Unmasking cryptococcal meningitis immune reconstitution inflammatory syndrome in pregnancy induced by HIV antiretroviral therapy with postpartum paradoxical exacerbation

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ABSTRACT

Cryptococcosis is the most common cause of meningitis in Africa due to the high burden of HIV. Immune reconstitution inflammatory syndrome (IRIS) is a frequent and deadly complication of cryptococcal meningitis. We report a fatal case of cryptococcal-IRIS in a pregnant woman that began after starting anti-retroviral therapy (unmasking IRIS) and markedly worsened postpartum after delivery (paradoxical IRIS).
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1. Introduction

Cryptococcal meningitis is the most common cause of meningitis in adults in Sub-Saharan Africa [1]. Immune reconstitution inflammatory syndrome (IRIS) due to cryptococcosis can occur in *paradoxical* or *unmasking* forms. *Paradoxical IRIS* describes a patient previously effectively treated for cryptococcosis who presents with a recurrence of symptoms as the immune system is restored (e.g. by antiretroviral therapy (ART) in HIV-infected persons or by removal of previously required immunosuppressive medications or conditions) [2]. *Unmasking IRIS* describes the presence of a previously subclinical infection being 'unmasked' by immune restoration resulting in an enhanced immune response [2]. Unmasking IRIS is readily preventable by cryptococcal antigen screening and pre-emptive therapy [3].

Paradoxical IRIS occurs in 13–30% of patients with HIV and cryptococcal meningitis who survive to receive ART [4]. Pregnancy induces a relative immune suppression in order to allow fetal development, and IRIS-like phenomena can develop in the postpartum period as the immune function normalizes [5]. This is commonly appreciated with respect to rheumatologic conditions, which can "flare" postpartum. We describe a unique case in which unmasking cryptococcal-IRIS in a pregnant woman was precipitated by starting ART with subsequent paradoxical deterioration after the delivery of her child.

2. Case

A 32 year-old pregnant female (G3P2) presented to the maternity ward of Mulago hospital in Kampala, Uganda, 29 weeks pregnant with a 7 day history of severe headache and right-sided numbness for 3 days. The patient reported a recent history of generalized weakness, mental status change, neck stiffness, and vomiting. She had no history of weight loss, fever, cough, or seizure. She had been recently diagnosed with HIV with a CD4 cell count of 67 cells/μL and had initiated ART with tenofovir, lamivudine, and efavirenz 30 days prior to presentation (end of second trimester). The patient had no history of tuberculosis, diabetes, or malignancy. Physical examination revealed a lethargic patient with a Glasgow Coma Scale (GCS) score of 15/15. She was afebrile with normal vital signs (Pulse 78, Respiratory

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18 breaths/min, blood pressure 110/70 mmHg) and a normal physical examination except for decreased strength (3/5) in the right upper and lower extremities and a fetal age-appropriate gravid uterus. The patient was admitted with a suspected diagnosis of meningitis due to *Cryptococcus neoformans* related to her advanced HIV/AIDS.

On admission (day 0), laboratory studies showed a positive serum cryptococcal antigen (CrAg) and a toxoplasmosis IgG titer

Table 1
CSF characteristics upon starting amphotericin B therapy.

CSF diagnostic test	Day +33	Day +34	Day +38	Day +42
White cell count (cells/µL)	< 5	< 5	–	125
Protein (mg/dL)	118	169	163	–
Quantitative CSF culture (CFU/mL)	5700	330	1200	120
Cryptococcal antigen titer	1:200	–	–	–
Opening pressure (mm H_2O)	510	210	250	84

The table displays CSF characteristics during the patient's hospitalization on the infectious disease ward beginning on hospital day +33 (post-partum day 3) at the start of amphotericin B deoxycholate-based therapy.
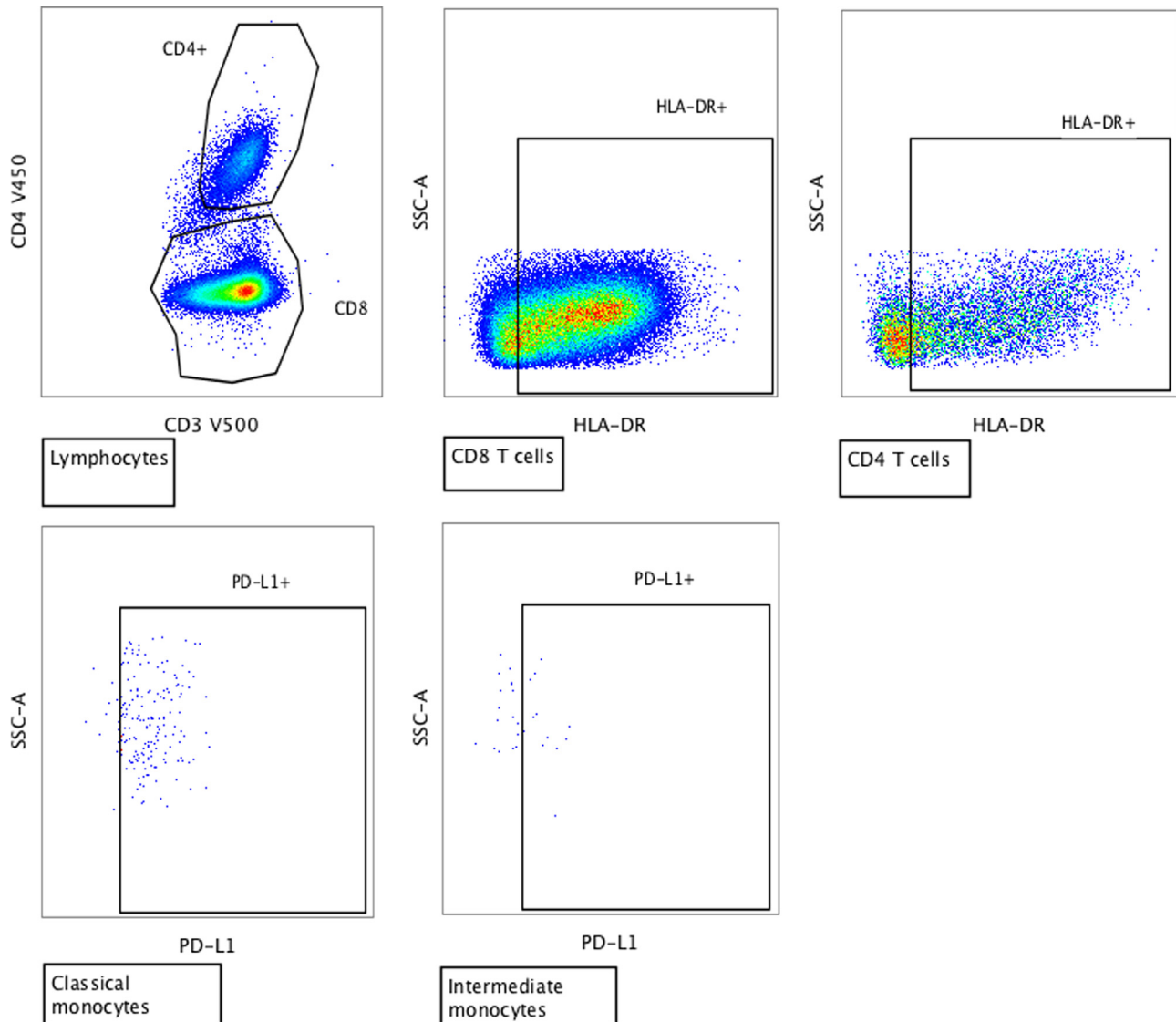
of 92 IU/mL (Ref: < 1.0 IU/mL). Microscopic examination of blood smears for *Plasmodium species* were negative, and complete blood count was unremarkable. ART was continued, and she received empiric antibiotics for suspected bacterial meningitis, glucocorticoids and trimethoprim-sulfamethoxazole for presumed pneumocystis pneumonia, and fluconazole 800 mg IV daily for possible cryptococcal meningitis. IV fluconazole was chosen (rather than amphotericin B deoxycholate) due to fears of amphotericin toxicity. Over the next 2 weeks the patient remained ill with fluctuating mental status (GCS ranging from 12 to 14 of 15).

On hospital day +30, a live female baby was delivered via normal spontaneous vaginal delivery with a birth weight of 1.9 kg, and Apgar scores 5/10. The baby was subsequently admitted to the neonatal intensive care unit (ICU) for respiratory distress requiring supplemental oxygen therapy and for further observation. A heel stick blood sample obtained from the neonate was CrAg negative. The 'baby's respiratory status improved after 5 days of oxygen therapy, and she was subsequently transferred out of the ICU with no apparent deficits (day +35).

Fig. 1. Cell phenotype and activation in CSF. Flow cytometry plots of T lymphocytes and HLA-DR expression (upper row) on CD4+ and CD8+ T cells. The bottom row shows PD-L1 expression on monocyte subsets. Of the CD45+ cells, 76% were lymphocytes, 0.2% were monocytes, and 1.2% were natural killer (NK) cells. CD8 T cells were the predominant lymphocytes (89.7%), and were highly activated with 84% expressing HLA-DR, while 9.6% were CD4+ T cells with 64% expressing HLA-DR. The classical monocytes were the predominant monocyte subset (74%) and showed high activation with 93% expressing PD-L1, while the intermediate and non-classical monocytes were equally present (13%) in the CSF. The predominant NK subset (56%) was CD56^{neg} cells with high expression of HLA-DR (95%).

On the third day post-partum (hospital day +33), the patient was transferred to the infectious diseases ward for further care as her mental status had worsened. Her physical examination was notable for positive Kerning's sign, nuchal rigidity, continued reduced strength in the right extremities 3/5, and altered mental status (GCS 12/15). Neurological examination revealed the patient was not oriented to person, place, or time and unresponsive to verbal orders. Initial vital signs were notable for a temperature of 36.3 °C (axillary), pulse 140, respiratory rate 16, blood pressure 115/87, and oxygen saturation of 95%. A diagnostic lumbar puncture was performed and the cerebrospinal fluid (CSF) CrAg was positive with a titer of 1:200.

The patient was immediately started on amphotericin 50 mg IV daily and oral fluconazole 400 mg twice daily. CSF examination showed no microorganisms on 'Gram's stain or Ziehl–Neelsen stain. A GeneXpert MTB/RIF (Cepheid) performed on the CSF was negative. A quantitative CSF culture on Sabouraud dextrose agar grew *C. neoformans* at 5700 colony forming units (CFUs) per mL of CSF. Repeat lumbar punctures were performed for relief of elevated CSF pressure on days 2, 5, and 9 of amphotericin therapy (days +34, +37, +41), results shown in Table 1. Retrospectively, CSF from day +41 was also evaluated for cell phenotype and activation by flow cytometry at the end of Amphotericin treatment and is described in Fig. 1. At the start of amphotericin therapy CSF white blood cell count was < 5 cells/μL and so flow cytometry was not conducted.

On hospital day +36 (day 3 of amphotericin therapy) the patient developed fevers, difficulty breathing and persistent vomiting. Her temperature was 37.8 °C, pulse 150, respiratory rate 36, blood pressure 100/58, and oxygen saturation 87%. On exam, she was in respiratory distress and had diffuse rhonchi present in the bilateral lung fields. She was treated with IV fluids, empiric antibiotics for aspiration pneumonia, and oxygen. Transfer to the ICU was indicated, but no beds were available. Laboratory evaluation revealed a plasma white blood cell count of 8.9×10^9 cells/L with 80% neutrophils. Hemoglobin, platelet count, renal, and liver function tests were within normal limits. Blood and urine cultures were negative. Unfortunately, the condition of the patient continued to deteriorate, and she died on the day 10 of amphotericin therapy (day +42 of hospitalization) due to respiratory failure.

3. Discussion

We report a case of unmasking cryptococcal meningitis in an HIV-infected pregnant woman who likely developed paradoxical IRIS in the post-partum period. Although published cases of cryptococcal infections in pregnant women are relatively rare [5–9], cryptococcal meningitis is estimated to cause 20–25% of AIDS-related deaths in sub-Saharan Africa accounting for approximately 350,000–400,000 deaths in 2011 [10,11]. *Cryptococcus* remains a major cause of morbidity and mortality in persons with AIDS, particularly in resource-limited settings with mortality rates of > 50% in routine care [11,12]. The burden of cryptococcosis is evident by the relatively high CrAg prevalence in asymptomatic persons with CD4 < 100 cells/μL ranges of 4–10% worldwide [3].

The patient described in this case had gestational cryptococcal meningitis that was diagnosed during the third trimester of pregnancy. Immunologic changes during pregnancy may increase the risk and severity of cryptococcal disease during pregnancy, leading to higher mortality rates [8]. Among the few reported cases of perinatal cryptococcal disease, most present during the third trimester or immediate postpartum period [7–9], as with our patient.

Initiating ART two months prior to her presentation likely led to unmasking IRIS in this patient. Her condition markedly worsened when her immune system recovered after she gave birth to her child, a paradoxical IRIS event, supported by her serial CSF WBC counts (Table 1). Cryptococcal IRIS has been reported in the post-partum period [5,6], and our patient's symptoms worsened following delivery making this a likely cause. What makes this a unique case is that she had two separate scenarios of IRIS, starting ART (unmasking) and giving birth to her child (paradoxical).

Despite all the measures taken, our patient died of respiratory failure. Even with potent antifungal therapy, cryptococcal disease continues to be associated with substantial morbidity and mortality [12]. Several factors are associated with mortality in central nervous system (CNS) cryptococcosis, these include: CSF white blood cell count < 20 cells/μL, high initial CSF CrAg titer > 1:32, untreated elevated intracranial pressure, and altered mental status [13–15]. Our patient initially had all these risk factors. The prolonged duration of altered mental status with initially untreated increased intracranial pressure coupled with vomiting, likely predisposed to aspiration. In a resource-rich setting, aspiration pneumonia would have been unlikely to be a fatal event, whereas in resource-limited settings, further supportive care and ventilator support is often unavailable.

With early diagnosis, cryptococcal meningitis often responds to therapy. Pregnant women with CNS or disseminated disease should be treated with amphotericin-based induction regimens whenever possible. Amphotericin rapidly clears the CNS of infection, is well distributed in the placenta [16], and better tolerated in children that it is in adults. Fluconazole, on the other hand, is fungistatic to minimally fungicidal and has been associated with birth defects in the first trimester [17,18]. However, fluconazole can probably be used safely during the second and third trimesters. In our case, the use of fluconazole monotherapy for initial management of this patient may have led to poor fungal clearance and increased risk of IRIS. Furthermore, pre-ART CrAg screening may have led to earlier diagnosis or prevented the development of meningitis altogether [3]. How to best manage asymptomatic CrAg+ women who are pregnant is unknown.

The predominance of CD8 T cells in this patient's CSF is similar to what has been found in the CSF of HIV-infected patients [19] and points to a poor CD4+ T cell response. The predominance of classical monocytes over intermediate monocytes in CSF at the end of Amphotericin therapy has been demonstrated by other investigators and may point to involvement of these subsets in the innate immune response to cryptococcal meningitis [20].

In conclusion, we present a novel case of a patient presenting with both unmasking CM IRIS induced by starting ART and paradoxical IRIS in the immediate post-partum period. Physicians must consider the immunomodulatory effects of giving birth and in the right circumstances, should consider IRIS.

Conflict of interest statement

The authors declare no conflict of interest.

Acknowledgments

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