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Case Report

Laryngeal cryptococcus infection: literature review and a case study

Xiaotong Lu, Quangui Wang, Shuifang Xiao

Department of Otorhinolaryngology, Head and Neck Surgery, Peking University First Hospital, No. 8 Xi Shiku Street, Xi Cheng District, Beijing 100034, China

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Abstract: Laryngeal cryptococcosis is a rare clinical condition. We review the cases reported in the literature and also discuss a case study from our department to highlight disease management. In our case report and literature review, we used the search terms "larynx" or "laryngeal" or "vocal cord" and "cryptococcus" or "cryptococcosis" or "cryptococcal" to identify the reported cases. We reviewed 23 cases. The median age of the patients was 61 years and males showed a higher rate of incidence. Among these patients, 14 (61%) showed a history of corticosteroid use, and four had human immunodeficiency virus (HIV) co-infection. All the patients presented with hoarseness with a median duration of 12 weeks. Vocal cord mass was the most common laryngoscopic finding. Histopathology indicated granulomatous inflammation in 11 cases (52%) and pseudoepitheliomatous hyperplasia in 9 cases (43%). Thirteen cases (68%) stained positive for mucicarmine for detection of fungal infection. Twelve (52%) received fluconazole antifungal therapy, of which 9 showed complete resolution. Histopathologic examination with appropriate stains provides clues for accurate diagnosis of laryngeal cryptococcus infection. Fluconazole (400 mg daily for 6-12 months) is recommended as the first-line treatment for this disease. Surgery with or without antifungal treatment is also effective in select patients.

Keywords: Laryngeal, cryptococcus, fungal infection

Introduction

After *Candida* and *Aspergillus*, *Cryptococcus* is the most common pathogen underlying invasive fungal infections. As an opportunistic pathogen, *Cryptococcus neoformans* infects mostly immunosuppressed hosts with oral corticosteroid use, HIV infection, organ transplantation and hematologic malignancies as the contributing factors. It often starts as a primary lung infection that disseminates to other regions such as central nervous system, meninges, skeletal and subcutaneous tissues.

Case report

This study was approved ethically by Peking University First Hospital (Beijing, China) (Approval ID: [2015] 988) and written informed consent was obtained from every participant. A 45-year-old man presenting with a 2-month history of persistent hoarseness, was studied. The symptom had gradually worsened over the past 2 months. The patient underwent renal transplantation 16 years ago and still received immunosuppressant treatment. He also had a history of smoking for 20 years. Physical examination and laryngoscopic findings suggested a lesion along the left vocal cord, which extended from the anterior commissure to the vocal process, and the lesion was covered with albuginea (**Figure 1**). Biopsy was performed under local anesthesia. The histopathologic examination showed pseudoepitheliomatous hyperplasia caused by numerous yeasts in the vocal cord squamous mucosa. The organisms stained positive with Gomori methenamine silver (**Figure 2**), periodic acid-Schiff stain and mucicarmine stain (**Figure 3**), suggesting a diagnosis of laryngeal cryptococcal infection. The latex agglutination test for serum antigen was also positive, further confirming the diagnosis of cryptococcosis. However, cerebrospinal fluid tests and imaging tests suggested no evidence of disseminated infection.

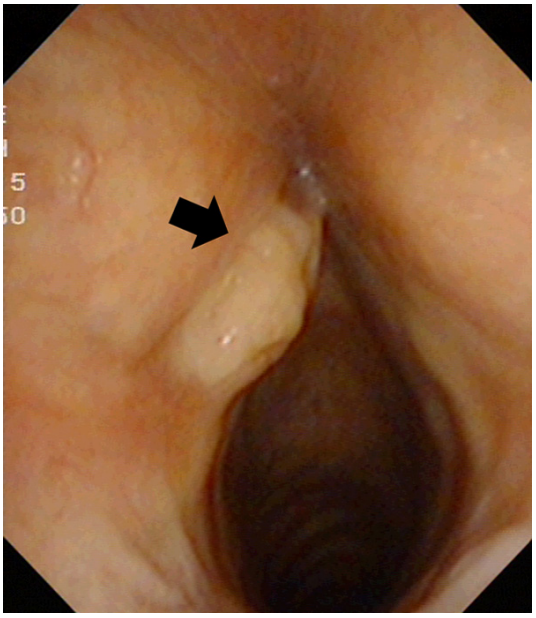

Figure 1. Lesion (arrow) along the left thickened vocal cord via anterior commissure toward the vocal cord process.

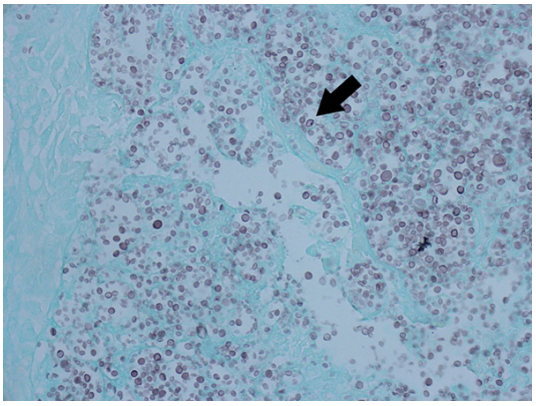

Figure 2. Cryptococcal yeasts stained (arrow) positive with Gomori methenamine silver stain (original magnification ×400).

Two months after the antifungal therapy, a follow-up laryngoscopy suggested significant improvement of the lesion in the left vocal cord (**Figure 4**). The patient completed a 6-month course of oral fluconazole therapy (200 mg daily) and obtained complete resolution.

Results

We reviewed 23 cases (22 from the database and one case study). **Table 1** summarized patients' general information and other risk factors contributing to the disease. The median

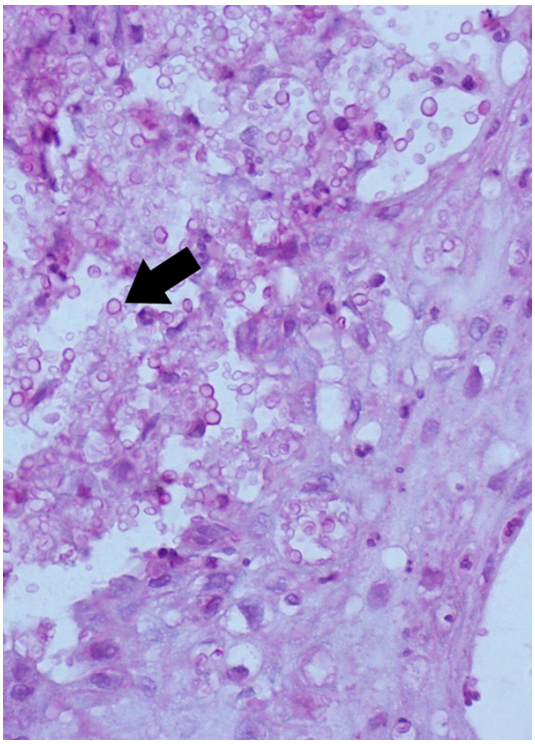

Figure 3. Yeast capsules (arrow) stained positive with mucicarmine stain (original magnification ×400).

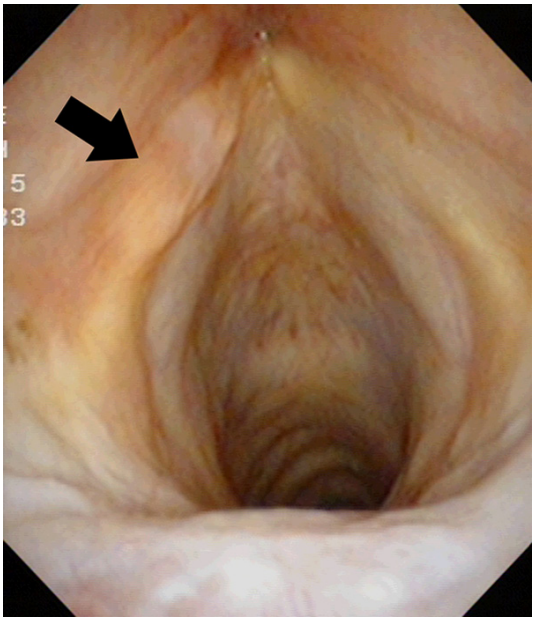

Figure 4. Two months after treatment, the lesion (arrow) in the left thickened vocal cord decreased significantly.

age was 61 years (range, 31-87 years) and males showed a higher rate of incidence. Nine of the 23 patients (39%) had a history of long-

Table 1. Clinical demographics and risk factors (n = 23)

Variable	Value
Age, median (range), years	61 (31-87)
Sex (male:female)	14:9
Possible risk factors	No. (%)
Long-term use of inhaled corticosteroids	9 (39)
Oral corticosteroid use	5 (22)
HIV infection	4 (17)
Diabetes mellitus	3 (13)
Tuberculosis	1 (4)
Meningitis	1 (4)
Previous or current cryptococcal pneumonia	2 (9)
Smoking	7 (30)
Exposure to bird manure	3 (13)

Table 2. Clinical and pathological findings

Characteristic	Value
Symptom (n = 23)	No. (%)
Hoarseness	23 (100)
Cough	5 (22)
Airway obstruction	2 (9)
Throat pain	1 (4)
Pharyngeal foreign body sensation	1 (4)
Duration of symptoms, median wk (range)	12 (3-104)
Reported findings from laryngoscopy (n = 23)	No. (%)
Vocal cord mass	10 (43)
Leukoplakia	6 (26)
Laryngeal erythema	6 (26)
Laryngeal edema	9 (39)
Histopathology (n = 21)	
Granulomatous inflammation	11 (52)
Inflammation without granulomas	5 (24)
Pseudoepitheliomatous hyperplasia	9 (43)
Squamous cell hyperplasia	3 (14)
Positive stains (n = 19)	
Gomori methenamine silver	15 (79)
Periodic acid-Schiff	5 (26)
Mucicarmine	13 (68)
Alcian blue	6 (32)
Positive serum antigen titer of isolated laryngeal cryptococcal infection (n = 12)	4 (33)
Abnormal findings on cerebrospinal fluid (n = 11)	0 (9)

term use of inhaled corticosteroids, 5 (22%) were documented with oral corticosteroid use before diagnosis while 4 (17%) had HIV co-infection. One case presented with meningitis and pulmonary localization at the time of diagnosis of laryngeal cryptococcosis. **Table 2** summarizes clinical symptoms and related examinations. All the patients presented with hoarseness. Ten cases (43%) were described as vocal cord or laryngeal mass, followed by laryngeal edema (39%). Histopathology indicated granulomatous inflammation in 11 of the 21 reported cases (52%) and pseudoepitheliomatous hyperplasia in 9 cases (43%). Gomori methenamine silver stain was positive in 15 of the 19 cases (79%) and 13 cases (68%) stained positive with mucicarmine. The treatments and outcomes of the reported cases are summarized in **Table 3**. Oral fluconazole (400 mg daily) was the most common regimen. Nine (75%) of the 12 patients who only received fluconazole showed complete resolution. A total of 15 patients (65%) had complete resolution. Four patients (17%) underwent endoscopic polypectomy alone, 2 of which were disease-free. Antifungal therapy with laser ablation was performed in 2 patients and only 1 patient achieved complete resolution.

Discussion

Cryptococcal laryngitis is uncommon. Only 22 cases have been reported in the literature to date [1-5]. Corticosteroid use is the most common predisposing factor for the development of this disease. Nine patients with COPD or asthma were exposed to inhaled corticosteroids alone. We found that the use of inhaled corticosteroids resulted in vocal cord impairment and increased the risk of infection. Male predominance was observed in the cases reviewed above. Our patient represented the first reported case of long-term immunosuppressant therapy following renal transplantation, which increased the risk of fungal infection. Husain S et al [6] showed that the incidence of cryptococcal infection was 2.8% in renal transplant recipients and the mortality rate reached 41%. Wu G et al [7] reported a higher risk of cryptococcal infection in male patients who underwent renal transplantation. Animal models suggested that multigenic con-

Table 3. Treatment and outcomes

Variable	Value
Treatment (n = 23)	No. (%)
Fluconazole only	12 (52)
Amphotericin B only	1 (4)
Itraconazole followed by fluconazole	1 (4)
Amphotericin B followed by fluconazole	2 (9)
Endoscopic polypectomy	4 (17)
Surgery and fluconazole therapy	3 (13)
Fluconazole treatment duration median (range), wk (n = 12)	10 (2-40)
Outcomes (n = 23)	No. (%)
Complete resolution	15 (65)
Improvement	7 (30)
Recurrence	1 (4)
Treatment resulting in complete resolution, (n = 15)	No. (%)
Anti-fungal therapy only	12 (80)
Fluconazole only	9 (60)
Endoscopic polypectomy only	2 (13)
Surgery and fluconazole	1 (7)

trol and location of the *XID* gene on the X chromosome increased the susceptibility to cryptococcosis [8].

Hoarseness was the most common symptom. Morphologically, lesions varied from vocal cord masses, leukoplakia, erythema or edema that occasionally resembled laryngeal neoplasia. Differential diagnosis included papilloma, tuberculosis of larynx, premalignant tumors and malignant tumors. The standard diagnostic approach included histopathological examination combined with special staining, such as Gomori methenamine silver and mucicarmine. Previous studies suggested that the detection of serum cryptococcal antigen by latex agglutination was negative for isolated laryngeal disease [9]. However, 4 positive cases were still reported following serum antigen test for isolated laryngeal cryptococcosis after excluding cryptococcemia or dissemination. Serological evaluation for cryptococcal antigen may facilitate the diagnosis and monitoring of the treatment.

According to the Infectious Disease Society of America clinical practice guidelines for the management of cryptococcal disease, organ transplant recipients with mild-to-moderate non-CNS disease, fluconazole (400 mg [6 mg/kg] daily) is recommended for 6 to 12 months. Immunosuppressive management should include sequential or stepwise reduction of immunosuppressants, to taper the corticosteroid dose [10]. However, no specific treatments for cryptococcus infection involving the vocal cords were addressed in current guidelines. Our patient completed a 6-month course of oral fluconazole (200 mg daily) treatment and achieved complete resolution. As the patient was receiving immunosuppressants following renal transplantation, dose reduction of immunosuppressive therapy was used to maintain a balanced immune system. Therefore, we suggest that the dose and the course of treatment should be determined by the patient's susceptibility and tolerance to therapy, as well as the severity of lesions. Meanwhile, it is reasonable to suggest dose reduction or withdrawal of inhaled corticosteroids while the patient suffered from laryngeal cryptococcus, according to the guidelines. In addition to antifungal therapy, 4 patients were treated with endoscopic polypectomy alone and 2 of them showed complete resolution. Among the 3 patients who received surgery and antifungal therapy, 2 reported laser ablation and only 1 was disease-free using the KTP laser. Compared with the other lasers, such as CO_2 and pulse-dye angiolytic laser, Jeng J Y et al [1] suggested KTP laser ablation for the management of laryngeal cryptococcus infection in select patients because of its curative effect. Laser ablation of the epithelial structures preserved the lamina propria that was associated with scarring and dysphonia. However, additional cases showing acceptable resolution are needed to establish the clinical efficacy.

Conclusion

Laryngeal cryptococcal infection is uncommon. The use of inhaled corticosteroids is a significant risk factor for the development of cryptococcal disease. Histopathologic examination with appropriate staining enables accurate diagnosis and excludes common laryngeal lesions. Oral fluconazole (400 mg daily) is recommended for 6-12 months as the first-line

treatment for laryngeal cryptococcosis. Surgery with or without antifungal treatment also yields satisfactory patient outcomes.

Disclosure of conflict of interest

None.

Address correspondence to: Quangui Wang, Department of Otorhinolaryngology, Head and Neck Surgery, Peking University First Hospital, No. 8 Xi Shiku Street, Xi Cheng District, Beijing 100034, China. Tel: +86-15011231675; Fax: +86-021-64085875; E-mail: quanguiwangmd@sina.com

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