Case Reports in Women's Health 34 (2022) e00399

Contents lists available at ScienceDirect

Case Reports in Women's Health

journal homepage: www.elsevier.com/locate/crwh

Diagnosis of disseminated coccidioidomycosis in pregnancy through placental pathology: A case report

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ARTICLE INFO

Keywords:
Pregnancy
Coccidioidomycosis
Placenta
Pelvic adhesions
Infertility
Fungal infection

ABSTRACT

There are more than 150,000 new cases of coccidioidomycosis annually in the United States and the incidence is increasing. Although the majority of cases result in mild or no symptoms, pregnancy is a risk factor for complicated and disseminated disease. Overall, coccidioidomycosis is rare in pregnancy and there have been few reports in the literature of dissemination into the placenta. This report describes a 31-year-old primigravida with coccidioidomycosis diagnosed by placental examination. In retrospect, she had mild symptoms in the antepartum period but otherwise had no immediate complications due to the infection apart from the adhesive pelvic disease. The clinician should have a high index of suspicion for coccidioidomycosis in a pregnant woman presenting with a persistent respiratory illness who resides in, or who has recently recent travelled to, an endemic area. Additionally, a diagnosis of disseminated coccidioidomycosis should be considered for a woman with adhesive pelvic disease residing in an endemic region and one should consider microscopic placental examination if these findings are noted at cesarean delivery.

1. Introduction

Coccidioidomycosis is a fungal infection native to the Southwest United States, including California, New Mexico, Nevada, Arizona, Utah, and Texas [1]. It is caused by inhalation of the arthroconidia of the dimorphic fungus *Coccidioides immitis* or *posadasii*. It was previously believed that less than 1% of patients infected with *C. immitis* develop extrapulmonary disease. However, more recent studies have shown that there may be dissemination rates as high as 22–37% [2].

Although clinically evident coccidioidomycosis in pregnancy is rare, acquiring or having a reactivation of coccidioidomycosis in the second half of pregnancy or the early postpartum period is a risk factor for disseminated disease [3–5]. This increased risk for disseminated disease is thought to be secondary to a blunted cell-mediated immune response in pregnancy. Additionally, elevated estrogen and progesterone levels in pregnancy stimulate the growth of *C. immitis* [6]. More importantly, disseminated coccidioidomycosis leads to higher maternal mortality if left untreated in pregnancy [3,5].

This is a report of a woman from an endemic area who was diagnosed with coccidioidomycosis by pathological examination of the placenta.

2. Case Presentation

A 31-year-old Hispanic primigravida from the southern San Joaquin Valley in central California became pregnant by in vitro fertilization due to occlusive tubal disease. During her infertility evaluation, bilateral tubal occlusion on hysterosalpingography was found in the absence of a known history of sexually transmitted infections. The early pregnancy was complicated by chronic hypertension, for which she took prophylactic baby aspirin for preeclampsia risk reduction. Prenatal labs were otherwise normal, including low-risk genetic screening results, and the fetal anatomic ultrasound was normal.

At the 25-week visit, the patient reported four weeks of cough and congestion without fevers, night sweats, weight loss or loss of appetite. She was diagnosed with a persistent upper respiratory tract infection. At 27 weeks, the patient was diagnosed with intrahepatic cholestasis of pregnancy (ICP) based on lower extremity pruritus and elevated serum bile acids and was treated with oral ursodeoxycholic acid.

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https://doi.org/10.1016/j.crwh.2022.e00399
Received 23 January 2022; Received in revised form 9 February 2022; Accepted 11 February 2022
Available online 16 February 2022

An ultrasound scan at 30 weeks of gestation showed a fetus with growth at the 43rd percentile and a cervical length of 1.5 cm with breaking of membranes. Two doses of intramuscular betamethasone were given due to the increased risk of preterm birth, and twice-weekly modified biophysical profiles were done starting at 32 weeks.

Given the increased risk of stillbirth with ICP, the patient underwent indicated preterm delivery at 36 weeks by cesarean for breech presentation. A healthy female infant was delivered, with Apgar scores of 8 and 8 at one and five minutes, respectively. At surgery, filmy adhesions were present over the entire serosal surface of the uterus, and the fallopian tubes were not visible due to dense adhesions. The ovaries appeared normal. A 4–5 cm fibroid was noted in the lower uterine segment at the level of the incision, so a myomectomy was also performed intraoperatively. The neonate had a normal postnatal course and was discharged with her mother. The infant had no clinical evidence of vertical transmission of coccidioidomycosis.

At placental examination (routinely done at the facility), the placental disc measured 17 cm in greatest dimension by 2.6 cm thick and weighed 381 g. Microscopic examination revealed decidua with granulomatous inflammation, including multinucleated giant cells and fungal organisms as spherules (Fig. 1). Grocott's methenamine silver stain (GMS), and periodic acid-Schiff stains were positive for fungal elements, which were morphologically compatible with coccidioidomycosis. There were also features of early acute chorioamnionitis and intervillous thrombi comprising less than 5% of placenta. There was also a normal 3-vessel cord.

Due to the placental findings of disseminated coccidioidomycosis, the patient had an infectious disease consultation a week into her postpartum course. Upon further questioning she reported having had a mild cough during the latter half of her pregnancy and denied a previous diagnosis of coccidioidomycosis. On exam she had no obvious signs of disseminated coccidioidomycosis, including skin lesions, enlarged lymph nodes, spinal tenderness, joint effusions or focal neurologic deficits. The laboratory workup was notable for weakly positive complement immunoglobulin gamma (IgG) and negative immunoglobulin M (IgM) with an antibody titer 1:4. The erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were elevated at 71 mm/Hr and 168 mg/L respectively. Liver function tests and chest radiography were normal, so she was started on oral fluconazole 400 mg daily.

At her follow-up visit with the infectious disease specialist, the patient was noted to be doing well. Repeat labs at that time were notable for positive complement IgG and weakly positive IgM and an increased antibody titer of 1:128. The CRP and ESR had decreased to 9 mm/Hr and 42 mg/L respectively and liver function tests were normal. Her fluconazole dose was then increased to 400 mg oral twice a day and continued for 4 months postpartum.

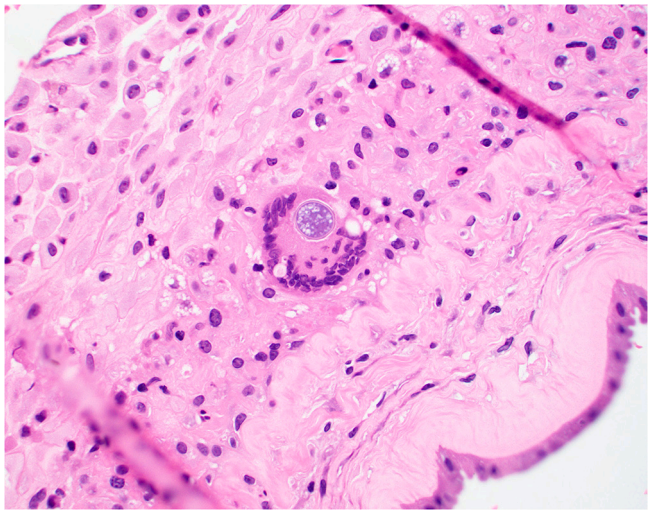

Fig. 1. Placental villus at 40× magnification with hematoxylin and eosin stain showing a granuloma with a spherule containing endospores of *Coccidioides immitis*.

3. Discussion

The incidence of coccidioidomycosis has increased every year since national reporting began in the 1990s [7]. More importantly, there are thought to be more than 150,000 new cases annually in the United States [8], but approximately 60% of patients with a primary coccidioidomycosis infection are asymptomatic [1]. The other 40% of primary infections typically present with mild to moderate flu-like symptoms, including cough, fever, night sweats, or pleuritic chest pain [1]. Like in our patient, coccidioidomycosis in pregnancy may be underreported and undiagnosed due to mild or absent symptoms. This may lead to increased morbidity and mortality if healthcare providers do not make a timely diagnosis and implement treatment.

Aside from pregnancy, other risk factors for complicated coccidioidomycosis, with chronic pulmonary infection and dissemination, include chronic health conditions that impact T-cell function, such as human immunodeficiency virus (HIV) (particularly if the patient has a CD4 cell count <250 k/mL or an AIDS diagnosis) and cancer (especially Hodgkin disease), and immunosuppressive agents used for transplant recipients [1,9]. Additional risk factors for disseminated disease include the extremes of age, and African American, Hispanic or Filipino race [2,5].

Coccidioidomycosis can be diagnosed in multiple ways, although serologic testing with enzyme-linked immunoassays (EIA) or immunodiffusion identifying immunoglobulin G (IgG) or M (IgM) and a chest radiograph are most common. If there is concern for disseminated disease, diagnosis can also be made with a coccidioidal antigen assay, which can be positive in the urine, blood or cerebrospinal fluid [10,11]. Additionally, older tests such as complement fixation (CF), fungal culture, or histopathology can be used [2,12].

Even though IgG antibody against coccidioidal CF is found in cord blood, there have been very few case reports of *C. immitis* invading the placenta [13–15]. According to a literature search, this is the fourth clinical case of pregnancy-associated disseminated coccidioidomycosis that was first diagnosed by histopathologic examination of the placenta [3,13,16]. It is thought that the spherules lead to a granulomatous reaction, whereas the endospores lead to a neutrophil-predominant reaction [14–16].

Disseminated disease, which can manifest weeks to months after a primary infection, can involve any organ, although the skin, bones, joints and central nervous system are the most common sites [2]. Moreover, there are very few case reports of pelvic coccidioidomycosis, which generally presents nonspecifically as a pelvic mass and is oftentimes mistaken for malignancy [17]. It is possible that the filmy intraabdominal adhesions found during the cesarean section of our patient were secondary to disseminated pelvic coccidioidomycosis. There is one other case report of a woman who initially underwent diagnostic laparoscopy during infertility workup and was noted to have her fallopian tubes fixed in the cul-de-sac and was ultimately diagnosed with pelvic coccidioidomycosis [18]. Additionally, the fallopian tubes of our patient were not visualized due to adhesions, a finding which corroborates the tubal occlusion diagnosed on prior hysterosalpingography during her infertility workup.

Longstanding coccidioidomycosis disease could have contributed to the infertility that our patient faced. This argument is bolstered by the fact that this patient had had no prior risk factors for intraabdominal adhesions such as pelvic inflammatory disease or intraabdominal surgery. There have been two other case reports of women with unexplained infertility who were subsequently diagnosed with pelvic coccidioidomycosis [19,20].

Management of coccidioidomycosis during pregnancy depends on

several factors, including the severity of illness and the presence of clinical comorbidities. Treatment for coccidioidomycosis outside of pregnancy consists of azoles for uncomplicated pulmonary disease [12]. Amphotericin B, with debridement or excision as needed, is more effective at treating complicated or disseminated coccidioidomycosis that is refractory to azoles [2,12]. However, for women who develop coccidioidomycosis during pregnancy, treatment recommendations largely depend on gestational age. Amphotericin B is recommended for women who develop initial nonmeningeal coccidioidal infection during their first trimester of pregnancy [12]. Azoles are avoided during the first trimester due to teratogenic concerns but can be considered in the second and third trimesters [12]. Breastfeeding is also discouraged in mothers who are taking azoles other than fluconazole [12].

Although studies performed decades ago showed that maternal and fetal mortality rates are higher if dissemination occurs in the later stages of pregnancy, with modern treatment maternal, fetal and neonatal outcomes are favorable [3–5]. Additionally, transplacental infection is thought to be rare, given numerous previous reports of placental invasion with coccidioidal spherules without subsequent neonatal infection [12,16].

In summary, a workup for disseminated coccidioidomycosis should be done for a woman, pregnant or not, with adhesive pelvic disease residing in an endemic region, and one should consider microscopic placental examination if these findings are noted at cesarean delivery. A persistent cough in a pregnant patient who has recently travelled to, or who resides in, a coccidioidomycosis endemic region should also alert the clinician to a possible infection.

Contributors

Adrian L. Hernandez Lopez was involved in performing background research for the article, drafting and formatting the article, and crafting the discussion.

Mon-Lai Cheung participated in the direct care of the patient.

Michael J. Fassett participated in the direct care of the patient and was involved in all critical elements of drafting the article.

All authors approved of the final article.

Funding

This work did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Patient consent

Obtained.

Provenance and peer review

This article was not commissioned. Peer review was directed by Professor Margaret Rees independently of Michael Fassett, one of the authors and a member of the editorial board of *Case Reports in Women's Health*, who was blinded to the process.

Conflict of interest statement

Dr. Fassett reports grants from Bayer AG and NIH/NICHD outside the submitted work. The other authors declare that they have no conflict of interest regarding the publication of this case report.

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