Unsuspected, Disseminated Coccidioidomycosis without Maternofetal Morbidity Diagnosed by Placental Examination: Case Report and Review of the Literature

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Historically, untreated disseminated coccidioidomycosis during pregnancy was thought to be associated with 100% maternal fatality and 50% fetal mortality and was the leading cause of maternal deaths in areas of endemicity. As recently as 1995, therapeutic abortions and early deliveries were advocated in certain contexts. This report describes an unrecognized case of disseminated coccidioidomycosis diagnosed at the time of placental examination in a woman who completed her pregnancy without significant maternofetal complications. This case suggests that abortion and early delivery may not be necessary, because the possibility of an uncomplicated pregnancy exists. It is likely that other similar cases exist but remain underreported or underdiagnosed because of the mild, nondescript nature of the illness and low clinical suspicion. Although this mother and infant had good clinical outcomes, thorough travel histories and consideration of the associated travel-related diseases are important because of the possibility of serious, potentially avoidable clinical consequences.

Historically, pregnant women with coccidioidomycosis were thought to be 40–100 times more likely to have disseminated disease, with maternal mortality estimates ranging from 20% to 90% and an associated increase in the incidence of negative fetal outcomes [1–5]. Because of these negative outcomes, therapeutic abortions or early deliveries were proposed in certain contexts [1]. However, subsequent anecdotal experience of physicians in areas of endemicity and more recent population studies during coccidioidomycosis epidemics do not support high maternofetal morbidity and mortality rates [6–9]. This may be attributable to a lower clinical suspicion in the majority of the mild disease forms, resulting in an overrepresentation of severe disease states in the older studies. Improvements in antifungal therapy may also have contributed to decreased morbidity and mortality rates. Consistent with the more recent publications, we report a case of undiagnosed, disseminated coccidioidomycosis in a woman who completed her pregnancy without serious complications.

CASE REPORT

Prenatal and antenatal course. A 30-year-old Hispanic woman (gravid, 3; para, 1; abortus, 1) presented to our institution at 18–19 weeks of gestation for prenatal care. Results of serological testing were negative for HIV infection and hepatitis B surface antigen.

At weeks 33–34 of gestation, the patient reported a 1-month history of left neck swelling, a pruritic facial rash, fever, night sweats, and a 4-month history of a cough with...
occasional hemoptysis. Chest imaging was not performed at this time.

On physical examination, a 4-cm, mobile, nontender lymph node was identified in the left cervical region, and a right cervical lymph node was also noted. However, a fine-needle aspiration was not performed at this time. A fine-needle aspiration of the left neck node was performed during week 37 and revealed a few poorly formed granulomas with multinucleated giant cells and necrosis, suggestive of an infectious process associated with mycobacteria or fungi. Fite’s and Grocott-Gomori methenamine–silver nitrate staining yielded negative results. Because of the paucicellularity of the aspirate and clinical suspicion for tuberculosis, the specimen was submitted only for a mycobacterial culture.

The following week, the patient presented in labor with spontaneous rupture of membranes and moderate meconium staining. At this time, because of the clinical suspicion of tuberculosis, tuberculin purified protein derivative testing was performed, and the result was subsequently determined to be negative. In addition, chest radiography was performed and revealed subsegmental atelectasis in the right lung base but was otherwise unremarkable. Because of nonreassuring fetal heart tones, a Cesarean section was performed. The 3560-g male infant was healthy (50th–75th percentile for estimated gestational age), and the Apgar score was 9 at 1 min and 5 min. Direct staining and culture of gastric lavage fluids from the newborn yielded negative results for mycobacteria. The infant was in good health and was discharged home on the second day of life with the mother. The placenta was submitted for pathological examination. Retrospective questioning, based on the results of the placental examination (see “Placental examination” below), identified a history of recent travel to Arizona and Mexico.

**Placental examination.** The 19.5 × 19.0 × 3.0–cm, 674-g (large for gestational age) placenta had meconium-stained fetal membranes but was otherwise unremarkable grossly, with a normal 3-vessel umbilical cord. Microscopically, there was chronic chorionic plate vasculitis and acute and chronic villitis, with a giant cell reaction and spherules of *Coccidioides* species (figure 1).

**Ancillary testing and therapy.** Within 1 week of the diagnosis of disseminated coccidioidomycosis by placental examination, the patient was examined in the dermatology clinic. On physical examination, multiple erythematous, papular, and verrucous lesions ranging in size from 2 mm to 1 cm were noted in the right postauricular area, right upper lip, chin, and right scalp. Examination of a punch biopsy of the upper lip revealed spherules and associated granulomatous inflammation, consistent with coccidioidomycosis. A portion of the skin biopsy specimen was submitted for culture tests. The patient began treatment with fluconazole (400 mg daily) for 3 months; improvement of the cutaneous lesions and decreased size of the bilateral cervical lymph nodes were seen.

Two months after completing the fluconazole course, the patient noted worsening of the pruritic lesions in the right postauricular region. Examination of a punch biopsy specimen of the right preauricular skin lesion was diagnostic for coccidioidomycosis. Fluconazole treatment at 800 mg daily for 2 months was reinstituted, to be followed by fluconazole at 400 mg daily for at least 1 year.

The maternal and newborn serum specimens were both positive for complement-fixing antibodies at a titer of 1:16. An enzyme immunoassay for anti-coccidioidal antibodies was not performed on the mother’s serum; however, the newborn’s serum tested positive for IgG (10.2 IV) and negative for IgM. These results indicate likely transplacental passage of maternal IgG antibodies to the newborn. Although the absence of IgM antibodies suggests that the infant was not infected, a negative
result due to a very early stage of infection or immaturity of the infant’s immune system cannot be excluded.

In view of the results of the placental examination, the initial mycobacterial broth culture from the lymph node aspirate was plated on fungal media and yielded a fluffy mold with arthroconidia consistent with Coccidioides species (figure 2). The upper lip biopsy specimen was also cultured and yielded Coccidioides species. Confirmatory DNA-based tests identified Coccidioides immitis in both cultures.

**DISCUSSION**

Disseminated coccidioidomycosis occurs in <1% of all symptomatic infections [10]. At particular risk are patients of African and Filipino ethnic backgrounds [11] and immunocompromised patients (pregnant women, especially those in the third trimester of pregnancy; transplant recipients; patients undergoing steroid therapy; and patients with AIDS) [12–15]. The increased incidence of dissemination during pregnancy is thought to be secondary to depressed cell-mediated immunity and the direct stimulatory role of increased estradiol and progesterone on the growth of Coccidioides species [16, 17]. Historical accounts of poor maternofetal outcomes associated with disseminated coccidioidomycosis during pregnancy [1–5] conflict with more recent reports of more favorable outcomes in similar situations [6–9].

In 2006, Crum and Ballon-Landa [15] performed an exhaustive literature search and identified 81 cases of pregnancy-associated coccidioidomycosis. They found that dissemination occurred in 75% of cases, of which 10% were associated with miliary disease. In addition, 51% of the women had abnormal results of chest radiographs or a recent pneumonia. Of the women with coccidioidomycosis, 50%, 62%, and 96% of the cases diagnosed in the first, second, and third trimesters of pregnancy, respectively, were disseminated disease. African-American women were found to have a 13-fold-increased risk of dissemination ($P = .007$). Eighty-one percent of the patients received their diagnoses intrapartum, whereas 9% received their diagnoses postpartum and 10% received theirs before pregnancy. Overall, 64% of the mothers and 69% of the infants survived, with the majority of deaths occurring before the availability of antifungal therapy. In comparison, only 6% of mothers and 6% of infants have died since modern antifungal therapy became available.

The discrepancy of morbidity and mortality rates between historical and more recent literature may relate to an underrepresentation of milder cases, which do not come to routine clinical attention, and improvements in antifungal therapy. Underdiagnosis may be even more likely for patients with mild coccidioidomycosis evaluated in regions where it is not endemic, as was seen in the present case. Cairns et al. [18] published a study on coccidioidomycosis in a group of 126 missionaries returning to Washington State from Tecate, Mexico. Sixteen members of this group visited 19 health care providers because of symptoms of coccidioidomycosis. Only 1 health care provider, an infectious disease physician from California, correctly diagnosed coccidioidomycosis. Other reported diagnoses included bacterial bronchitis, contact dermatitis, and viral infection.

This case also highlights the importance of placental histological evaluation. To the best of our knowledge, this is the third clinical case of pregnancy-associated disseminated coccidioidomycosis that was first diagnosed by microscopic examination of the placenta. The first case was reported in 1966 and involved a patient who developed fever and joint pain at

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**Figure 2.** Culture results. *Left,* Initial culture from the lymph node aspirate material and lip lesion; plating onto fungal media yielded a white fluffy mold. *Right,* Lactophenol blue preparation of the mold, illustrating septate hyphae and thick-walled, barrel-shaped arthroconidia flanked by thin-walled disjunctor cells consistent with Coccidioides species (magnification, ×400).
32 weeks of gestation. The results of skin tests for *C. immitis*, *Mycobacterium tuberculosis*, and *Histoplasma capsulatum* were negative. She delivered a healthy infant at 34 weeks of gestation via an uncomplicated vaginal delivery. The placenta was grossly normal, but histological examination demonstrated coccidioidomycosis. The patient died of respiratory failure 18 h after beginning amphotericin B therapy [5]. The second case was reported in 1976 and involved a white woman at 18 weeks of gestation. She had recently visited Arizona and developed blurred vision, headache, sinusitis, and a dry cough. She was admitted to the hospital and delivered a female infant who later died of causes secondary to extreme prematurity. The patient died on day 7 after admission. A frozen section of an apparent placental infarct revealed spherules morphologically consistent with *Coccidioides* species [19].

The first description of the characteristic features of coccidioidomycosis involving the placenta was by Mendenhall et al. [20] in 1948. They described the fungal spherules and endospores associated with areas of chorionic villi necrosis, epithelioid and giant cell reaction, and focal collections of segmented neutrophilic infiltration. The endospores were lodged in a heavy deposition of platelets and fibrin.

Since the report of Mendenhall et al. [20], a number of other authors have reported similar histological features [21–24]. It appears that the *Coccidioides* spherules elicit a granulomatous reaction, whereas the liberated endospores elicit a neutrophilic response. In addition, there may be associated coagulative necrosis of the villi.

It is generally thought that *Coccidioides* does not cross the placenta, because there are numerous accounts of coccidioidal placentitis that are not associated with fetal disease [4, 23, 25]. Potential mechanistic explanations for the lack of transplacental transmission include the large size of the spherules prohibiting transmission and the associated granulomatous reaction walling off the spherules from the villous circulation. However, significant rupture or manipulation of the placenta could circumvent these barriers and could theoretically lead to transplacental transmission [20, 22].

Indeed, coccidioidomycosis is rare in neonates. The mode of transmission is most often inhalation from the environment, although there are reports of postnatal cervical cultures positive for *C. immitis* [25–27] which have led some authors to suggest that neonatal infection may occur through exposure during vaginal delivery [4, 25, 27, 28].

Charlton et al. [29] suggested that *Coccidioides* may have been transmitted through swallowing or inhaling the presumed infected amniotic fluid in a fatally infected newborn delivered by cesarean section. However, the delivery of the infant was preceded by extraction of the anterior-lying placenta, later determined to be infected with *C. immitis*, and it is possible that the manipulation of the placenta may have contributed to the infant’s infection.

Management of coccidioidomycosis during pregnancy varies depending on the trimester, severity of disease, the presence of dissemination, and the site of dissemination. In general, patients with severe pulmonary involvement, disseminated disease, or meningitis require antifungal therapy with either amphotericin B, an azole, or a combination of the 2, depending on the scenario and trimester; however, azoles are contraindicated in pregnancy during the first trimester because of teratogenic effects, such as wavy ribs, abnormal craniofacial ossification, and limb deficiencies and during the second trimester because they may predispose infants to prematurity [30–33]. Use of azoles during the third trimester, when the risk of teratogenesis is lower, is not recommended at this time unless the life of the mother is at risk [33]. Instead, pregnant women may be treated with amphotericin B. Lipid-based amphotericin B is now preferred over the deoxycholate formula because of the former’s lower toxicity. Breast-feeding should also be avoided during azole therapy, because the levels of azoles in the breast milk are thought to exceed the dosage considered safe for infants [33]. Azoles are recommended in the postpartum period for women who are not breast-feeding. The duration of therapy varies with the disease presentation. Severe pulmonary disease is generally treated for at least 1 year, nonmeningeal disseminated disease is treated for at least 2 years, and therapy for meningitis is life-long.

In summary, we report a unique case of an unsuspected, pregnancy-associated disseminated coccidioidomycosis, with no serious maternofetal complications, diagnosed by placental examination in an area where coccidioidomycosis is not endemic. It is likely that other similar cases exist but remain underreported or underdiagnosed because of the mild, non-descript nature of the illness and low clinical suspicion in areas where coccidioidomycosis is not endemic. Although this mother and infant had good clinical outcomes, thorough travel histories and consideration of the associated travel-related diseases are important because of the possibility of serious, potentially avoidable clinical consequences. This case also emphasizes that therapeutic abortion or early fetal delivery may not be necessary in cases of disseminated coccidioidomycosis in pregnancy and demonstrates the importance of a thorough placental examination.

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