Coccidioidomycosis in pregnancy: Case report and literature review of associated placental lesions

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Abstract

Background: Coccidioidomycosis is an endemic fungal infection found most commonly in the Southwestern United States, Northwestern Mexico, and parts of Central and South America. Although infection is relatively uncommon during pregnancy, it is imperative to have an index of suspicion in order to diagnose and begin timely treatment to prevent dissemination and dire consequences. The right upper and middle lobes of the lung were resected due to continuous bleeding. A subsequent pregnancy was uneventful. Coccidioidomycosis titers remained negative throughout the second pregnancy.

Discussion: This case demonstrates the potential for severe pulmonary coccidioidomycosis and vascular strain of pregnancy-associated vascular expansion in the first trimester of pregnancy and the possibility of a favorable pregnancy outcome in subsequent pregnancies after appropriate treatment. The route of feto-maternal transmission and placental lesions in coccidioidomycosis are discussed.

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1. Introduction

Coccidioidomycosis also known as Valley Fever, is an infection caused by the fungi of the genus Coccidioides [1]. Coccidioides spp. are dimorphic, soil-dwelling fungi known to cause a broad spectrum of symptoms ranging from a mild febrile illness to severe pulmonary manifestations or disseminated disease [2,3]. The genus Coccidioides is comprised of two genetically distinct species: C. immitis and C. posadasii [4]. These two species cause similar clinical symptoms, however they are present in different geographic regions. C. immitis is found in central and southern California, with the San Joaquin Valley being the region of greatest endemicity [3]. The most concentrated region for C. posadasii is in Arizona and sporadic sites in southern Utah and Nevada. Outside the U.S., C. posadasii is present in parts of Mexico and Central and South America [3,4]. Cases of coccidioidomycosis in pregnancy are rare and were extensively described in a review by Crum and Ballon-Landa [5]. Maternal and fetal mortality, associated with the disseminated disease, is high. Medical pregnancy termination has been advised when disseminated infection is detected in early pregnancy [6,7]. Recent reports showed discrepancies between Coccidioidomycosis-related perinatal mobility and mortality and the disease-associated placental lesions. Here, we report a case of coccidioidomycosis in a woman with a non-viable pregnancy with a subsequent unaffected pregnancy and non-specific placental lesion. A literature review of placental findings associated with coccidioidomycosis cases, published since 1948, is provided.

2. Case report

A 30-year-old Hispanic female with an intrauterine pregnancy at 7 weeks of gestation was admitted to the hospital with mild
tion was performed at 37 weeks (due to 2 previous cesarean sections) and the patient remained negative throughout the pregnancy. An elective cesarean section was performed in triplicate. A standard curve was prepared from dilutions of a \textit{Coccidioides immitis} control DNA (VirCell, Granda, Spain). The dilutions used to make the standard curve were 60,000 copies/rxn, 6000 copies/rxn, 600 copies/rxn, and 60 copies/rxn. The placental tissue samples were negative for \textit{Coccidioides immitis} DNA (Fig. 1).

3. Discussion

Coccidioidomycosis is caused by \textit{Coccidioides immitis} or \textit{C. posadasii}, endemic to the Southwestern United States, northwestern parts of Mexico, Central and South America [10]. The exact incidence of coccidioidal infections is difficult to calculate because approximately 60% of infected individuals are asymptomatic or have subclinical disease and never seek medical attention. An estimated 150,000 infections occur annually in the United States [11]. The incidence of coccidioidal infections in Arizona, Nevada, California, New Mexico, and Utah has increased from 5.3 per 100,000 in 1988 to 42.6 per 100,000 in 2011 [12]. Around 75,000 deaths per year result from the infection. This increase in the disease occurrence requires particular attention in the pregnant population, since the consequences could manifest not only in the dissemination of coccidioidomycosis, but also result in fetal disease, congenital anomalies and other developmental sequels [5]. Despite the fact that coccidioidomycosis has been more common among men than women (55–66% of cases collected from surveillance data from Arizona [1993–2006] involved men), pregnant women experience dissemination 40–100 times more frequently than men [13–15]. Pregnancy alters the maternal immune system which potentially increases maternal and fetal vulnerability to common viral and parasitic infections [16]. The consequences could be far greater for women, than for men. The usual route of \textit{Coccidioides} transmission is through inhalation of spores that are found in the soil of endemic areas. Spores get lodged in the lungs and produce spherules [17]. After infection, a wide spectrum of manifestations is possible. Early symptoms such as cough, fever, and arthralgia are fairly common. Primary infections most commonly manifest as community-acquired pneumonia approximately 7–21 days after exposure. Complications of coccidioidomycosis include severe pneumonia with respiratory failure and bronchopleural fistulas requiring resection, lung nodules, and dissemination. Dissemination may be rapid with fatal consequences. Any organ of the body can be involved in dissemination, but \textit{Coccidioides} species have an affinity for the lungs, skin, soft tissue, joints, brain, and especially the meninges. Hemoptysis may occur and suggests the development of a pulmonary cavity. Cavities present in approximately 2 to 8% of adults infected with a \textit{Coccidioides} species. Pregnant women are at a higher risk for dissemination and re-activation of the infection [18], however not all pregnant women who develop coccidioidomycosis are at risk for dissemination – Wack et al. [3] reported only 10 cases of coccidioidomycosis in 47,120 pregnancies in an endemic area of Arizona in 1988 (2.1 cases per 10,000 pregnancies). Only 2
Fig. 2. (A) Microphotographs of the placenta, demonstrating villous calcification shown at 100× magnification, (B) increased number of syncytial knots shown at 100× magnification, (C) edematous villi shown at 100× magnification, and (D) necrosis (arrows) shown at 40× magnification.

Fig. 1. A. Melting curve for β-actin (pink color, melting temperature 87.5 °C) and Coccidioides spp. (blue color, melting temperature 85.5 °C) in the control DNA samples, placental samples (placenta, attached to placenta umbilical cord, fetal membranes) and soil samples. Note: placental samples do not show specific amplification. B. Standard curve for quantifying Coccidiosis spp. that was created by using 4 standards with the following dilutions: 60,000 copies/rxn, 6000 copies/rxn, 600 copies/rxn, and 60 copies/rxn.
| Age | Time of Diagnosis | Disseminated sites of disease in article | Titer | Treatment | Fetal outcome | Maternal outcome | Geographic area | Strain | Reference |
|-----|------------------|----------------------------------------|-------|-----------|---------------|-----------------|----------------|--------|-----------|
| 20  | Day of delivery  | Yes                                    | 1:64  | Amphotericin B, postpartum | Infected infant | Multiple foci of acute inflammation with numerous Coccidioides spherules. | Fatal | San Francisco, CA | C. immitis | [18]     |
| 38  | 34 weeks         | Disease reactivation during pregnancy | 1:04  | Amphotericin IV | Healthy infant | Normal placenta, weighed 310 g at 36 weeks. | Recovered | NR | C. immitis | [17]     |
| 30  | 18–19 weeks      | NR                                     | 1:16  | Fluconazole | Healthy infant | Unremarkable | Recovered | NR | Recent travel to Arizona and Mexico | C. immitis | [6]      |
|     |                  |                                        |       |            |               |                 | N/A            | N/A | N/A          | N/A      | [22]     |
|     |                  |                                        |       |            |               |                 | N/A            | N/A | N/A          | N/A      | [24]     |
|     |                  |                                        |       |            |               |                 | N/A            | N/A | N/A          | N/A      | [26]     |
| Week(s) | During pregnancy | Test Result | Treatment | Description |
|---------|------------------|-------------|-----------|-------------|
| 20      | 16 weeks         | 1:128       | NR        | Delivered by postmortem C-section, death after 10 h |
| 27      | Postmortem       | 1:128       | NR        | Coagulative necrosis of chorionic villi and an intense infiltration by neutrophils, lymphocytes, and plasma cells in the intervillous space. Spheres filled with round fungal endospores and scattered individual sporangiospores of *Coccidioides* were identified adjacent to areas of placental infarction. |
| 27      | 26 weeks         | NR          | Ampotericin B, vancomycin, and voriconazole | Fetal death at 26 weeks |
| 34      | 20 weeks         | Actidone    | NR        | Healthy infant delivered at term, titer 1:2 |
| N/A     | Third trimester  | N/A         | N/A       | N/A         |
| 38      | 32 weeks         | NR          | NR        | Healthy infant, weighed 2381 g. |
| 22      | 18 weeks         | 1:128       | Ampotericin B lipid complex (ABLC) | Multiple granulomas and large numbers of *Coccidioides* organisms. Abundant numbers of *C. Immitis* grew from placental and cervical cultures. |
| 21      | 24 weeks         | NR          | Metacortin | Normal placenta |
| 21      | 28 weeks         | NR          | Ampotericin after delivery | Healthy infant delivered preterm at 32 weeks |
| 37      | 24 weeks         | 1:8         | Ampotericin B | Healthy infant delivered at 38 weeks |
| 19      | 37 weeks         | NR          | NR        | Healthy infant, labor induced at 37 weeks |
| Animal report | Alpaca (Vicugna pacos) | 1:256 | N/A | Death |

**Notes:**
- *Coccidioides immitis*
- NR stands for not recorded.
- Placenta weighed 359 g, had necrosis, acute inflammation, presence of the spherules. The area between necrotic lesions was normal.
- **Recovered** indicates clinical recovery.
- **Fatal** indicates infant death.
of the 10 patients developed systemic illness that presented as fevers, pulmonary infiltrates and meningitis.

In a recent study of 32 cases of coccidioidomycosis in pregnant women residing in Kern County, California, dissemination developed in 3 women [19]. The risk of dissemination increases as the weeks of gestation advance, with the third trimester and immediate postpartum period having the highest risk. The mechanism of increased risk might be associated with depressed cellular immunity or changes in 17β-estрадiol and progesterone levels, which enhance the maturation and growth of C. immitis [20–22]. The question regarding the transplacental passage of the spherules is controversial [23–26]. The spherules were found in the placenta (Table 1) and documented to destroy the villi, however sporules were not found in fetal circulation [20]. The pathognomonic features of coccidioidomycosis in the placenta and the absence of inflammatory response were described by McCaffee and Benirschke [20]: “Coccidioides organisms were located in occasional microscopic foci of necrosis without inflammatory cell proliferation. Although this kind of bland necrotizing change is also characteristic of herpes simplex placenta, the two diseases are differentiated by the morphologic features of the respective organisms.” Taking into consideration multiple placental lesions, found in the cases of maternal coccidioidomycosis, it was suggested that placental insufficiency might contribute to fetal demise [27]. In the reviewed cases of placental lesions, acute placental inflammatory response was reported in three cases with the fatal outcome. Increased fibrin deposition is a common placental lesion associated with this disorder (Table 1).

This fibrin deposition is part of the pathogenesis of coccidioidomycosis: a fibrillar material, released by endospor, inhibits polymorphonuclear cell access to the emerging endospores [28]. The non-permissiveness of the placenta to coccidioidomycosis was also explained by the characteristic thrombotic segregation of the organism, which may “eliminate viable capillaries” and thus prevent transmission to the fetus [29,30]. The placental lesions described in present case were non-specific for coccidioidomycosis.

While the causative relationship between coccidioidomycosis and pregnancy loss cannot be determined, Coccidioides posadasii and immitis has been associated with abortion in animal examples [27,31]. African Americans, Filipinos, and Hispanics are known to be at higher risk for dissemination. In the present case, the patient had at least three risk factors making her more susceptible to a severe form of infection – Hispanic race, pregnancy, and diabetes. Treatments for coccidioidomycosis depend on the severity of the disease, presence of dissemination, and the site involved. Amphotericin B deoxyolate, azoles, or both are available as treatment options. Amphotericin B deoxyolate is considered to be the safest during pregnancy (category B). Lipid preparations of Amphotericin B are preferred over amphotericin deoxyolate due to reduced toxicity. Azoles have been used as treatment for coccidioidomycosis for over 20 years, however soon after their introduction it became evident that Azoles might be teratogenic [32]. Currently, fluconazole is a category D drug. The patient in the presented case was initiated on fluconazole as her pregnancy was considered to be nonviable during her admission at early gestation, indeed this pregnancy resulted in spontaneous abortion.

Women with a history of resolved pulmonary coccidioidomycosis have a minimal risk of disease reactivation during pregnancy, whereas in women with a history of disseminated coccidioidomycosis this risk is increased [18]. In agreement with the later observation, in the presented case the second pregnancy was not associated with reactivation of the disease and placental lesions were nonspecific for coccidioidomycosis.

In conclusion, the described case demonstrates the potential for severe pulmonary coccidioidomycosis and vascular strain of pregnancy-associated vascular expansion in the first trimester of pregnancy and the possibility of a favorable pregnancy outcome in subsequent pregnancies after appropriate treatment.

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