Disseminated Cryptococcosis with Marked Eosinophilia in a Postpartum Woman

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Abstract:
Disseminated cryptococcosis usually develops in immunosuppressed patients. A 33-year-old postpartum woman developed disseminated cryptococcosis with marked eosinophilia. She presented with a cough and a week-long fever. A computed tomography scan showed multiple pulmonary nodules randomly distributed. Eosinophils were observed to have increased in number in both her peripheral blood and bronchoalveolar lavage fluid. A transbronchial lung biopsy and cerebrospinal fluid specimens revealed findings consistent with cryptococcal infection. Disseminated cryptococcosis can present with marked eosinophilia of the peripheral blood and lung tissues. Additionally, the postpartum immune status may sometimes be involved in the development of opportunistic infections in previously healthy women.

Key words: Cryptococcus neoformans, eosinophilia, immune reconstitution inflammatory syndrome, postpartum period

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Introduction
Cryptococcosis usually manifests as localized infections of the lung or skin - sometimes of the central nervous system in a disseminated form - usually in immunosuppressed hosts. Peripheral blood and pulmonary eosinophilia associated with cryptococcosis is an uncommon manifestation. Additionally, the occurrence of cryptococcosis during the postpartum period suggests instability of the immune system. We herein report a case of disseminated cryptococcosis with marked eosinophilia in a postpartum woman.

Case Report
A healthy 33-year-old woman, who had delivered a child five months earlier, visited a clinic with a cough, wheezing, and a week-long fever. As she had hypereosinophilia in her peripheral blood and a computed tomography (CT) scan indicated multiple pulmonary nodules, she was admitted to our hospital for further evaluation. She did not look critically ill and had neither any appreciable disease, atopic disposition, or history of animal exposure. Her heart and respiratory sounds were normal. The superficial lymph nodes were not palpable. Cutaneous involvement was not identified. A blood examination revealed significant eosinophilia (17,887 cells/mm$^3$) and a modest elevation of C-reactive protein (Table 1). Chest X-rays showed multiple nodular opacities in the bilateral lung fields. Chest CT showed diffuse and randomly distributed small pulmonary nodules (Figure a and b).

We performed bronchoscopy. The cell numbers in bronchoalveolar lavage (BAL) fluids were significantly increased (14.66x10$^5$ cells/mL) with a high proportion of eosinophils (89%). No evidence of Mycobacterium tuberculosis or any malignant neoplasms was found in the BAL fluids and transbronchial lung biopsy specimens, respectively. Biopsy specimens showed the aggregation of eosinophils within alveolar spaces, and Grocott’s silver stain identified yeast-like fungus bodies (Figure c). A progressively worsening headache appeared after admission; therefore, we performed a lumbar puncture. A cerebrospinal fluid (CSF) analysis is shown in Table 2. The number of cells increased, with a predominance of eosinophils. India ink stain showed yeast-
Table 1. Laboratory Findings on Admission.

| Test                          | Value          |
|-------------------------------|----------------|
| White blood cells             | 26,500 cells/mm³ |
| Neutrophils                   | 21.0 %         |
| Lymphocytes                   | 11.0 %         |
| Eosinophils                   | 67.5 %         |
| Hemoglobin                    | 12.5 g/dL      |
| Platelets                     | 21.9x10⁴ cells/mm³ |
| Total protein                 | 7.2 g/dL       |
| Albumin                       | 3.6 g/dL       |
| Total bilirubin               | 0.5 mg/dL      |
| Aspartate aminotransferase    | 10 IU/L        |
| Alanine aminotransferase      | 12 IU/L        |
| Lactate dehydrogenase         | 247 IU/L       |
| Alkaline phosphatase          | 329 IU/L       |
| γ-glutamyl transpeptidase     | 11 IU/L        |
| Creatine kinase               | 40 IU/L        |
| Blood urea nitrogen           | 7 mg/dL        |
| Creatinine                    | 0.58 mg/dL     |
| Uric acid                     | 4.7 mg/dL      |
| Sodium                        | 142 mEq/L      |
| Potassium                     | 4.1 mEq/L      |
| Chloride                      | 106 mEq/L      |
| Calcium                       | 9.2 mg/dL      |
| Glucose                       | 85 mg/dL       |
| Hemoglobin A1c                | 5.1 %          |
| C-reactive protein            | 1.15 mg/dL     |
| Immunoglobulin G              | 1,683 mg/dL    |
| Immunoglobulin A              | 232 mg/dL      |
| Immunoglobulin M              | 176 mg/dL      |
| Immunoglobulin E              | 1,943 IU/mL     |

Figure. (a, b) Chest computed tomography images show many small pulmonary nodules and a few bilateral pleural effusions. The nodules are randomly distributed and on the pleura (white arrow), which suggests that they are distributed with a hematogenous spread. Cryptococcus sp. is detected from cerebrospinal fluid and lung tissue specimens. (c) A lung biopsy specimen shows many yeast-like cells. They are positive for Grocott’s silver stain. (d) India ink stain reveals capsules of yeast-like fungus bodies in cerebrospinal fluid specimens (magnification: ×1,000).

Table 2. Cerebrospinal Fluid Analysis.

| Test                  | Value  |
|-----------------------|--------|
| Opening pressure      | 46 cm H₂O |
| Cell counts           | 84 cells/mm³ |
| Neutrophils           | +/-   |
| Lymphocytes           | 1+    |
| Eosinophils           | 2+    |
| Protein               | 32.3 mg/dL |
| Glucose               | 49 mg/dL |

like fungus bodies in the CSF (Figure d). Cryptococcal antigen titers from serum and CSF were 1:8 and 1:256, respectively. Cryptococcus neoformans var. neoformans was then isolated from the CSF and urine. Finally, we diagnosed the patient to have disseminated cryptococcosis.

We confirmed that she was not immunosuppressed. Idiopathic CD4+ T lymphocytopenia was unlikely because her peripheral lymphocyte number was normal and the proportion of CD4+ cells was 52.1%. Anti-interferon-γ autoantibody-induced cellular immunodeficiency was ex-
eral blood eosinophilia in cryptococcal disease is a more frequent antifungal treatment. Fortunately, she recovered with subsequent antifungal treatment.

### Discussion

We discovered two important clinical issues based on the findings of this rare case. First, disseminated cryptococcosis can present with marked eosinophilia of peripheral blood and lung tissues. Eosinophilia is uncommon in cryptococcal infection. Although the mechanism underlying eosinophilia has not yet been fully elucidated, some basic research reports an allergic reaction to C. neoformans. The intratracheal injection of C. neoformans induced inflammatory cells, including eosinophils, in rodents (1). A recent study demonstrated that a C. neoformans infection induced pulmonary IL-33 production with the accumulation of type 2 innate inflammatory cells, in which IL-33 activates the pathogen. A review of cryptococcosis in the postpartum period without HIV infection is shown in Table 3. The time of onset after delivery was mostly within the range of one week to half a year (median: two months). The pathogens were one case each of C. gattii and C. lauren-
tii (18, 23), and the others were C. neoformans.

Marked eosinophilia with Th1 predominance could be inconsistent because Th2 cytokines induce eosinophil differentiation. Our patient developed cryptococcosis as late as five months after delivery, when the Th1 predominance might have been restored. In addition, excessive Th2 responses could be triggered by cryptococcal antigens while reconstituting immunity is unstable. Because disseminated C. neo-
formans infection is fairly uncommon in immunocompetent patients, we diagnosed the present case to have postpartum IRIS.

In conclusion, we herein reported a case presenting with disseminated cryptococcosis as postpartum IRIS with marked eosinophilia for the first time. This is a fairly rare case; however, it implies a protective role of eosinophilia and recognizes postpartum immune system instability. In fu-

### Table 3. Review of Cryptococcosis with Eosinophilia in Adolescents and Adults.

| Age/Sex | Eosinophil (cells/mm³) | Site of infection | Underlying disease | Treatment | Outcome | Reference |
|---------|------------------------|------------------|-------------------|-----------|---------|-----------|
| 23 M    | 42,559                 | Disseminated     | Sarcoïdosis       | AMPH-B+5-FC+MCZ | Recovered | 4         |
| 16 F    | 10,500                 | Disseminated     | Nothing           | AMPH-B    | Recovered | 5         |
| 64 F    | 3,400                  | Disseminated     | Unknown           | AMPH-B+5-FC+FLCZ | Recovered | 6         |
| 23 M    | 27,750                 | Disseminated     | Nothing           | AMPH-B+5-FC | Recovered | 7         |
| 22 F    | 16,811                 | Disseminated     | Nothing           | AMPH-B+5-FC | Recovered | 8         |
| 61 M    | 6,252                  | Lung             | Cancer            | FLCZ      | Recovered | 9         |
| 28 M    | 6,000                  | Lung             | Nothing           | L-AMB+5-FC | Recovered | 10        |
| 33 F    | 17,887                 | Disseminated     | Nothing           | L-AMB+FLCZ | Recovered | Present case         |

M: male; F: female; AMPH-B: amphotericin B, 5-FC: flucytosine, MCZ: miconazole, FLCZ: fluconazole, L-AMB: liposomal amphotericin B
ture studies, it is necessary to elucidate the precise mechanism and function of eosinophil aggregation in response to cryptococcal infection, and the risk factors and precautions that need to be taken to prevent the onset of postpartum IRIS.

The authors state that they have no Conflict of Interest (COI).

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Table 4. Review of Cryptococcosis in the Postpartum Period without HIV Infection.

| Age | Time after delivery | Site of infection | Underlying disease | Treatment | Outcome | Reference |
|-----|------------------|-------------------|------------------|-----------|---------|----------|
| 30  | 6 weeks          | Lung              | Nothing          | MCZ+FLCZ  | Recovered| 16       |
| 28  | 3 weeks          | Lung              | Nothing          | FLCZ      | Recovered| 17       |
| 18  | 5 days           | Disseminated      | Nothing          | AMPH-B+5-FC | Recovered| 18       |
| 29  | 4 months         | Lung              | Nothing          | FLCZ+5-FC | Recovered| 19       |
| 25  | 2 months         | Lung              | Nothing          | FLCZ      | Recovered| 20       |
| 25  | 1 week           | Brain             | Nothing          | FLCZ      | Recovered| 21       |
| 28  | 1 month          | Lung              | Nothing          | Resection | Recovered| 22       |
| 30  | 2 months         | Disseminated      | Nothing          | AMPH-B    | Dead     | 23       |
| 33  | 5 months         | Disseminated      | Nothing          | L-AMB+FLCZ| Recovered| Present case |

MCZ: miconazole, FLCZ: flucloxacalone, AMPH-B: amphotericin B, 5-FC: flucytosine, L-AMB: liposomal amphotericin B
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