Rare disease

'Fungal spondylodiscitis in a non-immunocompromised patient'

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Summary

Spondylodiscitis is an inflammatory disease, usually infectious, of one or more vertebral bodies and of corresponding intervertebral discs. The fungal aetiology is rare (less than 5% of cases), affecting mostly immunocompromised individuals. It is often a delayed diagnosis by the indolence of symptoms, presenting itself as a serious infection, which may result in important functional consequences. The authors present the case of a 75-year-old male, with constitutional complaints and intense back pain. Prior recent history of left hemicolectomy due to diverticulitis with multiple surgical complications, resulted in prolonged intensive care unit hospitalisation, and, later on, an episode of fungal endophthalmitis. The diagnosis of spondylodiscitis L5/S1 was performed by MRI. The patient underwent surgical disco-vertebral debridement and isolation of a *Candida albicans* was seen in the collected surgical material. No evidence of an immunosuppressive status was found. Treatment was complemented with liposomal amphotericin B in the maximum recommended dose.

BACKGROUND

Spondylodiscitis remains rare but its incidence is rising, due to an increasingly susceptible population and the availability of more effective diagnostic tools.¹ The growing problem of systemic disease caused by *Candida* species reflects the enormous increase of patients at risk, depending primarily of their immune status.² Fungal spondylodiscitis is relatively uncommon, mainly in a non-immunocompromised patient. The diagnosis and treatment of this entity is challenging, requiring a multi-disciplinary team. An illustrative case-report and literature review is presented.

CASE PRESENTATION

A 75-year-old male presented in the Medicine Clinics with a 3 months history of mechanical and intense low back pain, weight loss of 4 kilograms, non-selective anorexia, fatigue and nausea.

Denied falling or local trauma. No fever, night sweats nor relevant epidemiological context was reported. Personal background included hypertension, dyslipidaemia, hyperuricemia, depressive syndrome; Appendectomy (2003), partial prostatectomy for benign prostatic hyperplasia (2007) and left hemicolectomy surgery for complicated diverticulitis, requiring a Hartmann procedure (2010).

Physical examination was remarkable for pallor and bilateral positive Lasègue sign.

Lab investigation revealed a normocytic and normochromic anaemia (Hb: 9.5 g/dl), acute renal failure, elevated erythrocyte sedimentation rate (ESR) and β -2-globulin, probably associated with renal impairment (table 1).

Differential diagnosis included multiple myeloma, bone metastasis of solid tumours (lung, prostate, kidney and thyroid) and spondylodiscitis. The thyroid

and prostate ultrasounds, thoraco-abdomino-pelvic CT and bone marrow/bone biopsy revealed no significant changes. Conventional x-ray and sacral spine CT revealed only degenerative changes (figure 1). A bone scintigraphy showed an inflammatory/degenerative L5 hyperfixation, but neoplasia could not be excluded.

However, during his admission, the patient reported worsening of lumbar pain and became bedridden, despite the step-up of non-steroidal anti-inflammatory drugs and opioid analogues therapy. A cervico-dorso-lumbar MRI revealed a L5/S1 spondylodiscitis with a spinal epidural abscess (figure 2).

An orthopaedic consultant decided to repeat lumbar CT (figure 3) and that the best therapeutical approach was surgical cleansing, debridement and posterior fixation of L5-S1. A *Candida albicans* species was isolated in the surgical material collected, sensitive to fluconazole, amphotericin B and caspofungin.

A prolonged intensive care unit stay in the previous year due to major septic complications after diverticulitis surgery, along with parenteral nutrition, several central catheters and broad-spectrum antibiotics might be the predisposing factors to a fungal infection in a immunocompetent subject.

Subsequently, the patient had a fungal endophthalmitis without any microorganism isolated, with total recovery of visual acuity following antifungal therapy.

INVESTIGATIONS

Moreover, a thorough investigation proved his immunocompetence (negative HIV/P24 antigenemia, hepatitis serologies and normal lymphocyte populations, immunoglobulins, complement and immunological profile).

Table 1 Initial laboratory parameters

Parameter	Value
Haemoglobin	9, 5 (13, 5–18) g/dl
MCV (mean corpuscular volume)	94 (80–96) fl
MCH (mean corpuscular haemoglobin)	30 (27–31) pg
Leucocytes/neutrophils/lymphocytes	6600 (4–10) mm ³ ; 72, 6% (37–72); 16, 3% (18–50%)
Platelets	248000 (150–400) mm ³
C reactive protein	4, 4 (<1) mg/dl
ESR	109 (1–20) mm/1st h
AST	12 (14–36) U/l
ALT	33 (9–52) U/l
Alkaline phosphatase	139 (38–126) U/l
δ-GT	142 (12–43) U/l
LDH	394 (313–618) U/l
Urea	198 (15–45) mg/dl
Creatinine	2, 5 (0, 8–1, 5) mg/dl
Na+	138 (137–145) mEq/l
K+	5, 9 (3, 6–5) mEq/l
Cl–	107 (98–107) mEq/l
β-2-microglobulin	8, 3 (<2) mg/l
Electrophoresis of proteins/serum immunofixation	No monoclonal peak
Total PSA	2, 35 (<2, 35) ng/ml
HIV 1/2 (ELISA)	Negative
HBsAg/anti-HBs/anti-HBc	Negative
Anti-HCV	Negative

AST, aspartate aminotransferase; ALT, alanine aminotransferase; ESR, erythrocyte sedimentation rate; HCV, hepatitis C virus; LDH, lactate dehydrogenase; PSA, prostate-specific antigen.

TREATMENT

Our first antifungal choice was fluconazole 400 mg intravenously per day, during 1 week, later changed to liposomal amphotericin B 3 mg/kg/d due to development of fever, worsening back pain and aggravation of inflammatory parameters (table 2).

Repeated blood cultures were negative and no vegetations on echocardiogram were seen. A repeated lumbar-sacral CT revealed a root conflict at S1-S2 due to a right transpedicular screw (figure 4) urging for a new orthopaedic fixation and debridement procedure. Again, a *C. albicans* was isolated with the same sensitivity spectrum. Liposomal amphotericin B 3 mg/kg/d was maintained for 1 week, but the persistence of fever led us to up-titrate it to 5 mg/kg/d resulting in apyrexia, remarkable pain improvement and recovery of laboratory parameters, 1 week later.

OUTCOME AND FOLLOW-UP

After 22 days of a lipid formulation of amphotericin B, fluconazole (400 mg per os, per day, high enough because of systemic fungaemia) was started, due to good clinical recovery, regression of inflammatory parameters, including ESR (table 2) and to allow earlier discharge.

The patient was transferred to a rehabilitation clinic. He completed 6 months of antifungal therapy in an ambulatory basis. The new thoraco-pelvic CT, did not show any loci of infection and sacral spine CT only revealed sequelar changes.

DISCUSSION

The term ‘spondylodiscitis’ means primary infection of the intervertebral disc by a pathogen, with secondary infection of neighbouring vertebral bodies.³

Figure 1 AP lumbar spine x-ray showed only degenerative changes.

Spondylodiscitis is a rare disease accounting for 2–7% of all cases of pyogenic osteomyelitis, with incidence varying from 1 per 100 000/year to 1 per 250 000/year.⁴ Men are up to three times more often affected than women.⁴

Any age group can be affected, although spondylodiscitis is most frequent in the fifth to seventh decades of life.³ However, there is evidence that the incidence is rising due to longer life expectancy for patients with chronic debilitating disease, immunosuppressive therapy, increasing use of indwelling devices and spinal surgery.⁴

The haematogenous spread of pathogenic microorganisms into the bone marrow of the vertebral bodies is the most common source of infection in adults. It affects preferentially the lumbar spine, followed by the thoracic and cervical spine in decreasing frequency (58%, 30% and 11% respectively), possibly reflecting the relative proportions of blood flow.¹ Contiguous infection is less common and is difficult to distinguish from direct inoculation.⁵ Direct inoculation may occur during lumbar puncture, spinal anesthesia, discography, chemonucleolysis, infiltration treatment of low back pain by local anesthesia or after spinal surgery.⁵

The most important infecting organism in pyogenic spinal osteomyelitis is *Staphylococcus aureus*, accounting for more than 50% of cases in most series from developed

Figure 2 TW2 cervical-dorsal-lumbar MRI shows: severe oedema of L5/S1 disc and vertebral bodies; erosion of the cortical bone of the vertebral endplates, particularly in S1 vertebral body, and an enlarging soft tissue mass in the anterior epidural space highly suggestive of epidural abscess.

Table 2 Evolution of laboratory parameters

Parameter	Value		
	1 Week after the 1st surgery (beginning of liposomal amphotericin B 3 mg/kg/d)	2 Weeks after the 1st surgery. (beginning of liposomal amphotericin B 3 mg/kg/d and new surgery)	1 Month after the 1st surgery (beginning of fluconazole 400 mg/d)
Haemoglobin	9, 2 g/dl	9, 9 g/dl	10 g/dl
Leucocytes/neutrophils	5100 mm ³ ; 73, 7%	8600 mm ³ ; 80, 1%	7400 mm ³ ; 63, 9%
C reactive protein	12, 3 mg/dl	18, 2 mg/dl	3, 6 mg/dl
ESR	113 mm/h	110 mm/h	70 mm/h
Urea	26 mg/dl	25 mg/dl	49 mg/dl
Creatinine	1 mg/dl	1 mg/dl	0, 9 mg/dl

ESR, erythrocyte sedimentation rate.

countries, with a growing relevance of methicillin-resistant *Staphylococcus aureus* strains.^{6 7}

However, the range of reported pathogens is large; less common but important pathogens include: enteric gram-negative bacteria (39%), *Streptococci* (19%) and skeletal tuberculosis in 5% of HIV-negative patients and in 60% of HIV-positive patients.³ Brucellosis, the commonest zoonosis in endemic areas, can account for 21%–48% of spinal infections, representing the predominant cause in some series from the Mediterranean Basin and the Middle East.¹

Fungal infections of the spine are relatively uncommon (0, 5%–1, 6%, usually).^{8 9}

Candida species are normal flora that inhabit the skin and mucous membrane of human host.⁸ Invasive fungal infections caused by *Candida* species have increased significantly over the past two decades.¹⁰

Recently, the widespread use of antibiotics, central venous catheters, intravenous drugs and immunosuppressive chemotherapy have increased virulent infection by *Candida* species in immunocompromised individuals.⁸ Patients cronicly ill and malnourished, in particular if

they are receiving total parenteral nutrition or have had gastrointestinal injury or surgery (gastrointestinal tract perforations and anastomotic leaks), with HIV infection and injecting drug abuse, are also affected.^{11 12}

Other secondary sites of infection are also commonly found, for example, endophthalmitis in 18%.¹ On the other hand, the incidence of ocular candidiasis has been decreasing among inpatients with candidaemia, with

Figure 3 Lumbar CT scan shows erosion at L5 and S1 vertebral bodies, and paravertebral fat densification, compatible with spondylodiscitis at L5/S1.

recent incidence estimates of less than 2%.¹³ The most common species involved is *C albicans*.¹⁴ The clinical presentation may be very indolent, with progression from chorioretinitis to vitritis or frank endophthalmitis, and *Candida* endophthalmitis may occur as a late relapsing of candidiasis.¹³

Candida osteomyelitis is a recognised late complication of fungemia, occurring several months after the initial episode, and remains a rare condition.¹⁰ The species more frequently involved are *C albicans* (62%), *C tropicalis* (19%) and *C glabrata* (14%).¹⁰ *Candida* spondylodiscitis may occur by direct implantation of a contiguous infected site or by haematogeneous route.⁸

The diagnosis of *Candida* spondylodiscitis includes clinical features, laboratory results, radiological studies and microbiological tests.⁸ The clinical features are non-specific, and usually arise late in the course of the disease (2 to 12 months in 70% and more than 1 year in 10%).^{15–17} Involvement of the vertebral bodies can lead to vertebral compression fractures and deformity of the spine.⁹ The only 32% to 43% of patients presented with fever at admission and about 20% of patients complained of the neurological deficits.⁸ In addition, spread of infection along the anterior longitudinal ligament can lead to psoas muscle or paravertebral abscesses.⁹

Laboratory results frequently revealed elevated ESR and C reactive protein, whereas the white blood cell count is often normal.⁸ The elevation of ESR is a non-specific indicator that can be used to monitor the response to the treatment of fungal vertebral osteomyelitis.¹⁵

Microbiological analysis enables definitive diagnosis and may further define treatment via susceptibility testing.⁹ Patients with suspected fungal spondylodiscitis should have blood sent specifically for fungal cultures.⁹ Furthermore, specimens could be obtained by CT-guided fine needle aspiration.⁹

Figure 4 Lumbar-sacral CT revealed a root conflict at S1-S2 due to a right transpedicular screw.

Antigen assays as PCR, galactomannan and Western-blot can be used for rapid diagnosis of invasive fungal infections, detecting antibodies and fungal metabolites.¹³

Although plain radiograph frequently reveals erosive and destructive changes of the vertebral body, MRI is the diagnostic tool of choice for *Candida* spondylodiscitis.⁸ It has reported a sensitivity of 96%, specificity of 93% and accuracy of 94%.¹ Its advantage over other modalities lies with its superior ability to provide anatomical information, particularly relating to the epidural space and spinal cord.¹ Williams *et al* reported different imaging features, including absence of disc high signal intensity and preservation of the intranuclear cleft in T2-weighted images in the case of fungal spondylitis.¹⁸

CT is inferior to MRI with respect to the specificity and sensitivity in the diagnosis of spondylitis.³ It is worse than MRI in imaging neural tissue and abscesses but is the best modality at delineating bony abnormalities, including early endplate destruction (before they become visible on x-ray), later sequestra or involucrum formation, or pathological calcification.¹

Fluorine-18 fluorodeoxyglucose positron emission tomography is showing promise as a very sensitive modality. It can effectively distinguish infection from degenerative changes even when MRI is inconclusive, although it shows a low specificity for neoplasms.¹

Radioisotope studies may be a useful adjunct to diagnosis, when radiographic changes on plain films or CT scans are either absent or equivocal and the suspicion for osteomyelitis is high. Such studies are relatively sensitive but their specificity for infection is low.¹⁹

Optimal management of such cases may require surgical debridement and, after initial intravenous antifungal therapy, prolonged administration of oral azoles. Adequate antifungal drug levels are difficult to achieve in the bone.¹³

First choice antifungal agents include oral fluconazole 400 mg (6 mg/kg) daily for 6–12 months or lipid formulation of amphotericin B (3–5 mg/kg/day) for several weeks followed by oral fluconazole for 6–12 months. Alternative include an echinocandin (anidulafungin 200 mg loading dose, 100 mg/day; caspofungin 70 mg loading dose, 50 mg/day; micafungin 100 mg/day) or amphotericin B deoxycholate (0, 5–1 mg/kg) followed by oral fluconazole for 6–12 months.¹³

Although the optimal duration of therapy for *Candida* spondylodiscitis is not totally established, the current practice is to continue treatment until the resolution of clinical symptoms, recovery of laboratory data and amelioration of radiological features.⁸

Such medical treatment is generally effective. However, surgical treatment should be considered in a patient with neurological deficits, extensive collapse of the vertebral bodies, or persistent infection in spite of antifungal chemotherapy.²⁰

The overall prognosis for patients with *Candida* spondylodiscitis is good, with the full recovery rate ranging from 67% to 100%.²¹ However delayed diagnosis may therefore lead to poorer outcome in terms of neurological recovery.⁹

Learning points

- Nowadays, the growing of systemic diseases caused by *Candida* species is an enormous problem, associated to a longer life expectancy, immunosuppression and medical manipulation.
- Fungal spondylodiscitis is a rare entity, especially in a non-immunocompromised patient.
- It remains a diagnostic and therapeutic challenge, which may result in important functional consequences.

Competing interests None.

Patient consent Obtained.

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