Surgical Management of Fungal Vertebral Osteomyelitis

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Abbreviations: *AIS = American Spinal Injury Association Impairment Scale; CRP = C-Reactive Protein; ESR = Erythrocyte Sedimentation Rate; FVO = Fungal Vertebral Osteomyelitis*

Abstract

Introduction

Fungal vertebral osteomyelitis (FVO) is an uncommon but aggressive disease that may cause spinal instability, neurological insult, and possibly death. Little data about treatment strategies and patient outcomes exist. A retrospective review of medical and surgical management with follow-up of this disease was performed.

Methods

A retrospective review was conducted of patients with FVO treated with surgery and pharmacotherapy at a single institution over a 7-year period (1999 to 2006). Patients were included in analysis if they had biopsy and radiographically confirmed vertebral fungal infection. Analysis was constructed through office and medical records. Specific data points included age, gender, microbiology, treatment, clinical presentations and outcomes.

Results

Nine patients with FVO were identified (5 females and 4 males) ranging in age from 42 to 77 years (mean=57 years). Advanced age (n=4) and previous spine surgery (n=4) were the most commonly identified risk factors for FVO. Candida species (n=7), *Aspergillus fumigatus* (n=2), and *Saccharomyces cerevisiae* (n=1) pathogens were identified. The average pre-operative erythrocyte sedimentation rate (ESR) was 83.2 mm/hr (normal range is 0 to 20 mm/hr) and C-reactive protein (CRP) was 6.9 mg/dL (normal range is 0 to 1.2 mg/dL). Surgical debridement and stabilization procedures were performed in all 9 patients. The average antifungal prescription duration was 21 weeks. Revision surgical procedures (n=5) were the most commonly identified treatment complication, and the average duration between the initial surgery and the first subsequent procedure was 3.5 months (range, 3 weeks to 9 months). In comparison to pre-operative ASIA Impairment Scores, patient neurological status was improved (n=4) or stable (n=3) at latest follow-up. Average follow-up duration was 19 months. There was no mortality.

Conclusions

Aggressive surgical treatment with concurrent pharmacotherapy can successfully treat FVO and prevent neurological injury. Repeat surgeries are common in patients with progressive vertebral degeneration or persistent infection.

Introduction

Fungal vertebral osteomyelitis (FVO) is an uncommon but aggressive disease that may cause spinal instability, neurological insult, and death.[1,2] It is often difficult to diagnose and treat.[3] The incidence and prevalence of invasive fungal infections has increased since the 1980s, and is believed to be related to the growing population of immunocompromised patients.[4] However, there has been little attention given to the management and follow-up of FVO. Additional data about treatment strategies and patient outcomes is warranted. We reviewed our experience and the literature to highlight the surgical management and follow-up of this disease.

Methods

This study was Institution Review Board-approved. The medical records of 9 consecutive patients with fungal vertebral osteomyelitis (FVO) and combined surgical and pharmacological treatment between 1999 and 2006 were reviewed retrospectively. The following patient data were documented: Demographics, risk factors for FVO (Table 1), fungal pathogens identified, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) laboratory results, surgical and pharmacological treatments, clinical course, and American Spinal Injury Association (ASIA) Impairment Scale grades.

Results

Patients

There were 5 females and 4 males and patient ages ranged from 42 to 77 years (mean=57.4 years,). Table 2 outlines the clinical details of these cases.

Diagnoses and Laboratory Results

Vertebral osteomyelitis diagnosis in 8 patients was confirmed by radiologic imaging. Fungal pathogen diagnosis in 8 patients was confirmed by tissue biopsy at our institution. The most

Table 1. Recognized risk factors for spinal infections[6]

Risk factor
Advanced age
Diabetes
Human immunodeficiency virus
Chronic renal or hepatic disease
Intravenous drug use
Long-term steroid use
Malignancy or chemotherapy
Severe trauma
Previous surgery
Alcoholism
Rheumatoid arthritis

Table 2. Clinical details of FVO patients treated at our institution

Patient No.	Age at Diagnosis (Y)/Sex	Risk Factors	Pathogen/Antifungal Agent/Prescription Duration	Spinal Level of Pathology/ Surgical Treatments	AIS Grade at Initial Presentation/Last Follow-Up
1	65/F	Advanced age; previous spine surgery	*Candida tropicalis*/Diflucan, Voriconazole/1Y	L2-3/Anterior and posterior fusion with autograft*; 2 subsequent I&D procedures	ND/D
2	43/F	Inflammatory bowel disease**; Diabetes	*Aspergillus fumigatus*/ Fluconazole/6-8W	T8-9/Anterior and posterior fusion with autograft*	E/E
3	65/M	Advanced age; chronic hepatic disease; feeding tube**	*Candida albicans, Saccharomyces cerevisiae*/ Caspofungin/8W	L1-2/Stage 1: Posterior fusion*; Stage 2: Anterior fusion with autograft*	D/E
4	54/M	Alcoholism; chronic hepatic disease	*Candida albicans*/ Diflucan/8W	C5-6 and T11-12/Stage 1: Cervical anterior fusion with autograft*; Stage 2: Thoraco-lumbar anterior and posterior fusion with autograft*	B/E
5	65/F	Advanced age; previous spine surgery	*Candida albicans* (and MRSA)/Vancomycin, Rifampin, Fluconazole/8W	T9-10/Anterior and posterior fusion with autograft*	C/D
6	45/F	Previous surgery (lower lobectomy for Aspergillosis pneumonia)	*Aspergillus fumigatus*/ MK0991 (experimental therapy), Itraconazole/1.2Y	L1-5/Anterior and posterior fusion with autograft*; Subsequent thoracic anterior and posterior fusion with allograft*	E/E
7	77/M	Advanced age; previous spine surgery	*Candida glabrata*/ Voriconazole/ND	L4-5/Anterior and posterior fusion with autograft*	D/D
8	42/F	Inflammatory bowel disease**; peri-anal abcesses**	*Candida tropicalis*/ Caspofungin/4W	T7-8/Anterior fusion with autograft*; Subsequent I&D	E/E
9	57/M	Previous spine surgery	*Candida albicans*/Diflucan/ ND	L1-2/Posterior decompression and fusion with autograft*; 3 subsequent spinal fusions at varying levels*	D/C

Advanced age is defined as at least 65 years old; AIS = ASIA Impaiment Scale; FVO = Fungal Vertebral Osteomyelitis; I&D = Irrigation and debridement of post-operative wound infection; ND = No Data; W = Week; Y = Year; * = Instrumentation was implanted during this procedure; ** = Not a traditionally-recognized risk factor for spinal infection, but supported by data in Table 3.

commonly identified pathogens were *Candida* species (*C. albicans* (n=4), *C. glabrata* (n=1), *C. tropicalis* (n=2)), *Aspergillus fumigatus* (n=2), and Saccharomyces cerevisiae (n=1). Patient pre-operative laboratory results for ESR averaged 83.2 mm/hr (range, 25-130 mm/hr) (normal range at our institution is 0-20 mm/hr), and for CRP averaged 6.9 mg/dL (range, 0.5-14.1 mg/dL) (normal range at our institution is 0-1.2 mg/dL).

Treatments

Table 2 outlines the details of the surgical procedures performed. Five patients underwent additional, subsequent surgery, necessitated by disease progression and/or complications of their initial surgical procedures. Subsequent surgery was the most commonly identified surgical complication, and the average duration between the initial surgical procedure and the first subsequent procedure was 3.5 months (range, 3 weeks to 9 months, SD=3.8 months). Table 2 also outlines the antifungal medication treatments prescribed. The average antifungal prescription duration was 21 weeks (range, 4 to 62 weeks, mode=8 weeks, SD=24.6 weeks).

Outcomes

Table 2 outlines the neurologic status of each patient as recorded at pre-operative presentation and at latest follow-up with the Department of

Figure 1

Pre-operative MRI of patient 9 shows extensive vertebral degeneration with *Candida albicans* infection.

Neurological Surgery or Orthopedic Surgery. In 3 patients the ASIA Impairment Scale (AIS) grades improved following treatment; in 4 it remained constant; in 1 it worsened; and there was incomplete pre-operative data for 1 patient. The average follow-up duration, calculated as the time between the initial surgical procedure and the latest follow-up date, was 19.2 months (range, 1.5 weeks to 48 months, SD=18.7 months).

Discussion

Fungal infections of the spine are uncommon, and are especially rare among immunocompetent patients. However, in immunocompromised patients, such as transplant patients with immunosuppressant medications or patients with concurrent diseases like diabetes mellitus, fungal infections are increasingly prevalent.[5] Table 3 lists primary immunodeficiencies, acquired immunodeficiencies, and other factors related to immune system compromise that have been associated with fungal infections of the spine. In this study, 7 of 9 patients (78%) had at least one risk factor for fungal osteomyelitis related to immunosuppression or compromised immune system function.

Laboratory markers of host inflammation such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) also signal the close relationship between host immune system function and spinal osteomyelitis. Elevated ESR and CRP levels are associated with active vertebral osteomyelitis and decreasing levels are associated with response to treatment.[6] In one case series, 10 of 11 patients with fungal vertebral osteomyelitis (FVO) had elevated ESRs,[1] and in the present study the pre-operative ESR was elevated in every patient and the pre-operative CRP was elevated in 8 of 9 patients (89%).

Importantly, FVO may also occur in immuno*competent* patients, and laboratory markers may not universally be elevated. For instance, Al-Tawfiq and Ghandour[7] reported a case of *Cryptococcus* vertebral osteomyelitis and Levine et al8 reported a case of *Scedosporium* vertebral osteomyelitis, both in immuno*competant* patients. In the present study, the pre-operative CRP was normal in Patient [9]. Thus, while fungal infection of the spine and host immune system function are usually closely related, there are exceptions to the typical patient profile.

The most common fungal organisms that infect the spine include *Aspergillus*, *Candida*, and *Cryptococcus* species.[9] Several other pathogens associated with FVO have also been reported (Table 4). Because specific fungi such as *Coccidioides* and *Blastomyces* are limited to particular geographical regions, patient residence in or travel to endemic areas should be considered during clinical evaluation.[10]

Antifungal pharmacotherapy is the central component of FVO treatment and is universally indicated in the setting of invasive fungal infections. Delayed initiation of pharmacotherapy has been associated with poorer neurological outcomes,[1] and antifungal medication should therefore be promptly administered once a diagnosis has been made.

The development of an antifungal treatment regimen is a complex task that considers several variables including: (1) the drug or class of drugs that will appropriately target the pathogen of interest (e.g., Amphotericin B, Azoles, Echinocandins); (2) pharmacokinetics (e.g., absorption, excretion, etc.); (3) pharmacodynamics (e.g., therapeutic and toxic effects); and (4) patient-specific considerations. Furthermore, the maintenance of an antifungal treatment regimen over time is an equally complex and lengthy process.

Table 3. Reported risk factors for FVO

Risk factor
Primary immunodeficiencies
Chronic granulomatous disease[18]
Defect in monocyte killing[19]
Acquired immunodeficiencies
Bronchiectasis[20]
Chemotherapy[21]
Corticosteroids[1]
Cancer[1]
Chronic obstructive pulmonary disease[22]
Diabetes mellitus[23]
Human immunodeficiency virus[24]
Increased age[23]
Inflammatory bowel disease[13]
Malnutrition[1]
Neutropenia[25]
Rheumatoid arthritis[23]
Sarcoidosis[26]
Other factors
Antibiotic use[27]
Factor X concentrate infusion[28]
Hematopoietic stem cell transplantation[29]
Hemodialysis[30]
Indwelling central venous catheter[27]
Injection drug use[27]
Lumbar disc puncture[14]
Organ transplantation[31]
Previous spine surgery[1]
Trauma and wound contamination[32]

FVO = Fungal Vertebral Osteomyelitis

Table 4. Reported fungal pathogens associated with vertebral osteomyelitis

Genus
Aspergillus[18]
Blastomyces[33]
Blastoschizomyces[34]
Candida[27]
Coccidioides[35]
Cryptococcus[36]
Inonotus[37]
Mucor[38]
Pneumocystis[24]
Pseudallescheria[16]
Rhizopus[14]
Scedosporium[39]
Trichosporon[10]

Table 5. Literature summaries for FVO management with combined surgical and medical techniques

Author	Year	Total number of FVO patients	Number of FVO patients treated with combined surgical and medical techniques	Number (and percentage) of FVO patients treated with combined surgical and medical techniques			
				whose infection had resolved at latest follow-up	that experienced neurological stability or improvement	that had recurrent surgery	that died/Average follow-up duration
Frazier et al[1]	2001	11	11	9 (82%)	11 (100%)	3 (27%)	2 (18%)/6.3 years
Khazim et al[11]	2006	3	3	3 (100%)	3 (100%)	0	0/5.3 years
Wrobel et al[2]	2001	23	16	ND	13 (81%)	2 (13%)	2 (13%)/2.5 years
This study	2011	9	9	7 (78%)	7 (78%)	4 (44%)	0/1.6 years
Pooled total		46	39	19/23 (83%)	34 (87%)	9 (23%)	4 (10%)/3.6 years

Note: Table only includes studies with >1 patient. Single case reports were excluded. ND = No Data; FVO = Fungal Vertebral Osteomyelitis

The fundamental aims of FVO management with combined surgical and pharmacological treatment are (1) to eliminate the fungal infection, and (2) to prevent neurological injury and repair any neurological insult. Table 5 shows the consistent ability of surgical and pharmacological management to eliminate fungal infections in FVO patients. Table 5 also shows that the vast majority of VFO patients managed with surgical and pharmacological treatment experience neurological stability or improvement.

Combined medical and surgical treatment, therefore, is clearly preferable to no therapy, which leads to rapidly progressive disease.[11] Stratov et al[12] have shown that combined treatment is also preferable to isolated pharmacotherapy or surgery for many FVO patients. Furthermore, the follow-up mortality rate in this study and throughout the literature is very low (Table 5), and there was no operative mortality in this study. Thus, patients presenting with FVO and spinal cord or nerve root compression, spinal instability or deformity, or overwhelming infection should be managed with a combination of surgery and pharmacotherapy.

Management of FVO has been associated with moderate rates of surgical recurrence, or repeat procedures, as evidenced by numerous case reports.[13-17] Repeat surgeries are often necessary due to disease progression and/or complications of initial surgical procedures, such as post-operative surgical site infections. Frazier et al.[1] reported that 3 of 11 patients managed with combined treatment underwent subsequent surgery (Table 5). In this study, 4 of 9 patients (44%) underwent subsequent surgeries (Tables 2 and 5). Patient 8 had a subsequent irrigation and debridement procedure for a deep wound infection, and Patient 1 had 2 subsequent irrigation and debridement procedures, both for deep wound infections. Patient 6 had a subsequent spinal fusion at an entirely different level than the initial procedure, due to disease progression from the lumbar to the thoracic spine. Patient 9's initial surgery targeted infection of the lumbar spine (L1-L2) (Figure 1), but due to extensive infection progression he ultimately underwent two additional surgical procedures due to thoracolumbar instability. Indeed, fungal infections of the bony spine frequently prove to be difficult and persistent, and it is in this context of progressive infections that the prospect of new and more effective pharmacological antifungal agents is especially relevant.

This study had several limitations. The small number of patients may have skewed our results, and we therefore presented our findings in the context of pooled literature summaries (Table 5). The relatively short follow-up duration may have biased our rates of recurrent surgery and mortality. Ultimately, due to the rarity of FVO, additional series are needed to further define the optimal management of this disease.

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