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CLINICAL RECORD

Cryptococcal infection of the larynx: case report

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Abstract

Objective: Laryngeal cryptococcosis is a rare condition. In this report, we describe the findings for and treatment of a 58-year-old man with *Cryptococcus gattii* infection of the right vocal fold.

Method: Case report and review of the relevant English language literature.

Results: The patient presented with persistent hoarseness of voice. Laryngoscopy demonstrated an irregular, red lesion on the right vocal fold. Histopathological examination identified cryptococcus. The patient was treated with oral fluconazole 400 mg/day for eight weeks.

Conclusion: Laryngeal involvement by *Cryptococcus gattii* can result from prolonged inhaled corticosteroid therapy and proximity to eucalyptus trees. The clinical presentation, laryngoscopic findings and imaging results of laryngeal involvement may mimic a neoplasm. Histopathological examination can demonstrate the causative organism. Management consists of advice from an infectious disease specialist together with adequate treatment by antifungal agents.

Key words: Hoarseness; Cryptococcus Gattii; Eucalyptus

Introduction

There are numerous causes of hoarseness of voice, which fall into three categories: inflammatory lesions, benign proliferative disorders and malignant tumours.[1] The most common cause of laryngitis is viral infection; however, fungi can also infect the larynx. Mycotic laryngitis is important to keep in mind as it can resemble a malignant process on both clinical examination and imaging studies.[2,3]

Laryngeal cryptococcosis is very rare, with only 12 cases reported in the literature.[3] The most common presenting symptom of isolated laryngeal cryptococcosis is persistent hoarseness of voice.[3]

We describe the case of a non-immunocompromised patient in whom mycotic laryngitis was caused by cryptococcal infection which mimicked malignancy on laryngoscopy.

Case report

A 58-year-old man presented with a three-week history of a husky voice. He had a history of asthma treated with budesonide and formoterol inhaler therapy.

Laryngoscopic examination showed congested, red vocal folds.

A diagnosis of laryngitis was made and the patient was treated with cephalexin for 10 days.

However, his voice remained husky. A second laryngoscopy, one month later, showed that the right vocal fold was still red but the left vocal fold was normal. The patient was given a short course of oral prednisolone 25 mg and oral nystatin three times a day for possible fungal infection of the larynx.

The patient's symptoms persisted. A third laryngoscopy, one month later, showed increased mucus in the larynx and persistent redness of the right vocal fold. Antibiotics were changed to amoxycillin and clavulanic acid and the patient was advised to have steam inhalations. He was also referred for endoscopy as he had reflux oesophagitis, in order to assess reflux aspiration as a cause of vocal hoarseness. However, no abnormality was seen in the oesophagus or stomach, and biopsy histology was normal.

The patient's hoarseness still persisted. Further laryngoscopy with biopsy was arranged. This now revealed an irregular, red lesion on the right vocal fold (Figure 1), which was biopsied. Carcinoma of the larynx was suspected.

Histological examination of the biopsy specimen showed vocal fold squamous mucosa which was inflamed, thinned and partially ulcerated. The underlying tissue showed invasion by inflammatory cells. This included numerous macrophages containing rounded bodies which stained lightly with eosin (Figure 2). These rounded bodies stained positively with periodic acid Schiff stain (for mucopolysaccharides) (Figure 3). They were yeast-like in shape and had clear spaces around them. No pseudohyphae or true hyphae were seen. Alcian blue staining was performed in order to identify cryptococcus; this stained the specialised capsule, confirming the identity of the organism (Figure 4). The organisms also stained positive with Grocott methenamine silver fungal stain (Figure 5). There was no evidence of epithelial dysplasia or neoplasia (see Figures 1 and 2).

Following establishment of the histopathological diagnosis, the patient was referred to an infectious disease physician for further management. On further enquiry, the patient revealed a history of camping under eucalyptus trees in the Australian desert one year earlier. He had a normal leucocyte count, negative human immunodeficiency virus (HIV)

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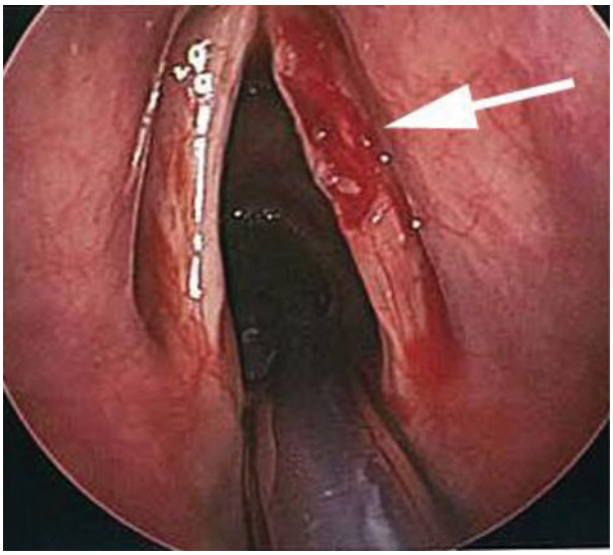

FIG. 1
View from the patient's third laryngoscopy, showing an irregular, red lesion on the right vocal fold (arrow).

serology, normal thyroxine results, negative blood cultures and negative blood results for diabetes. There were no enlarged liver, spleen or lymph nodes. The chest X-ray was normal and a test for cryptococcal serum antigen was negative. In view of the histological findings, he was diagnosed with localised vocal fold cryptococcal infection, with no systemic involvement.

The patient was treated with fluconazole 400 mg/day for eight weeks. At the time of writing, he was scheduled to undergo a further laryngoscopy in several months' time. It was intended to follow up the patient for a further 12 months to ensure that resolution was complete.

Discussion

The major species causing human cryptococcosis are *Cryptococcus neoformans* and *C gattii*.[4] *Cryptococcus neoformans* causes the vast majority of cryptococcal infections in immunosuppressed hosts, including patients with acquired immunodeficiency syndrome, whereas *C gattii* causes 70–80 per cent of cryptococcal infections among immunocompetent hosts. Although *C neoformans* is found worldwide, *C gattii* is usually identified in subtropical areas such as Australia, South America, Southeast Asia, and central and sub-Saharan Africa.[4] *Cryptococcus gattii* is closely associated with some eucalyptus trees.[5]

Cryptococcal laryngitis is uncommon. Twelve cases have been described in the literature to date.[3] *Cryptococcus neoformans* usually occurs as a primary pulmonary infection that can potentially disseminate in an immunocompromised host to sites such as the central nervous system, meninges, bone and subcutaneous tissue. Although the majority of cryptococcal infections occur in immunocompromised patients, hosts with a relatively intact immune system can

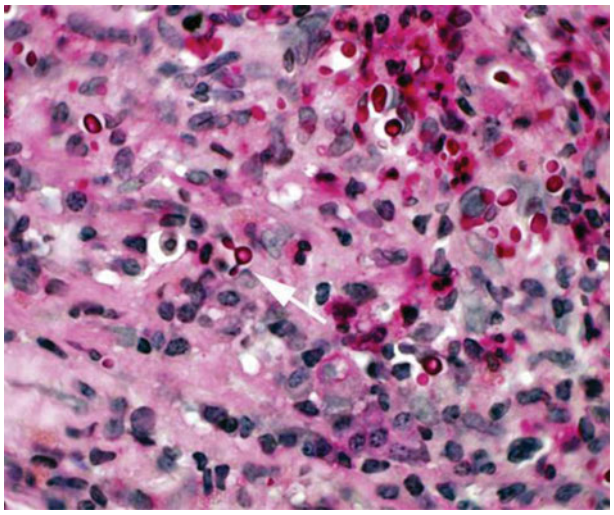

FIG. 3
Photomicrograph showing budding fungus (arrow) within granulation tissue. (Periodic acid Schiff; original magnification ×100)

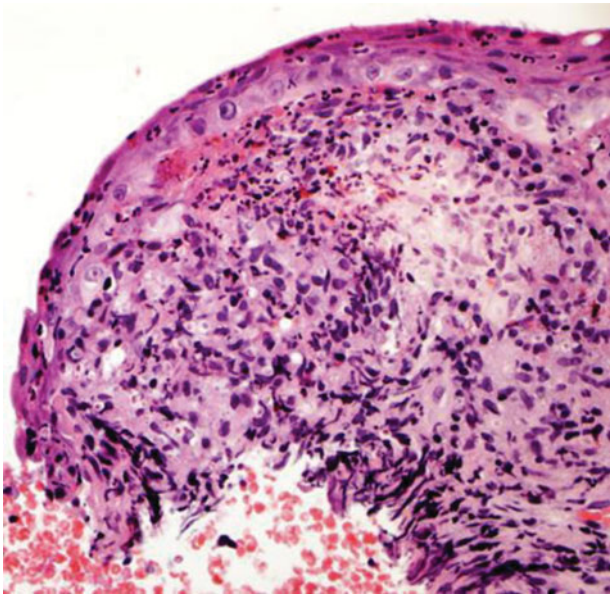

FIG. 2
Photomicrograph showing a granulomatous nodule with eroded surface epithelium. (H&E; original magnification ×40)

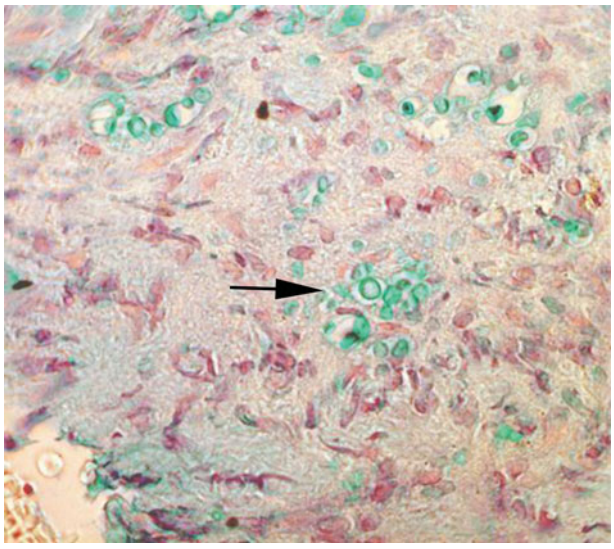

FIG. 4
Photomicrograph showing fungal capsules (arrow) staining positively on Alcian blue staining. (Original magnification ×100)

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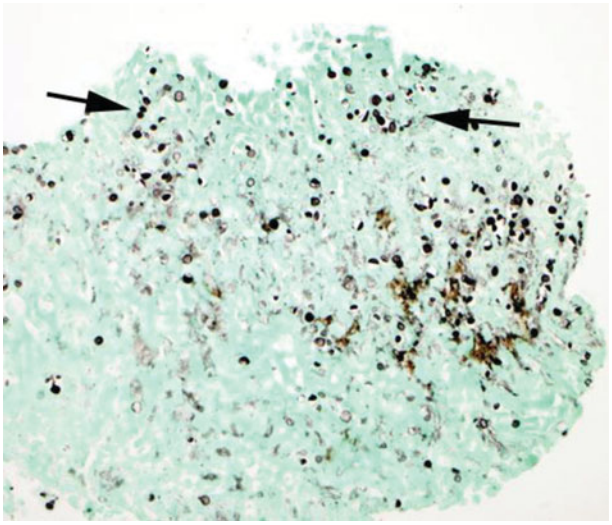

FIG. 5
Photomicrograph showing numerous fungal elements (arrows). (Grocott methenamine; ×40)

be infected as well.[2] Laryngeal cryptococcosis has been described in both immunocompetent and immunocompromised patients.[2,3,6] Our patient was not immunocompromised but had a long history of inhaled corticosteroid usage, which may have predisposed him to cryptococcal infection. In their case series, Gordon *et al.* described a similar history in one of their three patients.[3]

Laryngeal involvement may arise either from a haematogenous route, with spread from a primary focus such as the lung, or from direct implantation by inhaled, aerosolised organisms.[2] *Cryptococcus neoformans* is associated with avian habitats and droppings, while *C gattii* is found in association with several different species of eucalyptus trees such as the river red gum and the forest red gum.[4]

We believe it is likely that our patient was predisposed to cryptococcal infection by his inhaled corticosteroids, and presumably was exposed to a high level of *C gattii* while camping under eucalyptus trees.

- **Laryngeal cryptococcosis is rare and occurs in both immunocompetent and -compromised patients**
- **The presented patient had *Cryptococcus gattii* infection, predisposed to by inhaled corticosteroids and proximity to eucalyptus trees**
- **Histopathological examination established the diagnosis**
- **Treatment options for laryngeal cryptococcosis include oral fluconazole and endoscopic polypectomy**
- **It should be included in the differential diagnosis of persistent hoarseness, and can mimic neoplasia**

Hoarseness is the most common presenting symptom of laryngeal cryptococcosis (as seen in our patient), with an average duration of four months.[3] In laryngeal cryptococcosis, abnormalities of the vocal folds or subglottic space vary in appearance, with lesions being described variously as erythematous, oedematous, leukoplakic or cystic.[7] In our patient, the predominant finding on laryngoscopy was erythematous change of the right vocal fold with associated irregular nodularity, which led to the suspicion of a neoplastic aetiology.

On histological examination, laryngeal cryptococcosis biopsy specimens have been reported to show pseudo-epitheliomatous hyperplasia of the squamous mucosa overlying granulomatous inflammation in the submucosal region.[2,3] Histological examination of tissue sections shows cryptococcus as eosinophilic or lightly basophilic yeasts that vary in size from 2 to 20 mm. These yeasts possess capsules that stain positively with mucicarmine and cell walls that stain positively with methenamine silver. In immunocompetent patients, *C neoformans* usually elicits a granulomatous reaction; however, in anergic patients the host reaction may be greatly diminished.[8]

There are currently no evidence-based guidelines for the management of laryngeal cryptococcosis; thus, it is prudent to obtain advice from an infectious disease specialist, as in our case.[3] Assessment includes the exclusion of HIV or other systemic immunosuppressive disorders, and the exclusion of disseminated cryptococcal disease. Testing for serum cryptococcal antigen is only likely to be positive in cases with invasive disease; thus, it will usually be negative for isolated laryngeal disease. Treatment options include antifungal treatment with oral fluconazole (400 mg/day) and endoscopic polypectomy.[3] Pulse dye laser treatment at 585 nm has also been used to treat residual lesions, after a course of antifungals.[6]

Conclusion

We describe the findings in a rare case of laryngeal cryptococcosis. Our patient was likely to have been predisposed to this condition by prolonged use of inhaled corticosteroids and proximity to eucalyptus trees. Histological examination is essential to establish the diagnosis and to exclude other infectious cases and neoplasia.

References

1 Berke GS, Kevorkian KF. The diagnosis and management of hoarseness. *Compr Ther* 1996;**22**:251–5
2 McGregor DK, Citron D, Shahab I. Cryptococcal infection of the larynx simulating laryngeal carcinoma. *South Med J* 2003;**96**:74–7
3 Gordon DH, Stow NW, Yapa HM, Bova R, Marriott D. Laryngeal cryotococcosis: clinical presentation and treatment of a rare cause of hoarseness. *Otolaryngol Head Neck Surg* 2010; **142**(suppl 1):S7–9
4 Medscape Reference: Cryptococcosis. In: http://emedicine.medscape.com/article/215354 [20 August 2012]
5 Ellis DH, Pfeiffer TJ. Natural habitat of *Cryptococcus neoformans* var. gattii. *J Clin Microbiol* 1990;**28**:1642–4
6 Joo D, Bhuta S, Chhetri DK. Primary cryptococcal infection of the larynx in a patient with severe chronic obstructive pulmonary disease: a case report. *Laryngoscope* 2009;**119**(suppl S1):S169
7 Bamba H, Tatemoto K, Inoue M, Uno T, Hisa Y. A case of vocal cord cyst with cryptococcal infection. *Otolaryngol Head Neck Surg* 2005;**133**:150–2
8 Chandler FW, Watts J. Cryptococcosis. In: Connor DH, Chandler FW, Schwartz DA, Manz HJ, Lack EE, eds. *Pathology of Infectious Diseases*. Stamford: Appleton & Lange, 1997;I:989–97

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