Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.6559-20
Intern Med 60: 3003-3008, 2021
http://internmed.jp

【 CASE REPORT 】

Cryptococcosis in the Vocal Cords, Trachea, and Bronchi

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Abstract:
Laryngeal and endobronchial cryptococcosis are rare conditions, and to our knowledge, there have been only 23 cases of laryngeal cryptococcosis, and 18 cases of endobronchial cryptococcosis previously reported in the English literature. We herein report an extremely rare case of cryptococcosis with simultaneous laryngeal and endobronchial involvement. This case highlights the importance of paying close attention to possible occurrence of cryptococcosis of the airway tract in patients with asthma treated with high-dose inhaled corticosteroids.

Key words: laryngeal cryptococcosis, endobronchial cryptococcosis, asthma, inhaled corticosteroids, omalizumab

(Intern Med 60: 3003-3008, 2021)
(DOI: 10.2169/internalmedicine.6559-20)

Introduction

Laryngeal or endobronchial cryptococcosis is a rare condition. To our knowledge, 23 cases of laryngeal cryptococcosis and 18 cases of endobronchial cryptococcosis have been previously reported in the English literature (1-36). The important risk factors for these conditions were reported to include HIV/AIDS, hematological malignancy, systemic immunosuppressive therapy, cirrhosis, sarcoidosis, massive exposure to the *Cryptococcus* spp., exposure to aggressive strains, subtle host immune deficiency, localized immunosuppression, and a disruption of the local barrier (1, 37, 38).

We herein report a rare case of cryptococcosis in the vocal cords, trachea, and bronchi. In our patient, the regular inhalation of corticosteroids was considered to be a risk factor. We also present a summary of the previously reported cases of laryngeal and endobronchial cryptococcosis.

Case Report

A 68-year-old Japanese man presented with a 2-month history of progressive hoarseness. His medical history included hyperlipidemia, hypertension, and asthma. His asthma had been treated with inhaled corticosteroids (ICSs), long-acting beta-agonist (LABA), and long-acting muscarinic antagonist (LAMA) for more than 10 years. Mepolizumab had been started 13 months prior to this presentation and it had been prescribed for 8 months but had no effect. Therefore, mepolizumab was changed to omalizumab, which proved to be effective. His hoarseness developed and worsened three months after the initiation of omalizumab. He did not drink alcohol. He had a smoking history of 60 cigarettes per day for 34 years and had quit smoking 15 years previously. His regular medications were lansoprazole, torasemide, amlodipine, loratadine, montelukast, atorvastatin, dextromethorphan, fluticasone (500 μg/day)/formoterol inhaler, tiotropium inhaler, and omalizumab.

His initial vital signs were as follows: heart rate, 89 bpm; respiratory rate, 16 breaths per minute; blood pressure, 142/81 mmHg; body temperature, 36.7℃; and oxygen saturation, 97% on room air. Lung auscultation revealed wheezing in both lungs, and physical examinations were otherwise unremarkable. Initial laboratory tests were unremarkable, and both human immunodeficiency virus antibodies and human T-cell leukemia virus type 1 antibodies were negative. Chest X-ray and computed tomography (CT) showed no abnormalities. The results of pulmonary function testing were as follows: vital capacity, 3.99 L (100.8% of predicted value); forced vital capacity (FVC), 3.88 L; forced expiratory volume in 1 second (FEV 1.0), 2.68 L (85.1% of predicted value); and FEV 1.0/FVC ratio, 0.69. Laryngeal endoscopy

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Received: October 21, 2020; Accepted: February 10, 2021; Advance Publication by J-STAGE: April 5, 2021
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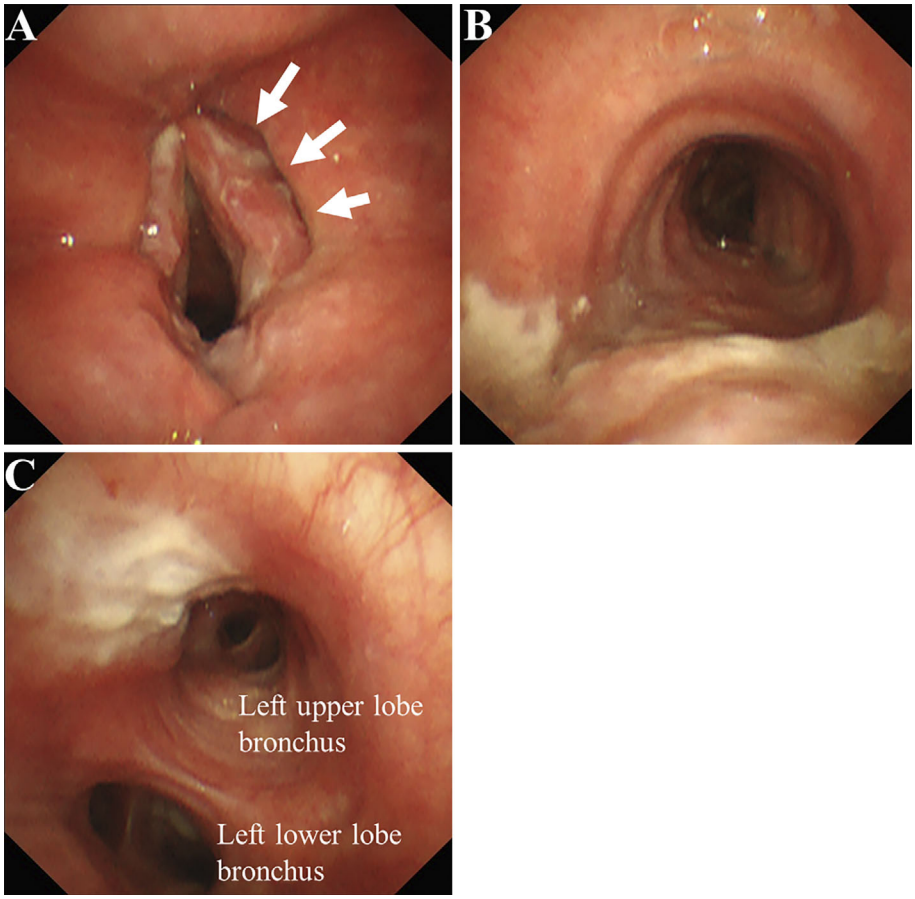

Figure 1. Laryngeal endoscopic and fiberoptic bronchoscopic findings. An elevated red lesion in the right true vocal fold with a normal left true vocal fold (arrows on A) and multiple white elevated lesions from the trachea to the left upper lobe bronchus (B, C) were found.

revealed an elevated red lesion in the right true vocal fold with a normal left true vocal fold (Fig. 1A) and multiple white elevated lesions in the trachea.

The patient underwent fiberoptic bronchoscopy, and multiple white and flat elevated lesions were observed from the trachea to the left upper lobe bronchus (Fig. 1B, C). A biopsy of the lesions of the vocal fold, trachea, and bronchus was performed, and the histopathological examination revealed squamous cell metaplasia, neutrophilic inflammation, and histiocyte-like cells with foamy cytoplasm under the epithelium (Fig. 2A, B). Hematoxylin and eosin (HE) (Fig. 2C) and periodic acid-Schiff (PAS) (Fig. 2D) of the specimens revealed a halo around the yeast cell, which means a polysaccharide capsule, and it was suspected to be associated with *Cryptococcus* organisms. The same pathological findings were found in both vocal fold and bronchial biopsy specimens. No microorganisms, including *Cryptococcus* and *Candida*, grew in any of the biopsy specimens (i.e., vocal fold, trachea, and bronchus) culture. Additional serum cryptococcal antigen latex agglutination test (BML, Saitama, Japan) that detects glucuronoxylomannan, the major capsular polysaccharide of *C. neoformans*, was positive (titer of 1:8), and the serum β-D-glucan level was within the normal limits. A lumbar puncture revealed cerebrospinal fluid with no white cells, and India ink stain revealed no *Cryptococcus* organisms. *Cryptococcus* were not grown in the cerebrospinal fluid, blood, urine, and sputum culture.

From these results, the patient was diagnosed with cryptococcosis in the vocal cords, trachea, and bronchi. Unfortunately, we were unable to detect *Cryptococcus* in culture and could not identify whether it was *C. neoformans* or *C. gatti*. Because *C. gatti* is extremely rare in Japan and the patient had no history of travel to endemic areas, his condition was therefore thought to be due to *C. neoformans*.

Treatment with fluconazole of 400 mg/day was started, and his symptoms improved gradually. After six months of treatment, the lesions of the vocal fold, trachea, and bronchus had almost completely improved (Fig. 3).

Discussion

Infections caused by *Cryptococcus* spp. occur mainly in immunocompromised hosts and most commonly present as either primary lower respiratory infections or secondary disseminated processes. A cellular immune deficiency has been reported to be an important risk factor for this condition, and predisposing conditions include HIV/AIDS, hematological malignancy, systemic immunosuppressive therapy (including corticosteroid therapy), cirrhosis, and sarcoidosis (37). However, cryptococcal infections sometimes occur

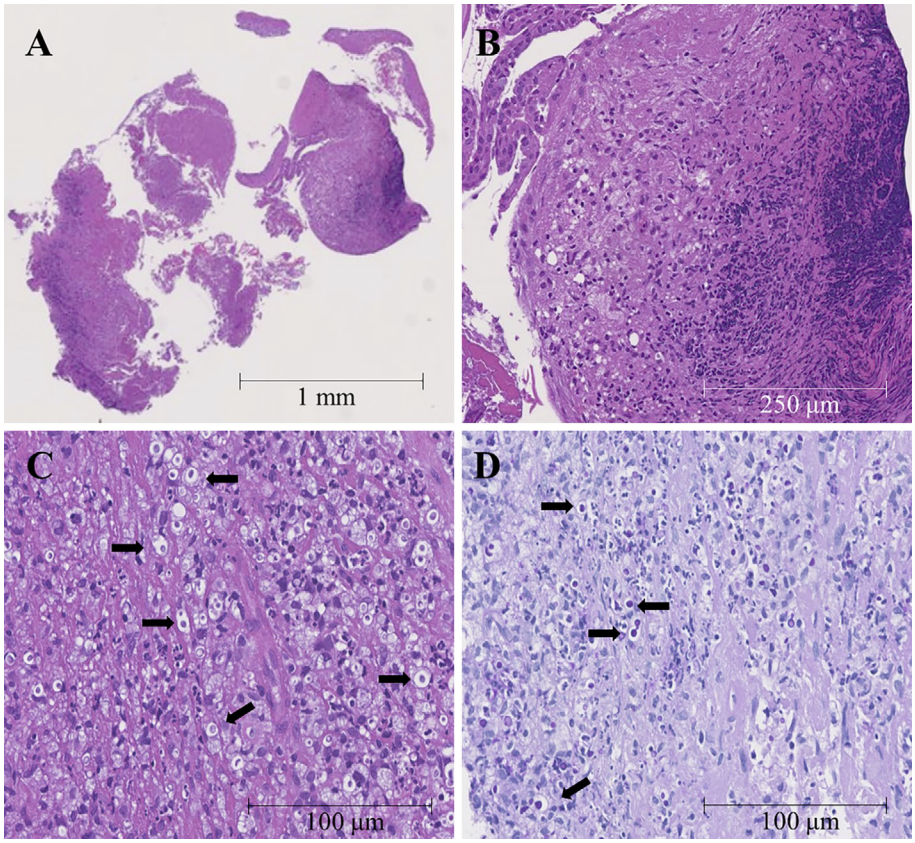

Figure 2. Histopathologic examinations of the biopsy specimens of the trachea. It revealed squamous cell metaplasia, neutrophilic inflammation, and histiocyte-like cells with foamy cytoplasm under the epithelium [A and B, Hematoxylin and Eosin (H&E) staining low-power field (2.5-fold) and high-power field (10-fold), respectively]. H&E staining (15-fold) (C) and periodic acid-Schiff (PAS; 15-fold) (D) of the specimens revealed a halo around the yeast cell, which means a polysaccharide capsule, which was suspected to be associated with *Cryptococcus* organisms.

in immunocompetent patients through some as-yet-undetermined mechanisms. Some possible factors include massive exposure to *Cryptococcus* spp., exposure to aggressive strains, subtle host immune deficiency (e.g., alcoholism, diabetes mellitus, pregnancy, and autoimmune conditions), localized immunosuppression (e.g., ICS), and disruption of the local barrier (e.g., radiotherapy, gastro-esophageal reflux, trauma, and smoking) (1, 38). In our patient, we repeatedly asked the patients and their families about exposure to birds, contaminated dust, trees, etc., but were unable to confirm this. In addition, no risk factors other than asthma and ICS were found.

To the best of our knowledge, 23 cases of laryngeal cryptococcosis 18 cases of endobronchial cryptococcosis have been reported since 1972 (1-36) (Table). For laryngeal cryptococcus, the mean age was 65 years old, a smoking history included 7 cases (30.4%), exposure to birds, chicken manure, or bird droppings were observed in 3 cases (21.7%), and a history of immunosuppression (i.e., HIV/AIDS or on systemic corticosteroid therapy) was seen in 11 cases (47.8%). In endobronchial cryptococcosis, the mean age was 44.5 years old, a smoking history was observed in 5 cases (27.7%), a bird exposure history included 4 cases (22.2%), and a history of immunosuppression was seen in 6 cases (33.2%). There have been no reports of cryptococcosis with simultaneous laryngeal and endobronchial involvement, making our patient the first known case with such a condition. Remarkably, ICSs were used in 11 cases (47.8%) of laryngeal cryptococcosis, while none of the reported endobronchial cryptococcosis cases had a history of using ICSs. Because our patient had quit smoking 15 years previously, ICS was thought to be a strong risk factor for his cryptococcal infection, especially on the larynx. However, ICSs have not been identified as an obvious risk factor for endobronchial lesions, and all reported cases had concomitant lung lesions.

Our patient had no concomitant lung lesions, and cryptococcal infections manifested after the initiation of omalizumab therapy. Omalizumab is a recombinant monoclonal antibody against human immunoglobulin E (IgE) used for the treatment of severe asthma, allergic rhinitis, and urticaria. Omalizumab reduces the response of the pro-inflammatory mediators and IgE activity (39). Very rarely, parasitosis (giardiasis) has been reported as an omalizumab-related infection (40), and no fungal infection has been reported. From these facts, fungus including *Cryptococcus* may be in-

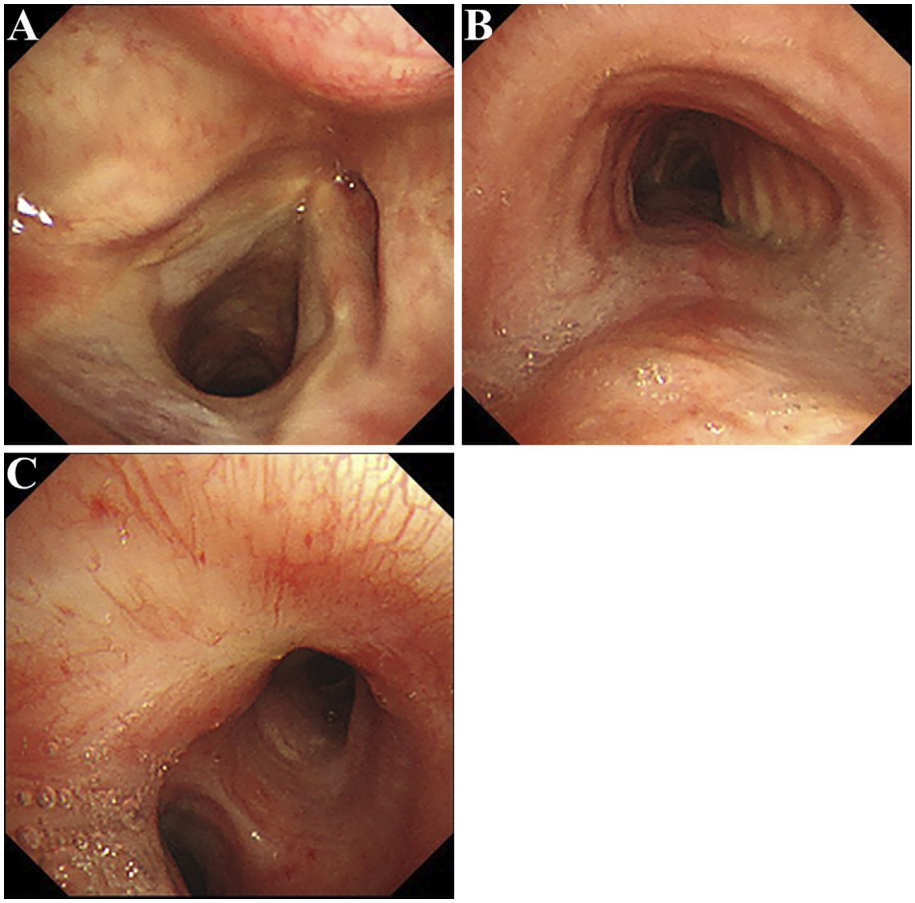

Figure 3. **Fiberoptic bronchoscopic findings after six months of treatment. The lesions of the vocal fold, trachea, and bronchus almost completely improved.**

Table. **Summary of the Previously Reported Cases of Laryngeal Cryptococcosis and Endobronchial Cryptococcosis.**

	Laryngeal cryptococcosis n=23	Endobronchial cryptococcosis n=18	Our case
Age (years) (median, range)	65 (31-87)	45 (19-73)	68
Male/Female	12/11	12/3 (unknown, 2)	Male
Lung lesion (n, %)	1 (4.3)	18 (100)	No
Meningitis (n, %)	1 (4.3)	5 (27.8)	No
Exposure to birds (n, %)	5 (21.7)	4 (22.2)	No
HIV/AIDS (n, %)	4 (17.3)	3 (16.6)	No
Systemic corticosteroid (n, %)	7 (30.4)	3 (16.6)	No
Smoking history (n, %)	7 (30.4)	5 (27.7)	Ex-smoker
Inhaled corticosteroids (n, %)	11 (47.8)	0	Yes
Omalizumab (n, %)	0	0	Yes

volved in severe asthma (i.e., fungus-related asthma and allergic bronchopulmonary mycosis) and therefore should be evaluated (41, 42).

The diagnosis was triggered by laryngoscopy performed for a close examination of his hoarseness. Hoarseness is a common symptom in patients using ICSs, so care must be taken not to overlook this possible association. The main endoscopic findings of laryngeal cryptococcosis are multiple white or reddish raised exudative lesions, warty lesions, mass, and erythema on the true cord (9). Accompanying findings include laryngeal edema and leukoplakia around the vocal cords (9). The findings of the fiberoptic bronchoscopy tend to vary, as follows: white plaque, white elevated lesion, white polypoid lesion, white lobulated lesion, cherry red plaque, reddish broad-based lesion, reddish elevated lesion, and mass lesion (25, 26). In our patient, all lesions in the vocal fold and bronchi were white, lobulated and raised, which was consistent with previous reports regarding the endoscopic findings.

A biopsy and histological examination are essential for

the diagnosis. The differential diagnosis of the laryngeal and endobronchial cryptococcosis includes other fungal infections (i.e., *Candida*, *Histoplasma, Blastomyces, Coccidioides*, or *Paracoccidiodes* species) and malignancy (i.e., squamous cell carcinoma, and granular cell tumor) (1). Most reported cases are treated with antifungal drugs (i.e., fluconazole, amphotericin B, flucytosine, and voriconazole) over a period of at least six weeks. Three cases of endobronchial cryptococcosis and six cases of laryngeal cryptococcosis received surgical excisions alone or in combination with drugs. In some case reports, the dose of ICS was reduced after the diagnosis of airway cryptococcosis, but our case improved with fluconazole treatment and thus continued the ICS dose.

Conclusion

We herein described a patient with asthma who had cryptococcosis in the vocal cords, trachea, and bronchi. To our knowledge, no such cases have so far been reported in the past. It is also important to point out that omalizumab may have caused this disease. This case highlights the importance of paying attention to cryptococcosis of the airway tract in patients with asthma treated with high-dose ICSs.

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

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