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【 CASE REPORT 】

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 (14.66×10^5 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-

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Table 1. Laboratory Findings on Admission.

White blood cells	26,500 cells/mm^3	Blood urea nitrogen	7 mg/dL
Neutrophils	21.0 %	Creatinine	0.58 mg/dL
Lymphocytes	11.0 %	Uric acid	4.7 mg/dL
Eosinophils	67.5 %	Sodium	142 mEq/L
Hemoglobin	12.5 g/dL	Potassium	4.1 mEq/L
Platelets	21.9×10^4 cells/mm^3	Chloride	106 mEq/L
Total protein	7.2 g/dL	Calcium	9.2 mg/dL
Albumin	3.6 g/dL	Glucose	85 mg/dL
Total bilirubin	0.5 mg/dL	Hemoglobin A1c	5.1 %
Aspartate aminotransferase	10 IU/L	C-reactive protein	1.15 mg/dL
Alanine aminotransferase	12 IU/L	Immunoglobulin G	1,683 mg/dL
Lactate dehydrogenase	247 IU/L	Immunoglobulin A	232 mg/dL
Alkaline phosphatase	329 IU/L	Immunoglobulin M	176 mg/dL
γ-glutamyl transpeptidase	11 IU/L	Immunoglobulin E	1,943 IU/mL
Creatine kinase	40 IU/L		

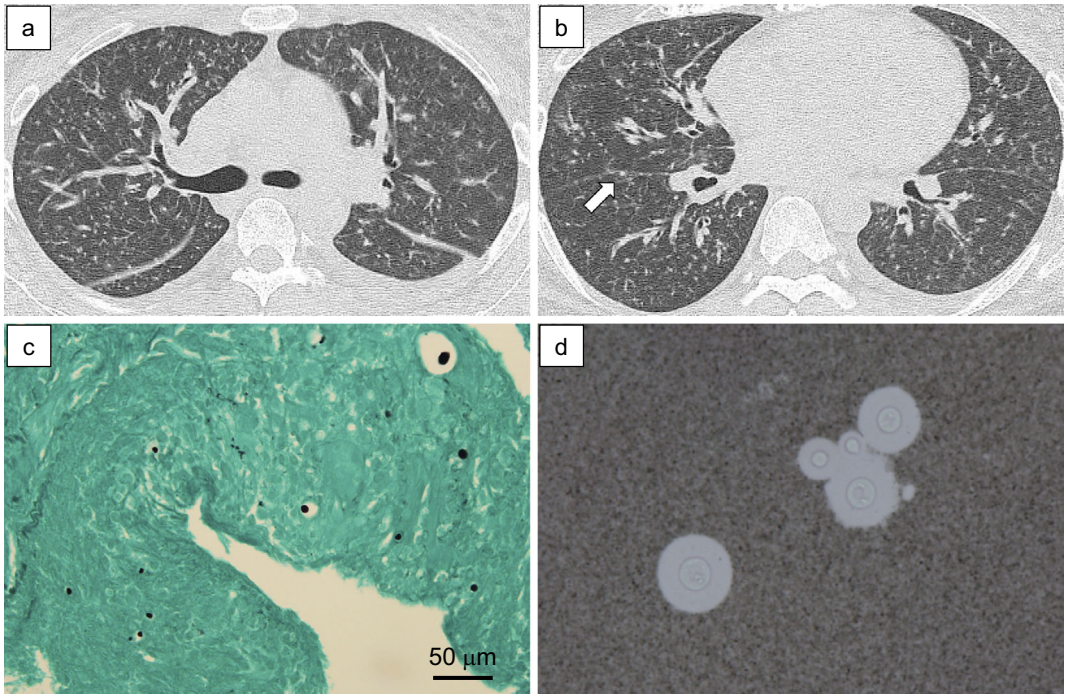

Figure. (a, b) Chest computed tomography images show many small pulmonary nodules and a few bilateral pleural effusions. The nodules are randomly distributed and on the pleura (white arrow), which suggests that they are distributed with a hematogenous spread. *Cryptococcus* sp. is detected from cerebrospinal 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.

Opening pressure	46 cm H_2O
Cell counts	84 cells/mm^3
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-

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

Age/Sex	Eosinophil (cells/mm^3)	Site of infection	Underlying disease	Treatment	Outcome	Reference
23 M	42,559	Disseminated	Sarcoidosis	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

cluded because no anti-interferon-γ autoantibodies were detected. In addition, human immunodeficiency virus (HIV) and human T-cell leukemia virus type 1 (HTLV-1) infection were negative.

An antifungal drug was started, but the patient was transferred to a highly specialized hospital to manage an acute episode of epileptic seizures and a disturbance of consciousness two days later. 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 lymphoid cells (ILC2) in mice (2). ILC2 is a major source of IL-5, a potent inducer of eosinophils, in a murine asthma model (3). We reviewed previous case reports of cryptococcosis with eosinophilia in adolescents and adults (Table 3). The identified pathogens were all *C. neoformans*; eosinophilia was seen in not only disseminated cases, but also in localized infections. No HIV-positive patients were reported. The most notable finding is that all patients with eosinophilia recovered, which indicates that eosinophils might play a protective role in cryptococcosis. Rat eosinophils are reported to opsonize *C. neoformans* phagocytosis and present *C. neoformans* antigens to trigger a fungal-specific Th1 immune response (11); this indicates the advantage of eosinophilia for cryptococcal infection. A recent retrospective study about pediatric cryptococcosis showed that peripheral blood eosinophilia was seen in 7 of 23 cases, especially in 5 of 11 disseminated cases (12), which indicates that peripheral blood eosinophilia in cryptococcal disease is a more common manifestation than generally recognized.

Second, the postpartum immune status may sometimes be involved in the development of opportunistic infections in previously healthy women. Cryptococcal infection is prone to develop during the postpartum period. We could not detect any evidence of immunosuppression in the present case except for her delivery five months earlier. Pregnancy causes a relatively immunosuppressed state for tolerating fetal antigens (13). The maternal immune system shifts from Th2 to Th1 after delivery, which can induce immune reconstitution inflammatory syndrome (IRIS) (13). IRIS is sometimes seen in immunosuppressed persons, which, paradoxically, worsens previously acquired asymptomatic and opportunistic infections during recovery of the host's immune system (14). Cryptococcal infection triggered by anti-retroviral therapy for HIV-positive patients is well documented (15). Although we could not identify precisely when the present case became infected, we speculate that she had been latently infected by *C. neoformans* before delivery, and the alteration of her immune status in the postpartum period subsequently activated the pathogen. A review of cryptococcosis in the postpartum period without HIV infection is shown in Table 4. 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. laurentii* (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. neoformans* 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 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: fluconazole, AMPH-B: amphotericin B, 5-FC: flucytosine, 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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