Head and Neck Histoplasmosis—A Nightmare for Clinicians and Pathologists! Experience at a Tertiary Referral Cancer Centre

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Abstract Histoplasmosis is a rarely reported deep mycotic infection in the Indian context. Oral or oropharyngeal manifestation can occur as an isolated symptom or as part of a disseminated process associated with immunosuppression especially with HIV and diabetes. Five cases of head and neck histoplasmosis accrued over 6 years in a tertiary referral cancer institute were reviewed. All these patients presented clinically as cancer. In three patients, the marked pseudoepitheliomatous hyperplasia led to a mistaken biopsy diagnosis of malignancy following which definitive surgical treatment was performed. The subsequent excision revealed typical features of histoplasmosis. Isolated oral presentation of histoplasmosis can mimic malignancy both clinically as well as pathologically, leading to potentially disastrous consequences. A high index of suspicion in those with overt or hidden immunosuppression and a deep wedge biopsy to demonstrate the organisms in the subepithelial tissue is recommended.

Keywords Oral · Histoplasmosis · Mimic · Malignancy · Immunosuppression · Pseudoepitheliomatous hyperplasia

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Key Messages

1. Isolated oral presentation of histoplasmosis can be treacherous especially when occurring in the absence of HIV infection.
2. It can mimic malignancy both clinically as well as pathologically, leading to over treatment in the form of radical surgery which can be disastrous.
3. A high index of suspicion for this entity especially in those with overt or hidden immunosuppression and a deep wedge biopsy to demonstrate the organisms in the subepithelial tissue is recommended.

Introduction

Histoplasmosis is a deep mycosis caused by inhalation of spores of *Histoplasma capsulatum*, a dimorphic fungus. These are converted to the yeast form which replicate within the reticuloendothelial system and disseminate in the absence of a good immune status [1]. Oral manifestations can be an isolated event or part of the disseminated process [2–4]. We present five cases of oral and oropharyngeal histoplasmosis and discuss the problems associated with this rare condition mimicking malignancy.

Materials and Methods

Five cases of head and neck histoplasmosis accrued over 6 years (2000–2005) in the pathology department in a tertiary referral cancer centre are presented.

Histopathology specimens received were biopsies (4 cases), excised specimens (3 cases) and both (2 cases). Clinical information was obtained from hospital records.

Table 1 Summary of clinical findings of the patients

No.	Age/Sex	Immune status	Clinical diagnosis	Histopathological diagnosis	Treatment
1	55/M	Diabetic (8 years) pyrexia of unknown origin, pancytopenia, hepatomegaly ^a	Indurated ulcers (1.5 and 0.3 cm) Leukopakia <i>Carcinoma—hard palate</i>	Squamous carcinoma	Right upper alveolectomy
2	41/M	HIV +ve	Indurated ulcer (3 cm) lateral border tongue, Level II nodes ++ <i>Carcinoma Tongue</i>	Squamous carcinoma	Near total glossectomy with neck dissection
3	50/M	HIV –ve ^b	Hoarseness of voice. Ulceroproliferative growth <i>Carcinoma larynx stage T2N0</i>	Squamous carcinoma	Laser excision of the growth
4	59/M	Diabetic	Hoarseness of voice, dysphagia, pooling of saliva. Ulceroproliferative growth - pyriform fossa, Level II nodes ++ <i>Carcinoma hypopharynx</i>	Histoplasmosis	Antifungal
5	59/F	HIV status unknown ^b Weight loss (6 kg–6 months)	Ulceroproliferative indurated lesions right lower lip—painful (2 months) Ill fitting dentures (9 years) <i>Carcinoma lip</i>	Histoplasmosis	Antifungal

^a Evidence of dissemination^b Patient had no other known immunosuppressive factors

Results

Details of these cases in terms of clinical presentation and course of treatment are summarized in Table 1.

The key histopathological features noted are as depicted (Figs. 1, 2a, b, 3, 4a, b). The first three cases showed florid pseudoepitheliomatous hyperplasia of the overlying epithelium which on a superficial biopsy was mistaken for a squamous carcinoma (Fig. 3) and these underwent radical treatment.

Fig. 1 Biopsy histopathology of the lesion in case 4 showing partly ulcerated oral mucosa with underlying dense mixed inflammation (H&E ×40)

To summarise, all patients clinically presented as carcinoma involving the oral cavity (3 cases), hypopharynx (1 case) and larynx (1 case). Two patients had corroborative findings with neck node enlargement. Immunosuppression was present in three patients (HIV: 1; diabetes: 2). All five patients were put on systemic antifungal treatment after primary diagnosis of histoplasmosis on biopsy or excision.

A 2-year follow-up was available in two of the patients, case 1 and 2 who are well and free of complications. The other three patients were lost to follow up.

Discussion

Documented cases of histoplasmosis have in general, been low in India with less than 50 cases being reported from 1968 till date [5–8]. It is also worthy to note that although nasal route is the usual portal of entry, extra pulmonary infections are more common than pulmonary infections [5].

It is well known that disseminated disease is frequently seen in immunocompromised states such as HIV [4], as well as with hidden chronic immunosuppressive conditions such as extremes of age, diabetes and alcoholism and post radiotherapy for malignancies [3, 6, 9]. In 20% of patients there is no identified risk factor for dissemination [2, 5, 10]. Overall the under diagnosis of this relatively rare disease is very likely. Early recognition is critical as this is a potentially fatal condition unless promptly treated [11]. Oral or oropharyngeal manifestations have been reported [11] in 66% of chronic, 31% of subacute and 19% of acute

Fig. 2 (a) Higher power of the biopsy in Fig. 1 showing infiltrate predominantly composed of histiocytes and lymphoplasmic cells. Histiocytes are stuffed with typical yeast forms of *Histoplasma capsulatum* (H&E $\times 1000$). (b) Gomori Methanamine Silver (GMS) stain from the same case to highlight the fungus (GMS $\times 1000$)

Fig. 3 Overlying squamous mucosa in case 2 showing marked pseudoepitheliomatous hyperplasia. A superficial biopsy from this lesion led to a mistaken diagnosis of squamous carcinoma on the biopsy (H&E X 40)

Fig. 4 (a) Section from the excision specimen in case 1 showing well formed epithelioid granulomas with giant cells containing an occasional yeast form of the organism (H&E $\times 400$). (b) Periodic acid Schiff (PAS) from the same case to highlight the fungus (H&E $\times 1000$)

disseminated disease in other parts of the world. In the upper aero-digestive tract, lesions commonly occur as multiple painful ulcers and verrucous excrescences in the tongue and buccal mucosa. They can also present as deep ulcers with infiltrative edges or hard irregular nodular lesions and may be accompanied by regional lymphadenopathy clinically strongly simulating carcinoma as was seen in our cases [3, 7, 11, 12].

In a cancer centre, immunosuppression is rampant following institution of toxic multi agent chemotherapy with opportunistic fungal infections such as aspergillosis, mucormycosis and candidiasis [12]. However it is a curious observation that histoplasmosis is rarely ever seen in this setting. Their ability to mimic malignancy results in their presentation in a cancer centre such as ours [7, 13].

Histological appearances as in our cases range from dense histiocytic response, well formed granulomas to extensive necrosis with subtle inflammation especially in

an immunocompromised host [11]. The latter appearance was not seen in any of our patients including the patient who was HIV positive. The florid pseudoepitheliomatous hyperplasia of the overlying epithelium coupled with a strong clinical suspicion may lead to a diagnostic pitfall of malignancy particularly in India where oral cancer is very common. This can lead to unnecessary radical treatment and morbidity in this potentially treatable infective condition. Two of our patients underwent radical treatment in the form of partial alveolectomy and hemiglossectomy with node dissection. This can be avoided with a deep wedge biopsy to adequately visualize the underlying stroma. *Histoplasma capsulatum* is classically described as elliptical, narrow based uninucleate budding yeast forms 2–4 µm in diameter [14]. Differentials include other fungi such as candida, cryptococcus, pneumocystis, toxoplasmosis and micro forms of blastomyces [15], and tuberculosis with a granulomatous morphology [3, 11].

Though diagnosis is usually adequately established in typical cases by cytology or biopsy, culture is the gold standard [3, 11]. Serologic methods also constitute complementary diagnostic tools [16]. In all our cases a careful morphology with the help of special stains was adequate to establish the diagnosis. Though treatment with systemic antifungals like amphotericin is the standard, chronic localized manifestations can be treated with a less toxic drug like Itraconazole [17]. Newer drugs have been described for very severe cases of disseminated disease [18].

To conclude the incidence of histoplasmosis is extremely rare in India and has not increased even with the explosive onset of the HIV epidemic [19]. This condition may be underdiagnosed and can be mistaken for malignancy in patients presenting with isolated oral or oropharyngeal manifestations leading to disastrous consequences. A high index of suspicion in those with overt or hidden immunosuppression and a deep wedge biopsy to demonstrate the organisms is recommended.

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