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Possible Pulmonary Cryptococcosis in a Patient with Crohn's Disease during Anti-Tumor Necrosis Factor-Alpha Treatment: a Case Report and Literature Review

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Tumor necrosis factor-alpha inhibitors are widely used as treatment agents for rheumatoid arthritis (RA) and Crohn's disease (CD). Infliximab (IFX) is a representative agent that has been used in Japan since 2002. Opportunistic infections by mycobacteria and fungi are well known in patients receiving IFX, and cryptococcosis, an invasive fungal infection, has been reported in RA with relatively high incidence, but it has rarely been reported in CD (1–11). In this study, we have reported a possible case of pulmonary cryptococcosis during IFX treatment in a patient with CD, and have reviewed previously reported cases (9–11).

A 35-year-old man was diagnosed with ileocolic-type CD at 2 years of age. On 3 separate occasions, he had undergone intestinal surgeries for fistula or stenosis of the intestine due to CD and colostomy. Although he was being treated with 5-aminosalicylic acid and prednisolone (10 mg/day, orally), his symptoms gradually worsened. Although his CD activity index (CDAI) did not indicate severe activity (CDAI, approximately 150), he had severe longitudinal ulcers in his residual intestine. Oral treatment with 5-aminosalicylic acid and prednisolone was insufficient to improve his symptoms; therefore, he began receiving IFX therapy in combination once every 6 weeks when he was aged 34 years. His symptoms gradually relieved.

In July 2011, after 8 infusions of IFX, he was referred to our respiratory medicine department presenting with high fever, which was refractory to antibiotics (ciprofloxacin), and a nodular lesion in the left lower lobe of the lung, as shown by the chest computed tomography (CT) images. Physical examination showed that his temperature and respiratory rate were 38.1°C and 16 breaths/min, respectively; the oxygen saturation level was 98% while inhaling ambient air. Respiratory sounds were normal upon auscultation. Abdominal,

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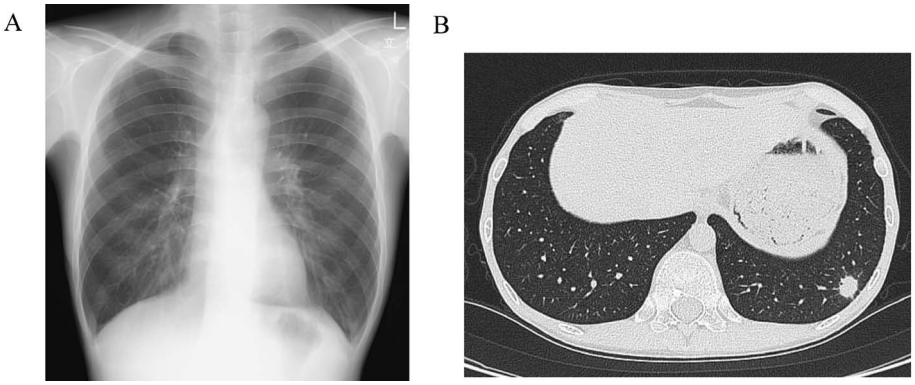

Fig. 1. (A) Chest radiograph at the first visit. No abnormal finding was observed. (B) Chest computed tomography (CT) at the first visit. Chest CT revealed a 14-mm nodule in segment 9 of the left lung. Cavity, daughter nodule, or tree-in-bud appearance was not observed.

cardiovascular, and neurological examinations did not reveal any particularly remarkable features.

The chest radiograph finding was almost normal, but CT of the chest revealed a 14-mm nodule just below the pleura of segment 9 of the left lung (Fig. 1A, B). Lung cancer, pulmonary mycobacteriosis, and mycoses were considered as differential diagnosis, but the solitary nodule lacked the features of typical lung cancer or pulmonary mycobacteriosis, such as daughter nodules and relevant pleural indentations. In addition, he was young and tumor markers, including carcinoembryonic antigen (CEA), cytokeratin fragment (CYFRA), and progastrin-releasing peptide (pro-GRP) were all negative. Accordingly, opportunistic infections, including pulmonary mycobacteriosis and mycoses, were strongly suspected although he did not have a history of relevant exposure to those pathogens. Laboratory tests showed normal leukocytes (7,200/mm^3) and increased C-reactive protein levels (3.71 mg/dl). Serum cryptococcal antigen (Eiken, Tokyo, Japan) and QuantiFERON®-TB Gold were negative, and the β-D-glucan test (Wako, Osaka, Japan) was slightly elevated (13.6 pg/ml). All other laboratory test results, including those for liver enzymes, creatinine, and blood urea nitrogen, were within normal ranges (Table 1).

Table 1. Laboratory findings at the first visit

Leukocyte	7200/μl	Na	135 mEq/l
Sg.	83%	K	3.8 mEq/l
Ly.	9%	Cl	103 mEq/l
Mo.	8%	BUN	17.0 mg/dl
Eo.	0%	Cre	0.92 mg/dl
Ba.	0%	TP	7.2 g/dl
Erythrocyte	418×10^4/μl	T.bil	0.3 mg/dl
Hb	9.7 g/dl	AST	12 IU/l
Plt	34.5×10^4/μl	ALT	10 IU/l
PCT	0.048 ng/ml	LDH	123 IU/l
β-D-glucan	13.6 pg/ml	CRP	3.71 mg/dl
Cryptococcal antigen	(—)		
QuantiFERON®-TB Gold	(—)		

Sg, segmented form; Ly, lymphocyte; Mo, monocyte; Eo, eosinophil; Ba, basophil; Hb, hemoglobin; Plt, platelet; PCT, procalcitonin; BUN, blood urea nitrogen; Cre, serum creatinine; TP, total protein; T.bil, total bilirubin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; CRP, C-reactive protein.

Bronchoscopy with bronchoalveolar lavage of the left lower lobe was performed for further examination. Transbronchial lung biopsy was not performed as the nodular lesion was not visible on the chest radiograph. The microscopy tests of the bronchoalveolar lavage fluids (BALF) did not reveal any bacteria, mycobacteria, fungi, or yeast; however, the BALF were positive for cryptococcal antigen ($\times$16). Polymerase chain reaction tests for *Mycobacterium tuberculosis*, *M. avium*, and *M. intracellulare* were negative, as was cytology diagnosis. At this point, IFX was discontinued, but aggressive treatment against cryptococcosis was not performed because the culture remained negative even after 2 weeks of incubation. The lung nodule deteriorated and infiltration was observed 3 weeks after the first visit. He underwent bronchoscopy again, and the second test for cryptococcal antigen in BALF was also positive ($\times$32), while the culture and serum cryptococcal antigen remained negative. Spinal fluid examination was not performed due to the lack of encephalomeningitis symptoms and signs and the negative serum cryptococcal antigen result. Accordingly, he was treated with 400 mg/day oral fluconazole (FLCZ) for possible pulmonary cryptococcosis, though the evidence was insufficient for definitive diagnosis. The clinical course of the present case is shown in Fig. 2. Due to the discontinuation of IFX, his CD symptoms such as diarrhea, abdominal pain, and high fever worsened, and the CDAI elevated to 234. Hence, IFX was restarted approximately a month after the initiation of FLCZ, following which his symptoms gradually relieved and the CDAI decreased. Infiltration of the left lower lobe of the lung gradually improved and was nearly eliminated after 3 months' FLCZ administration. The patient was treated with FLCZ for a total of 6 months, and no relapse has been observed thus far.

Serum cryptococcal antigen, in spite of its high sensitivity and specificity (12), tends to be negative when a nodule is 15 mm or smaller (13); thus, the small nodule may have been related to the negative serum cryptococcal antigen in our case. Consensus on the significance of cryptococcal antigen in BALF is not complete, and routine testing is not recommended; however, it is reported to have 100% sensitivity and 98% specificity when the titer exceeds $\times$8 (14,15). In our case, 2 separate BALF

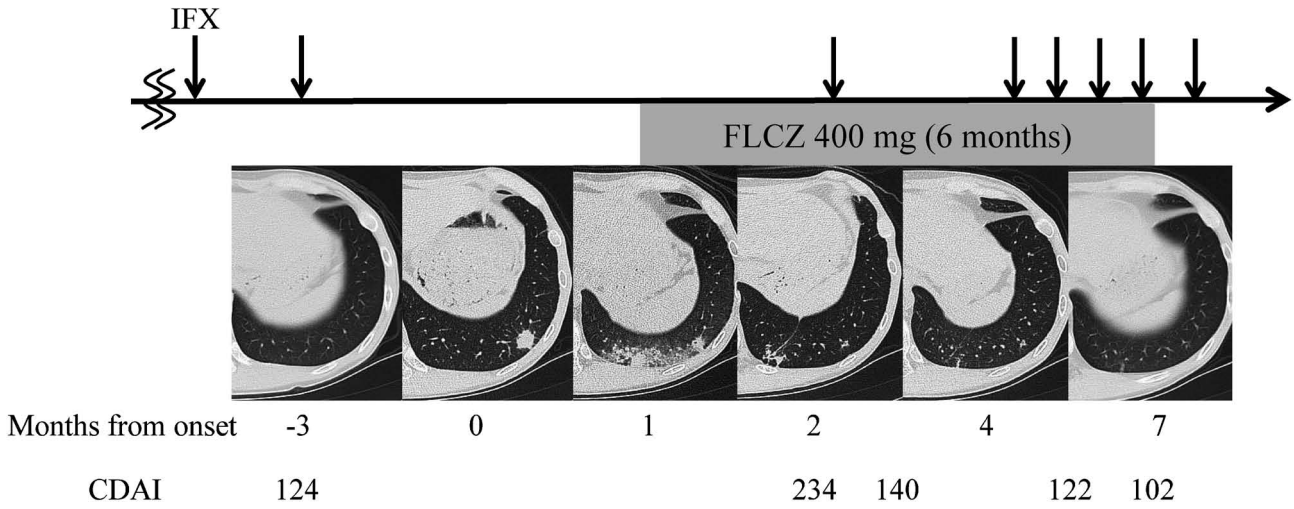

Fig. 2. Clinical course of the present case. A nodule in segment 9 of the left lung changed into infiltration (segments 9, 10) in 3 weeks. The infiltration gradually improved after initiation of fluconazole. The Crohn's disease symptoms worsened during the infliximab discontinuation period, but resolved when infliximab was restarted. FLCZ, fluconazole; ↓, infliximab (IFX); CDAI, Crohn's disease activity index.

Table 2. Clinical characteristics of pulmonary cryptococcosis in Crohn's disease patients receiving TNF-α inhibitor

Study group (ref no.)	Age/sex	Symptom	Disease duration of CD (yr)	IFX treatment	Concurrent medication	CT findings	Dissemination	Methods for diagnosis
Rehman et al. 2008 (11)	61/M	none	10	2.5 years	prednisolone, azathioprine	multiple nodules (max 6 cm)	−	biopsy
Osawa and Singh 2010 (10)	53/M	high fever, diarrhea	34	3 years	prednisolone, azathioprine	multiple nodules	+	biopsy
Hirai et al. 2011 (9)	39/M	none	8	5 times	none	nodule (left lower lobe)	−	histological finding (surgical specimen)
Present case	35/M	high fever	33	8 times	prednisolone	nodule (1.4 cm, left lower lobe) →infiltration	−	cryptococcul antigen in BALF

TNF-α, tumor necrosis factor-alpha; CD, Crohn's disease; IFX, infliximab; BALF, bronchoalveolar lavage fluids.

specimens demonstrated positive cryptococcal antigen with titers of ×16 and ×32, so contamination would be unlikely. In addition, the clinical course and CT findings were compatible with pulmonary cryptococcosis, though other mycoses, for which the antigen could have been false positive, should also be considered (15).

A post-marketing surveillance study of IFX in Japan revealed that 30 of the 5,000 RA patients developed fungal infections, including 5 cases of pulmonary cryptococcosis, while none of 2,820 CD patients developed invasive fungal infections. In addition, only 3 cases have been reported (3,9–11). The reason for this difference in the incidence rate is unclear, but the mean age is higher in RA (55.1 years) than in CD (32.2 years), and the rate of oral corticosteroid treatment in combination is higher in RA (88.3%) than in CD (35.9%); these factors may contribute to the higher incidence rate in RA.

Table 2 lists the clinical manifestations of 3 previously reported cases in comparison with our case. The disease durations of CD are relatively long, and all patients received multiple doses of IFX. Three patients out of 4, including the present case, received oral prednisolone, and multiple nodules and/or infiltration were observed in the radiographs. Toruner et al. demonstrated that the increased risk of opportunistic infections in inflammatory bowel diseases was statistically significant only when IFX was used in combination with both corticosteroids and azathioprine/6-mercaptopurine (16). Lichtenstein et al. also reported that an increased risk for serious infections observed in CD patients treated with IFX was due to disease severity and prednisone usage (17).

In conclusion, cryptococcosis in CD patients has been reported only rarely; nevertheless, patients receiving IFX, especially in combination with oral corticosteroid therapy, should always considered at risk of opportunistic infections, including invasive mycoses.

Conflict of interest None to declare.

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