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HOARSENESS SECONDARY TO LARYNGEAL HISTOPLASMOSIS: A CASE REPORT.

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ABSTRACT

Histoplasmosis usually occurs in immunocompromised patients through the dissemination of the fungus from lungs to other organs but laryngeal involvement is rare. We report a 52-year-old male chronic smoker who presented with hoarseness for 3 months was initially investigated for laryngeal carcinoma. However biopsy showed granulomatous inflammation. He was treated with anti-tuberculosis treatment for 2 months but symptoms persisted and a repeat biopsy revealed laryngeal histoplasmosis. There were no sign and symptoms of pulmonary or systemic involvement. Treatment with intravenous amphotericin B and oral itraconazole lead to complete resolution of symptoms and signs. Monitoring and early revisiting the diagnosis are important when a patient's symptoms do not improve with the treatment. Further investigation including a repeat biopsy of lesion is vital to establish the diagnosis and lead to appropriate management.

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ABSTRACT

Histoplasmosis usually occurs in immunocompromised patients through the dissemination of the fungus from lungs to other organs but laryngeal involvement is rare. We report a 52-year-old male chronic smoker who presented with hoarseness for 3 months was initially investigated for laryngeal carcinoma. However biopsy showed granulomatous inflammation. He was treated with anti-tuberculosis treatment for 2 months but symptoms persisted and a repeat biopsy revealed laryngeal histoplasmosis. There were no sign and symptoms of pulmonary or systemic involvement. Treatment with intravenous amphotericin B and oral itraconazole lead to complete resolution of symptoms and signs. Monitoring and early revisiting the diagnosis are important when a patient's symptoms do not improve with the treatment. Further investigation including a repeat biopsy of lesion is vital to establish the diagnosis and lead to appropriate management.

Keywords: Carcinoma, Granulomatosis, Histoplasmosis, Larynx, Tuberculosis.

INTRODUCTION

Histoplasmosis is caused by *Histoplasma capsulatum,* a fungus usually found in moist and fertile soil which prevalently in the river valleys in the central United States.[1] Laryngeal involvement of histoplasmosis usually occurs by the spread of the fungus from the lungs to other organs in immunocompromised patients. Primary laryngeal histoplasmosis in immunocompetent patient is rare.[2] It may mimic laryngeal malignancy or tuberculosis (TB) by common presentation symptoms of hoarseness and mucosal lesion of larynx. High index of suspicion is important to establish diagnosis in patient with persistent symptoms despite optimum medical treatments. We reported here a case of laryngeal histoplasmosis in a middle aged man who presented with 3 months history of hoarseness of voice and was

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initially missed diagnosed and treated as tuberculosis based on a laryngeal biopsy showing granulomatous inflammation. Final confirmatory diagnosis of histoplasmosis was made when symptoms did not improve after 2 months of treatment with anti-tuberculous drugs and repeat biopsy. Patient's symptoms and condition completely resolved with intravenous amphotericin B and oral itraconazole treatment. Learning point of this case report is to revisit the initial diagnosis if treatment is not effective and patient is still symptomatic with repeat biopsy to establish the correct diagnosis and apply appropriate management.

CASE REPORT

A 58-year-old man presented with progressive hoarseness for 3 months. He denied any fever, weight loss, haemoptysis, dyspnoea, odynophagia and dysphagia. He was a chronic smoker for the past 40 years, smoking on average 2 packs of cigarettes per day. There was no past history of TB and there was no known hypersensitivity to drugs or food. He worked as rubber tapper for the past 20 years.

Physical examination was normal except for the hoarseness. Blood investigation and chest radiograph were normal. Sputum was negative for acid-fast bacilli. Screening for syphilis, human immunodeficiency virus (HIV) and Hepatitis B virus were negative. Laryngoscopy disclosed a whitish fungating mass involving the whole length of left vocal cord extending from the anterior commissure to posterior commissure. Inferiorly mass extend to the left anterior part of subglottic and superiorly obliterating the left ventricle. Left false cord and right anterior two-thirds of true cord appeared irregular. Despite the provisional diagnosis of laryngeal carcinoma, biopsies of mass showed fragments of caseating epithelioid cell granulomas with many lymphocytes. Ziehl-Neelsen stain was negative. However, Grocott silver stain was not used routinely in all specimens. Based on the histopathological examination (HPE) result in a TB endemic region, a preliminary diagnosis of TB was made and the referred medical team decided to start with anti-TB therapy.

However, the symptoms persisted despite 2-month commencement of the treatment. Laryngoscopy showed similar lesion. As malignancy was the next in the list, a repeat biopsy was obtained.

Biopsies were taken and the HPE showed fragments of inflammatory cells which filled with tiny rounded capsulated yeasts in Haematoxylin and eosin (Figure 1) and Grocott silver stain (Figure 2) which consistent with fungal infection of *Histoplasma spp*. Surface squamous mucosa was unremarkable and there were no malignant changes. Diagnosis of histoplasmosis of the larynx was made and treatment with intravenous amphotericin B was commenced for 1 month. His symptoms improving after the treatment and laryngoscopy revealed complete resolution of fungating mass. He was discharged with oral itraconazole 200 mg twice daily and advised for subsequent follow up visits. At 3-month follow-up, the patient regained normal voice with no residual lesion seen on laryngoscopy.

DISCUSSION

Histoplasmosis is a very common granulomatous disease of worldwide distribution caused by dimorphic (existing as mycelial and yeast forms) fungus, *Histoplasma capsulatum.*[3] It was discovered in 1906 by Samuel Darling.[4] The organism was initially thought to be a protozoan but later proved to be a fungus and lives predominantly in the mycelial form in the environment. It is found usually in soils contaminated by faeces of bats or birds in the caves or houses. At room temperature, the fungus exists in the mycelial phase. However,

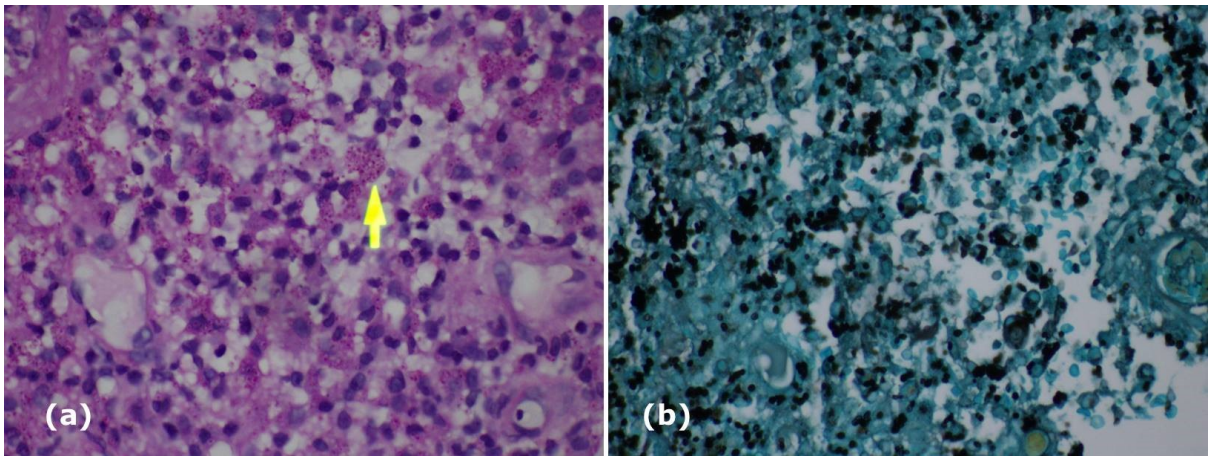

Figure 1: (a) Stain of laryngeal biopsy showing the presence of numerous small capsulated rounded organisms (Hematoxylin and Eosin (H&E), x 40), (b) (b) High power (x 40) Grocott silver stain of laryngeal biopsy showing the macrophages containing variable numbers numbers of round or oval bodies surrounded by a clear zone. (Click on image to enlarge)

once the spores are inhaled, the relatively high body temperature encourages the yeast form. This phase is responsible for the human infection,[5] which leads to pulmonary infection and complicated by haematogenous spread to other organs such as brain, heart, bone marrow and liver. Other factors that contribute to dissemination of primary infection are extremes of age, high load of organisms inhaled, immune-compromised and malnutrition.[6,7] Primary laryngeal histoplasmosis is rare and it can mimic carcinoma or TB. Our patient who was immune-competent might have inhaled the spores during working as rubber tapper, which lead infection of histoplasmosis, but confined to laryngeal involvement.

Primary pulmonary histoplasmosis is usually asymptomatic but chronic pulmonary histoplasmosis is clinically similar to pulmonary TB. Laryngeal involvement is usually secondary to disseminated histoplasmosis most likely by haematogenous spread. The symptoms include hoarseness, sore throat, cough, dysphagia and stridor.

Accurate diagnosis and non-surgical treatment will lead to resolution of the lesions and improvement of voice. However, the diagnosis is difficult as the lesions may resemble carcinoma or TB. In our case, the history of smoking along with the appearance of the lesion on the laryngoscopy suggested the diagnosis of a laryngeal carcinoma. Initial biopsy revealed chronic granulomatous features which was commonly associated with TB in local endemic region.

Despite anti-TB treatment, symptoms were persistent which require a repeat biopsy evaluation. Gomorimethenamine (or Grocott) silver stain is a histological stain that is used majorly for the identification of carbohydrates in fungal microorganisms. However, it was not initially used during first biopsy in view patient was immunocompetent and fungal infection was not suspected. The biopsy showed granulomatous tissue containing necrosis, with infiltration of giant cells, lymphocytes, plasma cells, macrophages. Grocott silver stain showed macrophages containing variable numbers of round or oval bodies surrounded by a clear zone led to diagnosis of histoplasmosis. Histoplasmosis which presents with only mucosal lesion must be further investigated likes sputum cultures, chest radiography and bone marrow aspiration biopsy to look for disseminated disease.[5] Other sites of oropharyngeal involvement include mucosal surfaces of the gingiva, tongue, lips and pharynx must be ruled out.

Histoplasmosis presenting with laryngeal symptoms is rare. A review of 606 histoplasmosis cases did not mention about hoarseness as a presenting symptom or laryngeal involvement.[1] The differential diagnoses are carcinoma, TB, syphilis, lymphoma and other granulomatous disease of head and neck regions such as cat-scratch disease and actinomycosis. Microscopically, histoplasmosis may be confused with TB and squamous cell carcinoma. Factors such as a living in endemic areas and occupational history may trigger clinicians' suspicion of histoplasmosis. Radiological assessment, immunohistochemistry test and positive culture of *Histoplasma capsulatum* are important foundation of which the clinical diagnosis is made.

Amphotericin B is the treatment recommended in the past. Currently, the preferred agent is itraconazole for treating patients without any known immunosuppression.[7] American Society of Infectious Diseases suggested itraconazole 200 mg administered twice a day for a year in mild to moderate disease lead to good success rate of cure. Surgical intervention of mass which causing airway obstruction can be consider in patients which symptoms do not improve after one to three months of medical therapy.[8,9]

CONCLUSION

Laryngeal histoplasmosis though rare should be considered in the diagnosis of a granulomatous lesion of the larynx in a patient presenting with hoarseness. Tissue biopsies of the suspicious lesions along with special stains such as Grocott silver stain helps to establish diagnosis of histoplasmosis and differentiate it from malignancy and tuberculosis. Anti-fungal medications such as amphotericin and itraconazole are the mode of therapy. Resolution of symptoms and laryngeal lesion within 4-6 weeks of antifungal treatment might avoid unnecessary interventions.

CONFLICTS OF INTEREST STATEMENT

The authors have no conflicts of interest to declare and consent has been obtained from patient and hospital authority to publish this article.

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