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Review

A rare case of *Candida glabrata* spondylodiscitis: case report and literature review

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ABSTRACT

Background: Spondylodiscitis is an infection of the vertebral column, the incidence of which is increasing due to an increase in the susceptible population and improved ascertainment. This disease has been associated with a wide range of microorganisms. Fungal spondylodiscitis is uncommon (0.5–1.6%) and strongly associated with immunosuppression and diabetes (Gouliouris et al., 2010). A rare case of *Candida glabrata* spondylodiscitis in a non-neutropenic diabetic patient is reported herein, along with a review of the literature.
Case report: A case of *C. glabrata* spondylodiscitis of L3–L4 metameres was diagnosed. The diagnosis was obtained through open biopsy of an abscess and culture examination. The patient was treated with anidulafungin and surgical debridement of the lesion.
Conclusions: The diagnosis of spondylodiscitis is often delayed or missed. Physicians should consider this entity in the differential diagnosis of lumbar pain in order to initiate an appropriate therapy to prevent spinal cord lesions and disability. This is particularly relevant in the case of a fungal aetiology, as there is a recognized global shift towards invasive candidiasis due to non-albicans *Candida* species, in particular *C. glabrata*, which has variable susceptibility to antifungal drugs.

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Introduction

Spondylodiscitis is an infection of the vertebral column, the incidence of which is increasing due to an increase in the susceptible population and improved diagnostic skills. Fungal spondylodiscitis is uncommon (0.5–1.6%) and is usually due to *Candida albicans* (Gouliouris et al., 2010; Berbari et al., 2015). *Candida glabrata*, formerly known as *Torulopsis glabrata*, is a common saprophyte in the gastrointestinal, genitourinary, and respiratory tracts and an opportunistic pathogen of low virulence (Berkowitz et al., 1979). There has been a recent significant increase in infections caused by *C. glabrata* due to the increase in the immunocompromised population (Seravalli et al., 2003).

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Risk factors for candidaemia are present in the majority of patients with fungal infections and include prior use of broad-spectrum antibiotics, central venous access devices, immunosuppression, neutropenia, chronic granulomatous disease, and intravenous drug use (Gouliouris et al., 2010; Berbari et al., 2015).

The case presented herein represents the fifteenth case of spondylodiscitis due to *C. glabrata* reported in the literature and the first treated with anidulafungin. Data reported in the literature concerning the diagnosis and treatment of *C. glabrata* spondylodiscitis are discussed and this newly reported case is compared to previously reported cases.

Case report

A 66-year-old male was admitted to the ward for lumbar pain, progressive difficulty in walking, and immobilization during the previous 2 months. He had a history of diabetes, spondyloarthrosis, hepatitis C virus (HCV) infection with liver sclerosis, depression, and segmental ileitis, and he was overweight (90 kg, body mass index (BMI) 28 kg/m^2). He had already been evaluated for lumbar pain in the emergency department, where he had undergone spine radiography that had not shown any evidence of pathology. During the following month, the pain had worsened and had not responded to non-steroidal anti-inflammatory drugs or opiates. The patient was therefore investigated with a computed tomography (CT) scan of the spine, which showed signs of lumbar spondyloarthrosis and suspected spondylodiscitis of L4. He was finally admitted to the ward.

Physical examination showed fever (37.5 °C), significant functional spine limitation for mobility, and weakness of the muscles of the legs. A blood test revealed a normal white blood cell (WBC) count, normochromic normocytic anaemia, and an increased erythrocyte sedimentation rate (ESR; 46 mm/h) and procalcitonin (12.69 ng/ml), while C-reactive protein (CRP) was within the normal range. Quantiferon and serology for Brucella, Echinococcus, and *Treponema pallidum* were negative. Blood cultures yielded no pathogens and electrophoresis of serum proteins did not show any monoclonal component. Electromyography (EMG) showed a sensitive and motor neuropathy of the L3–S1 fibres. It was decided to perform a spine magnetic resonance imaging (MRI) scan, which showed hypointensity in T1 sequences and hyperintensity in T2 and STIR sequences at the L3–L4 vertebral bodies, signs of oedema of the disc. Post gadolinium images detected a lesion suspicious of an abscess (Figure 1).

Based on the laboratory findings, the epidemiological data, and the aetiology of spondylodiscitis, the patient was started on a broad-spectrum antibiotic therapy; however, there was no improvement in his symptoms or the functional impairment. The case was then discussed with neurosurgeons, and a surgical exploration revealed a spinal abscess, which was treated with debridement and stabilization of the vertebrae involved. Biopsy specimens were sent for aerobic, anaerobic, fungal, and mycobacterial culture and yielded *C. glabrata*. Antifungal susceptibility testing indicated that the isolate was susceptible to caspofungin, anidulafungin (both minimum inhibitory concentrations (MICs) were 0.06 μg/ml), and micafungin (MIC 0.01 6μg/ml), according to Clinical and Laboratory Standards Institute (CLSI) guidelines. The patient was evaluated by an infectious diseases specialist and was started on treatment with anidulafungin 200 mg on the first day, followed by 100 mg daily thereafter. Within a few weeks, a progressive improvement in the lumbar pain, resolution of the fever, and a decrease in ESR were seen, and he was finally mobilized.

Figure 1. Spine MRI showing a lesion suspicious of an abscess.

Review of the literature

A MEDLINE search combining the keywords “Candida glabrata”, “Torulopsis glabrata”, “vertebral osteomyelitis”, “spinal osteomyelitis”, and “spondylodiscitis” was performed and the reference lists of identified articles were reviewed to find additional cases. For all reported cases, special attention was paid to risk factors, localization, methods of diagnosis, treatment, and outcome. This is currently the most complete review on *C. glabrata* spondylodiscitis (Table 1).

From the data in the literature, the mean age of patients at diagnosis was 61.5 years (range 43–74 years). Eight cases involved male patients and seven cases involved female patients (53.3% vs. 46.7%). The most prevalent risk factors were prior use of antibiotics

Table 1
Review of *Candida glabrata* spondylodiscitis.

Author	Age (years) and sex	Risk factors	Localization	Diagnosis	Medical therapy	Surgery	Outcome
Thurston and Gillespie (1981)	60 M	Diabetes mellitus Broad-spectrum antibiotics Obstructive uropathy Candiduria	L4–L5	Open biopsy	Amphotericin B 5-Fluorocytosine	–	Cured
Bruns et al. (1986)	63 F	Broad-spectrum antibiotics Obstructive uropathy Candidaemia	T7–T8	Open biopsy	Amphotericin B 5-Fluorocytosine Ketoconazole	Performed	Cured
Morrow and Manian (1986)	49 M	Broad-spectrum antibiotics Alcohol abuse Funguria	T11–T12	Needle biopsy	Amphotericin B	Performed	Paraplegic
Liudahl and Limbird (1987)	49 M	Alcoholic cirrhosis Broad-spectrum antibiotics	T11–T12	Open biopsy	Amphotericin B	Performed	Cured
Imahori et al. (1987)	66 F	Broad-spectrum antibiotics Candidaemia Central venous catheter	L2–L3	Needle biopsy	5-Fluorocytosine	–	Cured
Owen et al. (1992)	71 F	Diabetes mellitus Bowel resection Central venous catheter Parenteral nutrition Candidaemia	T9–T10	Open biopsy	Amphotericin B	Performed	Cured
Curran and Lenke (1996)	74 F	Colon resection Broad-spectrum antibiotics Central venous catheter Candidaemia	T7–T8	Needle biopsy	Amphotericin B Fluconazole	Performed	Cured
Bonomo et al. (1996)	85 F	Diabetes mellitus Rheumatoid arthritis Malignancy Broad spectrum antibiotics	C3–C4	Open biopsy	Amphotericin B Itraconazole	–	Cured
Bonomo et al. (1996)	44 F	Degenerative joint disease	T3–T11	Open biopsy	Amphotericin B	Performed	Paraplegic
Dwyer et al. (1999)	43 F	Gastric bypass Central venous catheter Parenteral nutrition Broad-spectrum antibiotics Fungaemia	L1–L2	Needle biopsy	Amphotericin B Fluconazole	–	Cured
Hendrickx et al. (2001)	72 M	Axillo bifemoral bypass Broad-spectrum antibiotics Central venous catheter Parenteral nutrition	L1–L2	Needle biopsy	Fluconazole Amphotericin B	–	Died
Seravalli et al. (2003)	64 M	Diabetes mellitus Gastric resection Spinal osteoarthritis Obstructive uropathy	L2–L3	Needle biopsy	Amphotericin B Fluconazole Amphotericin B lipid complex	Performed	Presumed cured
Dailey and Young (2011)	69 M	Candidaemia Colon resection Broad-spectrum antibiotics Central venous catheter Parenteral nutrition Alcohol abuse	L1–L2	Needle biopsy	Amphotericin B	Performed	Cured
Tan et al. (2014)	47 M	Psoriatic arthritis Immunosuppression Candidaemia	L3–L4	Needle biopsy	Caspofungin Posaconazole	–	Cured
Current case	66 M	Diabetes mellitus	L3–L4	Open biopsy	Anidulafungin	Performed	Cured

F, female; M, male.

(66.7%), previous candidaemia (46.7%), previous surgery (40%), central venous catheter (40%), and diabetes mellitus (33.3%).

Eight cases involved the lumbar spine, while one case involved the cervical spine and six cases involved the thoracic spine. The most frequently affected metameres were L2 (33.3%) and L3 (26.6%). The microbiological diagnosis was obtained after needle biopsy in 53.3% of cases and by open biopsy in 46.7% of cases. A needle biopsy failed in the detection of the pathogen involved in three cases and an open biopsy was therefore performed.

Treatment with amphotericin B plus another antifungal drug was used in 46.7% of the cases. A third of the cases were treated with amphotericin B alone. The remaining 20% of cases were treated with a single antifungal drug different from amphotericin B. Sixty percent of the patients underwent spinal surgery after starting medical therapy, while 40% were treated with medical therapy alone.

The majority of cases had a good outcome: 80% of the patients were cured at the end of therapy. One patient died and two patients had irreversible nerve damage. Only 46.7% of the cured patients underwent spinal surgery, while all of them were treated with antifungals. However, the literature regarding the treatment of *C. glabrata* spondylodiscitis is limited and the outcomes may have been affected by the clinical condition of the patient before surgical treatment. Further clinical observations are needed to provide more conclusive evidence regarding the management of these conditions, in particular the role of spinal surgery as a therapeutic option in addition to medical therapy.

Discussion and conclusions

The case reported here was a diagnostic challenge because back pain is a non-specific symptom among adults and *C. glabrata* is a very rare cause of spondylodiscitis. The patient's chronic ileitis probably contributed to the spinal infection, causing a barrier leakage that promoted the translocation of the pathogen from the bowel into the circulatory system, leading to secondary involvement of the lumbar spine. Nevertheless, further studies are needed to determine whether bowel inflammation could have a role in determining candidaemia.

The suspicion of spondylodiscitis came from physical signs including fever and neurological impairment, as well as the increase in ESR. Furthermore, risk factors such as diabetes, spondyloarthrosis, age >60 years, and male sex were present. ESR was increased, but as for the anaemia, this could have been explained by the chronic ileitis. The WBC count was within the normal range. A high serum value of procalcitonin (PCT) was found. Blood cultures have low sensitivity, and these were negative in the case patient. Based on the epidemiology, the PCT level, and the findings on spine MRI, the patient was started on a broad-spectrum antibiotic therapy that led to no effective improvement in the symptoms.

This experience suggests that a high PCT level – a well-known marker of bacterial infection (Pieralli et al., 2017) – does not necessarily rule out a fungal infection and has to be read in the clinical context.

According to the literature, MRI should be the first imaging modality used for patients suspected of native vertebral osteomyelitis; it has a sensitivity of 97%, specificity of 93%, and accuracy of 94%. Its excellent morphological resolution allows early recognition of spondylitis. Affected vertebral bodies and discs reveal typical alterations in T1- and T2-weighted images.

Nevertheless, MRI does not clarify the aetiology of the illness, which is crucial for initiating the appropriate therapy. A microbiological diagnosis should be established before any treatment. Biopsies (either open or percutaneous) are often reserved for patients with negative blood cultures and they often establish the microbiological and pathological diagnosis.

As reported in the literature, microbiological positivity is significantly higher when surgical sampling is provided, even through minimally invasive techniques. A CT- or MRI-guided aspiration biopsy should be the first invasive diagnostic step in the patient suspected of vertebral osteomyelitis. Biopsy samples should be sent for aerobic, anaerobic, fungal, and mycobacterial culture. However, the sensitivity of this procedure varies between 30% and 70%. Furthermore, prior treatment may affect the accuracy of culture (Berbari et al., 2015).

Once neurological impairment was proven by EMG and there was no clinical improvement with antibiotic therapy, it was decided to take a surgical biopsy of the abscess in order to establish the aetiology of the infection. According to this experience, open biopsy of the abscess was an effective method to obtain specimens for culture evaluation. The choice between needle and open biopsy was determined by the neurological impairment, which prompted the surgery.

The diagnosis of spondylodiscitis is often delayed or missed. It is generally misdiagnosed and mismanaged as a degenerative process (Berbari et al., 2015). Although spondylodiscitis is rare among adults, it should not be overlooked in patients with symptomatic back pain not responding to painkillers, especially in patients with risk factors.

Spondylodiscitis has a poor prognosis in terms of mortality and morbidity. There is a recognized global shift towards invasive candidiasis due to non-albicans *Candida* species, in particular *C. glabrata*, which has variable susceptibility to antifungal drugs (Andes et al., 2012) and a higher mortality rate (Fidel et al., 1999).

The 2016 recommendations of the Infectious Diseases Society of America for the management of Candida osteomyelitis favour initial therapy with fluconazole (6 mg/kg daily for 6–12 months) or an echinocandin (e.g., anidulafungin 100 mg daily) for at least 2 weeks followed by fluconazole (6 mg/kg daily for 6–12 months) (Pappas et al., 2016). However, there are also reports of resistance of *C. glabrata* to azoles, caspofungin, and amphotericin B (Thompson et al., 2008; Owen et al., 1992).

Surgical debridement is recommended in selected cases, with the goal of debulking the infected tissue, securing an adequate blood supply for tissue healing, and maintaining or restoring spinal stability. Indications for surgery may include the development of neurological deficits or symptoms of spinal cord compression and evidence of progression or recurrence despite appropriate antimicrobial therapy, instability, large epidural abscess, intractable back pain, or failure of medical treatment (Berbari et al., 2015).

The patient presented herein was the first with *C. glabrata* spondylodiscitis to be treated with anidulafungin. In this case, surgical debridement and anidulafungin were found to be effective in the treatment of *C. glabrata* spondylodiscitis. This experience could be useful in the case of *C. glabrata* infections with evidence of resistance to azoles or amphotericin B.

Conflict of interest

All authors deny any financial or personal relationships with other people or organizations that could inappropriately have influenced (biased) the work.

Ethical approval

No approval was required. All authors complied with the ethics and policy of the journal.

References

Andes DR, Safdar [55_TD$DIFF]N, Baddley JW, Playford G, Reboli AC, Rex JH, et al. Impact of treatment strategy on outcomes in patients with candidemia and

other forms of invasive candidiasis: a patient-level quantitative review of randomized trials. Clin Infect Dis 2012;54:1110–22.
Berbari [56_TD$DIFF]Elie F, Kanj Souha S, Kowalski Todd J, Darouiche Rabih O, Widmer Andreas F, Schmitt Steven K, et al. Infectious Diseases Society of America (IDSA) clinical practice guidelines for the diagnosis and treatment of native vertebral osteomyelitis in adults. Clin Infect Dis 2015;61:e26–46.
Berkowitz ID, Robboy SJ, Karchmer AW, Kunz LJ. *Torulopsis glabrata* fungemia a clinical pathological study. Medicine 1979;58:430.
Bonomo [57_TD$DIFF]RA, Strauss M, Blinkhorn R, Salata RA. *Torulopsis* (*Candida*) glabrata: a new pathogen found in spinal epidural abscess. Clin Infect Dis 1996;22:588–9.
Bruns J, Hemker T, Dahmen G. Fungal spondylitis: a case of *Torulopsis glabrata* and *Candida tropicalis* infection. Acta Orthop Scand 1986;57:563–5.
Curran MP, Lenke LG. *Torulopsis glabrata* spinal osteomyelitis involving two contiguous vertebrae. A case report. Spine 1996;21:866–70.
Dailey N[58_TD$DIFF]J, Young EJ. *Candida glabrata* spinal osteomyelitis. Am J Med Sci 2011;341(1):78–82.
Dwyer K, McDonald M, Fitzpatrick T. Presentation of *Candida glabrata* spinal osteomyelitis 25 months after documented candidaemia. Aust NZ J Med 1999;29:571–2.
Fidel PL, Vazquez JA, Sobel JD. *Candida glabrata*: review of epidemiology, pathogenesis and clinical disease with comparison to *C. albicans*. Clin Microbiol Rev 1999;12:80–96.
Gouliouris Theodore, Aliyu Sani H, Brown Nicholas M. Spondylodiscitis: update on diagnosis and management. J Antimicrob Chemother 2010;65(Suppl_3):iii11–24.
Hendrickx L, Van Wijngaerden E, Samson I, Peetermans WE. Candidal vertebral osteomyelitis: report of 6 patients, and a review. Clin Infect Dis 2001;32 (4):527–33.
Imahori SC, Papademetriou T, Ogliela DM. *Torulopsis glabrata* osteomyelitis: a case report. Clin Orthop Rel Res 1987;219:214–20.
Liudahl KJ, Limbird TJ. *Torulopsis glabrata* vertebral osteomyelitis: case report and review of the literature. Spine 1987;12:593–5.
Morrow JD, Manian FA. Vertebral osteomyelitis due to *Candida glabrata*. A case report. J Tenn Med Assoc 1986;79:409–10.
Owen PG, Willis BK, Benzel EC. *Torulopsis glabrata* vertebral osteomyelitis. J Spinal Disord 1992;5:370–3.
Pappas PG, Kauffman CA, Andes D[59_TD$DIFF]R, Clancy CJ, Marr KA, Ostrosky-Zeichner L, et al. Clinical practice guidelines for the management of candidiasis: 106 update by the Infectious Diseases Society of America. Clin Infect Dis 2016;4: e1–e50.
Pieralli [61_TD$DIFF]F, Corbo L, Torrigiani A, Mannini D, Antonielli E, Mancini A, et al. Usefulness of procalcitonin in differentiating *Candida* and bacterial blood stream infections in critically ill septic patients outside the intensive care unit. Intern Emerg Med 2017;12(5):629–35, doi:http://dx.doi.org/10.1007/s11739-017-1627-7.
Seravalli Laurent, Linthoudt [63_TD$DIFF]DanielVan, Bernet Christian, Torrenté Antoinede, Marchetti Oscar, Porchet François, et al. *Candida glabrata* spinal osteomyelitis involving two contiguous lumbar vertebrae: a case report and review of the literature. Diagn Microbiol Infect Dis 2003;45(February (2)):137–41.
Tan Aaron C, Parker Nicholas, Arnold Mark. *Candida glabrata* vertebral osteomyelitis in an immunosuppressed patient. Int J Rheum Dis 2014;17(February (2)):229–31.
Thompson III [64_TD$DIFF][45_TD$DIFF]George R, Wiederhold Nathan P, Vallor Ana C, Villareal Nyria C, Lewis II James S, Patterson Thomas F. Development of caspofungin resistance following prolonged therapy for invasive candidiasis secondary to *Candida glabrata* infection. Antimicrob Agents Chemother 2008;52:3783–5.
Thurston AJ, Gillespie WJ. *Torulopsis glabrata* osteomyelitis of the spine: a case report and review of the literature. Aust NZ J Surg 1981;51:374–6.