Cryptococcemia resulting in an incomplete abortion in an HIV-positive patient

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Cryptococcus is an encapsulated yeast that causes opportunistic infection in immunocompromised patients, involving typically the nervous and respiratory systems. Traditionally, risk groups have included patients with diabetes, renal failure or cirrhosis, patients with connective tissue disease, patients on steroids or monoclonal antibody therapy, solid organ transplant recipients, patients with hematological malignancies and pregnant women. The HIV epidemic has facilitated an increase in the incidence of this infection, with HIV coinfection implicated in 80% of cases of cryptococcosis worldwide (1). In addition, HIV infection often results in unusual clinical presentations of well-known organisms such as cryptococcus.

Cryptococcosis of the female genital tract is rare, with descriptions of involvement of the endometrium, ovary, vagina, uterus and placenta confined to case reports. In the present report, we document the presence of cryptococcal organisms in the dilation and curettage specimen of an incomplete miscarriage in an HIV-positive woman. This is the third case of cryptococcosis involving the female genital tract and is noteworthy because it was the initial presentation of the infection, resulting from presumed cryptococcemia.

**CASE PRESENTATION**

A 28-year-old African patient (para 2, gravida 3) presented to the emergency department complaining of acute abdominal pain and vaginal bleeding. On examination, the patient appeared to be in her first trimester, was shocked, there were no signs of fetal life and a dilation and curettage was performed to evacuate the pregnancy. Despite this intervention the patient died shortly thereafter. The patient did not have any antenatal records and presented for the first time as a medical emergency.

**Pathology**

The dilation and curettage specimen contained blood and fibrin with endometrial tissue fragments showing stromal decidualization and mixed, but predominantly chronic, inflammation (Figure 1). Focal cyto- and syncytiotrophoblasts were present admixed with hemorrhage (Figure 2). Encapsulated organisms consistent with cryptococcus were noted lying singly and in clusters within the decidual stroma and endometrial glands.

**Key Words:** Cryptococcus; HIV; Incomplete abortion
clusters enmeshed in the fibrin and hemorrhage with an associated granulomatous response (Figure 3). There were no organisms present in the endometrial tissue. A mucin stain highlighted the capsule of the organisms. Other fungi or tuberculosis were not seen on special stains.

**DISCUSSION**

Thus far, there have been two reports of cryptococcal placentitis. The initial case, reported by Kida et al (2), was of disseminated cryptococcosis in a HIV-positive patient with the subsequent case by Molnar-Nadasdy et al (3) occurring in a patient with systemic lupus erythematosus.

Both cases documented intervillous (maternal) space involvement by cryptococcal organisms associated with fibrin and neutrophils. Both specifically report the absence of chorioamnionitis, villitis or organisms within the villi (fetal compartment). In the case reported by Kida et al, the woman died on postpartum day 2. Postmortem examination revealed disseminated cryptococcus involving the lungs, liver and kidney but there was no documentation of uterine involvement. The infant was well and several months after birth had no clinical evidence of HIV or cryptococcal infection.

In the second case, the neonate died on day 5 but an autopsy was not performed. The mother did well. Having undergone a caesarean hysterectomy, histological examination of the uterus revealed no evidence of deciduitis and again, no organisms within the endometrium.

In our case, the yeasts were identified within the fibrin but did not involve the endometrium. This in conjunction with the other two reports documenting involvement of the maternal ( intervillous space) would suggest hematogenous dissemination of the organism.

In the veterinary literature, Petrites-Murphy et al (4) documented a case of equine cryptococcal endometritis and placentitis in which the foal died on day 9 due to cryptococcal pneumonia. In this case, the endometrium contained clusters of giant cells some of which contained cryptococcal organisms. Cryptococcal endometritis was not seen in the current case or in the two previous reports of cryptococcal placentitis.

Plaut (5) reported a case of cryptococcosis involving the cervix, endometrium and fallopian tube of a 31-year-old woman. Granulomatous lesions with giant cells containing fungal organisms were noted on microscopy, and on microbiological culture the organism was interpreted as being consistent with *Cryptococcus glabratus*.

Although it is recognized that cryptococcus can affect pregnant women, it is still controversial whether there is mother-to-child transmission. Sirinavin et al (6) reported a case of presumed mother-to-child transmission of cryptococcus, in which *Cryptococcus neoformans* was present in the cerebrospinal fluid of an infant at 92 days of age (6). They postulate it was acquired during labour or delivery basing this assumption on the fact that the mother had peripartum cryptococcosis and disease onset in the child was before three months of age.

Cryptococcal infection may be protean in its manifestations and this is particularly true in the setting of immune compromise, such as HIV. Even in the absence of immune compromise, unusual presentations have been documented. Chen et al (7) documented a case of isolated vaginal cryptococcal infection in an elderly patient treated for colon cancer nine years previously. The current case and the previous report of cryptococcal placentitis occurred in the setting of HIV infection. In addition, a case of cryptococcoma presenting as a tubo-ovarian abscess in an HIV-positive patient has recently been reported (8).

Pregnancy itself results in altered immune state possibly attributable to increased suppressor T cell function, decreased CD4 T cell function and stimulation and decreased production of cytokines. Disseminated fungal infections, which have been described in pregnancy in otherwise healthy women, include coccidioidomycosis, African histoplasmosis and blastomycosis. Several other fungi involving the placenta have been described in otherwise healthy pregnant women and in women with secondary causes of immune compromises. These organisms include histoplasma, candida, *Coccidioides immitis* and blastomyces.

Whitt et al (9) documented the first cases of transplacental transmission of *Histoplasma capsulatum* in humans, having previously only been diagnosed in horses. The case was of a woman with AIDS with disseminated histoplasmosis in whom
blood cultures were positive for H capsulatum. Culture of infant 
blood, cerebrospinal fluid and peritoneal fluid also grew H caps-
ulatum. Histological examination of the placenta showed focal 
yeast containing histiocytes within stem villi and trophoblasts 
but not within the intervillous space. The umbilical cord and 
membranes showed absence of chorioamnionitis and 
vacuolitis.

Lemos et al (10) reported three cases of blastomycosis in pregnancy 
and reviewed a further 16 cases from the literature. Overall 
the placenta was examined in only seven cases, six of which 
were negative for fungal organisms. In the one documented case of 
blastomycosis placentitis, the neonate was healthy.

Arnold et al (11) recently presented the third case of preg-
nancy-associated disseminated coccidioidomycosis in which 
the diagnosis was determined by histological examination of 
the placenta. Typical histological features include areas of 
necrotic villi, granulomatous reaction with giant cells, micro-
abscesses and endospores enmeshed in fibrin. Other findings 
include coagulative necrosis of the villi, chronic chorionic 
plate vasculitis and acute and chronic villitis. It is thought that 
coccidioides does not cross the placenta because there are 
numerous reports of placentitis without fetal disease. Postulated 
reasons for this include the large size of the organism and con-
tainment by the granulomatous inflammatory reaction. 
Coccidioidomycosis is rare in infants, although some authors 
speculate that neonatal infection may occur in vaginal delivery 
because of postnatal cervical cultures positive for C immitis.

Fitzhugh et al (12) described a case of a premature infant in which placentation revealed acute chorioamnionitis and organisms morphologically consistent with Actinomyces.

Causes of chronic endometritis of specific type include 
other fungal organisms, bacteria and viruses. Herpes simplex 
virus, cytomegalovirus (CMV) and HIV may infect the 
edometrium.

Rare infective causes of miscarriage that have been docu-
mented include syphilitic endometritis and CMV endometri-
tis. Lee et al (13) documented a case of syphilitic endometritis 
causing first trimester miscarriage in 30-year-old. Examination 
of the dilation and curettage specimen showed lymphoplasmacytic 
deciduitis and decidual necrosis with silver staining high-
lighting spirochetes diffusely involving endometrial glands and 
stroma.

Dehner et al (14) have reported a case of CMV endometri-
tis associated with spontaneous abortion, and work by Kleinman 
et al (15) showing estradiol induced reactivation of CMV in 
endometrial cells implicates the hormonal milieu of pregnancy 
in viral reactivation.

Placental changes in HIV are not well documented. In a 
prospective study of 51 placentas from treated and untreated 
HIV-positive women, chorioamnionitis (31.37%) and decidui-
tis (21.56%) were the most common inflammatory findings 
with noninflammatory lesions including cytotoxicplastic 
hyperplasia (76.47%), subchorionic fibrin (52.94%), calcifica-
tion (49.01%), perivillous fibrin (43.13%) and chorangiosis 
(29.4%) (16). Villitis has generally been reported to be rare in 
HIV-related pregnancies, and because this is an immunological 
phenomenon, this has been attributed to the lymphopenia.

CONCLUSION

We present an unusual case of cryptococcal-induced incom-
plete abortion in an HIV-positive patient as the initial prese-
ntation of this infection. This is the first documented case of 
cryptococcal-associated miscarriage and it expands the spec-
trum of HIV-related disease in pregnancy.

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