ABSTRACT

BACKGROUND AND PURPOSE: Coccidioides immitis is a dimorphic fungus endemic to the Southwest United States and Mexico, and at our institution, it is a relatively common pathogen presenting with a broad spectrum of associated spine diseases. We describe the various spinal manifestations resulting from coccidioidal infection and provide MR imaging examples from 41 pathologically proved cases.

MATERIALS AND METHODS: Retrospective electronic medical record and PACS searches were performed. Patients found to have both MR imaging findings positive for infection and confirmative biopsy and/or CSF studies were included. Abnormal MR imaging findings were identified, categorized, and quantified. Patient demographics and associated intracranial involvement if present were also recorded.

RESULTS: Forty-one patients were included. Positive findings were categorized as leptomeningeal enhancement (26 patients, 63%), arachnoiditis (22 patients, 54%), osteomyelitis-discitis (14 patients, 34%), cord edema (11 patients, 27%), and true syrinx (3 patients, 7%). Thirty patients had documented brain involvement (73%), most commonly in the form of basilar meningitis. Four patients were positive for HIV (10%). Fifteen patients had comprehensive review of both intrathecal and vertebral/paraspinal involvement of this magnitude.

CONCLUSIONS: C. immitis results in various spinal manifestations, most commonly leptomeningeal enhancement and arachnoiditis/adhesive disease followed by osteomyelitis, which may resemble tuberculous or pyogenic infection on MR imaging.

ABBREVIATION: T1+C = T1-weighted images with contrast

Coccidioides immitis is a dimorphic fungus well-known to be endemic to the Southwest United States and Mexico. At our institution, we experience C. immitis as a relatively common pathogen, presenting with variable pulmonary, intracranial, and spinal diseases regardless of immune status. The spectrum of spine disease reported in the literature is extensive, with involvement of the leptomeninges, epidural/paraspinal space, vertebral bodies both with and without disc involvement, and, rarely, the spinal cord. Although previous case reports and articles have discussed the imaging appearance of spinal coccidioidomycosis, to our knowledge, there has not been a comprehensive review of both intrathecal and vertebral/paraspinal involvement of this magnitude.

We describe the spinal MR imaging findings from 41 patients with pathologically proved Coccidioides infection.

MATERIALS AND METHODS

This retrospective study was approved by the St. Joseph Hospital and Medical Center institutional review board and was conducted in accordance with Health Insurance Portability and Accountability Act guidelines.

A broad retrospective search was performed using the electronic medical record for patients with a history of coccidioidomycosis during a 6-year period. Key words used for the search included “Coccidioides,” “coccidioidomycosis,” “cocc,” and “valley fever.” Patients were screened with spinal MR imaging and individually overread to evaluate abnormal findings. Patients with an abnormal spine MRI were then cross-referenced for evidence of true coccidioidal infection. True infection was defined as culture positive for C. immitis obtained from a paraspinal mass, fluid collection, or vertebral body or positive CSF complement fixation titers. Only patients found to have both MR imaging findings positive for infection and laboratory evidence of true infection were included. Abnormal MR imaging findings were categorized as cord edema, syrinx, cord enhancement, leptomeningeal...
enhancement, arachnoiditis, and osteomyelitis-discitis with or without epidural/paraspinal abscess/phlegmon. Cord edema and syrinx were differentiated from one another by the degree of hypointensity on T1, in which syrinx more closely followed the CSF signal. Patient demographics, immune status, and the presence of associated intracranial or pulmonary involvement were also recorded.

During the 6-year period, patients were scanned using either GE (GE Healthcare, Milwaukee, Wisconsin) or Phillips (Phillips Healthcare, Best, the Netherlands) magnets at 1.5 or 3T. All patients included received intravenous gadolinium. Patients did not require total spine imaging to be included in the study.

Patients with intrathecal disease were screened for brain MR imaging and intracranial involvement. In patients without brain MR imaging, the posterior fossa was reviewed on cervical spine MR imaging to assess basilar meningitis.

RESULTS

Forty-one patients with confirmed *C. immitis* were identified as having abnormalities on spinal MR imaging. Of the 41 patients, 34 were men (83%) and 7 were women (17%). Seventeen patients were white (41%); 12, African American (29%); 7, Latino (17%); 3, Native American (7%); and 2, Asian (5%) (Table 1). The average patient age was 42.0 ± 14.7 years.

Abnormal findings on intrathecal, vertebral/spinal, and intracranial involvement. In patients without brain MR imaging, the posterior fossa was reviewed on cervical spine MR imaging to assess basilar meningitis.

The distribution of intrathecal findings is summarized in Table 3. Leptomeningeal enhancement was most often diffuse and affected the cervical cord, thoracic cord, and conus medullaris/cauda equina fairly evenly (23, 20, and 19 patients, respectively). Adhesive arachnoiditis was most common in the lumbar spine where nerve root clumping was the most common finding (18 patients). Cervical and thoracic cord adhesive disease was observed in 14 and 11 patients, respectively. Collectively, cord edema and syrinx were observed equally in the cervical and thoracic cord (9 patients each). In total, 30/41 (73%) patients had intrathecal involvement.

Fourteen of 41 patients presented with vertebral osteomyelitis and/or discitis (34%, Fig 4). Disease distribution and characteristics are summarized in Table 4. Paraspinal involvement (Figs 5 and 6) was most common, occurring in 11 patients. Disc involvement, osseous destruction (Fig 4A), and skip lesions involving noncontiguous vertebral bodies occurred in 7 patients each. Epidural involvement (Figs 5 and 6) was identified in 6 patients. Well-circumscribed osteomyelitis was observed in 5 patients; 2 instances involved the disc space. Four patients had a well-circumscribed pattern of paravertebral/epidural phlegmon as well (Fig 4B). Sparing of the disc space and involvement of adjacent vertebral levels in a pattern resembling tuberculosis was observed in 2 patients (Fig 4C). Gibbus deformity (focal kyphosis) was observed in 1 patient (Fig 6). The thoracic spine was most commonly involved (11 patients).

Intracranial disease was identified in each (30/30) patient with intrathecal disease. Twenty-seven of 30 patients had MR imaging of the brain performed, while 3 other patients had evidence of posterior fossa involvement by cervical MR imaging. Nineteen of 30 (63%) had either exclusively basilar or basilar-predominant leptomeningeal enhancement, while 4 patients (13%) had diffuse leptomeningeal enhancement. Less typical intracranial manifestations identified included the following: middle cranial fossa

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| Table 1: Patient demographics | No. (%) |
|-------------------------------|--------|
| Ethnicity                     |        |
| White                         | 17 (41) |
| African American              | 12 (29) |
| Latino                        | 7 (17)  |
| Native American               | 3 (7)   |
| Asian                         | 2 (5)   |
| Sex                           |         |
| Male                          | 34 (83) |
| Female                        | 7 (17)  |
| Patient age (mean) (SD) (yr)  | 42.0 (14.7) |

| Table 2: Abnormal findings on spinal MR imaging | No. of Patients (%) |
|-------------------------------------------------|---------------------|
| Leptomeningeal enhancement                      | 26 (63)             |
| Arachnoid adhesive disease                      | 22 (54)             |
| Osteomyelitis/discitis                          | 14 (34)             |
| Cord edema                                      | 11 (27)             |
| Syrinx                                          | 3 (7)               |

| Table 3: Distribution of intrathecal disease | Leptomeningeal Enhancement | Adhesive Arachnoiditis | Cord Edema/Syrinx |
|---------------------------------------------|---------------------------|------------------------|-------------------|
| Cervical                                    | 23                        | 14                     | 9                 |
| Thoracic                                    | 20                        | 11                     | 9                 |
| Lumbar                                      | 19                        | 11                     | NA                |

Note: NA indicates not applicable.

| Table 4: Osteomyelitis-discitis distribution and characteristics | No. of Patients (%) |
|-----------------------------------------------------------------|---------------------|
| Segment                                                         |                    |
| Cervical                                                        | 5 (36)             |
| Thoracic                                                        | 11 (79)            |
| Lumbar                                                          | 9 (64)             |
| Characteristic                                                  |                    |
| Paraspinal involvement                                         | 11 (78)            |
| Disc involvement                                                | 7 (50)             |
| Skip levels                                                     | 7 (50)             |
| Destructive (osseous)                                           | 7 (50)             |
| Epidural involvement                                           | 6 (43)             |
| Well-circumscribed (osseous)                                    | 5 (36)             |
| Well-circumscribed (paraspinal)                                 | 4 (29)             |
| Disc sparing with involvement of adjacent levels                | 2 (14)             |
| Gibbus deformity                                                | 1 (7)              |

| Table 5: Disease involvement and overlap | No. of Patients (%) |
|-----------------------------------------|---------------------|
| Abnormality                             |                    |
| Intrathecal disease                     | 30 (73)             |
| Discitis-osteomyelitis                  | 14 (34)             |
| Overlap                                 | 3 (7)               |
pachymeningeal enhancement, diffuse pachymeningeal enhancement, prepontine abscess, Sylvian fissure leptomeningeal enhancement, interpeduncular/infundibular enhancement, and right temporal lobe intra-axial and leptomeningeal enhancement.

Only three (7%) patients in our study group had both intrathecal and vertebral disease (Table 5). Each of these 3 patients had intracranial disease.

Four patients were positive for HIV (10%). Fifteen patients had documented pulmonary involvement (36%).

Patient clinical manifestations varied. Four patients (4/30) with intrathecal disease presented with acute myelopathy. Clinical

FIG 1. Leptomeningeal enhancement. Sagittal cervical (A) and thoracic (B) spine T1+C MR T1-weighted imaging with contrast show abnormal leptomeningeal enhancement, confluent in the cervical spine and patchy in the thoracic spine. Axial cervical (C) and lumbar (D) spine T1+C MR imaging show cord, cervical nerve root, and cauda equina nerve root leptomeningeal enhancement.

FIG 2. Arachnoiditis/adhesive disease. Sagittal T2 (A) and T1+C (B) MR imaging of the lumbar spine show cauda equina nerve root clumping and enhancement. Note the dependent, nonenhancing purulent debris in the thecal sac on T2WI. Axial T1+C of the cervical spine (C) shows tethering and deformity of the cord in addition to leptomeningeal enhancement. Axial T2 of the lumbar spine (D) shows adhesive cauda equina nerve root clumping.

FIG 3. Cord edema and syrinx. Sagittal STIR images of the cervical spine show cord edema (A) and true syrinx (B). Sagittal T1 (C) shows true syrinx and exemplifies the utility of T1WI to differentiate true syrinx from edema states. Axial T1+C (D) shows no associated cord enhancement. Paraspinous enhancement in this image is related to postsurgical decompression.
These observations illustrate the importance of un-

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adhesive disease, but all patients with adhesive disease had lepto-

meningeal enhancement, implicating both as related processes in

which the antigen incites inflammation and inflammation plus

exudate formation across time leads to adhesions.

The pathophysiology of the relationship to syrinx and cord

edema is controversial. The Gardner hydrodynamic theory pro-

poses that pulsatile ventricular CSF pressure is transmitted from

the fourth ventricle to the central canal, eventually resulting in a

progressive dilation (water-hammer effect).4 Only 1 case in our

review demonstrated a dilated connection from the fourth ven-

triple to the central canal; however, it is most likely that syrinx and
cord edema in the remainder of our patients are better explained

by the theory that increased subarachnoid pressure due to CSF

flow disturbances results in excess interstitial intramedullary fluid

via the perivascular spaces.12 Increased intramedullary pulse pres-

sures also promote circulatory disturbances within the cord and

further intramedullary fluid accumulation. All patients with cord

signal abnormality and syrinx had evidence of leptomeningeal
disease.

Many patients with extensive leptomeningeal enhancement

and cord edema were not myelopathic. This is congruent with the

findings of Lammering et al,14 who noted that 7 of 8 patients with

intrathecal disease were without back pain or radiculopathy. The

4 patients with myelopathy had syrinx formation or severe adhe-

sion/cord deformity.

Meningitis is the most common and lethal form of dissemi-
nated coccidoidal disease, consisting of pyogranulomatous and

fibroblastic processes affecting the meninges as well as the small

vessels and perivascular zones.13 Once the intracranial meninges

are involved, CSF dissemination can and often does occur. In our

case review, 30/30 patients with intrathecal disease had evidence

of intracranial involvement, most commonly in the form of basi-

lar leptomeningitis (19/30). Lammering et al14 documented intra-

cranial disease in 19/19 patients with intrathecal disease. It would

appear that intrathecal involvement either does not or is highly

unlikely to occur in the absence of intracranial involvement.

Osteomyelitis-discitis seen in the study population often re-

sembled pyogenic spondylitis with aggressive endplate destruc-

tion and paravertebral phlegmon formation (7/14) (Fig 4A).13 A

common misconception is that coccidoidal spondylitis is identi-

cal to tuberculous disease. Osteomyelitis that clearly spares the
disc space commonly evokes the differential diagnosis of tubercu-

losis/fungal infection. This is not altogether incorrect; however, it

leads to secondary misperception by affiliation. It suggests that

because C immitis is a fungus, it cannot appear similar to pyogenic

disease. The origin of this error may stem from a survey report in

the 1960s in which the authors observed only a single Trichophy-
ton among 30 different fungal species that were capable of colla-
gen digestion. The group included all major dimorphic mycotic

pathogens, with the exception of C immitis.13,14,15 It was not until

1985 that a group in Nevada using different culture media ob-
served that C immitis could, in fact, digest collagen.16 The authors

postulated that a fungal-specific collagenase or a more broadly

functioning protease may be responsible. This finding appears to

be unique to C immitis among fungal species and explains the

appearance often similar to pyogenic osteomyelitis-discitis.

Spinal infection with Coccidioides uncommonly resembled tu-

berculous spondylitis in our population, with sparing of the disc

FIG 4. Osteomyelitis-discitis. Sagittal STIR of the lumbar spine (A)
shows destructive endplate changes similar to pyogenic disease at
L3/4 with paravertebral phlegmon. Sagittal STIR of the lumbar spine
(B) shows destructive endplate changes of L5/S1, but note the well-
circumscribed nature of L5 and the L4 skip lesion. Sagittal STIR of the
cervicothoracic junction (C) shows a well-circumscribed signal abnor-
mality of the vertebral bodies with paravertebral phlegmon that ap-
pears to skip disc spaces, similar to tuberculous disease.

FIG 5. Axial T2 (A) and T1C+ (B) sequences demonstrate right T8–9
paraspinal and epidural phlegmon, producing mild effacement of the
thecal sac and leftward cord displacement.

history was considered incomplete for 5 patients with intrathecal
disease (25 had sufficient information obtainable via the elec-

tronic medical record). The 4 are summarized as follows: quadri-

plegia secondary to severe cervical cord deformity/adhesive dis-

ease (Fig 7), quadripareisis secondary to a large loculated cervical
cord syrinx (Fig 3C), neuropathic pain and quadripareisis second-
ary to cord edema and intermittent syrinx, and bilateral foot

numbness secondary to extensive cord edema and arachnoid ad-

hesive disease. Many other patients with ataxia had hydrocephalus

along with other symptoms that could not be attributed solely to

spinal disease.

DISCUSSION

Spinal infection with C immitis is relatively common at our insti-
tution due to its location within a highly endemic region. Mor-

bidity is high, and treatment strategies are complex and often

lengthy.10,11 These observations illustrate the importance of un-

derstanding characteristic imaging findings to aid in diagnosis,

especially in areas where a high index of suspicion must be

maintained.

Osteomyelitis-discitis is a well-known association of infection

with C immitis.3,4,7,8 However, leptomeningeal disease is a more

common manifestation. Extensive leptomeningeal enhancement

involving the entire neural axis is common and requires complete

spinal and brain imaging to evaluate the full extent. Only 5 pa-

tients with leptomeningeal enhancement did not have evidence of

adhesive disease, but all patients with adhesive disease had lepto-

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spaces and involvement of adjacent vertebral levels (2/14) (Fig 4C). Most interesting, a common finding was that of a well-circumscribed osteomyelitis that does indeed involve the disc space (5/14) (Fig 4B), contrasting with typical aggressive pyogenic bone destruction. The authors of this study suggest the terminology of “clean” osteomyelitis-discitis when observing this pattern and considering coccidioidal disease, especially in endemic areas. Skip lesions are common, supporting the need for entire neuraxis imaging. Gibbus deformity, historically associated with tuberculous spondylitis, was observed in 1 patient.

Overlapping intrathecal/intracranial disease and spondylitis were observed in only 3 patients (7%). The lack of overlap suggests alternate routes of infection (eg, CSF seeding versus hematogenous spread).

Intramedullary spinal cord enhancement was not a finding associated with coccidioidal infection in our study population. Such involvement has been reported rarely in the form of intramedullary abscess and enhancing intramedullary lesions.18,19

Men are much more commonly affected, potentially secondary to environmental/work exposure. The military has studied this extensively due to marine base locations in the San Joaquin Valley and frequent engagement in outdoor exercises.20,21 According to the 2016 US Census Bureau, 5% of the greater Phoenix, Arizona, population is composed of African Americans, and our study population was composed of 29% African Americans.22 This suggests a disproportionate amount of African Americans in the study group, implicating a predisposition, possibly due to genetics or secondary to occupational/environmental exposure. This finding is in concordance with other observations.2 Associated pulmonary disease is common and agrees with other investigations.4 Immunocompromised state is not required. In fact, only a minority of patients in our study were immunocompromised, suggesting complex host-pathogen interactions.

A recent neurosurgical review of spinal coccidioidomycosis included 140 patients and yielded similar patient characteristics. Males were disproportionately affected (95%) as were African Americans (52%). One-third of patients had concurrent pulmonary disease.23

**CONCLUSIONS**

The pathology associated with *C. immitis* infection is most commonly manifested as leptomeningeal enhancement and arachnoiditis, followed by osteomyelitis. Osteomyelitis and leptomeningeal disease are uncommonly seen simultaneously, suggesting different pathophysiology leading to infection. Cord edema and true syrinx states are secondary findings commonly seen in association with leptomeningeal disease. Coccidioidal spondylitis is protean and can mimic pyogenic spondylodiscitis, though it can also appear as well-circumscribed spondylitis with or without discitis. Skip lesions are common, necessitating imaging of the entire neuraxis. Myelopathy was an uncommon clinical presentation in
our patient population, only documented in patients with syrinx or severe arachnoid adhesive disease.

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