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Head and neck involvement with histoplasmosis; the great masquerader

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ABSTRACT

Introduction: Head and neck involvement with histoplasmosis usually occurs as a part of the disseminated illness. There are no pathognomic features of the upper aerodigestive tract involvement and the lesion may mimic a host of other conditions. The current report presents our experience with head and neck histoplasmosis in a non-endemic tertiary care center.

Materials and methods: We present a case of disseminated histoplasmosis with oral symptoms and lesions as the chief complaints. A 10 years' retrospective institutional database search was undertaken to identify the patients with histoplasmosis affecting head and neck region treated at our institution. The demographic and treatment details of the patients were reviewed.

Results: In addition to the index patient, four more patients (two with gingivobuccal and one each with nasal and laryngeal histoplasmosis) were found. Out of the five patients, only one patient was found to have underlying immunosuppression. All of the patients were diagnosed with biopsy showing typical appearance of the intracellular organism. All the patients were satisfactorily treated with systemic antifungal treatment.

Conclusion: Upper aerodigestive tract involvement with histoplasmosis can present as an intriguing clinical puzzle. A high index of suspicion is needed and biopsy is the gold standard for the diagnosis. Intravenous Liposomal Amphotericin B and oral Itraconazole are standard treatment agents of choice and are highly efficacious in achieving cure.

1. Introduction

Histoplasmosis is a systemic deep mycosis associated with granulomatous host response. The disease, in general, tends to occur in certain endemic regions of the United States of America, Africa, and Southeast Asia and tends to affect the immunocompromised patients, especially individuals deficient in cell-mediated immunity. Head and neck involvement usually occurs as a part of disseminated mycosis [1]. The dominant manifestation in the head and neck region, especially in non-endemic areas may create a diagnostic dilemma since the morphological surface display of this deep mycosis may imitate a host of other infectious, inflammatory and neoplastic processes [2]. Keeping a high index of suspicion in an immunocompromised patient may help to reach the definitive diagnosis in a timely fashion resulting in a curative treatment with standard antifungal agents for an otherwise fatal course of the progressive disseminated disease.

We recently encountered a patient with disseminated histoplasmosis presenting with tongue lesion, the biopsy of which led to the diagnosis. A retrospective review of Otorhinolaryngology and pathology records at our institute revealed four additional patients with predominant or presenting complaints related to the otorhinolaryngologic domain. The current article highlights various presentations of histoplasmosis involving the upper aerodigestive tract and the patient characteristics in a non-endemic setting. The emphasis is on the part of physicians and surgeons alike, to keep the possibility of this great mimicker in mind and be prepared for an early biopsy from the generally accessible head and neck sites for timely management.

2. Case report

A 69 years old female patient was referred to our Dept. of Otorhinolaryngology and Head & Neck Surgery, with a history of painful oral ulcers, tongue swelling and burning sensation in the mouth along with difficulty in swallowing for one month. There was no history of breathing difficulty, voice change or bleeding from the mouth. The patient was a known case of seropositive rheumatoid arthritis for last 15 years, on treatment with oral hydroxychloroquine (200 mg daily), prednisolone (5 mg daily) and methotrexate (weekly, 12.5 mg).

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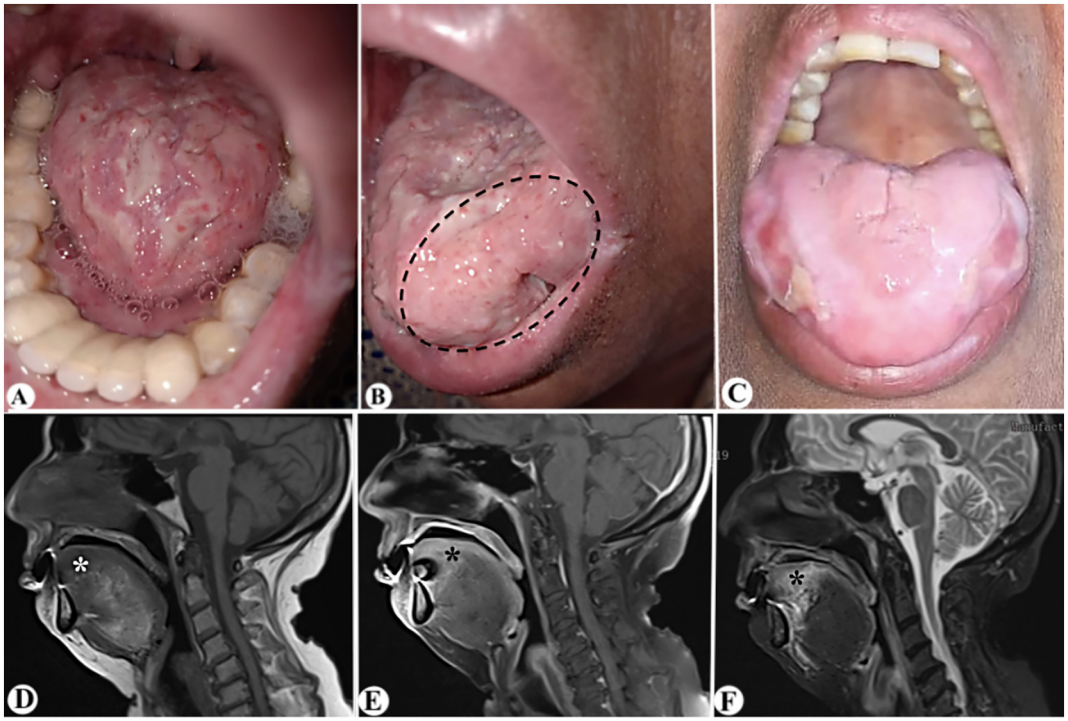

Fig. 1. (A) Diffuse nodular firm lesion involving the entire tongue dorsum with cobblestoned tongue and patchy areas of erythema and pallor. (B) The poorly demarcated ulceroindurated lesion (encircled) over the left lateral aspect of tongue showing the defect at the site of biopsy. (C) Significantly improved appearance of the tongue after one month of treatment with antifungals. MRI sagittal sequences showing tongue lesion (*) (D) hypointense on T1 without contrast, (E) diffusely enhancing on gadolinium administration, and (F) hyperintense on T2 weighted sequences involving the anterior and dorsal aspect of the tongue.

Preceding the onset of the oral symptoms, the patient had a flare-up of the rheumatoid arthritis disease activity for which she received a single intravenous injection of one gram of rituximab.

On oral examination, multiple, firm, mildly-tender nodules (size varying from 0.5 to 1.5 cm in size) were noticed involving the entire dorsal aspect of the oral tongue with areas of fissuring and superficial linear/nodular erythema (Fig. 1A). The largest of the nodules was a firm irregular lesion of about 1.5 × 1.5 cm on the left lateral border of the tongue (Fig. 1B). The tongue mobility was normal. The laryngoscopic findings did not reveal any abnormalities. A Contrast-Enhanced Magnetic Resonance Imaging (CE- MRI) of the face was performed, which showed an ill-defined, poorly marginated area of signal alteration showing diffuse contrast enhancement, involving intrinsic musculature of the tongue on either side of midline suggestive of inflammatory etiology (Fig. 1D–F).

An incisional biopsy was taken for diagnostic purpose from the edge of the nodule over the left lateral border of the tongue and sent for histopathology in formalin solution. The histopathology revealed ulcerated epithelium with sheets of macrophages, filled with tiny, capsulated organisms (Periodic acid schiff{PAS} + ve, Grocott-Gomori's methenamine silver{GMS} + ve), suggestive of histoplasmosis, with surrounding mixed inflammatory infiltrate (Fig. 2). The evaluation for systemic histoplasmosis revealed urinary antigenuria (> 25 ng/ml; normal < 2 ng/ml).

The patient was started on oral Itraconazole 200 mg twice daily but the symptoms worsened in the following two weeks and a nasogastric tube was put in view of severe dysphagia. Laryngoscopy showed severe pooling of secretions in the pyriform sinus. The patient was then started on intravenous Liposomal Amphotericin B (L-AMB) injections in a dose of 250 mg daily along with alternate day renal functions and serum electrolyte monitoring. The symptoms steadily improved after starting L-AMB and after two weeks (Cumulative L-AMB – 3.5 g), the patient was shifted back to oral Itraconazole with a loading dose of 200 mg thrice daily for three days followed by 200 mg twice daily. Two weeks later, the oral lesions subsided significantly (Fig. 1C) and the nasogastric tube was taken out. The patient is planned for treatment with oral Itraconazole in a dose of 200 mg twice daily for a total of one year with regular monitoring of the liver function tests.

3. Materials and methods

A retrospective search, for the patients diagnosed with head and neck/upper aerodigestive tract histoplasmosis, from the Dept. of Pathology database was undertaken, and the additional search was conducted from the ENT records from January 2010 to January 2019. The demographic, treatment and follow up related information was retrieved from the computerized record and patients were contacted telephonically for an outpatient follow up visit. The patient data including age, sex, presenting features, immune status, systemic involvement, treatment and follow up data were extracted and tabulated.

4. Results

The database search revealed four additional patients with histoplasmosis diagnosed on the basis of the biopsy taken from head and neck subsites. The patient demographics and treatment details are mentioned in Tables 1 and 2, respectively. All the patients in our series were adults ranging from 47 to 69 years old (mean age – 54.4 years). Four of the patients were males and one was female. Three of the patients were not found to have any underlying immunosuppressive condition, while one patient had underlying alcoholic chronic liver disease and another patient (the index case) was on immunomodulatory agents for rheumatoid arthritis. This patient received injection Rituximab preceding the onset of oral lesions, for flare-up of the rheumatoid arthritis systemic disease activity. Two of the patients had lesions involving the gingivobuccal/alveolus complex (Fig. 3) while laryngeal and nasal (Fig. 4) involvement was present in one patient each. All the patients were treated with oral Itraconazole with or without

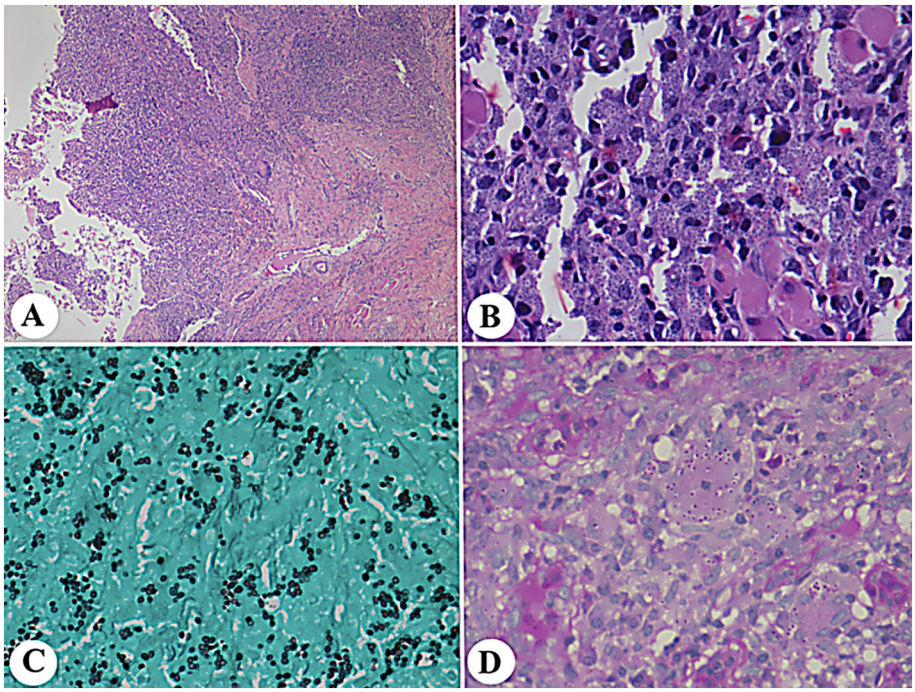

Fig. 2. (A) Ulcerated epithelium with epitheloid granulomas with variable caseation and intracellular round fungi. *Hematoxylin & Eosin (original magnification, 10 × 10 X).* (B) Isolated Histoplasma infiltrating into muscles. *Hematoxylin & Eosin (original magnification, 10 × 40 X).* (C) Capsulated isolated round fungi. *Grocott Methenamine Silver stain (original magnification, 10 × 40×).* (D) Capsulated isolated round fungi with perinuclear Halo. *Periodic Acid Schiff (original magnification, 10 × 40 X).*

intravenous L-AMB. One patient had to be shifted to oral Voriconazole in view of severe systemic reactions to AMB and inadequate response to Itraconazole. All the retrospectively reviewed patients received one year of antifungal treatment. The index case, after getting significant improvement with three months of antifungal treatment, is planned for one year completion treatment.

5. Discussion

Histoplasma is a thermally dimorphic fungus, which is found in the mold form in the environment and attains a yeast form at a temperature of 35–37^{0}C inside the human body. Histoplasmosis is an endemic mycosis and endemicity is seen in the region of Mississippi and Ohio River valley region, central and South America, West Africa and Southeast Asia [3]. There are two strains of Histoplasma affecting humans; H. *capsulatum* var. *capsulatum* (endemic in North and Central America) and H. *capsulatum* var. *duboisii* (predominant in West Africa). In these areas, it is disseminated by the bird excreta (birds and bat guano in nitrogen-rich soil acting as a reservoir) through the air currents and gains access into the human body via the inhalational route. The usual modes of disease presentation include acute/ chronic pulmonary and acute/ chronic disseminated forms. In immunocompetent patients, generally, it tends to be an asymptomatic or self-limited disease, while in immunocompromised patients it can disseminate in a fulminant fashion taking a potentially fatal course. The principal mechanism of defense in the human body against the organism is cell-mediated immunity and to a lesser degree the humoral immunity, resulting in histiocytic and granulomatous inflammation in the host [4]. From the portal of entry, the macrophages help in the dissemination of the yeast form to various organs via lymphatics. The gold standard of diagnosis is a direct demonstration of the organism using histopathology, cytopathology or culture. The organism can be detected inside the subepithelial macrophages in abundance and can be stained using Gomori Methenamine Silver (GMS) and Periodic Acid Schiff (PAS) stains. The appearance under the microscope is quite typical with intracellular, narrow-based, 2–4 μm sized (12–15 μm in case of H. *duboisii*) oval budding yeasts surrounded by a halo caused by retraction of the cytoplasm from the cell wall [3]. With verrucous appearing lesions, a deep biopsy is needed since a superficial biopsy may not show the diagnostic intracellular organism in histiocytes and the presence of pseudoepitheliomatous hyperplasia may result in incorrect diagnosis and overtreatment in lines of a malignant lesion [5]. Detection of antigen in serum and urine may help as contributory mycological evidence to help reach a probable diagnosis of histoplasmosis. Antigenemia and Antigenuria are present in high levels especially in HIV/AIDS with depressed cell-mediated immunity, and the specimen in these patients may give a high sensitivity of up to 95%. In addition to diagnosis, antigenemia and antigenuria serve to guide the therapy also [6].

The involvement of head and neck subsites usually occurs as a part of the disseminated disease in an immunosuppressed patient, and less often as an isolated disease. Interestingly, three out of five patients in our series did not have any evidence of immunosuppression. Upper aerodigestive tract involvement can take a mucosal or extra mucosal form. Involvement of the otolaryngologic subsites occurs in around 66% of chronic, 31% of subacute and 19% of acute disseminated histoplasmosis cases [7]. Mucosal involvement of oral cavity, sinonasal

Table 1
Demographic details of the patients.

SN	Age (y)/sex	Comorbidities and immune status	Presentation	Method of diagnosis
1.	69/F	Rheumatoid arthritis; on immunosuppressants	Oral ulcers	Tongue biopsy
2.	53/M	None	Right lower GBS and upper central arch lesion	Oral biopsy
3.	64/M	None	UPG involving left upper alveolus	Oral biopsy
4.	47/M	CLD with Portal Hypertension	Reddish nasal mass with ulcer at the tip of the tongue	Nasal biopsy
5.	55/M	None	UPG involving left true vocal cord	Direct Laryngoscopic Biopsy

(SN – serial number, y- years, M- male, F- female, GBS- gingivobuccal sulcus, UPG- ulceroproliferative growth, CLD- chronic liver disease).

Table 2
Treatment details of the patients.

SN	Evidence of dissemination	Treatment	Follow up and outcome
1.	Urinary antigenuria. No other organ involvement.	IV L-AMB (250 mg OD x 14 days; total- 3.5 g) ➜ Tab ITR (200 mg TDS ➜ 200 mg BD)	Symptoms improved significantly at 3 months follow up, planned for 1 year oral ITR treatment.
2.	Necrotic adrenal mass and Pulmonary nodules	Tab Voriconazole 200 mg BD for 1 year (severe systemic reaction to AMB and did not respond to ITR)	Follow up at one year shows no evidence of disease. Longer follow up not available since patient was lost to follow up.
3.	Hepatomegaly with deranged LFT	Tab ITR 200 mg TDS x 3 days ➜ 200 mg BD x 1 year	Hepatomegaly resolved and LFT returned to normal after 6 months of treatment. Asymptomatic at 18 months follow up.
4.	1) Papulonodular lesions over face. 2) PET-CT showing hypermetabolic areas involving -Right side tongue base and vallecula. -Mediastinal, retroperitoneal and mesenteric lymph nodes. -Bilateral adrenal glands.	IV L-AMB (250 mg OD x 20 days; total- 5 g)➜ Tab ITR (200 mg TDS x 3 days ➜ 200 mg BD)	No sign of residual infection after 6 months of treatment. Treatment completed for a total of 1 year. Diagnosed as Metastatic Hepatocellular carcinoma after 1 year.
5.	Hepatosplenomegaly	Tab ITR 200 mg TDS x 3 days ➜ 200 mg BD x 1 year	Disease free at 1 year follow up.

(SN- serial number, IV- intravenous, L-AMB- Liposomal Amphotericin B, ITR- Itraconazole, PET-CT – Positron Emission Tomography- computed tomography, LFT- Liver function tests, TDS –thrice daily, BD- twice daily, OD- once daily)

cavity and pharynx can mimic other infectious, mitotic and autoimmune processes quite closely and may present a diagnostic dilemma. The diverse presentation and deceptive appearance of the lesion have rightfully earned it the title of 'Syphilis of the Fungal world'. The differentials are site-specific and with upper aerodigestive tract mucosal involvement, the usual mimics [5,8–16] are described in Fig. 5.

Histopathology greatly narrows down the differentials but the similar appearance under the microscope may be exhibited by other pathogenic microorganisms including *Blastomyces*, *Coccidioidis*, *Candida*, *Pneumocystis*, *Cryptococcus*, *Toxoplasma*, *Leishmaniasis* and *Trypanosoma* species [4].

Since the head and neck involvement usually occurs as a part of the disseminated histoplasmosis, its treatment is undertaken in lines similar to the disseminated disease. Amphotericin B and Itraconazole are the agents of choice to treat the infection (Table 3). For mild-moderate disease, the treatment may be started with oral Itraconazole in a dose of 200 mg thrice a day for the first three days followed by 200 mg twice daily for at least one year. However, in case of failure with Itraconazole or for severe disease/life threating situations, the treatment should be initiated with Liposomal Amphotericin B (L-AMB) in a dose of 3 mg/kg/day for first 1–2 weeks followed by 'step down therapy' with oral Itraconazole with the same regimen as described above [17]. Regular serum electrolyte/renal functions monitoring with Amphotericin B is mandatory to detect and manage the nephrotoxicity at the earliest. While on Itraconazole, monitoring of liver function tests at one, two, and four weeks and thereafter every three months is mandatory in view of possible hepatotoxicity. The efficacy of Itraconazole is dependent on the appropriate serum concentration (1–10 μg/ml) and needs close monitoring of the serum drug levels. The multitude of significant drug interactions needs to be kept in mind before starting the patient on treatment with Itraconazole. In Immunocompromised patients, particularly for AIDS (Acquired Immunodeficiency Syndrome), the L-AMB has been shown to be significantly more efficacious with survival benefits as compared to the conventional deoxycholate preparation of Amphotericin B [18]. Azoles are contraindicated in pregnant patients and in this patient population, L-AMB is the drug of choice. Pediatric

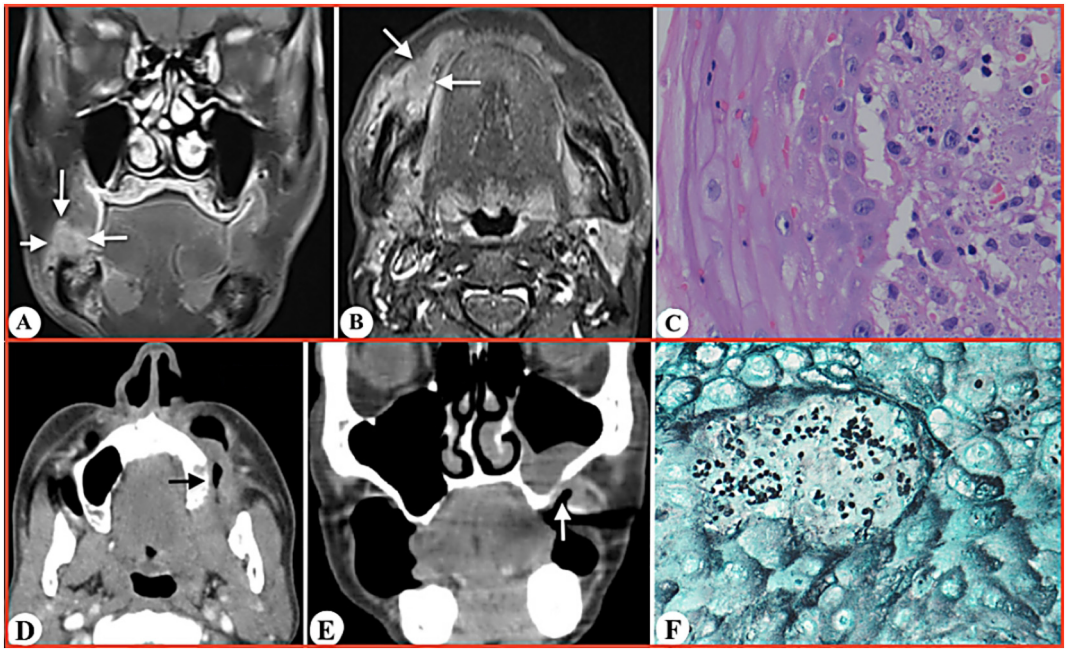

Fig. 3. (A) Coronal and (B) Axial T1 contrast enhanced MRI sequences showing heterogeneously enhancing soft tissue lesion (arrows) involving right side lower gingivobuccal sulcus region. (C) Isolated Histoplasma with perinuclear halo. *Hematoxylin & Eosin (original magnification, 10 × 40 X).* (D) Axial and (E) Coronal contrast enhanced computed tomographic images showing heterogeneously enhancing soft tissue density (arrows) involving left upper gingivobuccal sulcus and causing erosion of the upper alveolus. (F) Capsulated isolated round fungi. *Grocott Methenamine Silver stain (original magnification, 10x40X).*

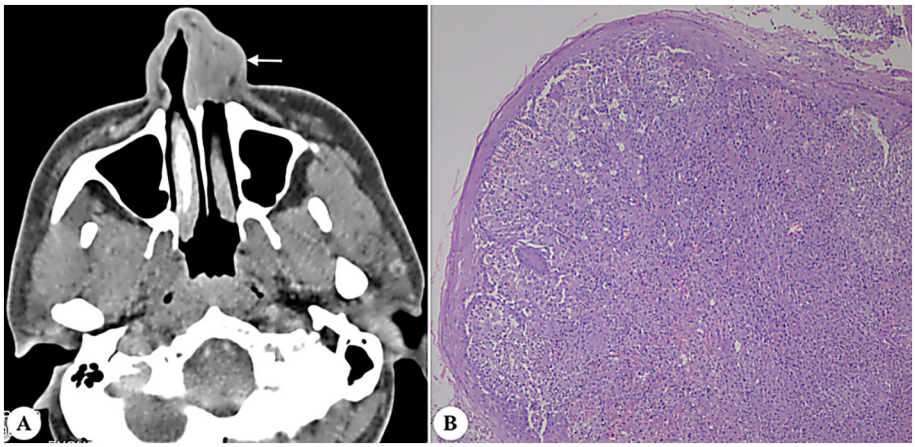

Fig. 4. (A) Axial contrast enhanced computed tomographic view of the paranasal sinus showing heterogeneously enhancing soft tissue lesion filling up the anterior nasal cavity (arrow) and based broadly over the cartilaginous nasal septum. (B) Ulcerated epithelium with epitheloid granulomas and intracellular round fungi. *Hematoxylin & Eosin (original magnification, 10 × 10 X).*

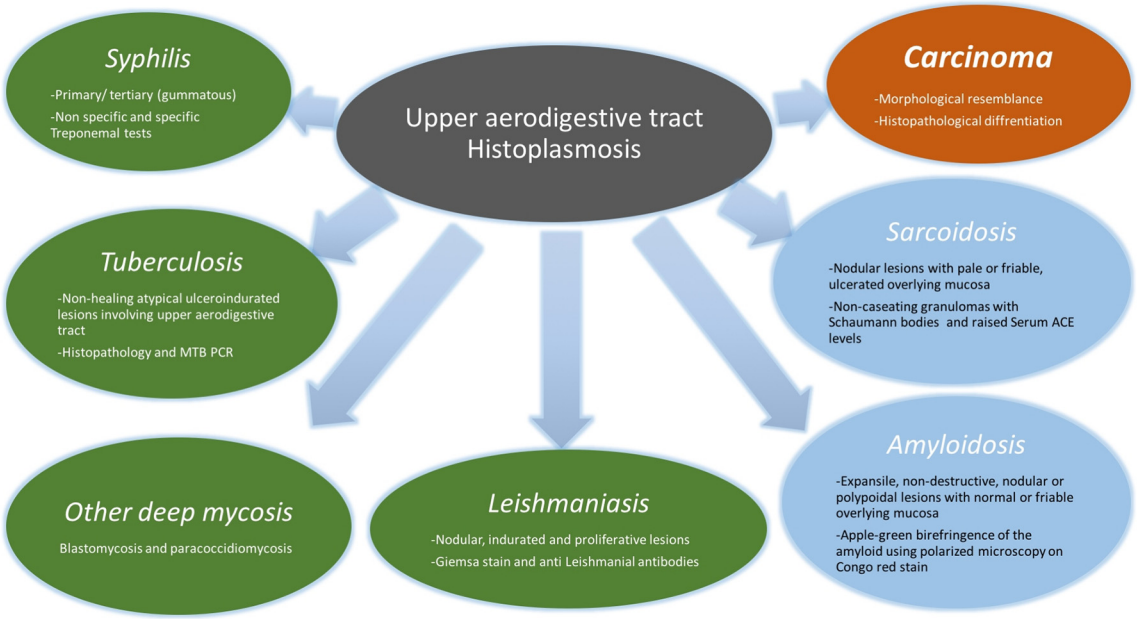

Fig. 5. The close mimics of upper aerodigestive tract affliction with Histoplasmosis. *(MTB PCR- Mycobacterium tuberculosis Polymerase chain reaction test; ACE- Angiotensin converting enzyme) (references:* 5, 8–16*).*

patients tolerate the deoxycholate preparation of Amphotericin (1 mg/kg/day) well and Liposomal preparation is not the preferred treatment agent in this age group [17].

6. Conclusion

- Histoplasmosis may present with upper aerodigestive tract lesions indistinguishable from other granulomatous infections, inflammatory conditions, and malignancies on clinical grounds.
- A high index of suspicion is needed to make the right diagnosis.
- Biopsy and direct demonstration of the organism with special stains and culture is the gold standard of diagnosis.
- A search for systemic dissemination and immunosuppression should be conducted in the diagnosed patient.

Table 3
The clinico-pharmacological description of the drugs commonly used for Histoplasmosis.

	Amphotericin B	Itraconazole
Dose	L-AmB in a dose of 3 mg/kg/day for 1–2 weeks (alternatives: AmB lipid complex- 5 mg/kg/d; AmB deoxycholate- 0.7-1 mg/kg/day) followed by ITR	200 mg TDS x 3 days followed by 200 mg BD
Duration	For 1–2 weeks followed by ITR (total of at least one year)	For at least one year
Side effects	1) Infusion related adverse events: hypersensitivity reactions; 2) Chronic toxicity: Nephrotoxicity and Bone marrow depression	1) Gastrointestinal side effects 2) Hepatotoxicity 3) Congestive Heart Failure
Monitoring	Regular (2–3 times/ week) Serum Electrolyte and RFT monitoring and weekly Hb Monitoring	1) LFT at 1, 2 & 4 weeks and thereafter every 3 months 2) Therapeutic drug level monitoring and drug-drug interactions

(L-AmB- Liposomal Amphotericin B; ITR- Itraconazole; TDS- Thrice daily; BD- Twice daily; RFT- Renal function tests; LFT- Liver function tests; Hb- Hemoglobin) (references: 6, 17).

- Liposomal Amphotericin B and Itraconazole are the drugs of choice for treatment and are highly effective in achieving a sustained cure.

Declarations

- This work was done at Medanta- The Medicity, Gurugram, Haryana, India.
- *Informed/Written consent*: was obtained from the individuals participating in the study
- *Conflict of interests*: None declared
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References

[1] Chee L. Histoplasmosis in the head and neck. Ann Acad Med Singapore 1997;26(4):510–3. [PMID: 9395822].
[2] Pincelli T, Enzler M, Davis M, Tande AJ, Comfere N, Bruce A. Oropharyngeal Histoplasmosis: a report of 10 cases. Clin Exp Dermatol. 2019 Feb 1; doi: https://doi.org/10.1111/ced.13927. [doi:10.1111/ced.13927].
[3] Kauffman CA. Histoplasmosis: a clinical and laboratory update. Clin Microbiol Rev 2007;20(1):115–32. https://doi.org/10.1128/CMR.00027-06.
[4] Azar MM, Hage CA. Laboratory diagnostics for histoplasmosis. J Clin Microbiol 2017;55(6):1612–20. https://doi.org/10.1128/JCM.02430-16.
[5] Viswanathan S, Chawla N, D'Cruz A, Kane SV. Head and neck histoplasmosis-a nightmare for clinicians and pathologists! Experience at a tertiary referral cancer Centre. Head Neck Pathol 2007;1(2):169–72. (doi:10.1007%2Fs12105-007-0034-1).
[6] Hage CA, Azar MM, Bahr N, Loyd J, Wheat LJ. Histoplasmosis: up-to-date evidence-based approach to diagnosis and management. Semin Respir Crit Care Med 2015;36(5):729–45. https://doi.org/10.1055/s-0035-1562899.
[7] Goodwin RA, Shapiro JL, Thurman GH, Thurman SS, Des Prez RM. Disseminated histoplasmosis: clinical and pathologic correlations. Medicine (Baltimore) 1980;59(1):1–33. [7356773].
[8] Gerber ME, Rosdeutscher JD, Seiden AM, Tami TA. Histoplasmosis: the otolaryngologist's perspective. Laryngoscope 1995;105(9 Pt 1):919–23. https://doi.org/10.1288/00005537-199509000-00009.
[9] Chroboczek T, Dufour J, Renaux A, Aznar C, Demar M, Couppie P, et al. Histoplasmosis: an oral malignancy-like clinical picture. Med Mycol Case Rep 2018;19:45–8. (doi:10.1016%2Fj.mmcr.2017.11.001).
[10] O'Connell Ferster AP, Jaworek A, Hu A. Histoplasmosis of the head and neck in the immunocompetent patient: report of 2 cases. Ear Nose Throat J 2018;97(9):E28–31. [PMID: 30273439].
[11] O'Hara CD, Allegretto MW, Taylor GD, Isotalo PA. Epiglottic histoplasmosis presenting in a nonendemic region: a clinical mimic of laryngeal carcinoma. Arch Pathol Lab Med 2004;128(5):574–7. https://doi.org/10.1043/1543-2165(2004)128%3C574:EHPIAN%3E2.0.CO;2.
[12] Pontes HAR, de Souza LL, Costa AMPE, da Silva AA, Gonçalves FLN, Fonseca FP, et al. An ulcer on the ventral tip of tongue. Oral Surg Oral Med Oral Pathol Oral Radiol 2019;127(2):92–6. https://doi.org/10.1016/j.oooo.2018.01.019.
[13] Ficarra G, Carlos R. Syphilis: the renaissance of an old disease with oral implications. Head Neck Pathol 2009;3(3):195–206. (doi:10.1007%2Fs12105-009-0127-0).
[14] Motta ACF, Lopes MA, Ito FA, Carlos-Bregni R, de Almeida OP, Roselino AM. Oral leishmaniasis: a clinicopathological study of 11 cases. Oral Dis. 2007; 13(3): 335–40. (doi:https://doi.org/10.1111/j.1601-0825.2006.01296.x).
[15] Pietruszewska W, Wągrowska-Danilewicz M, Klatka J. Amyloidosis of the head and neck: a clinicopathological study of cases with long-term follow-up. Arch Med Sci 2014;10(4):846–52. (doi:10.5114%2Faoms.2013.39206).
[16] Badhey AK, Kadakia S, Carrau RL, Iacob C, Khorsandi A. Sarcoidosis of the head and neck. Head Neck Pathol 2014;9(2):260–8. https://doi.org/10.1007/s12105-014-0568-y.
[17] Wheat LJ, Freifeld AG, Kleiman MB, Baddley JW, McKinsey DS, Loyd JE, et al. Clinical practice guidelines for the management of patients with histoplasmosis: 2007 update by the Infectious Diseases Society of America. Clin Infect Dis 2007;45(7):807–25. https://doi.org/10.1086/521259.
[18] Johnson PC, Wheat LJ, Cloud GA, Goldman M, Lancaster D, Bamberger DM, et al. Safety and efficacy of liposomal amphotericin B compared with conventional amphotericin B for induction therapy of histoplasmosis in patients with AIDS. Ann Intern Med 2002;137(2):105–9. https://doi.org/10.7326/0003-4819-137-2-200207160-00008.