Case Report
Primary Oropharyngeal and Laryngeal Histoplasmosis - A Diagnostic Challenge

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Citation

Open Access Archives
http://cogprints.org/view/subjects/OJHAS.html
http://openmed.nic.in/view/subjects/ojhas.html

Submitted: Aug 16, 2015; Accepted: Sep 22, 2015; Published: Oct 15, 2015

Abstract: Histoplasmosis is a rare tropical disease caused by Yeast-like dimorphic fungus *Histoplasma capsulatum*. Granulomatous diseases caused by infectious agents are being encountered more frequently nowadays. Infection by *histoplasma capsulatum* is one such granulomatous disease. In non-endemic areas, histoplasmosis poses a diagnostic challenge, especially since the presenting lesions can mimic carcinoma. The clinician should keep in mind histoplasmosis as a differential diagnosis when dealing with granulomatous lesions of oral cavity, oropharynx and larynx in both immunocompetent and immunocompromised patients. The histopathologist must be informed about the possibility of histoplasmosis, because special dyes have to be used to confirm this diagnosis. The treatment is mainly medical with Amphotericin B which remains the gold standard for treatment of this disease. The rarity of this disease in this part of country and variable clinical presentation prompted the authors to report this case.

Key Words: Histoplasmosis, Oropharyngeal, Laryngeal, Granulomatous.

Introduction:
Darling is accredited as the first to recognize and report three cases of Histoplasmosis in 1906.1 But it was De Monbreun who conclusively proved the fungal nature of the organism by culture, and reproduced the disease in monkeys.7 Its affinity for reticuloendothelial system and the intracellular habitat of the fungus differentiates it from majority of the other mycoses.

It is a worldwide systemic mycosis that has been isolated from soil contaminated with bird or bat droppings in endemic areas, as reported in Brazil and central United States.7 The course of histoplasmosis can be influenced by the immune status of the host and the quantity of infective propagules that the host is exposed to.3 Upper aerodigestive lesions are chiefly associated with systemic disease, especially affecting patients with immunosuppression. Disseminated Histoplasmosis (DH) refers to relentless growth of *H. capsulatum* in multiple organ systems. The most important risk factors are immunospression including organ transplantation, chronic renal disease, prolonged use of corticosteroids and HIV infection. In the last few years, Acquired Immuno Deficiency Syndrome (AIDS), has contributed to increased incidence of DH, as up to 25%.3 In the setting of DH, oral lesions are present in 30-50% of the patients. In some cases the oral lesions appear to be the only manifestation of the disease.4 Oral lesions along with constitutional symptoms like dysphagia, loss of weight, loss of appetite, irregular low grade fever, often mimic a clinical diagnosis of squamous cell carcinoma or a granuloma.5 The most common affected sites of oral cavity are the tongue, the palate and the buccal mucosa. Oral and oropharyngeal manifestations often coexist with laryngeal histoplasmosis.5 In India, histoplasmosis is uncommon, and is usually reported from the region of the Gangetic belt, beside this A few cases have been reported from other state of India. It is usually seen in immunocompromised conditions we report a cases of primary oral, oropharyngeal and laryngeal histoplasmosis in immunocompetent patient from Uttarakhand, a state of North India, where histoplasmosis is not a common diagnosis.

Case Report
A 62 year old male, chronic smoker presented with swelling over tongue and hoarseness of voice of four months duration. The swelling over the tongue and hoarseness were progressive and the tongue had become diffusely swollen along with swelling of both the lips and the buccal mucosa had ulcerated
lesion. The tongue became fissured over a period of time. There was mild dysphagia, with no loss of appetite or loss of weight. On examination, there was a diffuse swelling over the both lips and dorsum of tongue, with superficial ulcerations and fissures (Figure-1). Bilateral buccal mucosa had an ulcerative lesion of 2x2 cm in size, which was non tender, indurated, and had associated edema and erythema. Left submandibular lymph nodes were palpable, 3x3 cm in size, non tender, and mobile with regular and well defined borders. The hematological investigations were within normal limits. The general blood picture revealed normocytic, normochromic picture. The serology (HbsAg, HIV and HCV) were negative. The laryngeal endoscopy revealed multiple exophytic nodular lesions across the oropharynx, endolarynx and hypopharynx (Figure-2). The fine needle aspiration cytology revealed sialadenitis. The patient then underwent a biopsy under local anesthesia from the left buccal mucosa. Histopathological examination (Figure-3) of the biopsy using hematoxylin-eosin stain revealed chronic granulomatous inflammation, caused by histoplasma. There was a diffuse infiltrate of neutrophils, lymphocyte, and macrophages and few organisms. On oil immersion, scattered multiple organisms, within the macrophages seen with peripheral halo seen on Giemsa methenamine stain which was suggestive of histoplasma was seen. Disseminated histoplasmosis and an immunocompromised state were excluded by conducting all routine clinical investigations. The patient was managed conservatively on amphotericin B. A total of 100mg dose was given. There was periodic monitoring of electrolytes and creatinine. A pulse-blood pressure charting was done during whole infusion. No adverse effects were noted. The patient was discharged on oral itraconazole 200 mg twice daily for 3 weeks. The patient subsequently improved with healing of oral lesions and is voice also improved. The patient on subsequent follow-up for a year showed complete resolution of symptoms and dramatic improvement of oropharyngeal and laryngeal lesions.

**Discussion:**
Fungal infections, especially in immunocompetent patients, is often overlooked and misdiagnosed because it closely mimics carcinoma. However, the possibility of fungal infections should always be kept in mind, and biopsy should always be performed before resorting to radical surgery.\(^6\) Histoplasmosis is one such fungal infection, which can involve the upper aero digestive tract.\(^7\) Histoplasmosis is rarely reported from India, perhaps because of its varied presentation and lack of awareness among treating clinicians. Panja and Sen first reported histoplasmosis in India in 1959. Histoplasmosis is considered endemic in certain eastern states like West Bengal where the skin positivity is 9.4% to histoplasmin antigen.\(^8\) Infection is primarily acquired by inhalation, but there are rare cases where cutaneous inoculation of H. capsulatum has occurred. Soil is the natural habitat of H. capsulatum, and the fungus is often found in soils enriched by avian and bat excrement. Such soils may remain infectious for years. As histoplasmosis has varied presentations. The four main clinical variants are: acute pulmonary, acute disseminated, chronic disseminated and chronic pulmonary. Primary mucosal histoplasmosis is very rare. The primary lesion can occur on direct inoculation of the organism into mucosa. Primary lesion is a nodule or an indurated ulcer and there is local cervical lymphadenopathy with no systemic involvement. The primary mucosal lesions involutes spontaneously and do not usually occur in immunocompromised where disseminated histoplasmosis is more common.\(^8\) Otolaryngological manifestations of histoplasmosis are usually seen in the form of flat plaque-like non-tender elevations or nodules that later ulcerate and become painful.\(^9\) Mucosal surfaces of gingivae, tongue, lips, and pharynx are common sites of involvement. Lesions may also involve any area of the larynx, but the anterior part of larynx is more commonly involved. Sobrinho and colleagues made an extensive review of laryngeal histoplasmosis with diverse presentations.\(^10\) The common presenting manifestations of laryngeal histoplasmosis include sore throat, hoarseness, and dysphagia. Our patient had no systemic involvement and was immunocompetent. Our patient presented with lesions over the tongue (which is...
the most common site), ulceration over bilateral buccal mucosae, oropharynx and laryngopharynx with cervical submandibular lymphadenitis. Diagnosis is often confirmed by taking biopsies from suspicious areas for histological examination. This usually reveals macrophages containing yeasts, which stain prominently with periodic acid Schiff and Grocott (silver) procedures. Culture is the gold standard for the diagnosis of histoplasmosis but its utility is limited by the waiting period of two to four weeks and decreased sensitivity. There were no confirmed fungal cultures in our cases. Our patient underwent a buccal mucosal biopsy and staining which confirmed Histoplasma. Treatment for histoplasmosis has become considerably effective in recent years. Localized forms respond to oral Itraconazole (200mg once daily). Amphotericin B is effective in disseminated histoplasmosis with Itraconazole in follow up period. Our patient received 100mg of amphotericin B and this was followed by oral Itraconazole 200mg once a day. It is usually seen in immunocompromised conditions and a high index of suspicion should be kept in mind in cases of ulcerative lesions of the upper aero digestive tracts, where histological examination of the biopsies fails to show dysplasia or where there is a failure to respond to anti-tuberculosis treatment.

Conclusion
Histoplasmosis is a rare entity in India and it rarely affects seronegative non immunocompromised individuals. Oral and laryngopharyngeal lesions are common in disseminated histoplasmosis, but primary mucosal histoplasmosis is very rare hence the practicing Otorhinolaryngologist should not be ignorant of its presentation and high index of suspicion should be kept in mind in cases of ulcerative lesions of the upper aero digestive tracts.

References
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