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Fungal Spondylodiscitis: Review

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Abstract

The term spondylodiscitis is an entity that refers to an infection that affects the vertebral body and intervertebral disks. These are commonly caused by pyogenic infections, particularly by *Staphylococcus aureus*, which responsible for 60% of them. Fungal spinal infections remain a rare pathology, although an increased incidence has been reported due to a progressively more susceptible population (immuno-deficient patient). Fungal spondylodiscitis diagnosis currently relies on the presence of risk factors, microbiology, serological tests (Antigen detection and antibody testing) and imaging such as magnetic resonance with contrast, being the most useful study. The gold standard for establishing a diagnosis of fungal infection is to obtain tissue for histological confirmation or culture; endoscopy is currently the ideal method for sampling. Medical management is the initial approach for most fungal infections of the spine. This usually involves a multidisciplinary approach with anti-fungal therapy under the supervision of infectious disease specialists and bracing with early mobilization, but there are clear indications for surgical treatment where mechanical stabilization by posterior approach and drainage and placement of structured autologous grafts anterior approach, in the same act or a second surgical stage.

Keywords: Spondylodiscitis; Fungal; Spine; Infections; Discitis; Immuno-deficient patient

Introduction

The spine infections that enclose ligamentous, discal and bony structures of the spine are known as spondylodiscitis, vertebral osteomyelitis or discitis. These are commonly caused by pyogenic infections, particularly by *Staphylococcus aureus*, currently responsible for 60% of them [1]. Non-pyogenic infections include Mycobacterium tuberculosis, disease known as Pott`s Syndrome [1,2]. Fungal infections have become more common as the number of patients with immuno-deficiency disorders has grown, given that this type of patients need antibiotic treatment to fight opportunistic bacterial infections, and this favors the growth of fungal flora [1]. Fungal infections have been reported in patients with acquired immuno-deficiency syndrome (AIDS), use of medication that lowers native immunological defenses and patients in critical care. For the most part, the main agent isolated has been *Candida*, on second place *Aspergillus*, and also *Cryptococcus* or *Coccidioides* [1-3]. Hematogenous spread is the most common path of infection. There are two theories supporting this: the venous theory and the arteriolar theory. Wiley and Trueta [4] mention that the bacteria can conglomerate in the arteriolar network near the end plates. Batson [5] developed the venous theory, stating that retrograde flux of the pelvic venous plexus to the paravertebral plexus via veins from the meningoarachnoid complex can be given.

A fungal infection must be considered when the biopsies and cultures are negative and symptoms persist even after antibiotic therapy has been initiated [1,3].

Etiology

Fungal infections of the spine are uncommon. The frequently occur in immuno-suppressed hosts with mean age is 50 years old [1,3,6,7]. The incidence of fungal infections has risen markedly in recent years. Several factors have contributed to this increase; immuno-suppressive drugs, prolonged use of broad-spectrum antibiotics, widespread use of indwelling catheters, and AIDS [3,6,7]. Comorbids like diabetes, embolism or previous surgery are also relevant. After reaching bloodstream it reaches the vertebral body by the subcondral vascular heaves of the joint platforms, where it adheres given that the blood flow is slower [6,7].

Fungal infections of the spine are mainly caused by *Candidiasis* and *Aspergillosis* [1,8] for *Candida* organism to become pathogenic, the host must be immnucompromised [8].*Candida* species are part of the normal flora and are commonly found on the skin and gastrointestinal tract [9]. *Candida* may gain access to the vascular system of susceptible patients via IV lines or monitoring devices and the implantation of prosthetic materials [8-10]. *Candida* spondylodiscitis should be considered in any patient with spinal symptoms and a history of candidemia, the infection shows symptoms usually weeks or months after the first candidemia episode [9-12]. *Candida albicans* It is the most common species found, however the infection by *C. glabrata,* is becoming more common, this may be secondary to the general trend of increasing *Candida* infections and widespread use of azole antifungals [13-16].

Aspergillus spondylodiscitis is due to *Aspergillus fumigatus* in 80% of cases followed by *Aspergillus flavus*, the organisms is pathogenic only in immnuno-compromised host [8,17]. *Aspergillus* species are ubiquitous saprophytic fungi that produce numerous small spores. The small size of the spores allows for ready dispersion onto air currents from contaminated air-handling systems and deposition into human lung alveoli [1,8,17]. Patients with AIDS and chronic granulomatous disease, those on long-term antibiotics and IV drug abusers are especially at risk of developing the disseminated form [17-19]. Osseous involvement may occur by direct extension from the lung or by Hematogenous spread. The vertebral bodies are the most commonly infected sites by *Aspergillus* [18-21].

Other fungi are endemic and are limited to specific geographic areas; the two most common endemic fungi that give rise to spinal infections are *Coccidioides immitis* and *Blastomyces dermatitidis* [8,22,23].

Coccidioidomycosis is a fungal disease caused by *Coccidioides*

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immitis and *C. posadii.* The disease is localized to geographic regions with arid soil due to high temperatures and low humidity. *C. immintis* in endemic in parts of the south-western United States, Central America, and parts of South America [24-26]. Disease prevalence is increasing with the rise in tourism to those countries. The hicolum needed for infection can be quite small, even a few arthroconidia [27,28]. Spine lesion are frequently multiple and generally lytic, disease often develops through Hematogenous or lymphatic spread and can involve one or multiple sites [27,28].

The other endemic fungal infection is *Blastomyces dermatitidis* is a dimporphic fungus endemic in areas bordering the Mississippi and Ohio rivers. Primary infection in humans occurs by inhalation of conidia, the long bones, vertebrae, and ribs are the most common sites of osseous involvement [29-31].

Cryptococcus, *Candida*, and *Aspergillus* are found worldwide. *Cryptococcus neoformans* is found in the soil and in pigeon feces. The disease is the fourth most common infection in HIV-infected patients [32]. Cryptococcosis may be localized to the lung or generalized. Central nervous system involvement is common in the disseminated form [33]. Osseous involvement occurs in approximately 5% to 10% of patients [34,35].

In immuno-suppressed patients rare fungal infections may occur, *Blastoschizomyces capitatus* has been found in spondylodiscitis which is a normal human flora of the skin an GI track, it mimics candidiasis but with a fatal course [36,37]. *Scedosporium prolificans* with only 2 cases reported can cause disseminated disease on immuno-suppressed persons, resistant to antifungal therapy requiring extensive debridement for cure [38,39]. *Trichosporon fungemia* is a rare and fatal fungal infection that occurs in patients with prolonged neutropenia associated with hematologic malignancies. Individuals susceptible to this pathogen should be in constant evaluation because spondylodiscitis can manifest years after the infection has cure. Diagnosis can be difficult because no clinical or laboratory values suggest infectious process it can confuse with oncologic pathology, and make a therapeutic delay, so an open biopsy or closed needle aspiration should be consider [40-42]. (Table 1)

Clinical Presentation

A typical patient with fungal spondylodiscitis debuts as lower back pain or dorsal pain, with at least a month since initial onset. Insidious, progressive, intermittent pain that usually progresses to constant pain is a very common clinical manifestation of this disease [1,8,22,43]. Only a third of the patients present fever and approximately 20% present neurological symptoms and the most common presenting complaint is diffuse back pain [1,8,28,32,43,44]. Patient risk factors are usually related to an impaired immune system but may also be due to environmental factors [8,44]. Patients with a history of immune disorders, malignancies, corticosteroid use, receiving parenteral nutrition, diabetes, solid organ transplantation, IV drug use, and patients with prolonged IV access sites or previous surgery are at especially high risk [8,45]. A physical examination of a patient with a suspected fungal infection of the spine is mandatory. A baseline neurological examination documenting any sensory or motor deficits can be used to determine progression or resolution of the disease process.

Assessment of spinal balance, especially in the sagittal plane gives an idea of advanced infections, causing spinal deformity. Signs of recent significant weight loss and cutaneous sequelae of disease may also be suggestive of fungal infection. A detailed pulmonary exam is especially important with suspected *Aspergillus* infections but also with *Coccidioides* and *Cryptococcus* [43,44,45,46].

Diagnosis

Diagnosis of fungal spinal infections is often delayed and late initiation of antifungal therapy may be associated with a worse outcome, particularly in terms of neurological recovery [1,8,47]. A rise in inflammatory such as with cell count, erythrocyte sedimentation rates, and C-reactive protein levels can alert the possibility of a spinal infection [48,49]. However, these are not specific for fungal infections. Antibody and antigen tests are seldom helpful in the diagnosis of spinal infections for *Candida* and *Aspergillus* [48].

Blood culture is very accessible but has low sensitivity (50-70%), this can be improved with centrifugation, and nevertheless only 51% of the patients mentioned in the reviews have blood culture results [6]. Biopsy of the lesion must be done for diagnostic confirmation. (1→3)-β-D: -glucan (BDG) levels are useful with sensitivity and specificity reported up to 90% in patients with invasive candidiasis [49]. This test is positive in other fungal infections as aspergillosis and fusariosis, even though, high false positives rates have been reported. The detection of fungal nucleic acid via polymerase chain reaction (PCR) holds promise as a diagnostic tool. So fart technology has demonstrated high sensitivity and specificity for detecting isolates of *Candida* and *Aspergillus* [48,50].

Diagnosing fungal spondylodiscitis is currently based in risk

Fungus	most frequent	Location/ feature	Mode of transmission	Affected segment of the spine
Candidiasis	Albicans	Are normal commensals of humans and are found throughout the Gastrointestinal tract Sputum, disease skin.	For Candida organisms to become pathogenic, the host must be immune-compromised.	Lower thoracic or lumbar spine (95%)
Aspergillosis	Fumigatus	The organisms is pathogenic only in immune-compromised host	By inhalation of small spores (conidia)	Lumbar spine
Coccidioidomycosis	Immitis	Endemic, disease prevalence is increasing with the rise in tourism	By inhalation of the spores or through abrasion of the skin	Infection may involve multiple levels, the surrounding soft tissues, and the disc space.
Blastomycosis	Dermatitidis	Endemic, the organism exists in warm, moist soil rich in organic debris.	Inhalation of conidia	Thoracic and lumbar region
Cryptococcosis	Neoformans	Most commonly in pigeon feces and soil. Is the fourth most common life-threatening infection in patients with AIDS	By inhalation after the organisms is aerosolized	Thoracic mainly
Trichosporon	capitatum	Occurs in patients with prolonged neutropenia associated with hematologic malignancies	-------	Thoracic and lumbar

Table 1: General characteristics for fungal infection.

factors, microbiology, blood tests, antigen detection/antibody testing and imaging. The gold standard to establish a fungal infection diagnosis is to obtain a tissue sample for histological o culture confirmation [51,52]. The sample can be obtained by computed tomography guided needle aspiration (CT FNAC), the procedure can be repeated in case negative cultures are reported. If negative cultures persist, biopsy should be considered [53].

Endoscopic biopsy can be performed, accompanied by a discectomy at the same time and drainage. It has been demonstrated that the best sample is obtained when computed tomography (*CT*)-guided fine needle aspiration cytology (*FNAC*), which is why this is the preferred choice nowadays. The culture obtained by biopsy permits differentiation of the microorganism causing the infection in more than half of the patients [8,28,50-53].

If the first sample results as a negative culture, a second sampling is indicated and current recommendations are to obtain a minimum of 6 samples of different parts of the lesion [51]. Open biopsy will eventually be discouraged. The samples must be sent for stains in search of mycobacteria, fungi and histological analysis to dismiss malignancy [51-53].

Histology

Biopsy and histopathology assessments are critical in the diagnosis of fungal infections. Accurate diagnosis is dependent on the skill of the pathologist and adequacy of organisms received in aspirates or tissue biopsies. It is important that microscopic appearances are correlated with microbiology findings, as well as other tests for specific host antibodies, fungal antigens, and fungal antibodies [54,55].

Image Studies

The imaging of fungal infection is fairly nonspecific and mimics either tuberculous or pyogenic infection. Plain x-rays can be useful, nevertheless, visible changes can only be viewed after a few months after infection has taken place, and does not help differ infection from bony destruction. Certain patterns do occur more commonly with certain fungal infections, paravertebral soft-tissue swelling with involvement of the posterior structures is more common in late Coccidioides infections [56,57]. With *Blastomyces*, collapse and gibbous deformity tend to be seen more commonly [8,58]. In *Cryptococcus,* lytic lesions within vertebral bodies can resemble those in coccidioidomycosis or the cystic form of tuberculosis with discrete margins and surrounding abscess formation [57-60]. In fungal infections of the spine, CT (Figure 1) and MRI (Figure 2) are effective in determining the extent of disease spread. In contrast to pyogenic infections, fungal infections often spare the disc. When the causative agent is *Candida* or *Aspergillus*, the infection is focused on the intervertebral body space, decreasing its height, causing destruction of the end plates and adjacent bone and the presence of paraspinal abscesses [32,44,59]. A hypo-intense image is seen in T2 as in short-tau inversion- recovery (*STIR*) (more sensitive than T2) in the bony marrow, suggesting the presence of underlying fibrosis due to the indolent infectious process, very different from pyogenic infections that are significantly more aggressive [59,60] (Figures 3 and 4) (Table 2).

There are no radiological findings that can help differentiate fungal infections (*Candida and Aspergillus* mainly*)* from other discitis. The positron emitting tomography with fluorine 18 fluorodeoxyglucose (FDG PET) shows promising results when Magnetic resonance imaging (MRI) has no clear signs [11,12,50,60] (Figure 5).

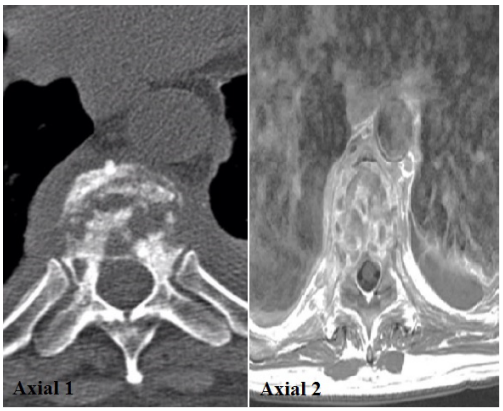

Figure 1: CT and MRI. Axial view of the spine with fungal infection.

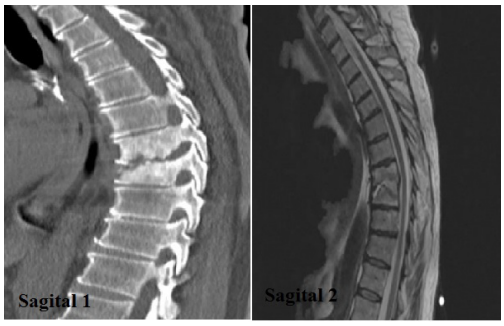

Figure 2: CT and MRI. Sagital view of the spine with fungal infection.

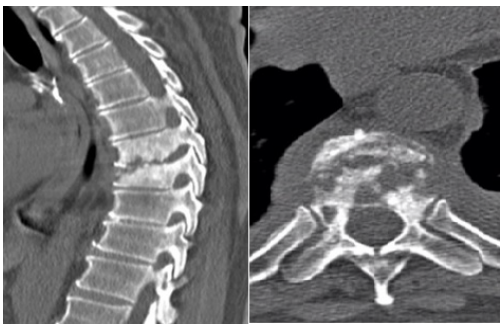

Figure 3: Sagittal and coronal views of the CT scan show the extent of bone fragmentation and sclerosis.

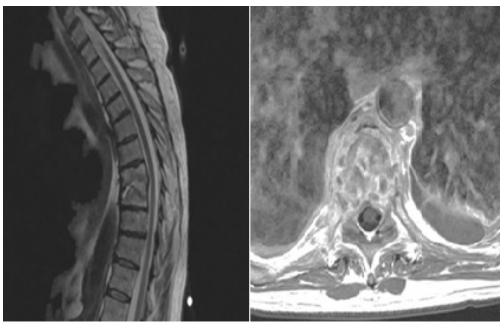

Figure 4: Magnetic resonance imaging of thoracic spine with contrast show involvement of T8, T9 vertebral bodies with associated pre-vertebral soft tissue inflammation.

Treatment

Antifungal treatment is the first choice of treatment in fungal

Disc space	T2 hyperintensity, enhancement, height loss
Vertebral body (VB)	Endplate destruction, T1 hypo, T2 hyperintensity, enhancement. Osteolysis/bone destruction/bone erosion
Paraspinal/epidural space involvement	Small paraspinal abscesses, ill-defined inflammation
Anterior sub-ligamentous spread	Common
Adjacent vertebral levels involvement	Uncommon
Multilevel involvement	Common (Coccidioidomycosis)
Deformity (Gibbous)	Mainly in Blastomycosis

Table 2: Fungal Spondylodiscitis: imaging findings.

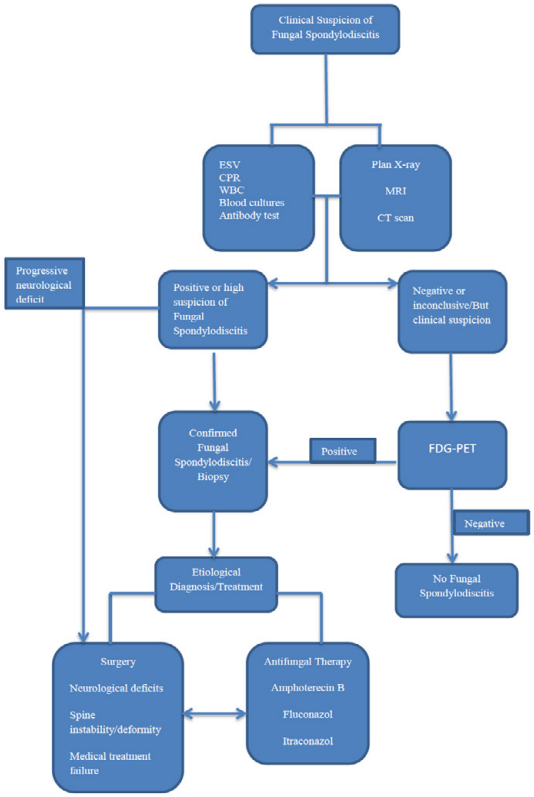

Figure 5: Fungal spondylodiscitis management algorithm. ESV: Erythrocyte Sedimentation Velocity, CPR: C-Reative Protein, WBC: White Blood Cell Count, MRI: Magnetic Resonance Imaging.

Indications for surgical intervention in fungal spondylodiscitis
1. Medical treatment failure
2. Significant or progressive neurologic deficits
3. Large paraspinal abscess with local mass effect
4. Progressive deformity with or without incapacitating spinal pain

Table 3: Indications for surgical intervention in fungal spondylodiscitis.

spondylodiscitis. Treatment guidelines establish that the primary regimen is the use of de amphotericin B for 2-3 weeks followed by fluconazole for 6-12 months [61]. Liposomal amphotericin B (AmBisome) is a lipid-associated formulation of the broad-spectrum polyene antifungal agent amphotericin B It is active against clinically relevant yeasts and moulds, including *Candida* spp., *Aspergillus* spp. and filamentous moulds [61]. There are reports of cases successfully being treated with azoles alone. The recurrence rate is high, and there are scarce cases reported [62-64]. Fluconazole has the best security and tolerance range compared to other azoles [63-65]. If mono-therapy is chosen with this drug, the recommendation is to have 4-6 weeks of i.v. fluconazole at 400 mg per day, followed by 2-6 months of oral treatment. Nevertheless, Gottlieb et al [66] mentions that itraconazole is the first choice and can be used in replacement of Amphotericin B, and the treatment period is shorter if surgical debridement is made. Currently resistance rates have increased, the widespread use of drug, even when it has not been indicated [67,68]. Once the medical treatment has been finished, the long term prognosis for functional recovery and pain relief continues to be uncertain. Some of the patients have residual chronic pain that can be incapacitating [62,64,66].

Isavuconazole a new option for treatment of fungal infections has a broad spectrum of activity, providing an advantage over other currently available broad-spectrum azole antifungals and a clinically useful alternative to voriconazole for the treatment of invasive Aspergillosis [69]. Isavuconazole has activity against a number of clinically important yeasts and molds, including *Candida* spp, *Aspergillus* spp, *Cryptococcus neoformans*, and *Trichosporon* spp [69] It has been proven that combined treatment (surgical and medical) relieves pain quicker, allows histological diagnosis and stabilizes the spine [62,64,65,70].

Medical treatment failure, the onset of neurological deficit or progression of symptoms, particularly when imaging studies demonstrate the nervous compression, are clear indications for surgical treatment, having to realize debridement, decompression and stabilization [71-73] (Table 3).

Also, significant deformity can be considered a surgical indication. Surgical treatment is accepted when abscesses are damaging neurological structures. Early decompression maximizes functional recovery but after 48 hrs the prognosis is uncertain [73]. The goal of surgical treatment is to debride, sample, drain, decompress and stabilize the spine, which can be done in the same surgery or in a second look [73,74]. Therefore, laminectomy without stabilization is contraindicated, because progression to kyphosis is a certainty and could cause further damage to the neurological structures [72,73].

Until very recently, minimally invasive techniques had a primary indication in mild cases with little bony destruction. Currently, this technique can be used in more severe cases. Currently, open surgery is the gold standard [73-75].

Surgical approach depends on the dominant side of the infection. Anterior approach is the standard procedure for debridement of the vertebral body and stabilization. Although, given the instability in these cases, posterior initial approach is recommended for mechanical stability followed by anterior approach [75].

Autologous iliac crest graft or fibular bone graft are the ideal structural grafts, given that the rib graft has been proven insufficient unless is vascularized [76,77]. Tricortical graft is needed for two reasons: as a biological matrix and as structural support. This prevents the kyphosis postoperatively [73-78].

Conclusions

Fungal Spinal infections remain a rare pathology, although an increased incidence has been reported due to a progressively more susceptible population (particularly in patients with immuno-compromised) and improved diagnostic acuity.

In an inmuno-deficient patient with lumbar pain, progressive onset that has atypical changes in the spine imaging, negative cultures and has persistent symptoms despite of antibiotic treatment, fungal infection should be considered.

Treatment of fungal spondylitis is often delayed because of difficulty with the diagnosis. Delay in the diagnosis led to poorer results in terms of neurologic recovery. Patients should be given a guarded prognosis and informed of the many possible complications of the disease.

The initial treatment should be medical, with antifungal drugs. The duration of treatment is important. Surgical treatment should be considered in patients with neurologic involvement, collapsed vertebrae, and persistent infection in spite of medical treatment. Questions remain whether instrumentation is necessary and safe in the surgical treatment of fungal infections of the spine.

Conflict of Interest

The authors, their immediate families, and any research foundation with which they are affiliated have not received any financial payments or other benefits from any commercial entity related to the subject of this article.

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