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Cryptococcal laryngitis in an immunocompetent asthmatic patient using inhaled corticosteroids

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ABSTRACT

We present a case of laryngeal *cryptococcosis* caused by *cryptococcosis neoformans* var. *grubii* affecting a patient using excessive inhaled corticosteroids. The patient experienced symptoms for several months prior to specialist review and the visualization of a mass lesion by nasopharyngoscopy. Fortunately a biopsy was performed and through histopathology & microbiological assessment a diagnosis of cryptococcal laryngitis was made. Treatment with 6 months of fluconazole resulted in clinical cure and resolution of symptoms. It is important to raise awareness of the risk of non-Candida fungal infections in patients on high dose corticosteroids, especially in the post covid era were steroids are more commonly prescribed.

1. Introduction

Laryngeal cryptococcosis presents in immunocompromised patients as a manifestation of disseminated disease or localised disease [1]. Rarely cryptococcal laryngitis occurs in immunocompetent patients who use inhaled and systemic corticosteroids [2]. Due to the lack of awareness of the association between inhaled corticosteroids and non-candida fungal infections, as well as the rarity of this disease entity, it may be unrecognised resulting in a delay in diagnosis and misinterpretation as a malignant lesion.

2. Case presentation

A 41 year old male with asthma presented with a nine month history of dysphonia in the setting of type 2 diabetes mellitus, obesity and hypertension. His dysphonia progressively worsened and was associated with the development of a productive cough. Intentional weight loss was also reported during this time. His symptoms did not respond to oral antibiotics or corticosteroids.

Our patient was a non-smoker with a history of severe asthma resulting in previous respiratory arrest. He reported regular use of salmeterol xinafoate 25mcg/, fluticasone 250mcg 3 puffs twice daily and frequent salbutamol nebulisers to manage his dyspnoea. He had been on this dose of fluticasone for over 20 years and high dose inhaled corticosteroids since childhood.

Upon review by Ear Nose Throat Head & Neck Surgeon (Day 0), nasopharyngoscopy was performed and demonstrated left sided supraglottic oedema and irregularity of the membrane of the supraglottic false cords with leucoplakia. Pan-endoscopy on Day 5 revealed oedematous supra-glottic tissues and vocal cords (Fig. 1). Biopsy of the larynx was performed and sent for bacterial and fungal cultures as well as human papilloma virus polymerase chain reaction (PCR). Tissue cultures showed yeast elements and gram-positive cocci on gram stain. *Staphylococcus aureus* and *Cryptococcus neoformans* var. *grubii* grew from culture. The Cryptococcus species grew on Sabouraud agar after 5 days and was identified by Matrix-Assisted Laser Desorption/Ionisiation Time of Flight (MALDI-TOF) mass spectrometry (BD™ Bruker MALDI Biotyper™) and confirmed by Internal Transcribed Spacer (ITS) sequencing. Histological examination showed yeast-like encapsulated intracellular organisms on hematoxylin and eosin (H&E) stain (Fig. 2a) and ulcerated lesions within the squamous epithelium with inflammatory cells including histiocytes and yeast organisms (Fig. 2b). No atypia or malignancy was identified. Human papilloma virus was not detected by PCR.

Further investigations including lumbar puncture, computed tomography (CT) chest and magnetic resonance imaging (MRI) brain

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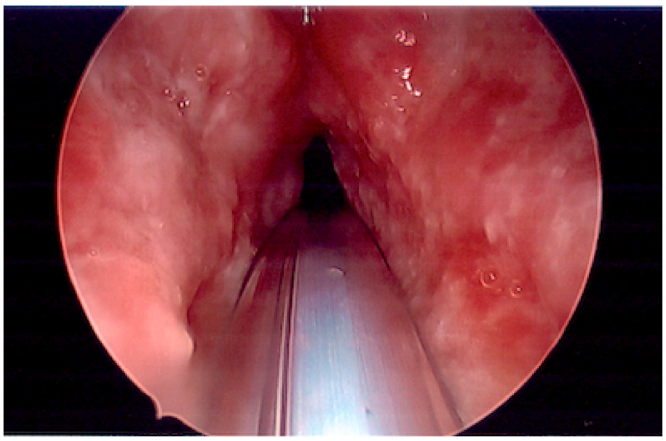

Fig. 1. Image of the larynx taken during pan-endoscopy at diagnosis showing oedematous supra-glottic tissue.

performed on days 11–16 did not show any evidence of disseminated cryptococcal infection. Serum and cerebrospinal fluid cryptococcal antigen was not detected using the IMMY lateral flow assay (Immuno-Mycologics Inc, Oklahoma). Investigations for underlying immunodeficiency including HIV, lymphocyte subsets and immunoglobulins were unremarkable. The patient also reported no history of opportunistic infections or recurrent childhood infections.

Susceptibility testing performed on the *C. neoformans* var. *grubii* isolate demonstrated a fluconazole minimum inhibitory concentration (MIC) of 1 μg/ml, amphotericin B MIC 1 μg/ml and flucytosine MIC 1 μg/ml. Fluconazole 400mg orally daily was commenced for treatment of cryptococcal laryngitis as per the Infectious Diseases Society of America guidelines with an intended duration of six months of therapy [3]. Inhaled corticosteroid therapy was changed to Budesonide 200mcg/formoterol 6mcg 2 puffs twice daily. After 3 months of fluconazole the patient's symptoms had resolved and the patient self-ceased fluconazole. A relapse of symptoms developed 3 months after discontinuation. The patient was recommenced on fluconazole for a further 3 months. The patient underwent a repeat endoscopy at the end of 6 months of treatment which was normal on macroscopic examination. The patient is now undergoing regular clinical monitoring.

3. Discussion

Cryptococcus infections in humans are caused by two main encapsulated yeast from the Cryptococcus genus: *Cryptococcus neoformans* and *Cryptococcus gattii* [1,4]. *C. neoformans* is ubiquitous and linked with rotting wood and avian hosts such as pigeon, chicken and turkey where the yeast may be found in their excreta [1,5]. *C. gatti* in Australia has been associated with Eucalyptus trees including the river red gum and other environmental niches in tropical and subtropical areas [6]. Infections caused by both *Cryptococcus species* cause similar clinical presentations including pulmonary and extrapulmonary disease [2]. Whilst invasive cryptococcosis are often regarded as opportunistic infections mainly affecting immunocompromised hosts, *C. gatti* has been associated with infections in immunocompetent patients [1,4].

Primary cryptococcal laryngitis is an uncommon condition, usually presenting with symptoms of dysphonia, cough and stridor [1,2]. Airway obstruction has been reported in severe cases [7]. Whilst primary cryptococcal laryngitis can occur in immunocompromised patients, haematogenous or contiguous spread to the larynx and disseminated cryptococcal infection is a more common presentation [2,8].

Case reports of primary cryptococcal laryngitis in immunocompetent patients have described a history of tobacco smoking and systemic corticosteroids and/or inhaled corticosteroid in affected patients [1,2,4,5,7,9].

In the literature, the dose of inhaled corticosteroids taken by patients with primary cryptococcal laryngitis varies from 1000ug to 2000ug of fluticasone per day [1,2]. Different corticosteroid formulations may confer a higher risk of fungal laryngitis [7]. Specifically fluticasone, has been linked with a higher risk due to the particle size and pattern of deposition on the glottis [7,10]. Inhaled corticosteroids and smoking are thought to cause localised disruption of the epithelial barrier of the larynx predisposing to fungal infection [1,2,7,9]. Systemic corticosteroid use further increases this risk [1,2,5].

The clinical presentation of laryngeal cryptococcosis with subacute symptoms and the appearance of a mass lesion often results in malignancy as the main differential diagnosis [5]. This is reflected in the majority of reported cases in the literature relying on histopathology alone for diagnosis [2,4,5]. The salient histology features seen in cryptococcal laryngitis include pseudoepithelomatous hyperplasia of the squamous mucosa and granulomatous inflammation in the submucosa with fungal elements detected by specialised fungal stains [2,5]. Tissue biopsy for histopathology and microbiological examination are essential to diagnosis and guiding antifungal treatment [5].

In the literature, *C. neoformans* has been implicated as the causative organism of all except one case of laryngeal cryptococcosis where an Australian patient with a history of exposure to Eucalyptus trees was assumed to have *C. gatti* without microbiological confirmation [4]. Our case report of an Australian patient residing in a rural setting with primary laryngeal cryptococcosis and confirmed *C. neoformans* from culture demonstrates that even with epidemiological risk factors for *C. gatti*, *C. neoformans* is more common.

Treatment of cryptococcal laryngitis reported in the literature include oral fluconazole, surgical resection, liposomal Amphotericin B and laser therapy [2,4,9]. In patients using inhaled corticosteroid medications, reducing exposure to corticosteroids and improving

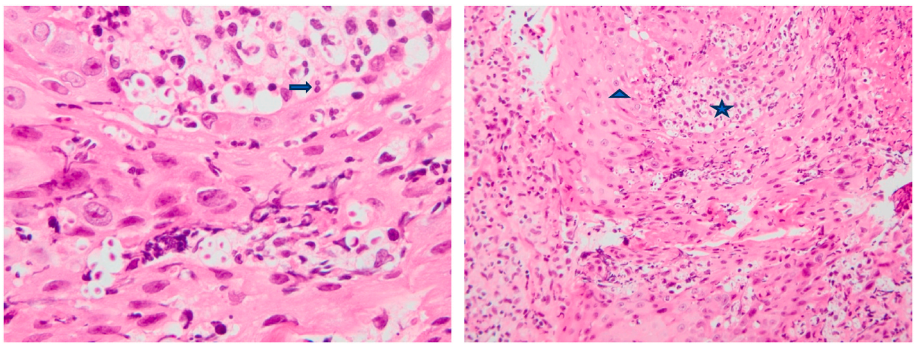

Fig. 2. Histology
Fig. 2a: High power (x400) H&E stain with yeast-like encapsulated intracellular organisms (arrow)
Fig. 2b: Medium power (x100) H&E stain showing ulcerated squamous cells (triangle) with inflammatory cells and yeast organisms (star).

inhaler technique to minimise local toxicity have been reported in the literature to be important aspects of management [1,2,9].

In summary, prescribers of inhaled corticosteroids should be aware of the risk of non-candida infections such as cryptococcal laryngitis in patients on high-dose therapy. In patients presenting with hoarseness, chronic cough and mass lesions on the larynx, cryptococcal laryngitis should be considered as a differential diagnosis. Laryngeal biopsy for histopathology and fungal culture are key in the diagnosis of laryngeal cryptococcosis. Exclusion of disseminated infection to other sites where Cryptococcus infection commonly occurs is important. Treatment with oral azole therapy can effectively cure patient with laryngeal cryptococcosis.

Ethical Form

Please note that this journal requires full disclosure of all sources of funding and potential conflicts of interest. The journal also requires a declaration that the author(s) have obtained written and signed consent to publish the case report/case series from the patient(s) or legal guardian(s).

The statements on funding, conflict of interest and consent need to be submitted via our Ethical Form that can be downloaded from the submission site www.ees.elsevier.com/mmcr. **Please note that your manuscript will not be considered for publication until the signed Ethical Form has been received.**

Sources of funding

There are none.

Declaration of competing interest

There are none.

Consent

Written informed consent was obtained from the patient or legal guardian(s) for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

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