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Laryngeal histoplasmosis mimicking glottic cancer in an immunocompetent host

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Abstract

We report an interesting case of laryngeal histoplasmosis which clinically mimicked a malignant glottic growth and is unusual in that it involved an immunocompetent host. Also, an isolated laryngeal involvement is very rare. A 63 year old farmer presented with complaints of hoarseness of voice. Indirect laryngoscopy revealed a friable growth in the middle of the right vocal cord. Histopathological examination of biopsy taken from the growth showed presence of numerous tiny intracellular organisms within collections of macrophages and epithelioid cells. Confirmation was done with periodic acid Schiff and Gomori's methanamine silver stain. The patient was administered amphotericin B 1 mg/kg body weight for 2 weeks followed by itraconazole 200 mg, twice a day for 8 weeks and discharged on oral itraconazole. A dramatic improvement in voice quality was seen in follow-up after two months. Repeat endoscopy showed regression of growth. The otolaryngologist should be aware of the existence of laryngeal histoplasmosis and consider it as one of the differential diagnosis when a patient shows signs of granulomatous inflammation or laryngeal masses, to perform specific diagnostic tests for fungi and provide optimal and timely treatment, avoiding unnecessary aggressive interventions.

Keywords: Laryngeal histoplasmosis, mimicking glottic cancer, immunocompetent host

Introduction

Case presentation

A 63 year old man presented to the department of otorhinolaryngology with complaints of hoarseness of voice of one month duration. The hoarseness was progressive in nature and was not accompanied by dysphagia or difficulty in breathing. The patient was a non-smoker, non-alcoholic and had been a farmer by occupation all his life. He denied recent travel, chronic disease or sick contacts. The general physical examination was normal except for notable hoarseness of voice. The examination of ear, nose, oral cavity did not reveal any significant finding. Significant lymphadenopathy was not found in the cervical region and elsewhere.

Throat examination by indirect laryngoscopy, however, revealed a friable growth in the middle of the right vocal cord (Figure-1). Both vocal cords were mobile. Laboratory investigations including complete blood count, liver and renal function tests, X-ray chest, hepatitis B surface antigen, anti-hepatitis C virus, HIV serology were within normal limits and non-reactive. The patient was taken to the operating room for microlaryngoscopy with biopsy. Pathologic findings: Gross: three tiny pale white soft tissue bits were received each measuring 0.2 cm in diameter. Microscopy: Sections from the same showed benign stratified squamous epithelial fragments. The underlying tissue revealed collections of macrophages and epithelioid cells (Figure-2). In higher resolution the macrophages showed presence of numerous tiny intracellular organisms, which was consistent with fungal infection of the *Histoplasma spp.* Confirmation was done with periodic acid Schiff and Gomori's methanamine silver stain (Figure-3). Ziehl- Nielson stain for Acid Fast Bacilli was negative. He was administered amphotericin B 1 mg/kg body weight for 2 weeks followed by itraconazole 200 mg, twice a day for 8 weeks and discharged on oral itraconazole. A dramatic improvement in voice quality was seen in follow-up after two months. Repeat endoscopy showed regression of growth (Figure-4).



Fig 1: Bronchoscopic images showing growth over right vocal cord and? leukoplakic patch over the left vocal cord

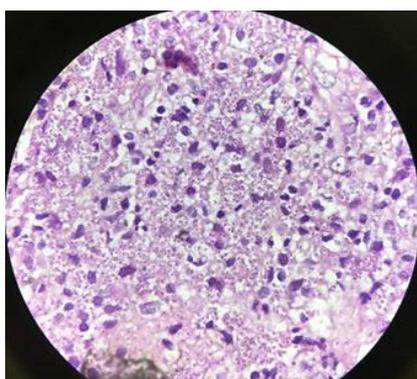


Fig 2: Collections of macrophages showing tiny intracellular organisms (H&E, 400X)

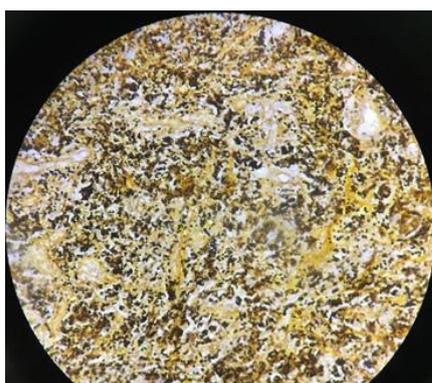


Fig 3: Intracellular Histoplasma organisms highlighted by Gomori Methanamine Silver (GMS, 1000X)



Fig 4: Bronchoscopic images of follow up bronchoscopy after over three months showing resolution of lesions following antifungal treatment

Discussion

Primary histoplasmosis of the larynx is an uncommon disease with few publications since it was first described in 1940 by Brown and coworkers [1]. Histoplasmosis is rare in India, but is endemic in regions of West Bengal, the Gangetic Plains and Western India [2, 3]. Kathuria *et al* also analysed that most of the cases published after 1994 were from Uttar Pradesh and West Bengal along the Gangetic plains [4]. Our patient also hails from the Gangetic plains of Uttar Pradesh.

Mycelia are the naturally infectious forms. The mode of infection is by inhalation of the mold microconidia which reach the alveolar spaces. They are phagocytosed by the macrophages where they transform to budding yeasts, multiply and reach the draining lymph nodes from where they spread throughout the reticulo-endothelial system [5]. Soil is the natural environment of *H capsulatum*. Soils enriched by avian and bat excrement harbor this fungus in large numbers and may remain infectious for years [6, 7].

It has been reported that disseminated histoplasmosis in India manifests commonly with fever, weight loss, and mucocutaneous involvement [8]. In the review presented by Kathuria *et al* the clinical presentation of disseminated histoplasmosis was analysed amongst 61 immunocompetent individuals. Adrenals were the most common organ to be involved followed by liver, skin and mucosa, spleen, lymph nodes, lung, pharynx, bone marrow, larynx, gastrointestinal tract, testis, kidney and epididymis [4]. In their review, larynx was not found to be very commonly involved by histoplasmosis, laryngeal presentation was seen in 3 of the 61 patients. According to Sobrinho FP and coworkers, about 40-75% of adults and 18% of children with progressive spread histoplasmosis have oropharyngeal involvement [9].

Most cases of laryngeal histoplasmosis result from hematogenous spread of disseminated disease usually originating in pulmonary involvement by the fungus [1]. Laryngeal histoplasmosis usually occurs in patient immunocompromised by the spread of the fungus from the lungs to other organs. Isolated laryngeal disease is rare [10]. Our patient tested negative for common immunosuppressive conditions and diseases such as diabetes mellitus. Therefore, in our case, this fungal infection presented in an immunocompetent individual.

Patients with laryngeal histoplasmosis usually exhibit low-grade fever, weight loss, sore throat, hoarseness, cough and dysphagia – symptoms which can mimic a malignancy [11]. On laryngoscopy, mucosa is pearly white, oedematous, inflamed or ulcerative, again mimicking the typical findings of malignancy [12]. Occasionally, this disease can present with leukoplakia like lesions, laryngeal exophytic masses and cervical lymphadenopathy [10]. Clinically as well as on microlaryngoscopy, in the present case, the mass was suspected to be a primary laryngeal carcinoma, as it was friable and no other buccal or oropharyngeal ulcers were identified.

The differential diagnosis of such lesions as seen on laryngoscopy includes, apart from malignancy, other granulomatous diseases such as tuberculosis, paracoccidioidomycosis, leishmaniasis, blastomycosis, leprosy, syphilis, or actinomycosis. Other conditions from which it should be differentiated are: gastroesophageal reflux, polychondritis, Wegener's disease, sarcoidosis, amyloidosis, rheumatoid arthritis, lupus, lymphoma or

papillomatosis^[10].

Depending on the immune status of the host, the histopathologic presentation of histoplasmosis is variable and may range from a dense histiocytic infiltrate to well-formed granulomas with or without necrosis^[13]. In the present case, diffuse infiltrate of macrophages was seen along with ill-defined collections of epithelioid cells. The tiny, intracellular, uninucleated organisms were highlighted using Gomori Methamine Silver stain and periodic acid Schiff stain. Microscopically, the differential diagnoses include, apart from leishmaniasis other fungal infections - blastomycosis, paracoccidiomycosis, candidiasis, *Pneumocystis carinii*, cryptococcosis from which it should be differentiated morphologically^[11]. For instance, yeast forms of *Histoplasma capsulatum* are small, uninucleated, and have single, narrow-based buds. Blastomyces dermatitidis is multinucleated, with broad-based buds, and accompanied with larger yeast forms^[11]. In cases with prominent granulomatous response and /or accompanying necrosis, careful search for fungal organisms is needed to avoid confusion with tuberculosis. Leishmania organisms, though of similar size as *Histoplasma*, lack peripheral halo and possess nucleus and kinetoplast. Additionally, periodic acid Schiff and Gomori's methanamine silver are positive only in histoplasmosis. Culture is the gold standard for the diagnosis of histoplasmosis, but utility is limited by the 4-6 weeks time it requires^[14].

According to the guidelines by the Infectious Diseases Society of America (IDSA), liposomal amphotericin B (3.0 mg/kg daily for 12 weeks), followed by oral itraconazole (200 mg three times daily for three days and then 200 mg twice daily for a total of at least 12 months) is recommended for the treatment of moderate to severe histoplasmosis^[15]. Our patient was treated initially by intravenous amphotericin followed by itraconazole, with dramatic resolution of symptoms and the lesion itself.

In conclusion, the diagnosis of histoplasmosis in the larynx requires a high index of suspicion, especially when it involves an immune competent host. The disease may mimic common laryngeal conditions as primary malignancy and tuberculosis. A high index of suspicion in endemic areas, work history, radiographic examination, immunological tests, histopathology and cultural demonstration of *Histoplasma capsulatum* may help in reaching the correct diagnosis.

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