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Review Article

A paradigm for the evaluation and management of spinal coccidioidomycosis

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Abstract

Background: Coccidioidomycosis is a fungal infection that is endemic to parts of the Southwestern United States. When infection involves the spine, the treatment strategies can be challenging. We have devised a management protocol for spinal coccidioidomycosis based on a review of the literature and our experience.

Methods: The electronic literature search of National Library of Medicine for publications from 1964 to 2014 was performed using the following keywords: Coccidioidomycosis and spine. The search yielded 24 papers. Treatment strategies were summarized into a treatment protocol.

Results: A total of 164 cases of spinal coccidioidomycosis were identified, ranging in age from <10 to >80 years. Males (n = 131) and African-Americans (n = 79) were strikingly over-represented. Medical therapy: Once a diagnosis of spinal coccidioidomycosis is established, antifungal therapy should always be started. Antifungal therapy with amphotericin B or azoles like fluconazole. Medical therapy needs to be continued for many years and sometimes indefinitely to reduce disease recurrence or progression. Surgical management is indicated in cases with mechanical instability, neurologic deficit, medically intractable pain, or progression of infection despite antifungal therapy.

Conclusions: This work provides a working protocol involving assessment and reassessment for the management of spinal coccidioidomycosis. Medical management with antifungal agents in some cases can provide satisfactory disease control. However, in patients with mechanical instability, neurologic deficit, medically intractable pain or disease progression disease control may only be achieved with surgical debridement and stabilization.

Key Words: Fungal infection, osteomyelitis, spinal coccidioidomycosis, spinal fusion, spine, stabilization, vertebral

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INTRODUCTION

Coccidioidomycosis, also known as San Joaquin Valley fever, is a fungal infection that is caused by *Coccidioides* spp. Infection is initiated by the inhalation of spores that originate in endemic soils within the Southwestern United States, Mexico, and Central and South America.[4,38,39] The organism typically causes a self-limited infection,

which commonly manifests as a community-acquired pneumonia or fever with fatigue.[63] Importantly, the incidence of coccidioidomycosis is increasing in the US and is estimated at 150,000 new cases/year, indicating a potential for more frequent cases involving vertebral infection in the future.[2,38,39]

Although 60% of infections are subclinical and self-resolving, 1% of them or approximately 5% of all diagnosed infections, result in hematogenous extra-pulmonary dissemination and the attendant increase in morbidity and risk of death.[48,50,53,54] Dissemination can potentially involve any organ system although the skin, lymphoid tissue, the musculoskeletal system, and the meninges of the brain are involved most frequently.[1,4,54] Spine involvement is distinguished for frequency and severity of the disease.[1] The treatment requires antifungal therapy but not infrequently surgery is necessary in patients with mechanical instability, compression of neural elements, or progression of perivertebral soft-tissue infection. Determining which patients to treat with antifungal drugs alone and which to employ one or more surgical procedures is a very important management branch point, and not clearly delineated in the medical literature. The purpose of this study is to review past published descriptions of the management of spinal coccidioidomycosis and from this to develop a management protocol. We also present several illustrative cases to demonstrate how the protocol could be implemented.

MATERIALS AND METHODS

The electronic literature search of National Library of Medicine for publications from 1964 to 2014 was performed using following keywords: Coccidioidomycosis and spine. The articles were reviewed using the following criteria for inclusion: Spinal coccidioidomycosis, surgical and medical management. The cases from all of the citations were considered because of the infrequent occurrence of this pathology.

The search was limited to the English language and yielded 21 papers. Bibliographies of publications were screened for additional citations. A total of 24 papers were selected (13 case reports and 11 case series) [Table 1].

Epidemiological characteristics (age, gender, race), clinical findings (comorbidities, segments involved, symptoms), treatment approach, and clinical outcomes were analyzed. Treatment strategies were summarized into the treatment protocol.

RESULTS

A total of 164 cases of spine coccidioidomycosis were identified (131 male and 26 female). Of these, 43 were derived from our institution (Szeyko, Bried). Their mean age at presentation was 28.3 years (range: 4–82 years). Most affected patients were in their third decade of life. Men were strikingly over-represented with this complication occurring more frequently than in women. Furthermore, nearly one-half of all infections occurred in African-Americans (48.5%) [Table 2]. Other risk factors include living or travel to cocci endemic areas. Various other comorbidities included recent corticosteroid use (8), HIV positive (2), cancer chemotherapy (1), and diabetes (3). Of note, a very large majority of the patients were not overtly immunosuppressed. Only 57 of the 164 cases were published from within the region endemic coccidioidomycosis, 43 of which from our institution.[10,58] This suggests that many acquired their infection from travel or relatively short residences there and underscores the utility of a travel history in assessing the etiology of destructive spinal lesions. Furthermore, only 16 were noted to have a recent or current respiratory illness, and the absence of this finding should not exclude spinal coccidioidomycosis from the differential.

Unfortunately, in only 28 patients was the precise method of diagnosis indicated: Serologic testing in 17 and computed tomographic (CT) guided biopsy in

Table 1: Number of reported patients per publication

Publication	Number of patients
Elgafy (2013)[22]	1
Tan (2013)[60]	1
Angelo (2013)[6]	1
El Abd (2012)[21]	1
Szeyko (2012)[58]	39
Kakarla (2011)[33]	27
Reach (2010)[50]	1
Prabhu (2004)[49]	1
Lewicky (2004)[41]	1
Kirk (2003)[34]	1
Copeland *et al.* 2003[14]	1
Wrobel *et al.* 2001[66]	23
Herron *et al.* 1997[31]	16
Kushwaha *et al.* 1996[36]	6
Zeppa *et al.* 1996[67]	10
Bried *et al.* 1986[10]	4
Delaney *et al.* 1982[17]	1
McGahan *et al.* 1980[45]	4
Halpern *et al.* 1979[28]	1
Winter *et al.* 1978[65]	12
Wasselius 1977[64]	1
Bisla *et al.* 1976[9]	3
Dalinka *et al.* 1971[16]	7
Jackson *et al.* 1964[32]	1
Total	164

11. If the cerebrospinal fluid analysis demonstrates an eosinophilic pleocytosis, this can be highly supportive to a *Coccidioides* meningitis or parameningeal infection.

Spinal levels

The thoracic and lumbar vertebras were the more commonly involved, followed by cervical spine and sacrum (83, 80, 43, and 14 cases, respectively) [Table 3]. Only 67 patients had reported involved spinal segments. 19 of them had single involved spinal segment and 48 had multiple.

Symptoms

About 40.8% of patients presented with local pain, and 42% had neurologic symptoms [Table 4].

Medical therapy

Antifungal therapy included administration of amphotericin B combined or followed by a triazole. In most of the reported cases, medical therapy was continued indefinitely to reduce disease recurrence [Table 5]. 29 patients had medical therapy only.

Table 2: Patient demographics

Age	Years
Mean	28.35
Range	4-82
Age distribution	**Number of patients**
0–10*	4
11–20*	19
21–30*	44
31–40*	21
41–50*	24
51–60*	7
61–70*	9
71–80*	1
81–90*	1
34 patients unreported*	
Sex	**Number of patients**
Male	131
Female	26
Male: Female ratio	5.04
7 patients unreported	
Race/ethnicity	**Number of patients (%)**
African-American	79 (48.2)
Mexican/hispanic	19 (11.5)
Caucasian	23 (14)
Native American	4 (2.4)
Asian	9 (5.4)
Unknown/not reported	30 (18.3)

Table 3: Number of involved spinal segments

Spinal segment	Number of patients
Cervical	43
Thoracic	83
Lumbar	80
Sacral	14

Table 4: Distribution of symptoms at presentation and comorbidities

Presentation/comorbidities	Number of patients
Back/neck pain	67
Radiculopathy	22
Sensory disturbance	21
Paraparesis	12
Myelopathy	9
Weight loss/anorexia	9
Fever	9
Diabetes	6
Respiratory issues	6
Chest/abdominal pain	4
Paraplegia	4
Long-term steroid treatment	4
Cough	3
Short-term steroid treatment	3
HIV/AIDS	2
Night sweats	2
HIV/AIDS	2
Quadriparesis	1
Chills	1
Sore throat	1

Table 5: Medical management of spinal coccidioidomycosis

	Number of patients
Monotherapy	
Amphotericin	72
Fluconazole	52
Itraconazole	18
Voriconazole	15
Ketoconazole	4
Posaconazole	2
Caspofungin	2
Miconazole	1
Polytherapy	
Amphotericin + fluconazole	12
Amphotericin + miconazole	3
Amphotericin + itraconazole	2
Fluconazole + itraconazole + amphotericin	2
Amphotericin + voriconazole	1
Amphotericin + ketoconazole	1
Itraconazole + fluconazole	1
Amphotericin + ketoconazole + itraconazole	1
Amphotericin + itraconazole + caspofungin	1
Itraconazole + amphotericin + voriconazole	1
Fluconazole + itraconazole + voriconazole	1
Amphotericin + itraconazole + caspofungin + voriconazole	1

Surgery

In patients with mechanical instability, neurologic deficit, medically intractable pain or disease progression surgical debridement, decompression of neural elements and stabilization was often necessary. 117 patients underwent surgical intervention [Table 6].

Outcomes

From 117 patients who underwent surgical intervention, only 102 had reported the clinical outcome. From those, 76.4% patients did not have a recurrence. 4.9% patient died due to the progression of disease despite treatment. 18 patients did not have reported treatment modalities and outcome [Table 7].

SURGICAL PROTOCOL

Patients with elevated specific antibodies against *Coccidioides* and confirmed with imaging spinal lesion require a CT-guided biopsy to rule out concurrent spinal tumor. Patients start antifungal therapy after diagnosis confirmation by histology and cultures. The early progression of disease does not necessarily indicate failure of medical treatment. Lesions can evolve with medical therapy even if fungal proliferation has been blocked. This is because of the persistence of pro-inflammatory fungal debris in the lesion. This is especially true if some lesions are stable or healing and one or more are worsening. The fact that surgery is added is not necessarily a reason to replace antifungal medication. It is imperative to assess the mechanical stability of affected spine, as well as the presence of neurologic deficit. Patients with acute neurologic deficit require emergency decompressive surgery, whereas mechanical instability and intractable pain can be addressed with an elective procedure. Goals for surgical intervention are decompression and stabilization. Follow-up imaging is critical to assess the effectiveness of treatment and disease progression. Magnetic resonance imaging (MRI) with and without gadolinium contrast can be obtained in 1, 3, and 6 months postoperatively or sooner if symptoms continue to progress. Figure 1 represents exemplified flowchart of the management of spinal coccidioidomycosis.

Table 6: Type of surgical approach

Surgical procedures*	Number of patients
Instrumentation and fusion	93
Irrigation/debridement	38
Corpectomy	20
Abscess drainage	11
Laminectomy	9
Discectomy	2

*Not all procedures were described in detail

Table 7: Clinical outcomes for patients with spinal coccidiomycosis

Outcome	Surgery + medical treatment	Medical treatment only
Improved or stabilized (no relapse)	78	6
Relapse	7	6
Relapsed but later improved	3	1
Worsened	2	1
Died (due to coccidiomycosis)	5	1
Died (unrelated to coccidiomycosis)	2	0
Died (cause not reported)	3	1
Terminally ill	1	0
Lost to follow-up	1	4
Unreported	15	9
Total	117	29

ILLUSTRATIVE CASES

Case 1

Forty-six-year-old Caucasian male, with past medical history of coccidioidal pneumonia treated for several months with fluconazole 6 years earlier, presented with a 3-month history of progressive mid back pain radiating to flank bilaterally. Symptoms were worse at night. The patient also had generalized joint pain, fatigue, weight loss. Physical examination did not reveal focal neurological deficit. MRI spine showed cystic lesions in T11/12 with

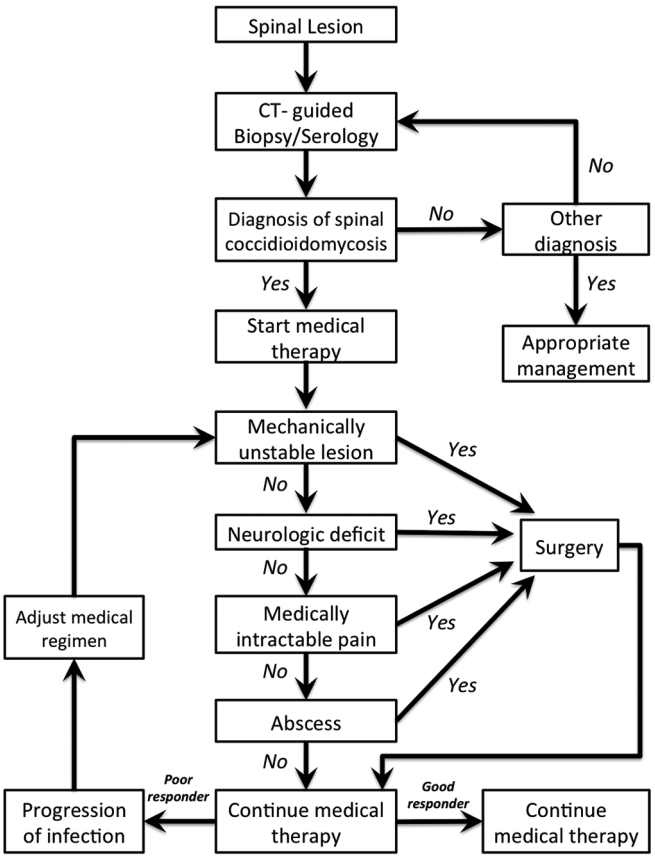

Figure 1: Protocol for surgical management of spinal coccidioidomycosis

vertebral body and disc space involvement, and minimal epidural involvement [Figure 2]. Patient had positive cocci IgG, and needle aspiration yielded *Coccidioides* spp. in culture. He was able to control back pain with over the counter pain relief medications. Since the patient did not have instability, neurologic deficit or intractable pain, he was managed medically with fluconazole 800 mg/day. Therapy was able to control disease, and there were stable MRI findings on subsequent MRI 3 months after treatment initiation.

Case 2

Twenty-two-year-old African-American male with no significant past medical history presented to emergency department with 3 months history of low back pain. Imaging studies revealed L1 lytic lesion. Although CT guided biopsy was negative for cocci, serologic studies were positive for cocci IgG. Patient was started with fluconazole and analgesics. Despite medical treatment patient's condition continued to worsen. He presented again after 4 weeks of medical therapy. He developed medically intractable low back pain and new onset bilateral lower extremity paresthesia. MRI showed a new L2 epidural infection with lumbar stenosis [Figure 3]. Given these findings of progression of the disease and severe lumbar stenosis on the MRI, a decision was made to take him to the operating room for posterior decompression. He tolerated that procedure well. The patient continued medical management with fluconazole. A follow-up MRI, in 14 days postoperatively demonstrated worsening of a pathologic fracture at the L2 level. Given the progression of disease as well as the progression of instability the decision was made to proceed with surgical debridement and stabilization of that segment. Postoperatively, patient continued to take fluconazole. The patient was discharged after recuperating and had regained his strength. He was noncompliant with follow-up.

DISCUSSION

Spinal coccidioidomycosis is a rare disease and associated with diagnostic and treatment challenges. In this review, we attempted to summarize existing knowledge about the nature of this disease. Furthermore, we devised detailed management protocol of spinal coccidioidomycosis.

Vertebral infection appears to be more prevalent in certain populations. Residents, former residents, or people who have traveled to endemic areas within the last 2 years are almost prerequisite history. However, in patients with prior pulmonary coccidioidomycosis who received antifungal therapy for this can have a longer interval between initial infection and their presentation of vertebral dissemination as illustrated in Case 1 above. We found that the vast majority of patients reported in the literature were male. Vertebral infections were also more in African-American patients. While immunocompromised patients, such as those taking immunosuppressant drugs (especially chronic corticosteroid use), those positive for HIV, pregnant women, and infants under the age of 1, are potentially at an increased risk of dissemination, it is critical to note that many patients with vertebral infection, if not the majority, were not immunocompromised.[5,8,46,48,58] In addition, although our findings agree with the literature reports of an average age in the 30–40s, we found twice as many of the reported patients to be between 21 and 30 years of age than any other decade of life.[33,58] Overall, however, patients ranged from 9 to 82 years of age and most were between 11 and 50.

Symptomatic patients with coccidioidomycosis commonly typically present with symptoms of primary lung infection.[4,18,21] Symptoms are similar to those of the flu or a mild pneumonia and include fever, cough, night sweats, headache, chest pain, rash, arthralgia, and myalgia.[18,21,32] Despite several patients presenting with symptoms of primary infection, we found that the most common symptoms of reported vertebral

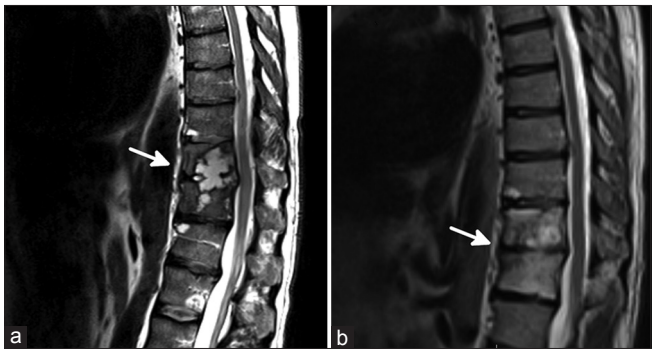

Figure 2: Sagittal magnetic resonance imaging reconstructions show T11/12 spinal coccidioidomycosis (arrow) at the presentation (a) and 3 months after medical management (b)

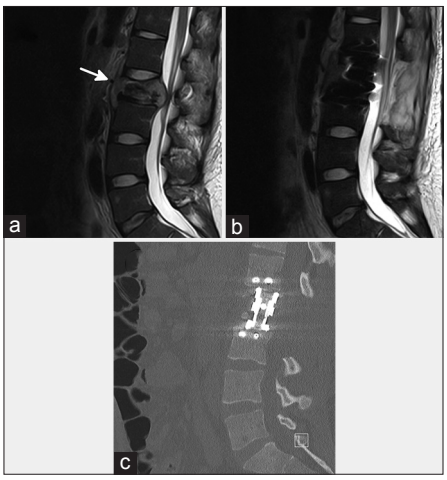

Figure 3: Sagittal magnetic resonance imaging reconstructions show L2 spinal coccidioidomycosis (arrow) at the presentation with severe spinal canal narrowing (a) and after surgical decompression of neural elements (b). Postoperative sagittal computed tomographic reconstruction shows L2 corpectomy (c)

coccidioidomycosis were radiculopathy, sensory disturbances, paraparesis (often progressive), and most frequently back/neck pain. Therefore, it is critical to note that although dissemination occurs more frequently in symptomatic patients, vertebral osteomyelitis due to disseminated coccidioidomycosis often occurs in patients who do not present with symptoms of primary infection.[58] Patients with a history of travel or residence to endemic areas who fail to improve from conservative treatment or who present with back pain, progressive weakness, and other neurological symptoms should raise strong suspicion of vertebral infection and receive a thorough work-up.[21,58,60]

Diagnosing vertebral coccidioidomycosis can be complicated but should be done as quickly as possible to prevent the infection from expanding and potentially worsening the patient's clinical condition. The inflammatory marker C-reactive protein and the erythrocyte sedimentation rate, while frequently elevated, are not specific for vertebral coccidioidomycosis, showing abnormal results for a variety of vertebral infections.[11,12,58] More useful early in the work-up are serology titers for *Coccidioides* species because their results are available relatively quickly. Elevation of immunoglobulins M (occurs 1–3 weeks after symptom onset) or G (occurs 2–28 weeks after symptom onset) antibodies above 1 in 16 is suggestive for disseminated disease and above 1 in 128 is suggestive for bone or joint infection.[15,53,58]

Imaging can expose erosive defects and/or sclerosis in vertebrae, vertebral endplates, or disks, as well as osteopenia, vertebral body collapse or paraspinal extension.[45,58] Several radiographic factors more common for vertebral *Coccidioides* infection than for tuberculosis or pyogenic infection. *Coccidioides* infection commonly causes continuous vertebral lesions, but often also causes skip-lesions.[58] In addition, the lack of a spinal gibbus deformity is more consistent with *Coccidioides* rather than tuberculosis infection.[45] Importantly, however, plain radiographs may appear normal in early infection.[58] Bone scintigraphy may also be useful for revealing disseminated lesions in the vertebrae by showing increased uptake in the vertebral bodies.[47,61] CT scans provide superior spatial resolution of lesions, which more clearly displays the degree of infection and destruction and, therefore, is a useful tool for planning biopsies and surgery.[6,58] Although CT may demonstrate abnormalities earlier than radiography, its sensitivity to early disease detection is still low.[21,58] In contrast, MRI is significantly more sensitive in detecting early vertebral, soft-tissue, paraspinal, and epidural dissemination and necrosis.[21,30,44,58] Thus, MRI is best for planning biopsies and surgery. Both active and necrotic lesions display low signal on T1-weighted sequences, but active lesions are hyperintense on T2-weighted sequences.[47,58,59,61] Nevertheless, like the other imaging modalities, MRI cannot diagnose coccidioidomycosis in the spine because findings can be similar to vertebral metastasis, tuberculosis, or other diseases.[47,50,67]

Diagnosis requires biopsy samples that either reveal *Coccidioides posadasii/immitis* spherules by microscopy or yield growth in culture. We recommend obtaining a tissue diagnosis unless the risk of the procedure is prohibitive. This is true even for patients who present with vertebral disease and coccidioidomycosis in other organ systems since the vertebral disease could have an alternate cause. Currently, obtaining a sample for pathogen identification can be done effectively by CT-guided biopsies.[24] The pathogens can be identified microscopically within 2 days by hematoxylin and eosin and periodic acid-Schiff stains, or by the preparations calcofluor white fluorescent and Gomori methenamine silver.[47,53,54]

Management of vertebral coccidioidomycosis has most frequently involved both pharmacological treatments and surgery. Of the reported cases we found, 3 of the 4 patients who did not undergo medical treatment died of sepsis (the other was lost to follow-up). All patients require medical therapy or risk progressive morbidity and eventual death. We found that historically, the various forms of amphotericin have been the standard of care. However, unless the vertebral lesions are very extensive and potentially unstable, the current medical approach has shifted to beginning treatment with azole antifungals for a minimum of 12–18 months after the patient begins to show evidence of response to treatment.[21,33,43,50] It is recommended that patients who are immunocompromised or who have meningitis should undergo lifelong azole treatment.[21,43,60] Definitive therapy for vertebral infections may also require lifelong antifungal treatment.[33]

We found that fluconazole was the most frequently reported antifungal used for therapy, followed distantly by voriconazole and itraconazole. In a comparison of fluconazole 400 mg/day and itraconazole 200 mg BID for progress coccidioidal infections, the subset with skeletal infections were twice as likely to respond to itraconazole.[25,26] Treatment with larger doses of fluconazole (800 mg/day or more) has not been reported but may improve this drug's efficacy as it appears to have done for our Case 1. A recent small salvage study suggested that voriconazole succeeded in treating disseminated infection when fluconazole or itraconazole failed.[58] Posaconazole, which was used in only two of the reported cases, has been shown to diffuse well into bone and may also be more effective than itraconazole.[7,13] Moving forward, studies should be conducted to address the efficacy of the various azoles.

Amphotericin or polytherapy, which usually included amphotericin, was the next step for patients who

responded poorly to azoles alone. A substantial number of reported patients underwent polytherapy, often due to resistance to monotherapy.[6,10,34,45,49,58,65,66] Polytherapeutic regimens consisted of 2, 3, or even 4 medications and almost always included amphotericin in addition to azoles. Importantly, amphotericin B may be preferred for pregnant women or in patients who present with lesions within the spinal canal or other critical locations.[21]

Repeated imaging should be used at regularly scheduled follow-ups to monitor lesions for stabilization, improvement or deterioration. Understanding this and communicating it to the patient is critically important to optimizing management. We found many that many patients were lost to follow-up, and also that poor compliance with the medical regimen was a major cause of relapse or clinical decline.[10,14,31,33,41,45,58,65-67] In contrast, most patients who underwent medical therapy improved or stabilized, although it should be noted that disease progression despite medical therapy is not uncommon.[21,58] Therefore, patient education is critical to improve patient understanding of the severity of the disease and the importance of proper treatment and monitoring.

In addition to pharmacological therapy, the vast majority of reported patients have also required and undergone surgical intervention. It can be difficult to determine when surgery is necessary, but generally the decision rests on the severity of the disease.[33] Surgery is warranted and should be strongly considered for patients who are unresponsive to medical regiments and present with progressive infection, abscess formation, osteolysis, intractable pain, motor weakness, spinal column instability, or neurologic compromise.[21,29,33,37,40,58] The goals of surgery are to eradicate infection, preserve neurologic function, and maintain spine stability.[21,29,33] The combination of medical and surgical treatments has been shown to be more effective in both symptom relief and disease arrest than either treatment alone.[9,30,33,50,58] Modern titanium constructs can be effectively used in the settings of active infection. Our review of the literature also indicated that the large majority of patients who underwent both surgical and medical treatment had a better outcome. In addition, those who were treated surgically generally had more progressive vertebral disease and involvement of multiple spinal levels.

Although medical hardware has been associated with biofilm production and infection, studies using metal hardware in spine surgery have also demonstrated infection eradication in most, and frequently all, study subjects.[19,20,23,35,42,51,52,55,57,62] In addition, a recent study on biofilms and persistent wound infections found that the presence of medical hardware was not a significant risk factor in the production of biofilms.[3] In particular, titanium hardware is especially resistant to biofilm formation and is frequently used for spine instrumentation.[56] Interestingly, recent studies have shown that antimicrobial-coated metal hardware can further inhibit microorganism growth and biofilm production.[2,27,57] The evidence suggests that titanium hardware use in spine surgery may be highly resistant to biofilm formation or infection, and moving forward, metal hardware may include antimicrobial coatings that provide even greater resistance.

Patients who are have resided in or traveled to endemic areas and present with flu-like symptoms, back pain, progressive extremity weakness, or other neurologic symptoms in the extremities should raise suspicion of vertebral coccidioidomycosis. These patients should receive a thorough work-up that likely includes MRI, especially in cases involving progressing neurological symptoms. Although MRI cannot be used for diagnosis, it is the most sensitive method of detecting vertebral lesions and aids in planning biopsies and surgeries. Patients diagnosed with vertebral coccidioidomycosis require long-term pharmacological treatment and may require surgery. Finally, it is imperative to educate patients about the seriousness of the disease to encourage them to adhere to their treatment regimen and follow-up regularly for disease monitoring.

CONCLUSIONS

This work provides a working protocol for the management of spinal coccidioidomycosis. Medical management with antifungal agents can provide satisfactory disease control. However, in patients with mechanical instability, neurologic deficit, medically intractable pain or disease progression surgical debridement and stabilization is often necessary.

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