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CASE REPORT

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Disseminated cryptococcal infection with eosinophilia in a healthy person

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Abstract A 23-year-old man with no recent medical history was hospitalized complaining of high fever and cough. In addition to very marked eosinophilia, chest X-ray revealed extensive bronchovascular bundle thickening. Transbronchial lung biopsy (TBLB) showed moderate eosinophil infiltration. *Cryptococcus neoformans* infection was diagnosed, based on blood culture, cerebrospinal fluid culture, urine culture, and lung biopsy specimens. The eosinophilia was successfully alleviated by treatment for cryptococcal meningitis. Furthermore, cryptococcal sepsis resolved with amphotericin B and 5-flucytosine treatment. Eosinophilia commonly occurs following chronic *Aspergillus* infection, but the present case suggests the involvement of *Cryptococcus* in another mechanism for eosinophilia.

Key words Eosinophilia · *Cryptococcosis* · Meningitis · Sepsis · Desensitization · Antifungal drug

Introduction

Cryptococcus is an encapsulated yeast that causes severe meningitis and disseminated infections in immunocompromised individuals.[1] It does not generally produce symptoms in healthy adults, although multiple nodular opacities may appear in the lungs.[2] Cryptococcal infection presenting with eosinophilia is rare in HIV-negative patients, but it has been reported.[3–5] We experienced a case of a healthy individual who developed cryptococcal infection with sepsis and meningitis, in addition to marked eosinophilia. Herein, we present this exceedingly rare case, with details of an immunological investigation and a literature review regarding eosinophilia.

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Case report

The case involved a 23-year-old male university student who had had atopic dermatitis in his childhood. He had had no close contact with pigeons or other birds. The patient developed cough and fever in late May 2004. Although he was given an antibiotic (tosufloxacin) and a nonsteroidal anti-inflammatory drug (loxoprofen) by a general practitioner on June 2, his symptoms were not alleviated. On June 5, he developed a headache and visited the clinic again, and he was diagnosed with *Herpes zoster* infection, but the basis of the diagnosis was unclear. He was medicated with valacyclovir hydrochloride. On June 7, his medication was altered to clarithromycin, which he took for 6 days. Blood tests conducted at the clinic on June 15 revealed elevated leukocyte (37000/μl) and eosinophil (75%) levels, while computed tomography (CT) showed extensive bronchovascular bundle thickening and mediastinal lymphadenopathy. Based on these findings, the patient was admitted to our hospital on June 21 for detailed tests and treatment.

On admission, his body temperature was elevated, at 38.8°C and oxygen saturation level was 92% in room air. With regard to physical findings, superficial lymph nodes were not palpable. Chest and abdominal examination revealed no abnormal findings. Skin examination showed no eruptions, and neurological examination also revealed no abnormal findings, including meningeal irritation.

Laboratory findings (Table 1) showed an elevated leukocyte count with eosinophilia, in addition to elevated C-reactive protein (CRP), erythrocyte sedimentation rate, and hepatic enzymes.

Blood gas analysis revealed hypoxemia, as indicated by the following results in room air: pH, 7.447; *P*aCO2, 39.9 mmHg; *P*aO2, 64.7 mmHg; HCO3-, 27.1 mmol/l.

Chest CT (high-resolution CT) on admission showed worsening of bronchovascular bundle thickening and

Table 1. Laboratory findings on admission

Hematology		Chemistry			
RBC	439×10^4/μl	TP	7.6 g/dl	ANA	<40
Hb	13.6 g/dl	Alb	4.1 g/dl	CH50	19.1 U/ml
Ht	40.3%	GOT	56 IU/l	C3	138 mg/dl
WBC	20600/μl	GPT	144 IU/l	C4	24 mg/dl
Neut	18%	LDH	357 IU/l	IgG	901 mg/dl
Lymp	10%	T. bil	0.7 mg/dl	IgA	189 mg/dl
Eosi	71%	ALP	2080 IU/l	IgM	119 mg/dl
Mono	1%	γ-GTP	147 IU/l	IgE	2200 mg/dl
Plt	39.1×10^4/μl	T. Chol	171 mg/dl	HIV (–)	
ESR	30 mm/h	BUN	8.8 mg/dl	HTLV-1 (–)	
		Cr	0.56 mg/dl	CD4	48%
Serology		UA	4.6 mg/dl	CD8	16%
CRP	11.3 mg/dl	Na	135 mEq/l	CD4/8	3
ACE	86.4 IU/l	K	4.4 mEq/l	ADA	42.4
CEA	1 ng/ml	Cl	96 mEq/l		
SCC	0.8 ng/ml	Ca	9.1 mg/dl		
sIL-2R	4320 U/ml				
				BALF	
Arterial blood gas analysis (room air)		Coagulation system		Total cell count	970×10^3/ml
pH	7.447	PT	13.0 s	(eosi, 73.4%; neut, 0.8%; lymph, 0.6%)	
*P*aCO2	39.9 mmHg	APTT	37.3 s	CD4/8	1.4
*P*aO2	64.7 mmHg				
HCO3-	27.1			DLST	
				Loxoprofen sodium	SI 160%
				Valacyclovir hydrochloride	SI 70%
				Tosufloxacin tosilate	SI 94%
				Clarithromycin	SI 125%

mediastinal lymphadenopathy (Fig. 1). To obtain a definitive diagnosis, transbronchial lung biopsy (TBLB) was performed on day 2 (Fig. 2). Although mild eosinophil infiltration was observed in the alveolar septum and alveolar space, bronchoalveolar lavage fluid (BALF) culture was negative for bacteria, acid-fast bacillus, and fungus. The total cell count in the BALF was 970×10^3/ml, and, among the cell fractions, eosinophils were elevated (73.4%; Table 1). No malignant cells were observed on cytology.

Although we considered the possibility that the eosinophilia observed on admission was drug-induced, drug lymphocyte stimulation tests (DLSTs) conducted for drugs prescribed by the local clinic were all negative (Table 1). Moreover, stool smear revealed no parasites.

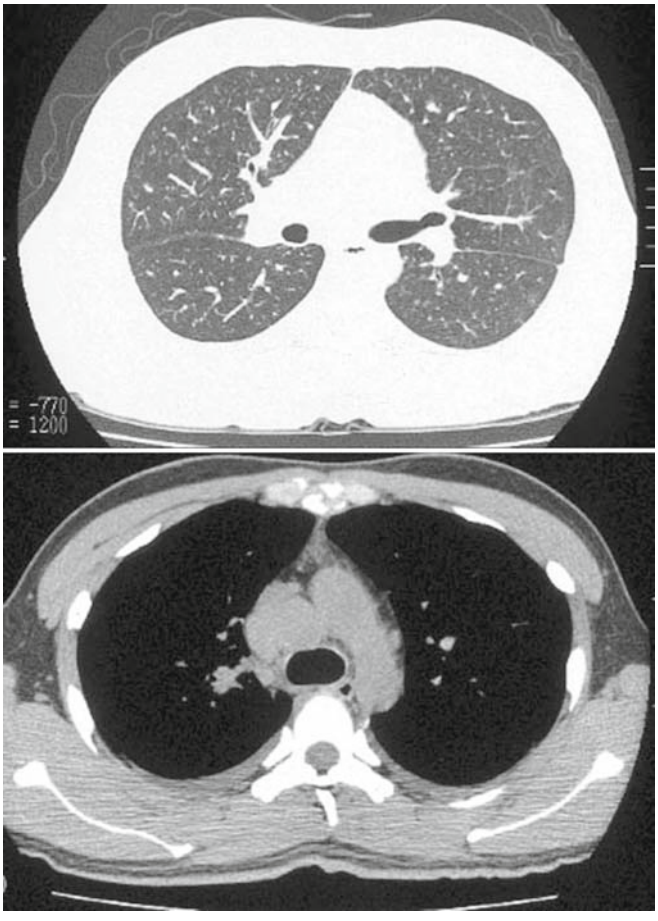

Fig. 1. Chest high-resolution computed tomography (HRCT) revealed bronchovascular bundle thickening and mediastinal lymphadenopathy

Post-admission course

Based on the medical history, in addition to blood tests and chest imaging findings, drug-induced pneumonia, eosinophilic pneumonia, and sarcoidosis were suspected. Because bronchoscopy performed on admission showed no findings that were strongly indicative of infection, and BALF demonstrated significantly elevated eosinophils (Table 1), the patient was thought to have a condition similar to acute eosinophilic pneumonia (AEP), and was thus given an adrenocortical hormone (prednisolone, 30 mg daily) from day 4. However, on day 5, *Cryptococcus* was detected in the blood culture obtained on admission, and cerebrospinal fluid and urine tests conducted on day 5 were also positive for *Cryptococcus*. Based on these findings, the patient was diagnosed with disseminated cryptococcosis, and was later found to be infected exclusively with *Cryptococcus* serotype

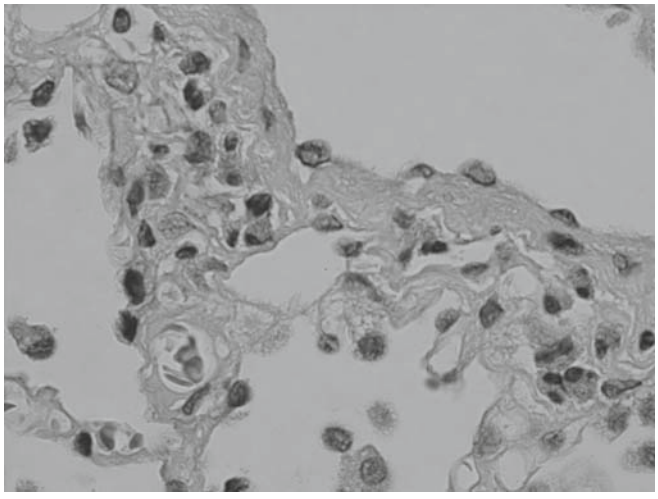

Fig. 2. Transbronchial lung biopsy (TBLB) specimen showed eosinophil infiltration with no malignant cells

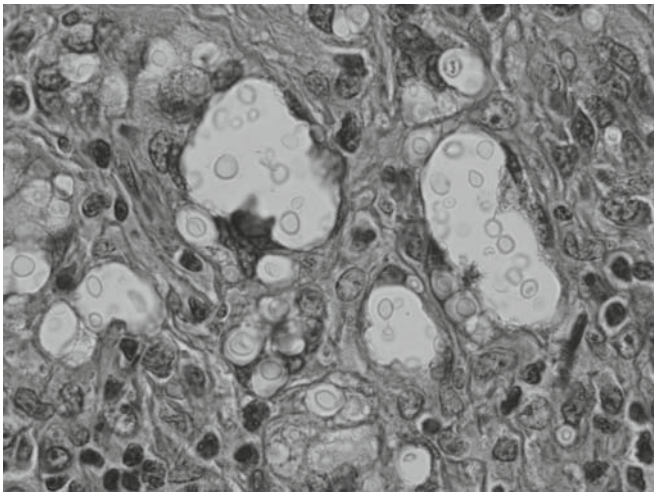

Fig. 3. Cervical lymph node biopsy was performed. On pathology examination, *Cryptococcus* was detected in the cervical lymph node biopsy specimen

A. Brain magnetic resonance imaging (MRI) did not demonstrate any abnormalities. He did not complain of pain suggestive of prostatitis. Cryptococcal antigen in serum was negative on day 5, but on day 9 it had become positive in serum and cerebrospinal fluid.

With regard to immune function, the patient had normal immunoglobulin levels and was negative for HIV and human T-lymphotropic virus (HTLV)-1, and thus was not thought to be immunocompromised (Table 1). The adrenocortical hormone treatment was discontinued after 4 days, and intravenous fosfluconazole (F-FLCZ) 800 mg/body was given from day 5 as treatment for cryptococcosis. However, the F-FLCZ was discontinued after the patient developed systemic urticaria with lowered blood pressure that was attributed to anaphylactic shock the day after its infusion.

Subsequently, the patient was given combination therapy with intravenous amphotericin B (AMPH-B) 0.75 mg/kg (50 mg/body) and oral 5-flucytosine (5-FC; 100 mg/kg). Furthermore, meropenem trihydrate (MEPM) 1 g/body was intravenously infused. After 4 days, the MEPM was switched to ampicillin sodium · sulbactam sodium (SBT/ABPC) 6 g/body, because of drug-induced liver dysfunction. The SBT/ABPC was continued for 20 days. The dose of AMPH was 10 mg on the first day of infusion, and was increased to the maintenance dose of 50 mg on day 13 of infusion. By day 26, with treatment solely for cryptococcosis, the patient's fever had declined and a reduction in eosinophils to 15% (1095/μl) was observed. Class 3-specific IgE antibodies were observed for *Candida* and *Aspergillus*. Subsequently, the patient tested negative for IgE antibodies specific for antigens isolated from *Cryptococcus*. Around the same time, a new lymphadenopathy 5 mm in size was observed in the left neck area. Cervical lymph node biopsy performed on day 30 showed diffuse infiltration of *Cryptococcus* into the lymph node (Fig. 3).

With the continuation of treatment, *Cryptococcus* was undetectable in blood and cerebrospinal fluid on day 26. On day 38, cryptococcal antigen was negative in both serum and cerebrospinal fluid.

Similarly, the extensive bronchovascular bundle thickening observed on chest CT was reduced, and the mediastinal lymphadenopathy also decreased in size. However, because an abnormal pulmonary shadow remained (Fig. 4), TBLB was performed again, and revealed the presence of *Cryptococcus* in the lymphatics along bronchial and vascular walls, as well as in the alveoli (Fig. 5).

After a cumulative dose of 2400 mg of AMPH-B had been administered, treatment was switched to an oral antifungal agent. Because allergic symptoms had been observed following intravenous F-FLCZ, desensitization therapy using an oral fluconazole (FLCZ) was provided as aftercare. The desensitization therapy was initiated at an FLCZ dose of 0.2 mg, which was increased to 400 mg over 15 days without the manifestation of any allergic symptoms. The patient was discharged on day 90 after recovery (Fig. 6). No relapse of symptoms such as fever and malaise occurred during home recuperation after he was discharged.

Discussion

The case we have reported may be a rare case of disseminated cryptococcal infection in a healthy young man who had an abnormal lung shadow, urinary tract infection, and meningitis. This patient did not complain of any urinary tract symptoms but there may have been a possibility of prostate infection by *Cryptococcus*. On admission, the patient presented with disseminated cryptococcosis associated with marked serum eosinophilia. The eosinophilia was attributed to either: (1) an allergic reaction to drugs given prior to admission, or (2) elevation of eosinophils associated with cryptococcal infection. Tosufloxacin and loxoprofen were unlikely to have been responsible for the eosinophilia because they had been discontinued 2 weeks

prior to his admission. Valacyclovir hydrochloride and clarithromycin may have been causative, as the patient was taking these medications until June 12 (9 days before admission to our hospital), but DLST was negative for these agents. Although a negative result on DLST does not rule out drug involvement, the frequency of eosinophilic pneumonia induced by tosufloxacin, clarithromycin, and loxoprofen is not particularly high.[6–8] Increases in leukocyte count to 37 000/μl are also rare. No reports on valacyclovir hydrochloride in relation to eosinophilia were found in searches of Japana Centra Revuo Medicina and PubMed.

Imaging showed extensive bronchovascular bundle thickening and mediastinal lymphadenopathy, which indicated lymphatic involvement. This type of dissemination along lymphatics is rare in drug-induced pneumonia. Another possibility was the activation of immune function by *Cryptococcus*. Allergic bronchopulmonary aspergillosis is known to lead to eosinophilia, in which IgE and IgG antibodies play central roles.[9] Although the present patient had IgE antibodies of Radio Allergo Sorbent Test (RAST) class 3 for *Candida* and *Aspergillus*, he was negative for IgE

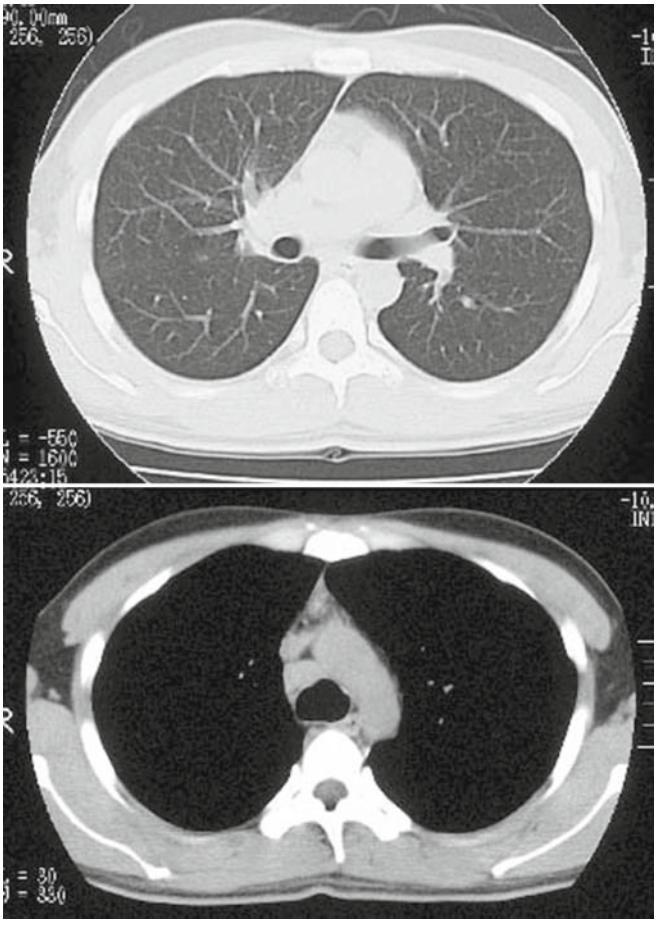

Fig. 4. The mediastinal lymphadenopathy remained, but it was reduced after 30 days' treatment with amphotericin B (AMPH-B) and 5-flucytosine (5-FC)

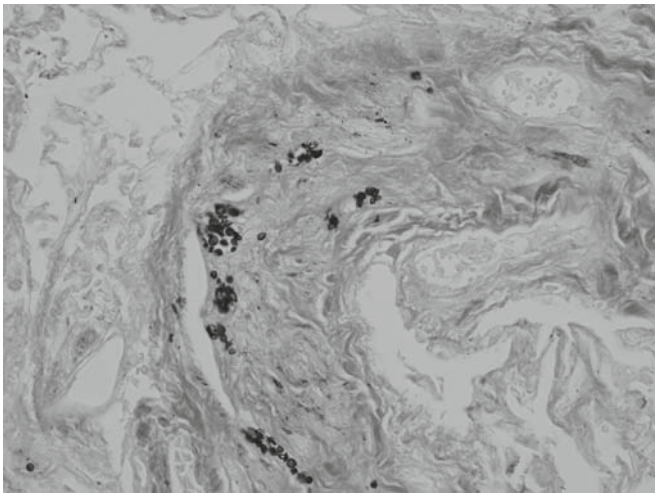

Fig. 5. *Cryptococcus* was detected in a pulmonary alveolus after 90 days' treatment with AMPH-B and 5-FC

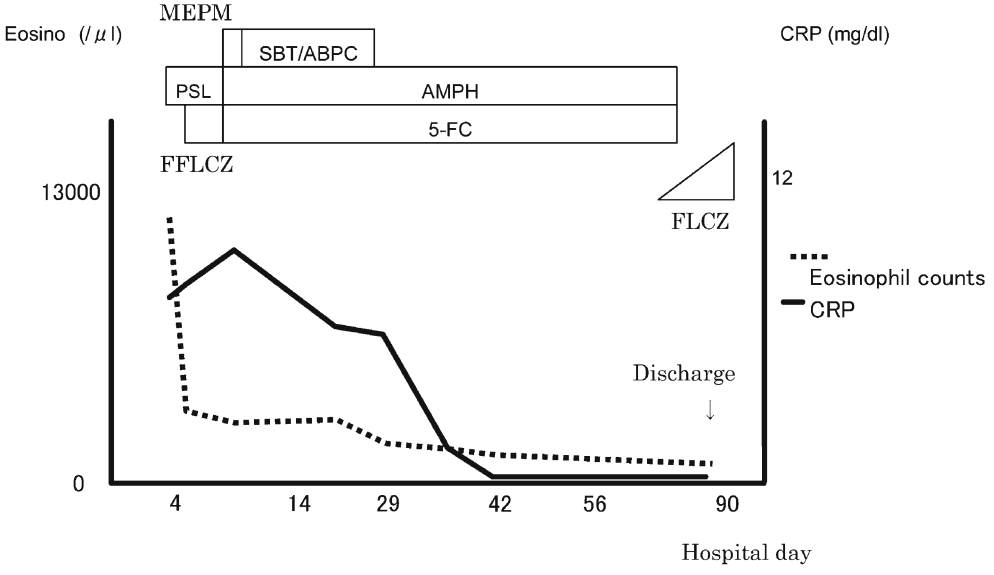

Fig. 6. Clinical course. *MEPM*, meropenem trihydrate; *SBT/ABPC*, ampicillin sodium · sulbactam sodium; *PSL*, prednisolone; *FLCZ*, fluconazole; *FFLCZ*, fosfluconazole; *CRP*, C-reactive protein

antibodies for cryptococcal antigens (isolated at the National Hospital Organization Sagamihara National Hospital). We thought that this negativity was because of the short duration of Cryptoccocal infection. Another possible reason for the IgE negativity could be related to the composition of the cell wall of *Cryptococcus*. *Cryptococcus* is normally covered in a layer of capsular polysaccharides, the main component of which is glucuronoxylomannan. In contrast, the cell walls of *Aspergillus* and *Candida* consist of the protein complexes galactomannan and mannan, respectively.[10] To date no specific IgE antibodies for *Cryptococcus* have been reported.

Although eosinophilia resulting from cryptococcal infection has been reported in a number of HIV-negative patients,[3–5] its cause has not been elucidated in these patients either. In the present patient, who had had an atopic disposition since childhood, eosinophilia may have resulted from the initiation of Th2 allergic reactions caused by the cryptococcal infection.

Serum IgE may become elevated not only as a result of allergic lung disorders but also as a result of chronic inflammatory lung disorders such as pulmonary cryptococcosis,[10] a disease that is closely linked to serum IgE. Specifically, a Th2-dominant immune status has been reported to cause increases in serum IgE, as well as susceptibility to cryptococcal infections in the lungs.[11] In addition, infections presenting with elevated IgE have been associated with a high risk of systemic dissemination, including meningitis.[12,13] Although cytokines such as interleukins 3 and 5 are thought to be involved in eosinophilia, this relationship was not investigated in the present study. Hematological diseases which cause an increase of eosinophils should also be considered. However, bone marrow aspiration and biopsy was not carried out in our patient because the eosinophils were reduced by the medical treatment of cryptococccal sepsis. Sometimes, an increase in eosinophils is detected in pernicious anemia, Hodgkin's lymphoma, chronic myeloid leukemia, and polycythemia, but our patient did not have specific clinical characteristics of these diseases.

In the present patient, extensive bronchovascular bundle thickening and mediastinal lymphadenopathy were observed on imaging on admission, and sarcoidosis and malignant lymphoma were considered in the differential diagnosis, based on the initial images. Diagnosis was difficult to confirm, as elevation of eosinophils in BALF indicated the possibility of AEP. Radiographic abnormalities associated with *Cryptococcus* include various shadows, such as infiltrative shadow, solitary or multiple nodular opacities, interstitial shadow, cavitary shadow, and pleural effusion.[14–16]

Healthy individuals, such as the present patient, rarely present with extensive bronchovascular bundle thickening and mediastinal lymphadenopathy. It was thought that cryptococcal septicemia was disseminated in the whole body. X-ray findings in cryptococcal infection have been reported to vary depending on the host's immune status.[17] In the present patient, although the steroids initially given for eosinophilia may have contributed to the disseminated course, their effects were thought to be small, considering that the patient was likely to have already had systemic infection on admission, as indicated by the detection of *Cryptococcus* in blood culture obtained on admission prior to steroid administration, in addition to the presence of gradually enlarging mediastinal lymphadenopathy on CT on admission.

Due to the detection of *Cryptococcus* in the lymphatics of the bronchial and vascular walls, as well as in alveoli, on the second TBLB, the extensive bronchovascular bundle thickening and mediastinal lymphadenopathy observed on chest CT was attributed to shadows created by *Cryptococcus*. Chest CT performed after the completion of treatment showed resolution of the extensive bronchovascular bundle thickening and mediastinal lymphadenopathy. Possible reasons for the absence of *Cryptococcus* on the TBLB performed on admission include differences that may have been related to the initial biopsy site and factors involved in pulmonary *Cryptococcus* invasion.

Although many types of antifungal agents are now available, the present patient was treated using 5-FC and AMPH-B, because new antifungal agents were unavailable at the time. At present, additional options include liposomal AMPH-B (L-AMB), itraconazole (ITCZ), and intravenous infusion of voriconazole (VRCZ).

Because the present patient was allergic to F-FLCZ, he was given desensitization therapy using FLCZ as aftercare. Although FLCZ is an azole antifungal agent, it has been associated with allergic side effects. When no other treatment is available, desensitization therapy must be given over a period of 15 days.[18] As the present patient did not develop allergic symptoms following desensitization therapy using oral FLCZ at an initial dose of 0.2 mg and final dose of 400 mg, desensitization therapy using FLCZ was considered to be useful.

Conclusion

Using combination therapy with amphotericin B and flucytosine, we successfully treated a previously healthy patient who had developed a disseminated cryptococcal infection presenting with eosinophilia.

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