CASE REPORT

Symptomatic hepatitis secondary to disseminated coccidioidomycosis in an immunocompetent patient

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SUMMARY

A young man from California presented with acute onset of cough, fevers, night sweats and pruritus with dark urine. Laboratory studies were notable for moderate transaminitis with elevated bilirubin and eosinophilia. Hepatitis panel, HIV screen and heterophile antibodies were negative. CT scan showed multiple bilateral focal opacities with hilar and mediastinal lymphadenopathy with no ductal dilation or gallbladder stones. The patient had positive coccidioidomycosis serologies and he was started on fluconazole with resolution of symptoms and improvement in transaminitis over the next month. This article highlights a rare manifestation of disseminated coccidioidomycosis with symptomatic hepatitis. Although an increasingly prevalent infection found in southwest USA, dissemination is rare in immunocompetent hosts. Postmortem studies suggest hepatic involvement is common in disseminated infection. However symptomatic hepatitis is rare, with only three cases of symptomatic hepatitis found in the literature.

BACKGROUND

Coccidioidomycosis, an increasingly prevalent infection, is caused by inhalation of the spores of *Coccidioides immitis*, a soil-dwelling fungus that is endemic to the desert regions of Mexico, Central America and southwestern USA. Although incidence is highest in endemic regions, significant exposure over a short period also confers risk.^{1 2} Infection is often asymptomatic, and those with symptoms only have a mild flu-like illness. Only a minority come to medical attention.³ More significant infection can manifest as an acute or chronic pneumonia. Dissemination is rare, occurring in 1% of immunocompetent patients although more common in those who are immunocompromised. Symptomatic hepatitis is an extremely rare complication of disseminated coccidioidomycosis with only 10 case reports in the literature.^{4–6} We present a case of disseminated coccidioidomycosis with symptomatic hepatitis in an immunocompetent patient following significant soil exposure.

CASE PRESENTATION

A 25-year-old Caucasian man presented to the emergency department following a recurrent flu-like illness with fevers, cough and myalgias. He lived in central California, and several weeks prior to presentation had significant soil and dust exposure associated with his occupation. Three days after exposure he experienced flu-like symptoms including fevers, chills and myalgias, which resolved without the patient seeking medical attention.

Figure 1 Chest X-ray showing right lower lobe opacity.

He had recurrent symptoms 2 weeks later with productive cough, night sweats, fevers, diffuse pruritus and intermittent dark urine. He subsequently presented to the emergency department where a chest X-ray (figure 1) showed right lower lobe opacity, and he was started on levofloxacin for presumed community-acquired pneumonia. Despite antibiotics the patient had progression of symptoms and returned to his primary care provider. Physical examination was notable for scleral icterus with no hepatosplenomegaly or lymphadenopathy.

INVESTIGATIONS

CT scan was performed (figure 2) and demonstrated multiple bilateral focal consolidated opacities with bilateral, bulky hilar and mediastinal lymphadenopathy.

Laboratory studies were notable for an alkaline phosphatase of 387 U/L, alanine aminotransferase 237 U/L, aspartate aminotransferase 83 U/L and total bilirubin 2.5 mg/mL. Complete blood count was notable for mild leukocytosis with 10 000 cells/ μ L and 18% eosinophils on differential. Hepatitis, heterophile and HIV antibody tests were negative. Serum coccidioidal complement fixation serology was positive at a 1:16 titre for IgG and IgM. Lumbar puncture was performed and showed no evidence of infection.

OUTCOME AND FOLLOW-UP

The patient was started on fluconazole 400 mg/day with reduction of his transaminitis as well as his eosinophilia over the next week. Given his rapid clinical improvement decision was made to defer liver biopsy or bronchoscopy. During the 3 months of therapy he continued to have mild transaminitis,

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Figure 2 CT of the chest showing multiple opacities with hilar and mediastinal lymphadenopathy.

with an alanine aminotransferase of 126 U/L, aspartate aminotransferase 56 U/L, alkaline phosphatase 215 U/L and bilirubin 0.8 mg/dL. He also continued to have mild eosinophilia with 2000 cells/ μ L. Patient transferred care and was continued on therapy for 1 year with resolution of his symptoms although no labs are available.

DISCUSSION

Although hepatic involvement in disseminated coccidioidomycosis is common, it is usually clinically silent and found only on postmortem studies.⁴ Symptomatic hepatitis in an immunocompetent host is a rare manifestation of disseminated coccidioidomycosis and of the 10 cases of hepatitis reported in the literature, only three occurred in immunocompetent hosts.^{4–7} Hepatic involvement in coccidioidomycosis most commonly is associated with abdominal pain, moderate transaminitis (aspartate transaminase 2–7 times upper limit of normal and alanine transaminase 4–15 times upper limit of normal) and hepatomegaly.^{5–6} Bilirubin elevations between 2 and 3 mg/dL were common in those with underlying immunosuppression, but rare in those with intact immune systems. All cases were associated with hepatomegaly, which was not present in our patient.^{5–6} Scleral icterus was only observed in one patient who had undergone renal transplant and was on chronic immunosuppressant medications. Similar to our patient, peripheral eosinophilia was present in all but one case, and it has been suggested that peripheral eosinophilia is a marker of dissemination.⁸ In most cases liver biopsy was performed to prove the diagnosis. Liver biopsy showed minimal disruption of the hepatic architecture, poorly formed granulomas, eosinophils, as well as mature *Coccidioides* spp. spherules.^{5–6}

Hepatopulmonary involvement is associated with a milder clinical course as well as improved mortality compared with other sites of dissemination including the central nervous system (CNS).⁶ Most of the reported patients were treated with 2–5 g of amphotericin B, however many of these cases were treated prior to the availability of fluconazole. In one case the patient was treated with fluconazole 600 mg daily which resulted in clearing of his blood cultures in 5 days although no long-term follow-up was available.^{4–6} Of the two patients with known hepatic involvement who died, one patient was immunocompromised and also had CNS involvement and the other was a child who died from acute respiratory distress syndrome.^{5–6}

Amphotericin B is often not well tolerated; up to 30% of patients develop some degree of renal dysfunction and up to

14% need to stop treatment due to adverse effects.⁹ Further, between 14% and 20% of patients develop liver injury; however this is usually mild and reversible.⁹ Fluconazole by contrast is much better tolerated with less than 3% of patients discontinuing therapy due to adverse effects. Fluconazole also has less overall risk of transaminitis than amphotericin B.⁹ Current guidelines recommend fluconazole as the first-line therapy for disseminated coccidioidomycosis, with at least a 9-month treatment course and lifelong therapy if there is CNS involvement due to risk of recurrence.³

Disseminated coccidioidomycosis rarely can cause a symptomatic granulomatous hepatitis most commonly reported in immunosuppressed patients.^{5–10–11} Hepatopulmonary involvement carries a better prognosis than other sites of dissemination, most notably the CNS.⁶ Treatment is first with fluconazole due to its efficacy and tolerability, but in rapidly progressive disease amphotericin B is the preferred agent.³

Learning points

- ▶ Coccidioidomycosis is an increasingly prevalent infection in those who live in and travel to endemic areas.
- ▶ Dissemination occurs in about 1% of patients with intact immune systems.
- ▶ Hepatic involvement is common on postmortem studies, however symptomatic hepatitis is rare.
- ▶ Amphotericin B has been historically used however fluconazole has been shown to have similar efficacy, is better tolerated and now is the recommended first-line therapy for at least 9 months.

Contributors The patient was initially seen and evaluated by CS and SB, with follow-up by MK. Manuscript was initially written by MK with editing and modifications by CS and SB. Final version of the manuscript was reviewed and approved by all three authors.

Competing interests None.

Patient consent Obtained.

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