MAEDICA – a Journal of Clinical Medicine
2023; 18(2): 209-215
https://doi.org/10.26574/maedica.2023.18.2.209

MÆDICA - a Journal of Clinical Medicine

ORIGINAL PAPER

Spinal Infections Caused by *Coccidioides* Species

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ABSTRACT

Introduction: *Spinal Coccidioidomycosis, although rare, represents the most frequent osseous presentation of* Coccidioides *spp infection. The present review aims to describe the anatomical distribution, the epidemiological characteristics, and the diagnostic and therapeutic approach of this severe infection.*

Methods: *A meticulous review of all published spinal Coccidioidomycosis cases was carried out. The studied population's demographics and the anatomical distribution of the infection were recorded. Furthermore, the medical and operative management as well as the disease outcome were studied.*

Results: *Seventy-six cases (of which 78.9% males) with a mean age of 35.5 years were located. Regarding the anatomical distribution of the infection, the thoracic area was the most commonly affected spine region (26.3%). Among the studied patients, 14 (18.4%) were immunocompromised. Pain was the most commonly reported symptom (21.1%). Regarding the diagnostic approach of this infection, plain x-ray or CT scan indicated the disease in the majority of cases (44.7%). Pathology (48.7%), serology (42.1%) and*

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Article received on the 18th of April 2023 and accepted for publication on the 24th of May 2023

microbiological examinations (35.5%) further established the firm diagnosis, with Coccidioides *immitis being the most frequently isolated fungus. Medical management included mainly amphotericin B (in 57.9% of cases), followed by fluconazole (in 38.2% of cases). The disease required surgical intervention in the majority of cases (76.3%), while the infection had a successful outcome in 80.3% of cases.*

Conclusions: *Spinal Coccidioidomycosis seems to require prolonged medical treatment, including proper antifungal therapy and, in most cases, operative management. Multidisciplinary approach, including infectious disease specialists, orthopaedic and/or spine surgeons, microbiologists and radiologists seems to be of utmost important for yielding favorable outcomes.*

Keywords: fungal infection, vertebral infection, spondylodiscitis, immunosuppression, spondylodiscitis anatomical distribution.

INTRODUCTION

Coccidioidomycosis represents an obscure infection, with a plethora of possible presenting signs and symptoms (1). Cultures and/or histopathology are the most commonly used diagnostic tools in clinical practice, while serology testing may also be helpful. Patients with this fungal infection may either be completely asymptomatic or present with numerous signs, symptoms, manifestations and clinical entities such as pneumonia, as well as other disease foci such as the soft-tissues and bones (2, 3).

Coccidioidomycosis, also known as "Valley fever", appears with symptoms from the respiratory tract which are frequently imitating community-acquired pneumonia. Infection is usually acquired by inhalation of aerosolized arthroconidia. Direct inoculation may also occur but it is relatively uncommon, while the disease usually presents similarly to community-acquired pneumonia (2). Clinical examination as well as detailed medical history is crucial for diagnosis (1, 3).

Extra-pulmonary disease occurs in most cases of hematogenous or lymphatic spread and may involve the skin, muscles and/or meninges (1, 2). Regarding the musculoskeletal involvement, osteomyelitis is the most frequently encountered infection, while numerous osseous regions could be affected, with the axial skeleton being the most commonly infected site (3, 4).

Spinal Coccidioidomycosis seems to be the most frequent osseous extra-pulmonary manifestation, and it is also a severe and even life-threatening infection (2, 3). However, only few reports in the literature have evaluated such infections, their diagnosis, medical and surgical management and outcomes.

The present review aims to present the anatomical distribution, the epidemiological characteristics and the diagnostic and therapeutic approach of this severe infection. ❑

METHODS

PubMed and MEDLINE databases were thoroughly searched, aiming to locate all spinal Coccidioidomycosis cases from January 2000 to February 2023. The search was performed by two independent researchers (CK and SN). The researchers used the following key-words: "fungal spondylodiscitis", "Coccidioidal spinal infections", "*Coccidioides* spondylodiscitis", "*Coccidioides* vertebral infection", "Coccidioidal spondylitis", "Coccidioidal immitis spondylodiscitis", "vertebral coccidioidomycosis", "Coccidioidal posadasii spondylodiscitis" for retrieving all articles reporting on spinal Coccidioidomycosis. Furthermore, additional cases were identified from the reference list of each initially retrieved article.

Articles in non-peer-reviewed journals, non-English articles, book chapters, conference proceedings, cadaveric animal *in vivo* and *in vitro* investigations were all excluded.

Demographics, including age and gender, site of the infected spine, presence of immunodeficiency, signs and symptoms of the disease, co-infections, prior surgical intervention and/or antimicrobial treatment, type and length of antifungal regimen(s), type of surgical management, imaging findings contributing to diagnosis and, finally, outcome of follow-up results were separately evaluated for each case.

If all signs and symptoms of Coccidiomycosis had disappeared with no recurrence during the follow-up, the provided medical and/or surgical management was considered successful.

Statistical analysis was carried out with Microsoft Excel 2019 (Microsoft Corporation, Redmond, WA, USA). ❑

RESULTS

Seventy-six cases (60; 78.9% males) with spinal Coccidiomycosis during a 23-year period were located (5-19). The majority of them were reported from the USA (97.4%). The mean age of the sample was 35.5 years [standard deviation (SD)=13.9] (Table 1).

Regarding the anatomical distribution of the infection, the most frequently involved spine region was the thoracic area (20; 26.3%), followed by the lumbar (15; 19.7%), cervical (9; 11,8%), iliac (1; 1.3%) and sacral area (1; 1.3%). In eight cases (10.5%), two or more spinal regions were affected, while in 39 cases (51.3%) the exact injured spinal region was not reported.

Among all studied cases, there were two patients with co-infection (2.6%), one case with *Enterobacter cloacae* and another one with concomitant *Staphylococcus aureus*, *Klebsiella pneumonia* and *Enterobacter cloacae* infection.

Fourteen patients (18.4%) presented with immunodeficiencies; more particularly, the majority of them received corticosteroids systematically (10; 71.4%) or suffered from diabetes mellitus (3; 21.4%). Most patients (16; 21.1%) presented with pain, six with fever (7.9%) and five (6.6%) with local infection signs and another five with neurological symptomatology.

TABLE 1. Main characteristics of the studied population (SD=standard deviation)

Total number of cases	76
Gender	60 males (78.9%); 16 females (21.1%)
Mean age	35.5 years (SD=13.9)
Concomitant bacterial infection	Two cases (2.6%)
Immunocompromised conditions	14 cases (18.4%)
Anatomical distribution	Cervical: nine cases (11.8%) Thoracic: 20 cases (26.3%) Lumbar: 15 cases (19.7%) Sacral: one case (1.3%)
Surgical intervention	58 cases (76.3%)

Before the current infection, only in one case (1.3%) antimicrobial treatment had been given during the previous six months; in particular, azithromycin had been prescribed for upper respiratory infection within a month before the spinal infection. Regarding previous surgical procedures, only in one case (1.3%) a shoulder surgery was reported (case no 73).

Regarding the diagnostic approach, plain x-ray or CT scan was utilized in 34 cases (44.7%), followed by magnetic resonance imaging (MRI) in 32 cases (42.1%) and bone scan in six cases (7.9%). Further evaluation with pathology (37 cases; 48.7%), serology (32 cases; 42.1%) and/or microbiology (27 cases; 48.7%) led to the diagnosis of infection. Cultures yielded *Coccidioides immitis* in nine cases (11.8%), while in the remaining 64 cases (84.2%) the fungus was not identified to species level. In some cases, more than one diagnostic method was used. More particularly, histopathology and cultures have both confirmed the diagnosis in 19 cases (25%), serological examinations and cultures in 20 (26.3%) cases, while all three diagnostic modalities led to the diagnosis of infection in 13 cases (17.1%).

Regarding medical management, antifungal monotherapy was used in 35 cases (46.1%), while two antifungal drugs, simultaneously or consecutively, were used in 30 (39.5%) cases and three or more in 11 (14.5%) cases. Antifungal treatment (AFT) was continued for a mean of 23.3 months (SD=20.9).

Table 2 exhibits details regarding the medical treatment. Most cases were commenced on Amphotericin B (44; 57.9%) and fluconazole (29; 38.2%). Itraconazole and voriconazole were used in 16 (21.1%) and eight (10.5%) cases, respectively. Moreover, ketoconazole was initiated in three cases (3.9%), while caspofungin and posaconazole were chosen in one case each (1.3%).

TABLE 2. Summary of the medical treatment

Antifungal agent	Number of cases
Amphotericin B	44 (57.9%)/11 (25%) as monotherapy
Fluconazole	29 (38.2%)/20 (69%) as monotherapy
Itraconazole	16 (21.1%)/4 (25%) as monotherapy
Ketoconazole	3 (3.9%)/1 (33.3%) as monotherapy
Caspofungin	1 (1.3%)
Posaconazole	1 (1.3%)

Furthermore, in the majority of cases (58; 76.3%) surgical intervention was necessary.

The disease had a successful outcome in 61 cases (80.3%), while mortality was found to be 2.6%. ❑

DISCUSSION

Cocciodiomycosis is an endemic infection, mainly presenting as pneumonia in the USA, more particular in Arizona and California (20). Nevertheless, easy communications and transportation may lead to the spread of infection in non-endemic geographical areas; thus, physicians should familiarize with the diagnostic and therapeutic approach of the disease. Furthermore, the increasing number of elderly populations as well as that of immunocompromised individuals may be a cause of a high incidence of Cocciodiomycosis and other deep fungal infections (21, 22). The disease is mainly transmitted through air currents and inhalation of dust from construction working sites (21-23).

The incidence of Cocciodiomycosis has been steadily growing, while 25.000 hospitalizations and more than two billion USD have been associated to this infection during the previous decade (20).

Extra-pulmonary Cocciodiomycosis is rare (<1% of cases), while many risk factors have been reported, including immunodeficiencies, advanced age, gender (male dominant infection) as well as natural disasters such as tsunamis, that may lead to environmental unleash of arthroconidia (fungal spores) (1, 2, 24, 25).

The present thorough review studied all published cases of spinal Cocciodiomycosis during a 23-year-period. More particularly, the aim of our study was to present the anatomical distribution, epidemiological characteristics, and diagnostic and therapeutic approach of this severe infection.

A total of 76 cases with spinal *Coccidioides* spp infections were recorded, while the studied population was quite young (mean age 35.5 years), with the majority of patients being males (78.9%). It has been reported that immunosuppression played an important role in the clinical gravity by multiplying the risk of dissemination (26, 27). It is remarkable that the majority of the included patients (81.6%) did not suffer from some type of immunodeficiency, neither had any co-existing medical condition that could facilitate complications.

Regarding the prolonged use of antimicrobial agents, antimicrobials are believed to be iatrogenic risk factor for invasive fungal infections, since they modify the normal flora of the host (1-3, 28). In this study, only in one case (1.3%) an antimicrobial agent had been administered before the current infection.

Musculoskeletal infections represent 10 to 50% of extra-pulmonary Cocciodiomycosis cases, with about 20% of them referring to axial skeleton involvement (3, 19, 20).

Regarding the axial skeleton, there were almost always vertebral lesions. In the present study, the most common anatomical areas of the spine affected by infection were the thoracic region (26.3%), followed by the lumbar (19.7%), cervical (11.8%), iliac (1.3%) and sacral (1.3%) regions, while in eight cases (10.5%) more than one region was infected.

Non-specific symptomatology frequently prohibits a prompt diagnosis of musculoskeletal fungal infections such as spondylodiscitis, while histology, serology and/or microbiology are essential for excluding other causative organisms such as bacteria, which are much more commonly encountered (19, 22, 28, 29, 39). The studied population presented mainly with pain (21.1% of cases), followed by pyrexia (7.9%), local inflammation signs and neurological deficits (6.6% each). All these signs and symptoms may very well be present in spinal infections caused by bacteria (29, 39). Furthermore, although imaging studies may indicate spinal infections, they are also non-diagnostic for specifically fungal spinal infections (30, 31).

C. immitis and *C. posadasii* have been held responsible for Cocciodiomycosis in humans (20, 31). *C. immitis* could be isolated in nine (11.8%) of the reported cases, while in the remaining 64 (84.2%) cases the fungus was not identified to the species level. However, this may not be necessary, since, although there have been reported variations of these species' genomes, there is no difference regarding the diagnostic and therapeutic approach of these infections (20, 31).

Histopathology, cultures and/or serology have been used in the reported cases for isolation of the fungus causing the spinal infection. In the majority of the cases (48.7%), histopathology was used for definite diagnosis, while in 26.3% of the studied population serological examination and cultures were positive and in 25% of cases serological examination and histopathology have both esta-

blished the diagnosis. Finally, in 17.1% of cases all three laboratory diagnostic modalities were positive. Serology testing plays an important role in Cocciodiomycosis (33-35). Serology was used in 42.1% of the present sample, a relative high use of this particular diagnostic modality when compared to its use in other fungal musculoskeletal infections (33-35). Nevertheless, this examination may be false negative, especially in the early course of the infection and in immunocompromised patients (33-36). Moreover, in many cases, cultures yielding the organism may be the one and only diagnostic modality (35-44).

Regarding treatment, the reported cases seem to show that prolonged AFT in combination with surgical intervention represents the cornerstone of treatment. More particular, the majority of these cases were treated with monotherapy (46.1%), while Amphotericin B was the drug of choice (57.9%). Data about the exact type of Amphotericin B were not available in most cases. It should be noted that the more recently available lipid and liposomal amphotericin B compounds have reduced the nephrotoxicity which was associated with the long-term use of this drug, especially with the deoxycholate-traditional Amphotericin B (45-48). Since the study reports on the last 23 years, it could be safe to assume that the deoxycholate-traditional Amphotericin B was not used. Fluconazole represented the second most used antifungal drug in the present study (38.2% of cases), while it was given mainly as a single-agent (69%). This low-cost drug is easy to use, while it may be combined with Amphotericin B in difficult to treat fungal musculoskeletal infections (49-54).

In addition to medical management, surgical intervention was necessary in the majority of cases (76.3%). Operative management plays an important role in the eradication of musculoskeletal infections. More particular, regarding spinal infections, neurological deficits, abscesses and/or failure of medical treatment represent are the main indications (48).

The present study has some limitations. The dosages, serum levels, fungal MICs of antifungal drugs and their adverse effects were not documented in most cases. Nevertheless, the present study provides detailed information regarding the epidemiology, signs and symptoms, management and outcome of 76 cases of spinal Cocciodiomycosis cases during a 23-year period. ❑

CONCLUSION

In conclusion, spinal Cocciodiomycosis represents an endemic infection in the USA, affecting mainly the thoracic and lumbar anatomical spinal regions. Due to migration and frequent transportation, these infections may appear outside the USA and physicians should be familiar with the disease diagnostic and therapeutic approach. Multidisciplinary management, involving infectious disease specialists, microbiologists and spine surgeons, seems to be of utmost importance, while long-term medical treatment and surgical intervention represent the therapeutic approach of choice. ❑

Conflicts of interest: none declared.

Financial support: none declared.

Authors' contributions: Conception and design: all authors; data collection: CK, SN; writing the original draft: all authors; manuscript review and editing: all authors. All authors have read and agreed to the published version of the manuscript.

Acknowledgments: The present study was supported by the Hellenic Society of Medical Mycology.

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