walking and weight bearing. At that time, he denied any trauma to the area or any direct injury to any related area.

A Magnetic Resonance Imaging (MRI) of right hip was done and showed evidence of osteomyelitis of the right sacral iliac joint. He underwent a biopsy of the right iliac joint. The gram stain of biopsy did not show any bacteria/organism with normal White Blood Cell (WBC) and Red Blood Cell (RBC) count. However, the pathology revealed extensive fibrosis, focal necrosis and osteomyelitis. In addition, the culture grew *Aspergillus fumigatus* species. Further workup did not reveal the primary source of infection especially in the lung. Susceptibility studies were not done unfortunately.

A bronchoalveolar lavage was done because a small speculated lesion in the right lower lobe. This was unremarkable for malignant cells, fungal organisms or acid-fast bacilli. Complete blood count and comprehensive metabolic panel was unremarkable. Erythrocyte Sedimentation Rate (ESR) was 90 mm/hour and C-Reactive Protein (CRP) was 4.5.

The patient was started on oral Voriconazole 200 mg once a day for six months. He tolerated the therapy without much problem. The MRI done of the right hip six months later revealed stabilization of the osteomyelitis.

Discussion

Fungal osteomyelitis, mainly caused by *Candida sp* and *Aspergillus sp*, is a severe and debilitating disease [1]. It is primarily a disease of the immunocompromised patients, even though it can affect immunocompetent patients. The majority of the cases have been reported in developed regions with outstanding healthcare systems, such as North America (47% of the reported cases) and Europe (33% of the reported cases). The most common mode of transmission of *Aspergillus* osteomyelitis is contiguous spread from pulmonary infection and/or from contiguous skin infection. This may be the reason why the vertebrae and the ribs were the most common sites affected [2]. In adults, vertebrae is also the most common infection site but most of the time due to hematogenous spread or direct inoculation due to trauma with penetrating injury/surgical procedures [2-7]. Most cases of *Aspergillus* osteomyelitis appeared to be affecting immunocompromised hosts with chronic granulomatous infections and immunodeficiency condition [2,4-6,8-10]. Among adults, prolonged and high dose immunosuppressive drug therapy is considered the most important predisposing condition [2,4].

In a paper published in 1999, a review of the literature on fungal osteomyelitis was done, which revealed less than 40 cases of *Aspergillus* osteomyelitis. Noticeably, the increased usage of chemotherapy, immunomodulator and steroids may indirectly cause the increased incidence of Invasive Aspergillosis, in particular *Aspergillus* osteomyelitis. Other important risk factors that should be considered are the use of central venous catheters and abdominal surgery. Therefore, in our case, it is possible that the history of bilateral inguinal hernia repair may have played a role as an entry route of *Aspergillus fumigatus*.

The incidence of *Aspergillus* affecting the bone among all cases of invasive Aspergillosis is thought to be around 3% [11,12]. In a series by Horn et al, the incidence of invasive Aspergillosis was 2.6%, similar to those reported by Denning and Stephen in 1990 [12]. In most cases it appears to present as diskitis or osteomyelitis of the spine. Involvement of the long bones and hip etc. has rarely been documented [3,4].

Aspergillus infection remains extremely rare in immunocompetent hosts [13]. In 1987, Brown et al reported 2 cases of seemingly immunocompetent adults who used intravenous drugs [14]. Vaishya et al reported a case of vertebral osteomyelitis in an immunocompetent adult; noting only 4 other cases have been previously reported [15]. In 2005, Mouas et al discussed 20 cases of osteomyelitis, 6 of which were immunocompetent [13].

Our case is particularly unique not only because the patient is immunocompetent, but also this is one of a few case of *Aspergillus* osteomyelitis that affecting long bone, particularly hip joint. There were no history of penetrating trauma/surgical event to the hip joint nor any signs of affected portal of entry of *Aspergillus* infection; which are lung, skin, gastrointestinal tract or sinuses [8].

It requires three major criteria to document that the osteomyelitis is secondary to a fungus:

1. Accurate identification and isolation of the pathogen from the actual site of infection.
2. Direct microscopic demonstration of the pathogenic invasive form of the fungus from the site where the cultures were obtained.
3. Correlation of the results of the culture to the osteomyelitis process. Concomitant bacterial infections can occasionally occur in these fungal bone infections.

Aspergillus fumigatus was the most commonly isolated species followed by *Aspergillus flavus*, *Aspergillus niger*, *Aspergillus terreus* [4,5,7]. Unlike *Candida*, which is the most common organism causing mycotic infections [16,17], *Aspergillus* is slow growing, difficult to isolate and most of the time is a contaminant since the spores are really small [9,18]. Therefore, a culture and histopathological examination are still important to obtain the correct diagnosis [7,9,18]. Another proposed method for diagnostic are Galactomannan (GM) and (1→3)- β -D-glucan (BG) antigen quantification by enzyme-linked immunosorbent assay and detection of fungal DNA by PCR methods or single nucleotide polymorphism (SNP) markers. This test is not easily available and has not been studied as an indicator for osteomyelitis caused by *Aspergillus*.

Treatment for *Aspergillus* osteomyelitis include Amphotericin B [2,19,20], Itraconazole [12,21] and Voriconazole [10,13,17,21,22]. Antifungal therapy in combination with surgical debridement of the bone involved is indicated, especially in advanced cases [12].

Recent studies of patients with invasive Aspergillosis have shown that treatment with Voriconazole is more effective than treatment with Amphotericin B [7,10,23,24]. Length of therapy is generally between 6-12 weeks [1,7]. Many of the literature supports the use of prolonged therapy for up to a year [13]. Recurrences are not uncommon [25].

REPORTED CASES OF INVASIVE ASPERGILLUS INFECTIONS

Source	Age/Sex	Sites of infection	Predisposing condition	Diagnosis	Treatment	Course
Agarwal et al.	34/M	Nasal polyp, right maxillary antrum and orbit	Not specified	Histology and culture of nasal polyp and orbital tissue	Surgery, X-radiation, Iodine & Hyamycin	Poor response
Allen et al.	67/F	Sternum	Hodgkin's Disease in remission	Histology and culture of open biopsy of sternum	Surgery debridement, liposomal Amphotericin B and oral Itraconazole	Recovered
Asare et al.	69/M	Sternum and left 3 rd costal rib	None	Histology and culture of open biopsy of sternum	Surgery debridement, intravenous and oral Voriconazole	Recovered
Asdamongkol et al.	57/M	C6-T4 vertebrae and disk space	Remote history of TB, DM	Histology and culture of open biopsy material from T4-5 disk space	Intravenous Amphotericin B and oral Itraconazole	Recovered
Baez-Escudero et al.	75/M	Sternum	Chronic Lymphocytic Leukemia with chemotherapy	Histology and culture of open biopsy material from sternum	Intravenous Amphotericin B, oral Voriconazole and multiple surgery debridement	Recovered
Bathoorn et al.	19/M	Left Maxilla	Non-myeloblastic stem cell transplantation for graft failure	Histology and culture of the bone fragments	Intravenous Amphotericin B and oral Voriconazole	Recovered

REPORTED CASES OF INVASIVE ASPERGILLUS INFECTIONS

Source	Age/Sex	Sites of infection	Predisposing condition	Diagnosis	Treatment	Course
Brown et al.	30/M	T6-7 vertebrae and disk space	IV drugs abuse	Histology and culture of the biopsy material from T6-7	Amphotericin B	Recovered
Byrd et al.	52/F	L5 vertebra and disk space	Renal transplant, long term use of steroid	Histology and culture of open biopsy material from L5 vertebral body	Amphotericin B	Deceased of Disseminated Intravascular Coagulation
Camargo et al.	71/M	L2-3 vertebrae and disk space	Status-post steroid epidural injection	Histology and culture of biopsy material from L3 vertebral body	Oral Voriconazole	Recovered
Cimerman et al.	22/M	Left Femur	Left femur closed transverse fracture	Histology and culture of the bone fragments	Intra-articular Amphotericin B	Recovered
D'sa et al.	45/F	Right 9 th -10 th ribs	DM	Histology and culture of the bone fragments	Oral Voriconazole	Recovered
Golmia et al.	58/F	Left Sacroiliac joint	Diffuse systemic sclerosis	Histology and culture of the synovial fluid	Surgical drainage, Caspofungin acetate and Voriconazole	Recovered
Grossman	44/M	L2-3 vertebrae and disk space	Renal transplant, long term use of steroid	Histology and culture of open biopsy material from L2 vertebral body	Amphotericin B	Deceased of Myocardial Infarct
Ingwer et al.	49/M	T8-10 vertebrae and disk space	Renal transplant, long term use of steroid	Histology of open biopsy material from laminectomy	Amphotericin B	Deceased of GI hemorrhage
Mahgoub et al.	40/M	Cervical Lymph Nodes	Unknown	Histology and culture of lymph node biopsy material	Iodine	Deceased
Mershon et al.	15/M	"Almost every organ"	Postmitral valvuloplasty, multiple antibiotics	Culture of tissue at autopsy	No specific antifungal therapy	Deceased
Mohammadpour et al.	9/M	Skull, superolateral left orbit	Chronic Granulomatous Disease	Culture of excisional biopsy of the skull mass	Intravenous Amphotericin B, Itraconazole and Voriconazole	Recovered

REPORTED CASES OF INVASIVE ASPERGILLUS INFECTIONS

Source	Age/Sex	Sites of infection	Predisposing condition	Diagnosis	Treatment	Course
McKee et al.	22/M	T10-12 vertebrae and disk space	Glucose 6-Phosphate-Dehydrogenase Deficiency and Hemoglobin-S trait	Histology and culture of open biopsy material from T11 vertebral body	Amphotericin B	Recovered
Nusair et al.	49/F	T8-9 vertebrae and disk space	Hepatitis C, IV drugs abuse	Histology and culture of open biopsy material from T8-9 disk space	Intravenous and oral Voriconazole	Recovered
Rippon et al.	28/M	Meninges	Postlumbar laminectomy, intrathecal steroids	Culture of 3 successive spinal taps	Intravenous and intrathecal Amphotericin B	Recovered
Roselle and Baird	54/M	L3-4 vertebrae and disk space	Cerebral Edema, steroids use in the past	Histology and culture of open biopsy material from L3-4 laminectomy	Amphotericin B	Recovered
Seligsohn et al.	42/F	L1-2 vertebrae and disk space	Cirrhosis, concurrent drugs abuse	Histology and culture of open biopsy material from L1-2 disk space	Amphotericin B	Recovered
Sethi et al.	25/M	L4-5 vertebrae and disk space	None	Histology and culture of open biopsy material from L4-5 disk space	Oral Itraconazole	Recovered
Siciliano et al. [26]	59/M	3 rd – 8 th bilateral ribs	Poststernotomy CABG, DM	Histology and culture of open biopsy material of bone fragments	Intravenous Itraconazole	Recovered
Tack et al.	64/M	Left Hip Joint	Prior total left hip replacement (9 yrs ago)	Histology and culture of open biopsy of hip joint	Amphotericin B	Recovered
Vaishya et al.	35/F	T11 vertebra	None	Histology of open biopsy corpectomy T11	Amphotericin B	Deceased
Van Tol et al. [27]	81/M	Right Mastoid	None	Histology and culture of open biopsy material right mastoid	Local Miconazole and oral Voriconazole	Recovered
Antony et al.	70/M	Right Sacro-iliac joint	None	Histology and culture of biopsy material from right sacro-iliac joint	Oral Voriconazole	Stable

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