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Case Report

Disseminated cryptococcosis in an HIV-negative pregnancy: a case of cryptococcal septic abortion complicating an immunocompetent pregnancy

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ABSTRACT

Cryptococcus neoformans, a well-known pathogen of the immunocompromised host, is rarely reported as a cause of disseminated infection in the immunocompetent pregnant woman. Reported herein is the case of a young gravid woman, who initially presented with vague systemic symptoms that evolved into a disseminated cryptococcosis, which was resistant to standard parenteral antifungal therapy and resulted in abortion. Experience from this case suggests that cryptococcal infection should be considered in the differential diagnosis of pregnant women presenting with vague systemic symptoms such as fever, abdominal pain, and generalized lymphadenopathy.

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1. Introduction

Cryptococcus neoformans is an opportunistic pathogen with great affinity for the immunosuppressed (usually the HIV-positive) host, and whose primary tropism is the central nervous system and the lungs. It maintains a widespread geographic distribution. Little is known about cryptococcosis in the HIV-negative host. The case of an HIV-negative pregnant woman who was the host of a latent infection of *C. neoformans* that developed into disseminated cryptococcosis, leading to systemic events including cholecystitis, pneumonia, and fungal sepsis, and to miscarriage, is presented herein.

2. Case report

A 27-year-old, gravida 4 para 3003, at 14 weeks of an uneventful gestation, initially presented with persistent fever of two-day duration, and headache, chills, and lower abdominal pain of one-day duration. She was admitted to the hospital with a presumptive diagnosis of urinary tract infection, resistant to treatment with amoxicillin. Initial triage disclosed vaginal spotting for three weeks, recent weight loss, chest pain, and nonproductive cough for two days.

Antenatal testing from the first visit had been normal except for significant anemia (hemoglobin 6.0 g/dl, hematocrit 17.2%), which had not responded to iron supplementation. Her past obstetrical history was significant for three full-term normal spontaneous vaginal deliveries, each requiring transfusions in the postpartum period. Her past gynecological history was limited to heavy menstrual periods. There was a family history significant for thalassemia of unknown subtype in the father.

Vital signs upon admission were temperature of 37.7 °C, heart rate of 101 bpm, respiratory rate of 20 rpm, and blood pressure of 114/41 mmHg. Physical examination was notable for pain on deep palpation in the left lower quadrant with mild rebound tenderness and guarding. A pelvic examination revealed a tender uterus and a closed cervical os. There was a 4-mm mobile non-tender lymph node in the right inguinal region, a 3-mm mobile non-tender lymph node in the left inguinal region, and a 1.5-cm tender mobile lymph node in the left supraclavicular region, which had become painful in the last two days. Treatment with intravenous ceftriaxone was started and she was transfused with three bags of fresh frozen plasma.

An abdominal ultrasound performed in the emergency room showed a normal pregnancy. A chest X-ray revealed marked mediastinal and hilar adenopathy. Lactate dehydrogenase and all coagulation studies were abnormally elevated, accompanied by the presence of fibrinogen degradation products. Fibrinogen levels were elevated at 882 mg/dl. Urinalysis showed 100 g of protein, a large presence of blood, urobilinogen, and many white blood cells

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Figure 1. Extensive lymphadenopathy of ground glass consistency spread throughout the lungs, kidney, gallbladder, peripancreatic area, and uterus.

(WBC). A complete blood count (CBC) showed prominent neutrophilic leukocytosis (absolute count of $20 \times 10^9/l$, 94%).

Two days after admission, the patient had a complete miscarriage, confirmed by bedside transabdominal ultrasound, which showed no intrauterine pregnancy and an endometrial stripe of 2.3 cm. She developed moderate dyspnea later that night. CBC continued to show a high WBC count, elevated liver function tests (LFTs), and aberrant coagulation studies; a high fever (40.6°C) persisted. The patient was moved to the intensive care unit. A full body computed tomography scan demonstrated diffuse lymphadenopathy of ground glass consistency, spread out around the lungs, kidney, liver, gallbladder, and the uterus. An emergency D&C was performed while continuing antimicrobial therapy with metronidazole and piperacillin/tazobactam. The recovered products of conception (POC) were sent for pathologic diagnosis.

A worsening productive cough with white sputum and evidence of bilateral pleural effusion prompted intravenous therapy with imipenem (Figure 1). The WBC count was elevated at $49.6 \times 10^9/l$. Blood and urine cultures, purified protein derivative (PPD), and HIV ELISA and antibody were all negative. Within the next 24 h she

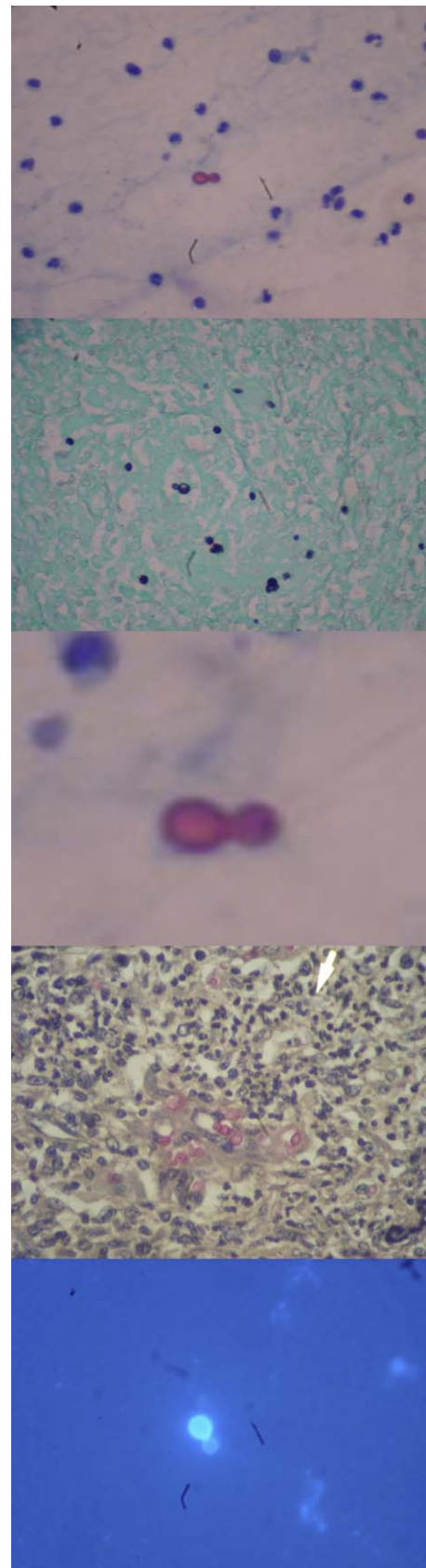


Figure 2. *Cryptococcus neoformans* exhibiting its characteristic structural appearance of narrow-based budding yeast with capsules.

developed a very diffusely tender abdomen. Abdominal ultrasound was suggestive of gangrenous acalculous cholecystitis. A laparoscopic cholecystectomy was performed under antimicrobial prophylaxis with cefazolin and metronidazole.

Fine needle aspiration of the increasingly tender left supraclavicular lymph node was performed, showing fungal organisms suggestive of *Cryptococcus* (Figure 2). Fluconazole was started immediately and all other antibiotics were discontinued. Specimen cultures (gall bladder, POC, intraoperative lymph node dissection) returned positive for growth of *C. neoformans* with sensitivity to fluconazole and itraconazole at minimum inhibitory concentrations (MICs) of 4 and 0.06 µg/ml, respectively. Daily blood cultures were negative for growth. Cryptococcal antigen was positive with a quantity of 1:512. The fever persisted for five days despite continuous administration of intravenous fluconazole; this prompted a change to IV amphotericin. Fever gradually resolved over the following two days.

The patient was discharged after a 25-day hospital stay, following remission of fever and marked progress in clinical status, although laboratory values (CBC, coagulation markers, LFTs) never reached 'normal' ranges. The patient did not consent to a bone marrow biopsy at a later time.

3. Discussion

Disseminated cryptococcosis is extremely rare in the immunocompetent individual. It has been identified in immunocompetent pregnant women in only two past reports, all in the form of pulmonary cryptococcosis.^{1,2}

One epidemiologic study at an urban hospital reported that 10–40% of those with a cryptococcal infection have no apparent immune deficiency.³ Interestingly, a population-based register in Australia reported near-equal incidence of infection with *C. neoformans* var. *gattii* in the immunocompetent and immunosuppressed (HIV-negative persons being treated for autoimmune disease), while the incidence of infection with *C. neoformans* var. *neoformans* markedly rose in HIV-positive persons with the spread of the AIDS epidemic in the early 1990s.⁴

Due to the natural tendency of *C. neoformans* to assume latency,⁵ infection may mimic a self-limiting illness and, as a result, be under-diagnosed. In this case, exposure to *C. neoformans* was not associated with any single event, though the exposure to old, dried pigeon excretus, the most significant source of the pathogenic fungus, is difficult to identify in retrospect. A journey into the history of cryptococcal disease revealed that it was not and still is not an uncommon encounter in the immunocompetent host, who may be asymptomatic or never seek medical attention due to the vague nature of its symptoms. It is possible that the contemporary association of HIV and *Cryptococcus* has over-

shadowed its diagnosis in those with an apparently normal immune system.

The case described above is dissimilar from the previous reports in that our patient had a much more extensive form of disease complicating pregnancy, leading to septic abortion with identifiable fungal forms within the POC. The two cases of pulmonary cryptococcosis in pregnancy have both attributed this susceptibility to infection to the immunotolerant state of pregnancy.^{1,2} Pregnancy gives rise to a state well-known as 'immune tolerance of pregnancy'. Though there is no clinically identifiable immunosuppression during pregnancy, there has been speculation of a slight down-regulation of immune mechanisms. Decreased T-cell function and natural killer (NK)-cell function have been consistently observed in pregnant women.^{6,7} It has been hypothesized that the physiologically altered Th1–Th2 balance during pregnancy facilitates the survival of a semiallogeneic fetus within the mother. An intact cell-mediated immunity is required for controlling the advancement of cryptococcal spores in persons inoculated by inhalation. However, during the state of pregnancy, colonization (or, in severe cases, infection) may be facilitated by the slightly down-regulated Th1 surveillance, especially in gravidas with comorbidities that might contribute to an overall decline in immune function.

Because cryptococcal mechanisms of achieving latency may be more effective in the environment of physiologic immunotolerance of pregnancy, special consideration must be given to the pregnant woman with vague symptoms suggestive of systemic disease, namely cryptococcosis. Prompt recognition and therapy may impede dissemination and prevent possible obstetric complications such as septic abortion.

Conflict of interest

No conflict of interest to declare.

References

1. LaGatta MA, Jordan C, Khan W, Toomey J. Isolated pulmonary cryptococcosis in pregnancy. *Obstet Gynecol* 1998;**92**(4 Pt 2):682–4.
2. Ely EW, Peacock JE, Haponick EF, Washburn RG. Cryptococcal pneumonia complicating pregnancy. *Medicine (Baltimore)* 1998;**77**:153–67.
3. Diamond RD, Bennett JE. Disseminated cryptococcosis in man: decreased lymphocyte transformation in response to *Cryptococcus neoformans*. *J Infect Dis* 1973;**127**:694–7.
4. Speed B, Dunt D. Clinical and host difference between infections with the two varieties of *Cryptococcus neoformans*. *Clin Infect Dis* 1995;**21**:28–34.
5. Ma H, Croudace JE, Lammas DA, May RC. Direct cell-to-cell spread of a pathogenic yeast. *BMC Immunol* 2007;**8**:15.
6. Petrucco OM, Seamark RF, Holmes K, Forbes IJ, Symons RG. Changes in lymphocyte function during pregnancy. *Br J Obstet Gynaecol* 1976;**83**:245–50.
7. Vaquer S, de la Hera A, Jorda J, Martinez C, Escudero M, Alvarez-Mon M. Diminished natural killer activity in pregnancy: modulation by interleukin 2 and interferon gamma. *Scand J Immunol* 1987;**26**:691–8.