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ABOUT COVER

Editorial Board Member of *World Journal of Gastroenterology*, Angela Peltec, PhD, Associate Professor, Department of Internal Medicine, Discipline of Gastroenterology, State University of Medicine and Pharmacy "Nicolae Testemitanu", Chishinev 2019, Moldova. apeltec@yahoo.com

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Pulmonary cryptococcosis after immunomodulator treatment in patients with Crohn's disease: Three case reports

Yan-Fei Fang, Xiang-Han Cao, Ling-Ya Yao, Qian Cao

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Abstract

BACKGROUND

Corticosteroids and anti-tumor necrosis factor α mAbs are widely used to treat Crohn's disease (CD). However, one disadvantage of this treatment is impairment of normal immune function, leading to an increased risk of infection. Cryptococcus infection is an opportunistic infection that occurs mainly in immunocompromised patients and poses a significant diagnostic challenge in patients with CD.

CASE SUMMARY

Here, we report three cases of pulmonary cryptococcosis in patients with CD after receiving immunomodulatory treatment. The patients presented with no or mild respiratory symptoms. Chest computed tomography scans revealed pulmonary nodules in the unilateral or bilateral lobes. Diagnoses were made using pathological examination and metagenomic sequencing. The patients were treated with fluconazole 400 mg once daily for 1 to 6 mo, and symptoms were resolved. Literature searches were conducted in PubMed, Web of Science, and Embase to retrieve previously reported cases and summarize patient characteristics.

CONCLUSION

The incidence of cryptococcus infection has increased along with immunomodulator use. Clinical vigilance is required for early identification and standardized treatment.

Key Words: Crohn's disease; Immunomodulator; Infliximab; Opportunistic infections; Pulmonary cryptococcosis; Case report

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Core Tip: Corticosteroids and anti-tumor necrosis factor α mAbs are commonly used to treat Crohn's disease (CD). However, they may also contribute to an increased risk of opportunistic infections. In this article, we report three cases of pulmonary cryptococcosis in patients with CD after receiving immunomodulatory treatment. Pathogen identification mainly depends on pathological examination findings, but metagenomics can serve as an alternative tool. Patients with timely diagnosis generally have a good prognosis, but clinical alerts should be raised in those who are elderly and have comorbidities and dissemination phenotype.

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INTRODUCTION

Crohn's disease (CD), a chronic inflammatory disease that may involve any part of the digestive tract, is characterized by periodic clinical relapse and remission[1]. Treatment medications include mesalamine, corticosteroids, small-molecule immunosuppressants, and biologics such as mAbs[2]. However, these drugs also affect normal immune function and may contribute to an increased risk of opportunistic infections.

Pulmonary cryptococcosis is a type of subacute or chronic fungal infection caused by the genus *Cryptococcus*, and is found mostly in immunocompromised patients. It usually presents with isolated pulmonary granulomatous lesions but can also disseminate to other organ systems[3]. Here, we report three cases of pulmonary cryptococcosis in patients with CD who received immunomodulatory treatment, and review previously reported cases. Literature searches were conducted in PubMed, Web of Science and Embase databases using the keywords "Crohn's disease", "pulmonary cryptococcosis", and "cryptococcus". The search was restricted to full-text journal articles and conference abstracts published in English between January 1980 and May 2022. The bibliographies of the included articles were manually reviewed.

CASE PRESENTATION

Chief complaints

Case 1: A 65-year-old man was admitted to a local hospital for recurrent abdominal distension and pain 10 years ago.

Case 2: A 20-year-old man was admitted to our hospital for perianal pain with fever 5 years ago.

Case 3: A 59-year-old man was admitted to a local hospital for recurrent abdominal pain and diarrhea 13 years ago.

History of present illness

Case 1: The patient was referred to our hospital and diagnosed with CD. Before treatment initiation, chest computed tomography (CT) showed small nodules in the bilateral upper lobes with a benign tendency, pulmonary sac in the right upper lobe, and fibrous foci in the right middle lobe and bilateral lower lobes. The patient received four doses of infliximab (IFX; 300 mg) and achieved clinical remission.

Case 2: The patient was diagnosed with CD and was treated with IFX for 2 years (22 doses; 300 mg), which was discontinued due to secondary loss of response. He complained of night sweats and right-sided chest pain during deep breathing.

Case 3: The patient was diagnosed with CD 5 years ago and had been treated with methylprednisolone (MP; 0.75 mg/kg) for 3 years. He complained of productive cough for 1 mo.

Laboratory examinations

Case 2: The carbohydrate antigen 125 (CA-125) level was 54.2 U/mL. The G test, galactomannan (GM) test, and sputum fungal test results were negative.

Case 3: Vitamin B12 and folic acid levels were normal. Hepatitis B virus surface, core and E antibodies, antinuclear antibodies, vasculitis antibodies, sputum acid-fast (AF) staining, bronchoscopic brush

cytology, and bronchoalveolar lavage fluid (BALF) cytopathology showed negative findings.

Other laboratory examination results are summarized in [Table 1](#).

Imaging examinations

Case 1: A repeat CT scan after the fourth dose of IFX revealed an increased number of bilateral nodules and a large nodule in the left upper lobe with possible inflammation ([Fig. 1A](#)). Electromagnetic navigation bronchoscopy revealed a clear trachea and no neoplasm in the principal and segmental bronchi. A biopsy was performed in the anterior segment of the left upper lobe. Fibrinobronchoscopic AF staining, fungus, culture, brush cytology, BALF Gram staining, exfoliative cytology, and X-PERT assay (simultaneous detection of *Mycobacterium tuberculosis* and resistance to rifampin) results were negative. Biopsy revealed focal granuloma formation in the alveolar tissues ([Figure 1B](#)). Periodic acid-Schiff (PAS) staining and AF staining were negative; however, periodic acid-silver methenamine (PASM) staining revealed suspicious positive bodies ([Figure 1C](#)).

Case 2: Chest CT revealed patchy lesions in the right upper lobe and right interlobar fissure, and multiple bilateral nodules with inflammatory propensity ([Figure 2A](#)). Bronchoscopy revealed clear segmental bronchi with no apparent stenosis or neoplasm in the lumen. Fibrinobronchoscopy was performed, and the BALF *Aspergillus* GM level was 0.840 µg/L. AF staining, fungus, brush cytology, and culture results were negative. BALF was sent for metagenomic sequencing and *Cryptococcus* was detected.

Case 3: Chest CT tomography revealed nodules in the posterior segment of the right upper lobe ([Figure 3A](#)). Tumor presence could not be ruled out. Bronchoscopy revealed no neoplasm in bilateral bronchi. Considering the difficulty of bronchoscopic biopsy, thoracoscopic lobectomy of the posterior segment of the right upper lobe was performed. Postoperative pathology revealed negative AF staining results but positive PAS and PASM staining results ([Figure 3B](#) and [C](#)). Tuberculosis- DNA (TB-DNA) test was negative.

FINAL DIAGNOSIS

Case 1-3: A diagnosis of CD combined with pulmonary cryptococcosis was confirmed.

TREATMENT

Case 1: IFX was discontinued, and the patient was administered fluconazole (FLCZ) 400 mg once daily for 6 mo.

Case 2: Medications for CD were discontinued. The patient was given FLCZ 400 mg once daily for 5 mo.

Case 3: MP was switched to pan-enteral nutrition therapy. The patient was administered FLCZ 400 mg once daily for 1 mo.

OUTCOME AND FOLLOW-UP

Case 1: A chest CT upon completion of anti-fungal therapy showed reduced size of the pulmonary nodule in the left upper lobe.

Case 2: During anti-fungal therapy, the patient was started on thalidomide for CD treatment and reported no apparent abdominal pain. One month after anti-fungal therapy, he achieved symptom resolution, and a repeat chest CT scan showed lesion absorption ([Figure 2B](#)).

Case 3: IFX was initiated 7 years later because of the progression of CD. Regular follow-ups have revealed no recurrence so far.

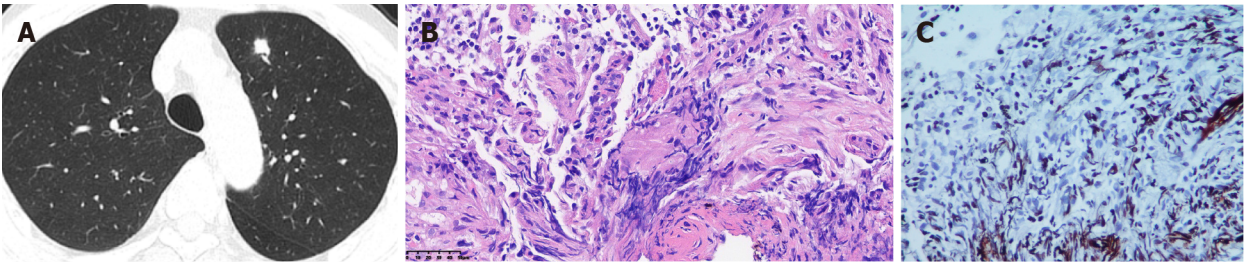
The clinical courses of the three cases are summarized in [Figure 4](#).

DISCUSSION

Cryptococcus infection is an opportunistic fungal infection caused by *Cryptococcus neoformans* or *Cryptococcus gattii*. These pathogens are ubiquitously distributed, with the respiratory tract being the primary portal of entry. Cryptococcosis often occurs in immunocompromised individuals, such as human

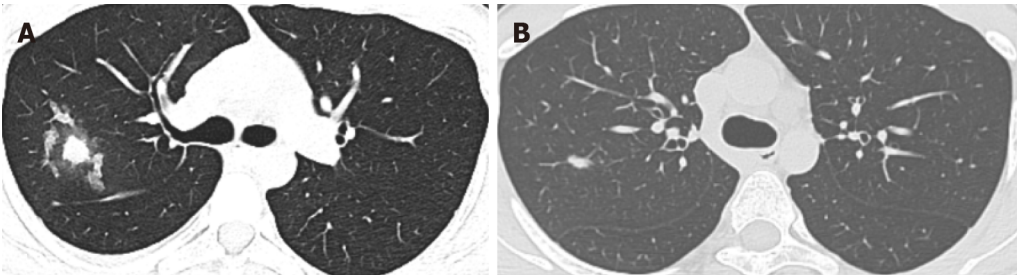
Table 1 Laboratory examination			
Case	1	2	3
WBC count (× 10 ⁹ /L)	10.0	9.4	2.5
Neutrophil count (× 10 ⁹ /L)	8.13	8.0	1.6
Platelet count (× 10 ⁹ /L)	305	282	220
Hemoglobin (g/L)	120	139	97
Albumin (g/L)	34.3	42.8	12.0
CRP (mg/L)	23.3	17.4	34.9
ESR (mm/hr)	19	16	14
Tumor markers	Negative	Negative	Negative
T-SPOT.TB	Negative	Negative	Weak positive
EBV IgM	Negative	Negative	-
Cytomegalovirus IgM	Negative	Negative	Negative
HIV	Negative	Negative	Negative
TPPA test	Negative	Negative	Negative

WBC: White blood cell; CRP: C reactive protein; ESR: Erythrocyte sedimentation rate; T-SPOT.TB: T-cell spot of tuberculosis test; EBV: Epstein-Barr virus; IgM: Immunoglobulin M; HIV: Human immunodeficiency virus; TPPA: Treponema pallidum particle agglutination.



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Figure 1 Imaging and pathologic findings of case 1. A: Chest computed tomography scan showing multiple nodules in bilateral lobes and a large one in the left upper lobe; B: Hematoxylin-eosin staining showing focal granuloma formation in alveolar tissues; C: Periodic acid-silver methenamine staining showing suspicious positive organisms.



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Figure 2 Imaging findings of case 2. A: Chest computed tomography (CT) scan before fluconazole treatment showing patchy lesions in the right upper lobe and right interlobar fissure and multiple nodules in bilateral lobes; B: Chest CT scan showing lesion absorption 6 mo after initiation of anti-fungal therapy.

immunodeficiency virus-infected patients, organ transplant recipients, and those with indications for immunosuppressants[3]. However, it has also been reported in immunocompetent patients[4]. A total of 21 studies reporting CD cases complicated by *Cryptococcus* infection were identified (Table 2)[4-24]. Among them, one was a retrospective analysis[21] (197 males and 69 females) and another reported relapse of a previously reported case[13]. The remaining 19 patients comprised 13 males and 6 females; 9 of the cases were disseminated cryptococcosis[4,5,8,12,15-19]. Infection sites

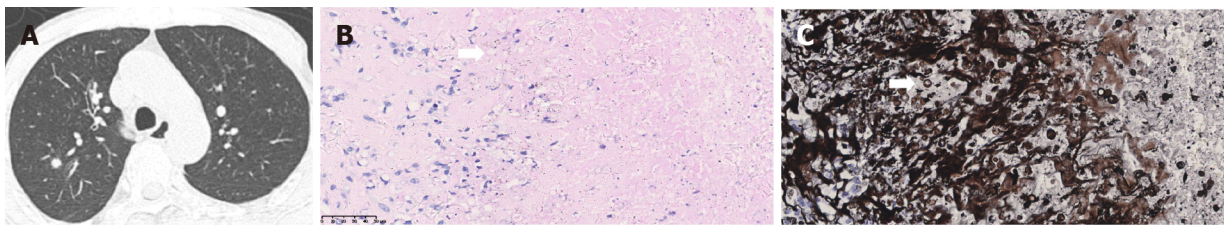
Table 2 Clinical characteristics of cryptococcus infection in patients with Crohn's disease

Ref.	Age/sex	Comorbidity	CD medication	Symptom	Infection site	Treatment	Outcome
Lerner <i>et al</i> [5], 1988	65/M	Ankylosing spondylitis	Prednisone	Calf ulcer	Lungs, skin	AmB, 5FC	Died
Hrncicek <i>et al</i> [6], 2003	51/M	None	IFX, prednisone, MTX, ciprofloxacin	Cough, fatigue, headache, fever, chills	Lungs	Surgery, FLCZ	Recovered
Rehman <i>et al</i> [7], 2008	61/M	None	IFX, prednisone, budesonide, AZA	None	Lungs	AmB, 5FC → FLCZ	Recovered
Osawa <i>et al</i> , 2010 [8]	53/M	Silicosis	IFX, prednisone, AZA	Abdominal pain, diarrhea, fever, night sweats, headache	Lungs, GI, CNS	AmB → LAmB, 5FC → FLCZ	Recovered
Sciaudone <i>et al</i> [4], 2011	26/F	None	None	Diarrhea, abdominal pain, weight-loss, headache, cough	Lungs, GI	Surgery, LAmB → FLCZ	Recovered
Hirai <i>et al</i> [9], 2011	39/M	None	IFX	None	Lungs	Surgery	Recovered
Takazono <i>et al</i> [10], 2012	35/M	None	IFX, prednisolone, mesalazine	Fever	Lungs	FLCZ	Recovered
Fraison <i>et al</i> [11], 2013	54/M	Ankylosing spondylitis	ADM, AZA	Fever, anorexia, cough, chest pain, dyspnea, arthralgia, myalgia	Lungs	LAmB, 5FC → FLCZ	Recovered
Wysocki <i>et al</i> [12], 2015	46/M	None	IFX, AZA → ADM → CZP	Abdominal and back pain, fever, headache	Omentum, CNS	LAmB, 5FC	Recovered
Takazono <i>et al</i> [13], 2016	35/M	None	IFX, prednisolone	Fever, fatigue, night sweats	Lungs	FLCZ → ITCZ	Recovered
Zhou <i>et al</i> [14], 2016	66/M	Cryptogenic organizing pneumonia	Prednisone	Dyspnea, cough	Lungs	FLCZ	Recovered
Saad <i>et al</i> [15], 2016	71/M	None	IFX, AZA	Meningitis	CNS	-	-
Vasant <i>et al</i> [16], 2016	74/F	Posterior reversible encephalopathy syndrome	IFX, prednisolone	Headache, confusion, fever, rigor, body ache	CNS	LAmB, 5FC → VRCZ	Died
Lee <i>et al</i> [17], 2017	70/F	<i>Klebsiella pneumoniae</i> and <i>Pneumocystis jirovecii</i> infections	IFX	Pyrexia	CNS	AmB → VRCZ	Died
Chavapradit <i>et al</i> [18], 2018	64/F	None	Prednisolone, AZA, mesalazine	Abdominal pain, diarrhea	Lungs, GI	AmB → FLCZ	Recovered
Maleb <i>et al</i> [19], 2019	45/M	None	Steroid, AZA	Shock, abundance of ascites, fever	Pleural fluid, ascites	FLCZ	Died
Santo <i>et al</i> [20], 2019	23/M	Tuberculosis	IFX, AZA	Fever, headache	Lungs	FLCZ	Recovered
Yeh <i>et al</i> [22], 2021	57/F	Systemic lupus erythematosus	ADM, prednisolone, mesalazine	Pneumonia	Lungs	AmB, 5FC	Recovered
Hussein <i>et al</i> [23], 2021	54/M	None	IFX, prednisolone, MTX	Fever, fatigue, cough	Lungs	FLCZ	Recovered
Yeoh <i>et al</i> [24], 2022	52/F	Autoimmune hepatitis	Prednisolone	Dyspnea, chest pain, cough, lethargy	Lungs	Surgery	Recovered

M: Male; F: Female; IFX: Infliximab; MTX: Methotrexate; AZA: Azathioprine; ADM: Adalimumab; CZP: Certolizumab pegol; GI: Gastrointestinal tract; CNS: Central nervous system; AmB: Amphotericin B; LAmB: Liposomal amphotericin B; 5FC: 5-fluorocytosine; FLCZ: Fluconazole; ITCZ: Itraconazole; VRCZ: Voriconazole; -: Not reported.

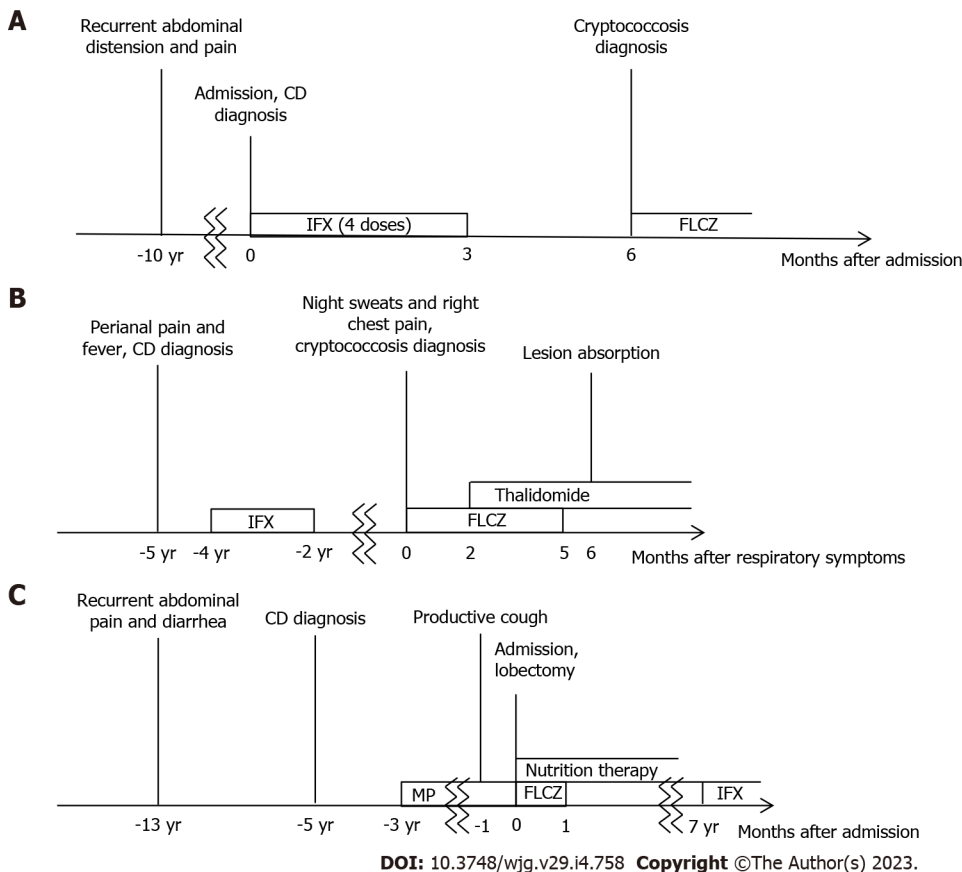
included lungs (15 cases), central nervous system (CNS; 5 cases), gastrointestinal tract (GI; 3 cases), skin (1 case), omentum (1 case), and pleural fluid and ascites (1 case).

Infected patients had been treated with different combinations of CD drugs, including anti-tumor necrosis factor α (TNF- α) agents, such as IFX, adalimumab and certolizumab pegol, corticosteroids, and other immunosuppressants. Symptoms ranged from asymptomatic lung granulomas to severe



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Figure 3 Imaging and pathologic findings of case 3. A: Chest computed tomography scan showing nodules in the posterior segment of right upper lobe; B and C: Periodic acid-Schiff and periodic acid-silver methenamine staining showing positive organisms (white arrows).



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Figure 4 Clinical courses of the three cases. A: Case 1; B: Case 2; C: Case 3. CD: Crohn's disease; IFX: Infliximab; FLCZ: Fluconazole; MP: Methylprednisolone.

pneumonia. Patients with disseminated cryptococcosis may also present with symptoms of other organ systems, such as colitis[8], meningitis[12], or skin ulcers[5]. Chest imaging typically revealed single or multiple pulmonary nodules. Diagnosis mainly relies on pathological examination, with accessory methods including fungal culture and the cryptococcal polysaccharide capsular antigen test. The most commonly used anti-fungal medications are amphotericin B (AmB), liposomal AmB (LAmB), 5-flucytosine (5FC), FLCZ, itraconazole, and voriconazole. Patients with mild symptoms generally recovered after treatment with triazole, while AmB and 5FC were intended for deep fungal infections; however, AmB and LAmB may cause serious adverse events[4,8]. Patients with disseminated cryptococcosis have a relatively poor prognosis, particularly when the CNS is involved.

Anti-TNF- α antibodies have been widely administered among CD patients with high efficacy, but concerns remain regarding their immunogenicity, skin toxicity, and increased risk of infection, such as the possible activation of latent TB. Therefore, current guidelines suggest that TB screening should be conducted before medication infusion[25]. TNF- α also plays a role in clearing pulmonary *Cryptococcus* infections by inducing interleukin-12 and interferon γ to promote a T1-cell-mediated immune response [26]. Anti-TNF- α agents, among other immunomodulators, may interfere with this process and increase the risk of *Cryptococcus* infection.

In this paper, we report three male patients diagnosed with CD, aged 20–65 years, who developed pulmonary cryptococcosis after being treated with anti-TNF- α agents or corticosteroids. The patients presented with asymptomatic or mild pneumonia with pulmonary nodules. One patient (case 2) showed elevated CA-125 level, which might be due to intestinal inflammation. G test and GM test were both negative, possibly because of low sensitivity of the tests for *Cryptococcus*. One patient (case 3) underwent surgery because of difficulty in biopsy. Diagnosis depended on postoperative pathological examinations since BALF might fail to detect *Cryptococcus*. All patients achieved symptom resolution after FLCZ treatment, consistent with other studies[6,10,23].

CD complicated with pulmonary cryptococcosis is relatively rare, but its incidence has increased in recent years with the use of various immunomodulators, particularly biologics, in CD management. Diagnosis is challenging because clinical symptoms and chest imaging both lack specificity, and GI manifestations can resemble CD progression, leading to misdiagnosis. Therefore, high clinical vigilance is required for early identification of infection, discontinuation of immunomodulators, and standardized treatment.

CONCLUSION

Our three case reports and literature review suggest that patients with timely diagnosis generally have a good prognosis. However, comorbidities, advanced age, and dissemination phenotype should raise clinical alerts. Metagenomic sequencing can be an alternative approach for pathogen diagnosis when biopsy is unfeasible.

FOOTNOTES

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