Review

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Review

Coccidioidomycosis Osteoarticular Dissemination

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Abstract: Valley fever or coccidioidomycosis is a pulmonary infection caused by several species of coccidioides (Cocci) fungi that is endemic to California and Arizona. Skeletal coccidioidomycosis accounts for about half of disseminated infections, with the vertebral spine being the preferred site of dissemination. Most cases of skeletal coccidioidomycosis progress to bone destruction or spread to adjacent structures such as joints, tendons, and other soft tissues causing significant pain and restricting mobility. Manifestations of such cases are usually non-specific, making diagnosis very challenging, especially in non-endemic areas. In this review, we explore case reports of dissemination of coccidioidomycosis to bones and/or joints to highlight key differential features with other conditions or diseases and highlight opportunities for mechanistic and pre-clinical studies that can help improve diagnostics, prognostics, and treatments.

Keywords: coccidioides; coccidioidomycosis dissemination; skeletal infection; fungal osteomyelitis; fungal synovitis; arthritis; knee joint

1. Introduction

Recently estimated at 350,000 infections annually in the United States, Coccidioidomycosis, also known as Valley Fever, continues to expand its clinical footprint from established endemic areas such as Arizona and California to several new hotspots in the northern areas of Mexico, and select regions in Central and South America potentiating new endemic areas [1], likely as a result of both climatic and populational changes [2,3]. This neglected disease is caused by inhalation of aerosolized spores of two dimorphic fungi *Coccidioides immitis* and *C. posadasii*. While most cases (60%) are asymptomatic, resolve spontaneously, and fail to be accounted for in the clinic, ~40% of infections present a pulmonary disease ranging from a self-limited flu-like illness to more severe pneumonia [4]. Uncommonly, but instigating significant burden on the health care system, 0.5-2% of cases progress to a disseminated and life-threatening disease, especially among immunosuppressed individuals (e.g., transplant recipients, HIV patients, and pregnant women), and non-Caucasian races (especially African Americans and Filipinos) [5]. The most common organs or sites for extrapulmonary coccidioidomycosis include the central nervous system (CNS), skin, bones, and joints. Skeletal coccidioidomycosis, which accounts for up to 50% of extrapulmonary infections, generally requires long term medical treatment, with the possibility of relapse if not properly managed [4].

Although widely described in clinical reports as individual case studies, disseminated skeletal coccidioidomycosis is still not well understood and remains uncharacterized mechanistically in animal models of dissemination. Most importantly, the genetic and molecular mechanisms that define susceptibility to a coccidioidal infection that progresses to disseminated disease rather than the typical self-limited pneumonia is yet to be determined.

In this review, we will discuss disseminated coccidioidomycosis with an emphasis on skeletal infection and describe the clinical and animal studies that define current understanding of skeletal coccidioidomycosis.

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2. Extrapulmonary Coccidioidomycosis

Disseminated coccidioidomycosis is defined as coccidioides infections that spread to organs outside of the pulmonary system and pleura space after the rupturing of spherules causing release of endospores that are carried by the blood or lymph stream to distal sites [5]. There are two types of dissemination: lymphatic and hematogenous, with the latter being the more common type. Disseminated infection can develop shortly after pulmonary infection or years later and has been associated with significant morbidity and mortality that can be reduced with an early diagnosis, effective systemic antifungal therapy and follow up [6]. According to a report by Fraser at al. [7], 95% of patients identified with fungal dissemination died within an average of 210 days after the dissemination occurred. In these patients, the clinical manifestations of disseminated coccidioidomycosis varied widely, and resembled many different unrelated conditions, making the diagnosis very challenging [6]. In addition to individual underlying health risks and susceptibilities, the severity of the illness was also likely to depend on the location of the dissemination. Disseminated coccidioides mostly affected the skin, the skeleton (bones and joints), and the central nervous system (CNS) (**Figure 1**) but was also identified at other anatomic sites such as lymph nodes, spleen, subcutaneous tissues, liver, kidneys adrenal glands, and myocardium. **Table 1** presents the distribution of case counts for the most common sites of dissemination of coccidioidomycosis as described by Adam and colleagues [6] in their retrospective analysis of 207 patients with disseminated coccidioidomycosis from the University Medical Center (UMC) in Arizona. Most cases involved one disseminated site only, although in few instances, multisystem dissemination, where 2 or more distinct systems or sites were affected, was described [6,8]. Osteoarticular infections constituted 20% to 56% of disseminated cases [9] and will be reviewed in detail in this article.

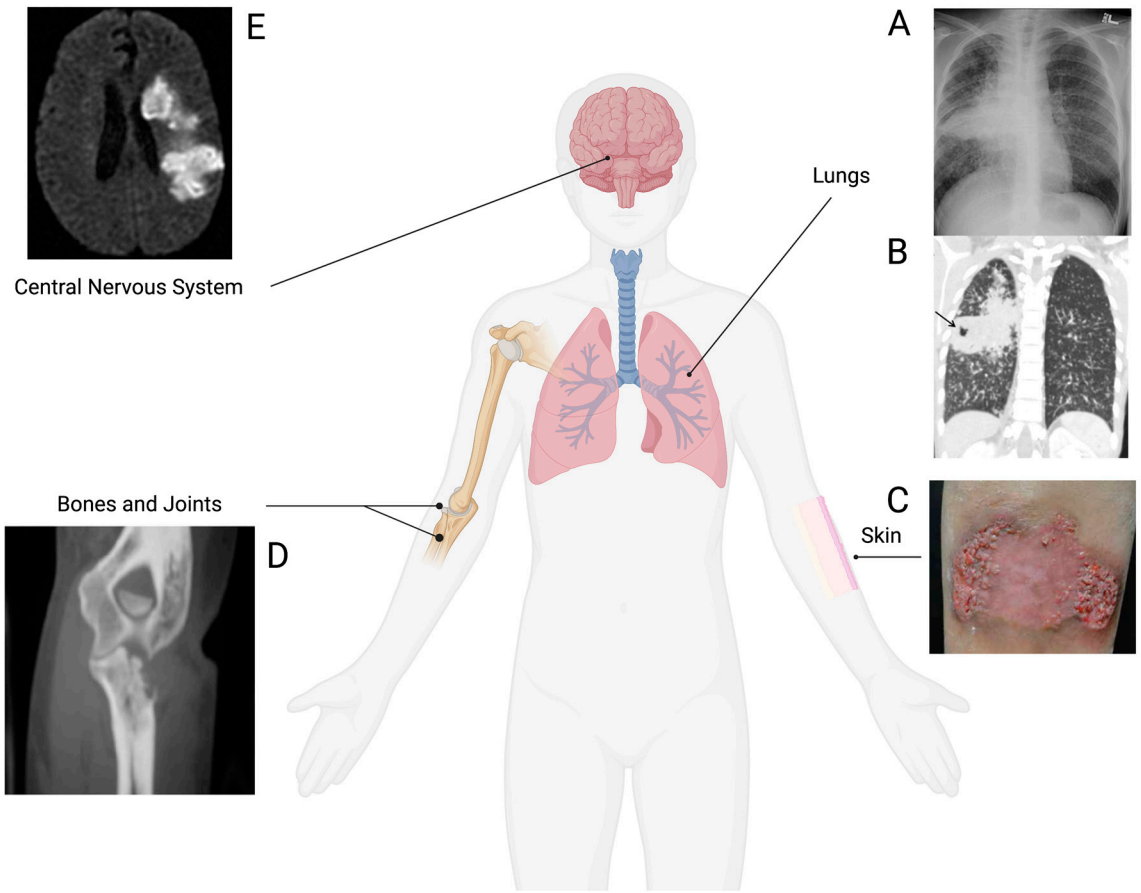

Figure 1. Common coccidioides infection sites. From the lung, coccidioidomycosis can spread to many different sites as highlighted above. Lungs chest radiograph and CT image of a patient with pulmonary coccidioidomycosis infection (A) & (B) [Reproduced from Adam et al. with permission [6]]. Skin infection appearing as verrucous plaques on a Coccidioidomycosis patient (C) [Reproduced

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from Garcia et al. with permission [2]]. CT image of the patient right elbow with eroded ulna, due to coccidioides dissemination (D) [Reproduced from Capoor et al. with permission [10]]. MR image showing coccidioidomycosis induced-cerebral infarction (E) [Reproduced from Lammering et al. with permission [11]]. Created using BioRender.com.

Table 1. Classification of disseminated coccidioidomycosis cases by common sites of dissemination among 207 patients described by Adam and colleagues [6].

Classification	Numbers of patients
Central nervous system	71
Skeleton	70
Joints	14
Soft tissues (muscle or lymph node)	15
Skin	16

3. Risk factors for extrapulmonary coccidioidomycosis

Certain groups of individuals exposed to Cocci display higher rates of dissemination and are therefore considered to be at higher risk for severe disease. These groups include African Americans, Asians, Hispanics, and those of Filipino descent, patients with compromised immune status (patients on immunosuppressive medications, human immunodeficiency virus patients, third trimester pregnant women, and organ transplant recipients), patients with diabetes, tobacco smokers [12–14] and people aged over 60 years [6].

Higher rates for both pulmonary and disseminated coccidioidomycosis were reported among Filipinos, Asians, and Hispanics, while patients of African descent were mostly associated with increased rates of disseminated coccidioidomycosis but not pulmonary disease [15]. This variation in susceptibility among different ethnic groups has suggested that genetic factors may influence the progression from a localized mild disease to a more severe and disseminated coccidioidomycosis infection. In support of this hypothesis, a study on host genetic polymorphisms found that blood types A and B were associated with an enhanced predisposition to symptomatic pulmonary and severe disseminated coccidioidomycosis, respectively, among Hispanics. The human leukocyte antigen (HLA) polymorphism (HLA class II DRB1*1301 allele) was however linked to higher predisposition to severe disseminated disease not only among Hispanics, but also among African Americans and Caucasians [12,13].

Late stage of pregnancy is considered as a high-risk factor for severe or disseminated infection, presumably due to the combined effect of reduced cell-mediated immunity and the influence of sex hormones during pregnancy [12]. High levels of estrogen and progesterone during pregnancy were reported to stimulate *C. immitis* and favored the progression towards disseminated disease, which in turn contributed to a higher rate of maternal mortality if left untreated [16–18]. The management of coccidioidomycosis in pregnant women is critical yet very challenging as most antifungals, excepted from Amphotericin B, are teratogenic [19].

Immunosuppressed persons, especially those with impaired T-cell function were also shown to be more vulnerable to developing severe or disseminated coccidioidomycosis. Among these patients, individuals with diagnosed diabetes, inflammatory arthritis, hematologic/lymphatic malignancies (e.g., chronic lymphocytic leukemia), HIV and those that have experienced solid organ transplantation were at higher risk [20–23]. The risk of severe and disseminated coccidioidomycosis was also elevated with certain medical therapies that are known to alter cellular immunity, such as corticosteroids, tumor necrosis factor-α inhibitors and antineoplastic products [24–26]. While few reports have established diabetes as a risk factor for disseminated coccidioidomycosis, most clinical and scientific reports have argued that diabetes is mostly associated with complicated pulmonary coccidioidomycosis rather than with disseminated disease [6]. In one retrospective review of 39 patients with vertebral coccidioidomycosis, Szeyko and colleagues [27] supported the idea that diabetes is not to be considered as a risk factor for disseminated coccidioidomycosis, yet several

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clinical reports have mentioned diabetes mellitus as part of the medical history of the patients with disseminated coccidioidomycosis [3,8,28,29].

Although disseminated coccidioidomycosis affects all ages, it is most common in adults. However, additional studies on the role of age as a risk factor still need to be conducted to conclusively determine functional links [12,15]. Higher incidence rates of coccidioidal infection were documented among men than women. Previous reports have linked this observed gender disparity to occupational hazards, suggesting that men engage in outdoors activities or agricultural jobs at higher frequencies than women. The disseminated disease was also reported to occur at higher rates in men than in women, suggesting that there may also be a genetic or hormonal basis to this gender disparity [12,30].

4. Osteoarticular coccidioidomycosis

4.1. Clinical reports

Skeletal coccidioidomycosis generally arises from hematogenous dissemination and can often progress to the destruction of bones or adjacent structures such as joints, tendons, and other soft tissues [4,9]. Skeletal sites of infection do not have a location bias, as any bone could be involved in dissemination, but the reported sites with the most severe disease manifestation have been in the axial skeleton, including the skull, sternum, ribs, and vertebrae [4,27,31,32], with the latter being slightly favored (especially the lumbar and thoracic areas), where *C. immitis* frequently disseminates [5,27,31]. Most clinical cases describe vertebral coccidioidomycosis as osteomyelitis (limited to the vertebral bodies) and discitis (intervertebral disc space involvement), with symptoms including vertebral body compression and height loss, worsening back and neck pain, lower extremities weakness, weight loss, night sweats [27,29,33–37], epidural enhancement and abscess [27,29,35,37], paraspinal abscess [37] vertebral body complete destruction with focal kyphosis as well as retropharyngeal abscess [34].

One complicating factor in the diagnosis of vertebral coccidioidomycosis is that patients do not always present either symptom of pulmonary coccidioidomycosis nor do they display a significant past medical history of elevated rates of respiratory infections [29,34,36,38]. Although some reports describe the presence of primary lung infection in patients with vertebral coccidioidomycosis [29], a retrospective review study by Szeyko and colleagues [27], showed that the pulmonary disease, even when present, did not correlate with the severity of vertebral infection. When the infection of the skull occurs from vertebral coccidioidomycosis [39], it can spread to the pachymeninges and the subarachnoid space and cause neurologic compromise characterized by symptoms such as motor deficits, mechanical instability, neural compression, sensory disturbances, leptomeningeal enhancement, and arachnoiditis. The clinical studies reporting neurologic symptoms in patients with vertebral coccidioidomycosis cases have also highlighted the necessity of surgical management to prevent further spread in addition to pharmacological therapy [33–35,40] due to the fatal nature of coccidioidal infection in the brain.

Some rare reported cases of coccidioidal osteomyelitis included infection of the first toe in a young patient with a medical history of diabetes insipidus and obesity [38], the facial bone involvement such as the jaw osteomyelitis in an infant [31], infection of the patella (anterior bone of the knee) in immunocompetent males [41], and orbital bone osteomyelitis with associated periorbital abscess [42]. Coccidioidal osteomyelitis in those rare sites highlights the importance of considering *C. immitis* and *C. posadasii* as potential pathogens during the diagnosis of patients with bone diseases, especially patients living in endemic region or patients with a travel history to endemic regions, whether they are immunocompetent or immunocompromised.

Skeletal coccidiomycosis cases often appear with nonspecific features, mimicking other conditions such as malignant tumor, tuberculous osteomyelitis, as well as bone infections caused by other microorganisms [4,9]. Caraway and colleagues described two different cases of coccidioidal osteomyelitis that were misdiagnosed as primary bone tumors [43]. In the first case, the patient with a right hip pain was diagnosed with an epithelioid hemangioendothelioma after a core biopsy

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showed histiocytoid cells. For the second case the patient presented a mass in the manubrium that was initially described as lymphoma with metastases based on radiographic findings. In both cases, a subsequent fine needle aspiration (FNA) biopsy helped correctly diagnose coccidioidomycosis osteomyelitis.

Similarly, vertebral coccidioidomycosis may also be misdiagnosed, being mistaken for spinal metastasis [44,45], tuberculous spondylitis (Pott's disease: tuberculosis with spine involvement), pyogenic spondylitis (spinal infection from other bacteria origin such as *Staphylococcus aureus*) [27] or other granulomatous diseases [45]. One report by Wesselius *et al*. [46] examined a case of vertebral coccidioidomycosis that appeared with similar clinical and radiological features as those of vertebral tuberculosis yet indicated differences to distinguish the conditions. Although both conditions can present with similar roentgenologic changes, coccidioidomycosis produces greater bone destruction with a rapid progression and symptom onset than tuberculous spondylitis, which appears with an indolent symptom onset [47]. The summary of distinctive clinical features for spinal metastasis, vertebral coccidioidomycosis, pyogenic and tuberculous spondylitis are presented in **Table 2** [27,47–49].

Table 2. Distinctive clinical features of spinal metastasis, vertebral coccidioidomycosis, pyogenic and tuberculous spondylitis.

Variables	Vertebral coccidioidomycosis	Pyogenic spondylitis	Tuberculous spondylitis	Spinal metastasis
Location on the spine	Thoracic and lumbar	Thoracic and lumbar	Thoracic	Thoracic and lumbar (and rarely cervical)
Associated microorganisms	*Coccidioides spp*	*Staphylococcus aureus*, Streptococci, Enterococci, *Escherichia coli, etc....*	*Mycobacterium tuberculosis*	No microorganisms associated
Route of spread	Hematogenous	Hematogenous arterial route, direct inoculation from surgery.	Venous, Batson's paravertebral venous plexus	Venous hematogenous (the most common route), arterial, direct tumor extension, and lymphatic
Vertebral bodies	High number	Few vertebral bodies involved	High number	Few vertebral bodies involved (some rare cases showed > 5 vertebrae involved on the cervical spine
Disc involvement	Always	Always	Disk destruction occur at late stage of the disease	Sparing of intervertebral disc space
ESP, CRP*	Mildly increased	Markedly increased	Mildly increased	Mildly increased

* ESR, erythrocyte sedimentation rate; CRP, C-reactive protein.

Some cases of bone infections can spread from adjacent soft tissues rather than through hematogenous dissemination [50]. Soft tissue infections are relatively rare in Valley fever patients but can be very severe and often behave as invasive neoplasms [51,52]. Coccidioides dissemination to the bones often occurs with simultaneous involvement of the associated joints [4,31,53], with joint infection typically occurring via spread from the bone and rarely as the result of the hematogenous spread [54]. In their retrospective clinical analysis, Adam and colleagues [6] found that all 14 patients with joint disease exhibited evidence of skeletal disease in bone adjacent to the joint, suggesting that the majority of patients with joint infection most likely present adjacent osseus infection. Nevertheless, although rare, cases of coccidioidal arthritis with no bone involvement exist. An

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example of coccidioidal synovitis localized to the knee joint with no osseus destruction was presented in the clinical report by Coba and colleagues [8].

The most common manifestations of joint dissemination are arthritis and synovitis with effusion, with the lower extremities such as the knees being the most affected articulated joint, followed by the ankles and the wrists [5,55]. Ahmad and colleagues [55] reported a well-managed case of knee joint effusion and synovitis, with no bone involvement, caused by both *C. immitis* and *C. posadasii*, in a 49-year-old man from Texas. This case was resolved after antifungal treatment together with synovectomy, arthrotomy and drainage, without further relapse after 6 months follow-up.

Cases of coccidioidomycosis with the involvement of both joint and bone (osteoarthritis) are the most severe, and the contiguous bones often represent potential sites of relapse. Their management requires aggressive surgical procedures, in addition to lifelong antifungal therapy. One report on coccidioidal infection of the knee of a 62-year-old man has shown the chronicity of this fungal infection, evaluated during 24 years of follow-up with 4 different relapses, the longest one occurring after 11 years [56]. It was only on the 4th relapse that advanced diagnosis has shown the presence of existing bone infection, suggesting a possible site of relapse. The case has been finally resolved after debridement and synovectomy, followed by an arthrodesis with an external fixation and a long-term azole therapy.

While most cases of joint coccidioidal septic arthritis appear in only one site of infection, such as the case described by Weisenberg [53], in which the patient, a 78-year-old man, had no other systemic symptoms apart from knee pain and swelling, in a minority of patients the dissemination of coccidioidomycosis can involve more joints. Nasrawi and colleagues [57] described a case of coccidioidal polyarticular septic arthritis involving the right wrist, left elbow, left ankle, and left knee joints as well as the associated bones and soft tissues. The patient was initially diagnosed with chlamydia infection, which misled his case to reactive arthritis, a painful inflammation of joints occurring as part of the response to infection by *Chlamydia trachomatis*. The involvement of many joints resulted in this case being mistaken for "desert rheumatism," a condition affecting joints bilaterally and causing a symptom called "erythema nodosum". The absence of both the bilateral joint involvement and the symptom of erythema nodosum in that case, and the fact that the culture of fluids obtained from the knee, elbow and wrist joints grew *C. immitis*, directly excluded the possibilities of reactive and rheumatoid arthritis. The management of the case was made possible by the choice of the appropriate fungal and bacterial therapy. This case report presents the challenge of managing cases that manifest with multiple pathologic options and suggests that coccidioidomycosis infection should always be considered as a potential cause in monoarticular or polyarticular septic arthritis, especially if patients are linked to Valley Fever endemic regions.

4.2. Diagnosis

Some reports of skeletal coccidioidomycosis have highlighted the potential diagnosis complications that can arise from the presence of additional superimposed bacterial, fungal, and viral infections in patients with pre-existing coccidioides infection. In the case of coccidioidal polyarticular septic arthritis mentioned above as described by Nasrawi [57], the fluid from the patient's wrist grew Methicillin-resistant *Staphylococcus aureus* (MRSA), in addition to *C. immitis*, making the patient's condition significantly more difficult to manage. In a similar case [7], a 52-year-old man diagnosed with pulmonary tuberculosis developed swelling and infection on his right calcaneus and left tibia from which wound-draining fluid grew *Mycobacterium tuberculosis*. Further examination of biopsies from the soft tissues around the infected bones showed *C. immitis* that he had probably contracted when he travelled to Arizona a few years before diagnosis. Nassif and colleagues [58] reported a case of disseminated skeletal coccidioidomycosis in a 67-year-old woman in southwestern United States, previously diagnosed with COVID-19. After the resolution of COVID-19, the respiratory symptoms persisted, and the imaging revealed bone infection in the chest wall, mimicking metastatic disease. Subsequent biopsies from the chest wall confirmed coccidioidomycosis, and the patient was put on oral fluconazole. This case highlights that potential co-infection with cocci and SARS-CoV-2 in

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COVID-19 positive patients, and especially in endemic areas should be considered as part of the diagnostic routine.

These clinical findings demonstrate that the coccidioidal dissemination, in particular skeletal dissemination, can mimic many other diseases, making the diagnosis very challenging and unspecific [7,51,59]. Differentiating coccidioidomycosis infection from those other diseases is of utmost importance given the therapeutic and prognostic implications. Accurate diagnosis of skeletal coccidioidomycosis requires a very high level of rigor and a multidisciplinary approach combining laboratory analysis (histopathology, immunology, and microbiology) and imaging (such as Radiographs and MRI), especially in immunocompetent patients, and people from endemic areas [9,31,55,60].

Culture and/or serological testing are considered the gold standard for the diagnosis and confirmation of coccidioidomycosis in suspected Valley Fever patients [14,55,60]. Culture of clinical specimens from any location can confirm the fungal infection. However, when skeletal dissemination is suspected, isolation of the coccidioides followed by histopathologic examination is performed on the involved bone, obtained by either percutaneous biopsy, CT-guided needle biopsy, or surgical debridement. In case of joint involvement, the culture is done from joint fluid obtained by arthrocentesis [4]. Histopathologic testing can be assisted by molecular techniques such as in situ hybridization (ISH), which can bring more specificity in tissue analysis. Other techniques such as polymerase chain reaction (PCR) have also been considered recently to assist the histopathologic examination [61] and confirm the presence of specific pathogen species.

The serologic testing methods used to confirm the coccidioidal infection include the Enzyme Immunoassays (EIA), Immunodiffusion and complement fixation (CF) titers [31]. CF testing is the mostly used serologic method, due to its specificity and correlation with disease severity. CF titer in patients with disseminated infections is generally higher than 1:16 and its variation can inform on the therapeutic response in patients or the disease relapse [14,31]. An extremely high CF titer is predictive of failure of medical treatment alone and the need for surgical intervention [4].

Although imaging can sometimes result in misdiagnosis as other conditions such as cancer, bacterial infections, and fungal infections, it remains a very useful tool in the evaluation of the extent of skeletal dissemination and the necessity of surgery [4,55]. While radiographs can show bony lesions at late stage of the disease progression, CT scan instead can visualize bone abnormalities with more specificity at any stage of the disease. MRI is generally used to orient the decision of surgical debridement by identifying the areas of abnormalities with more precision and clarity, the damage of soft tissues as well as the abscess formation [4,28,60]. In the case of radiography and MRI failure, technetium Tc^{99m} bone scan is the imaging method of choice, due to its high sensitivity and ability to determine multicentric osteomyelitis [4,62].

4.3. Management of osteoarticular coccidioidomycosis

Successful management of osseous and/or joint coccidioidomycosis requires the combination of an early detection, a good choice of treatment, a timely decision on surgery, and a lifelong suppressive therapy. Current guidelines for the treatment of coccidioidomycosis recommend azole therapy for bone and/or joint dissemination [63]. Preferences have been given to Itraconazole than Fluconazole for skeletal diseases [29,53,55]. However, for good bone penetration, Posaconazole was found superior to Itraconazole [64]. Amphotericin B is recommended for severe osseous disease but is less used in the clinic due to unwanted side effects on kidney function [57]. The severity and progression of the disease generally indicates the need for surgical intervention, in addition to lifelong antifungal therapy, especially in patients with vertebral coccidioidomycosis.

4.4. Animal Studies

Most animal studies of coccidioidomycosis have focused on localized infection (pulmonary disease) rather than the disseminated disease. To mimic human dissemination, the intravenous and intraperitoneal routes of infection have been used, although these generally require large numbers of arthroconidia to establish infection and are less lethal than pulmonary infection [65,66]. The few

existing murine studies on the dissemination of coccidioidomycosis have focused on the spleen, lungs, liver, kidneys, and brain. These include studies of the immune response to systemic *C. immitis* infection of the lungs, spleen, and liver [67], *C. immitis* tissue invasiveness in lungs, liver, spleen, and kidneys [68] as well as the drug efficacy against disseminated coccidioidomycosis in lungs, spleen, liver and CNS [69–71]. To our knowledge, no investigation using rodent animal models has been performed to study the dissemination of coccidioidomycosis to bones and joints. The use of animal models for the osteoarticular coccidioidomycosis dissemination will provide important insights into the complex pathophysiology of skeletal coccidioidomycosis.

4.5. Conclusion

Manifestations of coccidioidomycosis dissemination to bones and/or joints are often non-specific. Although existing knowledge of coccidioidomycosis infection and the patient's medical history may be helpful, the initial diagnosis of osteoarticular dissemination can be difficult and is often confounded by other inflammatory and infectious conditions or diseases. Successful management of osteoarticular coccidioidomycosis will therefore require a very high index of suspicion. Confirmation of the diagnosis is obtained either by histopathologic identification or by cultures, methods which delay patient management and promote dissemination to other organs including difficult-to-treat bone and joint infections. Early detection will require the use of methods that deliver the results in timely efficient manner such as PCR and genomic analysis, which, although available, are not yet widely used. In addition, imaging tests may show abnormalities and provide information on the existence of a bone infection but cannot distinguish osteoarticular coccidioidomycosis from other bone infections. To avoid confusion, they should be used as secondary tests to confirm coccidioidal infection, but not as primary tests.

Most reports of complicated cases of osteoarticular coccidioidomycosis have also presented coinfection with *Staphylococcus aureus*. Developing an assay of coccidioidal coinfection with *Staphylococcus aureus* may help in understanding the pathogen and host factors that foster their coexistence and provide insight into the requirements for the proliferation of each microorganism and thus inform therapeutic development.

The lack of a murine model recapitulating the dissemination of coccidioides to bones and joints has hampered the understanding of the mechanisms involved in dissemination and penetration to these sites. Establishing a murine model that mimics osteoarticular coccidioidomycosis using mouse strains of differing susceptibility can help identify not only the kinetic patterns of infection and bone/joint destruction and the fungal load required to induce lesions, but also the fungal virulence or host resistance factors that are involved in the pathogenic process. Moreover, although they cannot reproduce the complexity of the *in vivo* environment, *in vitro* assays of the interactions of lung cells and coccidioides species can provide insight into fungal pathogenesis, possible pathways involved in the dissemination to other organs, and factors defining the tropism for targeted organs of the extrapulmonary infection.

Finally, in the era of COVID-19, care should be taken to not overlook respiratory diseases of similar presentation, such as coccidioidomycosis, especially in patients with a history of travel to endemic areas.

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References

1. Castro-Lopez, N. and C.Y. Hung, *Immune Response to Coccidioidomycosis and the Development of a Vaccine.* Microorganisms, 2017. **5**(1).
2. Garcia, S.C.G., et al., *Coccidioidomycosis and the skin: a comprehensive review.* Anais Brasileiros De Dermatologia, 2015. **90**(5): p. 610-619.
3. Koutserimpas, C., et al., *Skeletal Infections Caused by Coccidioides Species.* Diagnostics (Basel), 2022. **12**(3).
4. Blair, J.E., *State-of-the-art treatment of coccidioidomycosis skeletal infections.* Ann N Y Acad Sci, 2007. **1111**: p. 422-33.
5. Crum, N.F., *Coccidioidomycosis: A Contemporary Review.* Infect Dis Ther, 2022. **11**(2): p. 713-742.
6. Adam, R.D., S.P. Elliott, and M.S. Taljanovic, *The spectrum and presentation of disseminated coccidioidomycosis.* Am J Med, 2009. **122**(8): p. 770-7.
7. Fraser, C.G., S.E. Monroe, and J.E. O'Hare, *Coccidioidomycosis and tuberculosis in the same bones; a case report.* Ann Surg, 1951. **133**(1): p. 116-22.
8. Coba, A.J., et al., *Pandora's Box: Disseminated Coccidioidomycosis Associated with Self-Medication with an Unregulated Potent Corticosteroid Acquired in Mexico.* Trop Med Infect Dis, 2021. **6**(4).
9. Ricciotti, R.W., et al., *Surgical Pathology of Skeletal Coccidioidomycosis A Clinical and Histopathologic Analysis of 25 Cases.* American Journal of Surgical Pathology, 2014. **38**(12): p. 1672-1680.
10. Capoor, M.R., et al., *Coccidioidomycosis masquerading as skeletal tuberculosis: an imported case and review of coccidioidomycosis in India.* Tropical Doctor, 2014. **44**(1): p. 25-28.
11. Lammering, J.C., et al., *Imaging spectrum of CNS coccidioidomycosis: prevalence and significance of concurrent brain and spinal disease.* AJR Am J Roentgenol, 2013. **200**(6): p. 1334-46.
12. Brown, J., et al., *Coccidioidomycosis: epidemiology.* Clin Epidemiol, 2013. **5**: p. 185-97.
13. Louie, L., et al., *Influence of host genetics on the severity of coccidioidomycosis.* Emerging Infectious Diseases, 1999. **5**(5): p. 672-680.
14. Twarog, M. and G.R. Thompson, 3rd, *Coccidioidomycosis: Recent Updates.* Semin Respir Crit Care Med, 2015. **36**(5): p. 746-55.
15. Rosenstein, N.E., et al., *Risk factors for severe pulmonary and disseminated coccidioidomycosis: Kern County, California, 1995-1996.* Clin Infect Dis, 2001. **32**(5): p. 708-15.
16. Drutz, D.J. and M. Huppert, *Coccidioidomycosis - Factors Affecting the Host-Parasite Interaction.* Journal of Infectious Diseases, 1983. **147**(3): p. 372-390.
17. Bercovitch, R.S., et al., *Coccidioidomycosis during pregnancy: a review and recommendations for management.* Clin Infect Dis, 2011. **53**(4): p. 363-8.
18. Weinberg, E.D., *Pregnancy-Associated Depression of Cell-Mediated-Immunity.* Reviews of Infectious Diseases, 1984. **6**(6): p. 814-831.
19. Welsh, O., et al., *Coccidioidomycosis.* Clinics in Dermatology, 2012. **30**(6): p. 573-591.
20. Blair, J.E., J.D. Smilack, and S.M. Caples, *Coccidioidomycosis in patients with hematologic malignancies.* Archives of Internal Medicine, 2005. **165**(1): p. 113-117.
21. Masannat, F.Y. and N.M. Ampel, *Coccidioidomycosis in Patients with HIV-1 Infection in the Era of Potent Antiretroviral Therapy.* Clinical Infectious Diseases, 2010. **50**(1): p. 1-7.
22. Mertz, L.E. and J.E. Blair, *Coccidioidomycosis in rheumatology patients - Incidence and potential risk factors.* Coccidioidomycosis: Sixth International Symposium, 2007. **1111**: p. 343-357.
23. Santelli, A.C., J.E. Blair, and L.R. Roust, *Coccidioidomycosis in patients with diabetes mellitus.* American Journal of Medicine, 2006. **119**(11): p. 964-969.
24. Rutala, P.J. and J.W. Smith, *Coccidioidomycosis in potentially compromised hosts: the effect of immunosuppressive therapy in dissemination.* Am J Med Sci, 1978. **275**(3): p. 283-95.
25. Bergstrom, L., et al., *Increased risk of coccidioidomycosis in patients treated with tumor necrosis factor alpha antagonists.* Arthritis Rheum, 2004. **50**(6): p. 1959-66.
26. Smith, J.A. and C.A. Kauffman, *Endemic fungal infections in patients receiving tumour necrosis factor-alpha inhibitor therapy.* Drugs, 2009. **69**(11): p. 1403-15.
27. Szeyko, L.A., et al., *Vertebral Coccidioidomycosis: Presentation and Multidisciplinary Management.* American Journal of Medicine, 2012. **125**(3): p. 304-314.
28. Ellerbrook, L. and S. Laks, *Coccidioidomycosis osteomyelitis of the knee in a 23-year-old diabetic patient.* Radiol Case Rep, 2015. **10**(1): p. 1034.

29. Nakhla, S.G., *Complications and Management of a Rare Case of Disseminated Coccidioidomycosis to the Vertebral Spine.* Case Reports in Infectious Diseases, 2018. **2018**.
30. Drutz, D.J., et al., *Human sex hormones stimulate the growth and maturation of Coccidioides immitis.* Infect Immun, 1981. **32**(2): p. 897-907.
31. Crum, N.F., et al., *Coccidioidomycosis - A descriptive survey of a reemerging disease. Clinical characteristics and current controversies.* Medicine, 2004. **83**(3): p. 149-175.
32. Zeppa, M.A., et al., *Skeletal coccidioidomycosis: Imaging findings in 19 patients.* Skeletal Radiology, 1996. **25**(4): p. 337-343.
33. Crete, R.N., et al., *Spinal Coccidioidomycosis: MR Imaging Findings in 41 Patients.* American Journal of Neuroradiology, 2018. **39**(11): p. 2148-2153.
34. Elgafy, H., et al., *Disseminated coccidioidomycosis of the spine in an immunocompetent patient.* Am J Orthop (Belle Mead NJ), 2014. **43**(8): p. E181-4.
35. Kim, J.M., S. Pervaiz, and G. Sivasubramanian, *Extensive spinal disease from disseminated coccidioidomycosis.* Am J Med Sci, 2022. **363**(6): p. e59.
36. Pillsbury, M.M., et al., *Coccidioidomycosis Presenting with Fever and Back Pain.* J Gen Intern Med, 2020. **35**(6): p. 1887-1888.
37. Ramanathan, D., N. Sahasrabudhe, and E. Kim, *Disseminated Coccidioidomycosis to the Spine-Case Series and Review of Literature.* Brain Sciences, 2019. **9**(7).
38. Khalid, A., et al., *A Case of Osteomyelitis of the toe caused by Coccidioidomycosis in a 17 year-old with Diabetes Insipidus.* IDCases, 2017. **9**: p. 14-16.
39. Forbus, W.D. and A.M. Bestebreurtje, *Coccidioidomycosis; a study of 95 cases of the disseminated type with special reference to the pathogenesis of the disease.* Mil Surg, 1946. **99**(5): p. 653-719.
40. Martirosyan, N.L., et al., *A paradigm for the evaluation and management of spinal coccidioidomycosis.* Surg Neurol Int, 2015. **6**: p. 107.
41. Li, Y.C., et al., *Coccidiomycosis infection of the patella mimicking a neoplasm - two case reports.* Bmc Medical Imaging, 2014. **14**.
42. Reed, D.S., et al., *Disseminated Coccidioidomycosis With Orbital Osteomyelitis and Periorbital Abscess.* Ophthalmic Plast Reconstr Surg, 2021. **37**(5): p. e173-e176.
43. Caraway, N.P., et al., *Coccidioidomycosis osteomyelitis masquerading as a bone tumor - A report of 2 cases.* Acta Cytologica, 2003. **47**(5): p. 777-782.
44. Wilde, G.E., C. Emery, and J.F. Lally, *Radiological reasoning: miliary disease, vertebral osteomyelitis, and soft-tissue abscesses.* AJR Am J Roentgenol, 2008. **190**(3 Suppl): p. S11-7.
45. Arora, N.P., et al., *Coccidioidomycosis masquerading as malignancy.* BMJ Case Rep, 2012. **2012**.
46. Wesselius, L.J., R.J. Brooks, and E.P. Gall, *<verterbral coccidiomycosis presenting as pott's disease.pdf>.* JAMA. , 1977. **238**((13)): p. 2.
47. Lee, K.Y., *Comparison of pyogenic spondylitis and tuberculous spondylitis.* Asian Spine J, 2014. **8**(2): p. 216-23.
48. Endrit, Z., K.V. Vibhu, and B.M. Fassil, *Spinal Metastasis.* 2022: StatPearls Publishing LLC.
49. Lee, C.-M., S. Lee, and J. Bae, *Contiguous Spinal Metastasis Mimicking Infectious Spondylodiscitis.* Journal of the Korean Society of Radiology, 2015. **73**(6).
50. Carter, R.A., *Infectious granulomas of bones and joints, with special reference to coccidioidal granuloma.* Radiology, 1934. **23**(1): p. 1-16.
51. Garvin, G.J. and C.G. Peterfy, *Soft-Tissue Coccidioidomycosis on Mri.* Journal of Computer Assisted Tomography, 1995. **19**(4): p. 612-614.
52. Johnson, R.H., et al., *Coccidioidomycosis: a review.* Journal of Investigative Medicine, 2021. **69**(2): p. 316-323.
53. Weisenberg, S.A., *Coccidioides immitis septic knee arthritis.* BMJ Case Rep, 2018. **2018**.
54. McConnell, M.F., et al., *Disseminated coccidioidomycosis with multifocal musculoskeletal disease involvement.* Radiol Case Rep, 2017. **12**(1): p. 141-145.
55. Ahmad, F., et al., *Disseminated Coccidioidomycosis of the Knee Joint Requiring Synovectomy and Arthrotomy.* J Orthop Case Rep, 2021. **11**(2): p. 76-80.
56. Lantz, B., et al., *<Coccidioidomycosis of the knee with a 26-year follow-up evaluation. A case report.pdf>.* Clin Orthop Relat Res

a. , 1988 **234**: p. 4.

57. Nasrawi, F., et al., *Disseminated Coccidioidomycosis Presenting as Polyarticular Septic Arthritis: A Case Report.* Journal of Investigative Medicine High Impact Case Reports, 2020. **8**.

58. Nassif, E.F., et al., *Disseminated Coccidioidomycosis Following COVID-19 Mimicking Metastatic Thoracic Relapse of Well-Differentiated Liposarcoma: A Case Report.* Front Med (Lausanne), 2021. **8**: p. 715939.
59. Smith, J., G. Brown, and R. Barbee, *Coccidioidomycosis in Patients with Diabetes-Mellitus.* American Review of Respiratory Disease, 1978. **117**(4): p. 286-286.
60. Ho, A.K., et al., *Diagnosis and Initial Management of Musculoskeletal Coccidioidomycosis in Children.* Journal of Pediatric Orthopaedics, 2014. **34**(5): p. 571-577.
61. Bialek, R., et al., *PCR assays for identification of Coccidioides posadasii based on the nucleotide sequence of the antigen 2/proline-rich antigen.* Journal of clinical microbiology, 2004. **42**(2): p. 778-783.
62. Holley, K., M. Muldoon, and S. Tasker, *Coccidioides immitis osteomyelitis: a case series review.* Orthopedics, 2002. **25**(8): p. 827-31, 831-2.
63. Galgiani, J.N., et al., *2016 Infectious Diseases Society of America (IDSA) Clinical Practice Guideline for the Treatment of Coccidioidomycosis.* Clin Infect Dis, 2016. **63**(6): p. e112-46.
64. Anstead, G.M., et al., *Refractory coccidioidomycosis treated with posaconazole.* Clinical Infectious Diseases, 2005. **40**(12): p. 1770-1776.
65. Capilla, J., K.V. Clemons, and D.A. Stevens, *Animal models: an important tool in mycology.* Med Mycol, 2007. **45**(8): p. 657-84.
66. Clemons, K.V., J. Capilla, and D.A. Stevens, *Experimental animal models of coccidioidomycosis.* Ann N Y Acad Sci, 2007. **1111**: p. 208-24.
67. Clemons, K.V., C.R. Leathers, and K.W. Lee, *Systemic Coccidioides immitis infection in nude and beige mice.* Infect Immun, 1985. **47**(3): p. 814-21.
68. Miyaji, M., *Animal models in medical mycology*. 2018: CRC Press.
69. Sass, G., et al., *Nikkomycin Z against Disseminated Coccidioidomycosis in a Murine Model of Sustained-Release Dosing*. Antimicrob Agents Chemother, 2021. **65**(10): p. e0028521.
70. Sass, G., et al., *Efficacy of nikkomycin Z in murine CNS coccidioidomycosis: modelling sustained-release dosing.* J Antimicrob Chemother, 2021. **76**(10): p. 2629-2635.
71. Shubitz, L.F., et al., *Evaluation of VT-1161 for Treatment of Coccidioidomycosis in Murine Infection Models.* Antimicrob Agents Chemother, 2015. **59**(12): p. 7249-54.