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

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°C; 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 (FEV1), 2.68 L (85.1% of predicted value); and FEV1/FVC ratio, 0.69. Laryngeal endoscopy re-
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 from the trachea to the left upper lobe bronchus (Fig. 1B-C).

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 histiocye-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 Inc., 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
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.

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.

To the best of our knowledge, 23 cases of laryngeal cryptococcosis 18 cases of endobronchial cryptococcosis have been reported since 1972 (1-36). 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 involved in severe asthma (i.e., fungus-related asthma and al-
ergic 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 Paracoccidioides 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 thatomalizumab 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).

**References**

1. Wong DJY, Stanley P, Paddle P. Laryngeal Cryptococcosis Associated With Inhaled Corticosteroid Use: Case Reports and Literature Review. Front Surg; 4: 63, 2017.
2. Browning DG, Schwartz DA, Jurado RL. Cryptococcosis of the larynx in a patient with AIDS: an unusual cause of fungal laryngitis. South Med J 85: 762-764, 1992.
3. McGregor DK, Citron D, Shahab I. Cryptococcal infection of the larynx simulating laryngeal carcinoma. South Med J 96: 74-77, 2003.
4. Smallman LA, Stores OP, Watson MG, et al. Cryptococcosis of the larynx. J Laryngol Otol 103: 214-215, 1989.
5. Joo D, Bhuta SM, Chhetri DK. Primary Cryptococcal Infection of the Larynx in a Patient with Severe Chronic Obstructive Pulmonary Disease: A Case Report. The Laryngoscope 119: S169, 2009.
6. Mittal N, Collignon P, Pham T, et al. Cryptococcal infection of the larynx: case report. J Laryngol Otol 127 Suppl 2: S54-S56, 2013.
7. Chongkolwatana C, Suwanagool P, Suwanagool S, et al. Primary cryptococcal infection of the larynx in a patient with AIDS: a case report. J Med Assoc Thai 81: 462-467, 1998.
8. Reese MC, Colclasure JB. Cryptococcosis of the larynx. Arch Otolaryngol 101: 698-701, 1975.
9. Jeng JY, Tombinson CM, Ocal IT, et al. Laryngeal cryptococcosis: Literature review and guidelines for laser ablation of fungal lesions. Laryngoscope 126: 1625-1629, 2016.
10. Tamagawa S, Hotomi M, Yuasa J, et al. Primary laryngeal cryptococcosis resembling laryngeal carcinoma. Auris Nasus Larynx 42: 337-340, 2015.
11. Nadrous HF, Ryu JH, Lewis JE, et al. Cryptococcal laryngitis: case report and review of the literature. Ann Otol Rhinol Laryngol 113: 121-123, 2004.
12. Gordon DH, Stow NW, Yapa HM, et al. Laryngeal cryptococcosis: Clinical presentation and treatment of a rare cause of hoarseness. Otolaryngol Head Neck Surg 142 (3 Suppl 1): S7-S9, 2010.
13. Bamba H, Tatamoto K, Inoue M, et al. A case of vocal cord cyst with cryptococcal infection. Otolaryngol Head Neck Surg 133: 150-152, 2005.
14. Isaacson JE, Frable MA. Cryptococcosis of the larynx. Otolaryngol Head Neck Surg 114: 106-109, 1996.
15. Bergeron M, Gagné AA, Côté M, et al. Primary Larynx Cryptococcus neoformans Infection: A Distinctive Clinical Entity. Open Forum Infect Dis 2: ofv160, 2015.
16. Frisch M, Gnepp DR. Primary cryptococcal infection of the larynx: a case report. Otolaryngol Head Neck Surg 113: 477-80, 1995.
17. Zeglaoui I, Belcadhi M, Mani R, et al. Laryngeal cryptococcosis revealing AIDS: a case report. Rev Laryngol Otol Rhinol (Bord) 130: 307-311, 2009.
18. Kerschner JE, Ridley MB, Greene JN. Laryngeal cryptococcus. Treatment with oral fluconazole. Arch Otolaryngol Head Neck Surg 121: 1193-1195, 1995.
19. Chang YL, Hung SH, Liu CH, et al. Cryptococcal infection of the vocal folds. Southeast Asian J Trop Med Public Health 44: 1043-1046, 2013.
20. Chechani V, Kamholz SL. Pulmonary manifestations of disseminated cryptococcosis in patients with AIDS, Chest 98: 1060-1066, 1990.
21. Town GI, Seeman R. Pulmonary cryptococcosis: a report of two cases and review of the literature. N Z Med J 98: 894-895, 1985.
22. Kashiyama T, Kimura A. Endobronchial cryptococcosis in AIDS. Respiriology 8: 386-8, 2003.
23. Long RF, Berens SV, Shambhag GR. An unusual manifestation of pulmonary cryptococcosis. Br J Radiol 45: 757-759, 1972.
24. Carter EA, Henderson DW, McBride J, et al. Case report: complete lung collapse—an unusual presentation of cryptococcosis. Clin Radiol 46: 292-294, 1992.
25. Inoue Y, Miyazaki Y, Izumikawa K, et al. Pulmonary cryptococcosis presenting as endobronchial lesions in a patient under corticosteroid treatment. Intern Med 46: 519-523, 2007.
26. Odashima K, Takayanagi N, Ishiguro T, et al. Pulmonary cryptococcosis with endobronchial lesions and meningitis. Intern Med 53: 2731-2735, 2014.
27. Mahida P, Morar R, Goolam Mahomed A, et al. Cryptococcosis: an unusual cause of endobronchial obstruction. Eur Respir J 9: 837-839, 1996.
28. Chang YS, Chou KC, Wang PC, et al. Primary pulmonary cryptococcosis presenting as endobronchial tumor with left upper lobe collapse. J Chin Med Assoc 68: 33-36, 2005.
29. Emmons WW 3rd, Luchsinger S, Miller L. Progressive pulmonary cryptococcosis in a patient who is immunocompetent. South Med J 88: 657-660, 1995.
30. Zhou Q, Hu B, Shao C, Zhou C, et al. A case report of pulmonary cryptococcosis presenting as endobronchial obstruction. J Thorac Dis 5: E170-E173, 2013.
31. Shimizu H, Miyashita N, Obase Y, et al. An asymptomatic case of pulmonary cryptococcosis with endobronchial polypoid lesions and bilateral infiltrative shadow. J Infect Chemother 14: 315-318, 2008.
32. Thomas R, Christopher DJ, Balamugesh T, et al. Endobronchial pulmonary cryptococcosis and tuberculosis in an immunocompetent host. Singapore Med J 53: e32-e34, 2012.
33. Nakashima K, Kamatsumi H, Endo M, et al. Endobronchial cryptococcosis induced by Cryptococcus gattii mimicking metastatic lung cancer. Respir Case Rep 2: 106-110, 2014.
34. Mitto K, Kawanou H, Yamakami Y, et al. Primary pulmonary cryptococcosis with endobronchial lesion. Nihon Kokyuki Gakkai Zasshi 38: 302-306, 2000.
35. Handa H, Kurimoto N, Mineshita M, et al. Role of narrowband imaging in assessing endobronchial cryptococcosis. J Bronchology Interv Pulmonol 20: 249-251, 2013.
36. Murakami M, Yoshimatsu H, Uozumi T, et al. A case of primary pulmonary cryptococcosis with formation of an endobronchial tu-
mor and meningitis. Nihon Kyobu Shikkan Gakkai Zasshi 2: 122-126, 1985 (in Japanese, Abstract in English).

37. Mandell GL, Bennett JE, Dolin R. Chapter 261: Cryptococcus neoformans. In: Principles and Practice of Infectious Diseases. 6th ed. Perfect JR, Ed. Elsevier Health Sciences, 2005.

38. Brouwer AE, Siddiqui AA, Kester MI, et al. Immune dysfunction in HIV-seronegative, Cryptococcus gattii meningitis. J Infect 54: e165-e168, 2007.

39. Belliveau PP. Omalizumab: A monoclonal anti-IgE antibody. MedGenMed 7: 27, 2005.

40. Yalcin AD, Bisgin A, Cetinkaya R, et al. Clinical course and side effects of anti-IgE monoclonal antibody in patients with severe persistent asthma. Clin Lab 59: 7-17, 2013.

41. S A Nachman. Potential role of Cryptococcus neoformans in the pathogenesis of asthma. Thorax 61: 2006.

42. Neelkamal Chaudhary, Kieren A Marr. Impact of Aspergillus fumigatus in allergic airway diseases. Clin Transl Allergy 1: 4, 2011.

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