Cutaneous Histoplasmosis: An Unusual Presentation with Nasal Obstruction

Abstract

Histoplasmosis is a systemic fungal disease that may be presented with a variety of clinical manifestations, usually as an opportunistic infection in immunocompromised individuals. We present an HIV seropositive patient with a large fleshy growth causing left-sided nasal obstruction, as an unusual presentation. The lesions shrunk dramatically and almost completely on intravenous amphotericin-B lipid complex (ABLC) given for 2 weeks followed by long-term oral itraconazole.

Keywords: *Histoplasmosis, HIV, immunosuppressed, nose*

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Introduction

Histoplasmosis is an invasive mycosis, mostly acquired through the respiratory route. Most pulmonary infections heal spontaneously in an immunocompetent host but disseminated histoplasmosis (DH) may occur in settings of HIV positivity and other immunosuppressed states. DH is considered an AIDS-defining illness. Mucocutaneous involvement is seen in 10–25% and is a very important diagnostic evidence in DH.

Case Report

A 34-year-old unmarried male from New Delhi, India, presented with a 4-month long history of a reddish raised painless growth on the left side of the nose, with similar nodules covering the left nostril. The lesions used to bleed on touching. He also had a few smaller and similar lesions on the right side of the nose. He had been diagnosed as HIV-1 seropositive 8 years ago after an episode of Herpes zoster ophthalmicus which had left him blind in the right eye due to the formation of corneal opacity. However, he had discontinued antiretroviral treatment after a mere 6 months course. The patient admitted to having had multiple unprotected anal intercourses with a male casual acquaintance 10 years ago. He did not have any respiratory or systemic symptoms.

On examination, the patient appeared emaciated. Mucocutaneous examination revealed a large fleshy growth, almost entirely covering the left side of the dorsum of the nose, bleeding profusely on manipulation [Figure 1a]. Three similar smaller nodules were present, one obstructing the left nostril and the other two on the apex and right ala of the nose [Figure 1b]. There was no significant lymphadenopathy. Nasal endoscopy did not reveal any nasal or paranasal polyp/mass.

Routine biochemical and hematological investigations were largely normal. HIV-1 antibody testing was reactive by ELISA [CD4 count - 34 cells/cu.mm (2%)]. He was also reactive for Hepatitis B. Mantoux and rK39 antigen were negative. Lesional fine needle aspiration cytology (FNAC) showed foamy macrophages and many tiny oval yeast forms (PAS-positive). Fungal culture from a skin biopsy sample revealed *Trichosporon* spp., which is known to be an occasional contaminant. A repeat fungal culture did not show any organism's growth. Histopathology of the skin lesion revealed dense lymphohistiocytic infiltrate in superficial and mid dermis with yeast forms on hematoxylin and eosin staining [Figure 2a]. PAS staining showed both intra and extracellular, round to oval, 2–4 µm yeast forms with narrow-based budding and chromatin clumped at periphery in an arc-like manner and surrounded by clear spaces, suggestive of *Histoplasma capsulatum* [Figure 2b].

Ultrasound of the abdomen showed hepatosplenomegaly and multiple enlarged periportal, peripancreatic, retroperitoneal,

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and mesenteric lymph nodes. A chest radiograph showed an ill-defined radio-opaque lesion with lobulated margins in the left-lower zone, adjacent to the left cardiophrenic angle. CECT chest also showed a lobulated, heterogeneously enhancing mass in the lingular segment of the left upper lobe abutting the pericardium. Bronchoscopy could not be attempted as the lesion was too peripherally located. Sputum obtained after nebulization was negative for acid-fast bacilli by CBNAAT assay, thus ruling out pulmonary tuberculosis. Fundoscopy showed a leucomatous opacity in the right eye.

The patient was thus diagnosed as progressive disseminated histoplasmosis (PDH) with HIV-1 infection. He was started on HAART (tenofovir, lamivudine, and efavirenz). Intravenous amphotericin B lipid complex (ABLC) (5 mg/kg/d) was given for 2 weeks following which the growth dramatically reduced in size [Figure 3a] The smaller nodules too decreased in size but still obstructed the nostril [Figure 3b]. He was then switched to oral itraconazole 200 mg thrice daily for 3 days followed by 200 mg twice daily, as per recommendations, which led to near-complete shrinkage of the growth [Figure 4a] resulting in removal of the obstruction of the nostril [Figure 4b].[1,2]

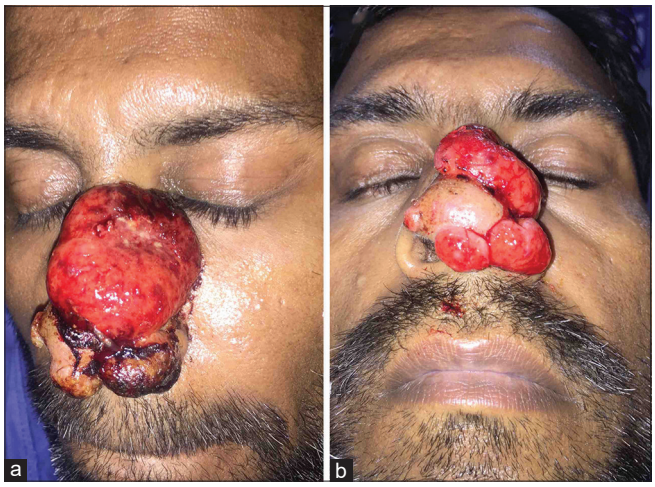

Figure 1: Clinical photographs of the patient at presentation (a) large noduloulcerative growth with the hemorrhagic surface over the left dorsal aspect of nose, (b) similar smaller growths over the left ala and tip of nose obstructing the left nostril

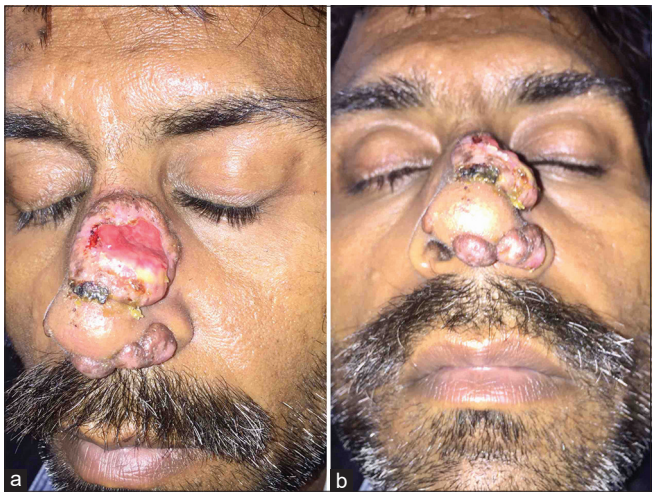

Figure 3: Patient after 14 doses of amphotericin B lipid complex (ABLC) (a) Visible reduction in the growth over the dorsum of nose with no bleeding on manipulation, (b) shrinkage of smaller nasal nodules too

Discussion

A proliferative growth on the nose can develop due to diverse disorders, both infectious and noninfectious. It may originate from the nasal/paranasal sinus mucosa or may

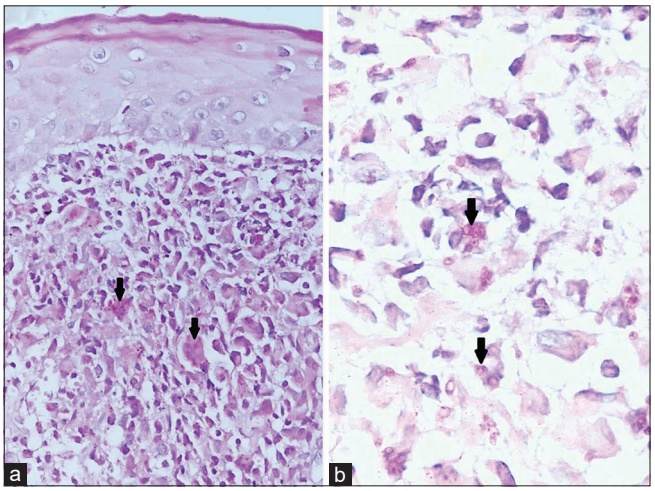

Figure 2: (a) Dense lymphohistiocytic infiltrate abutting the epidermis with intracellular yeast forms. (H and E × 400), and (b) PAS stained section showing both intracellular and extracellular budding yeast forms round to oval 2–4 μm yeast forms with narrow-based budding and chromatin clumped at periphery in an arc-like manner and surrounded by clear spaces (PAS × 1000)

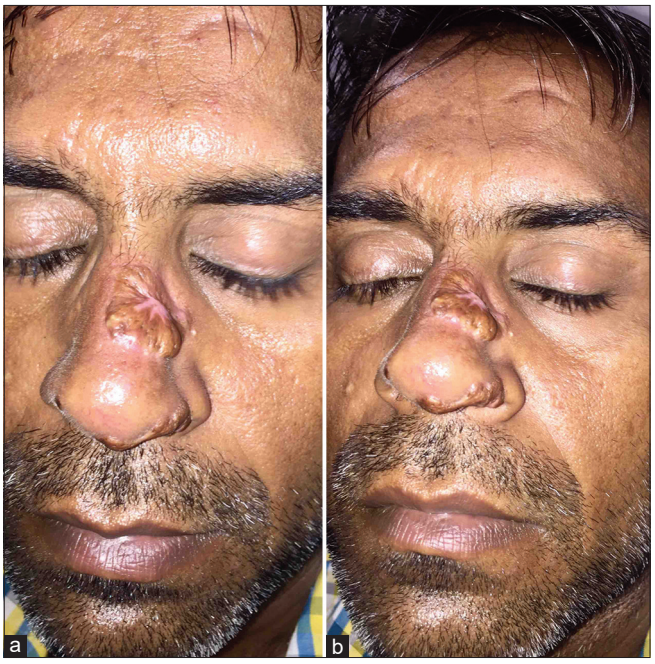

Figure 4: Patient after 6 weeks of oral itraconazole therapy (a) and (b) Near-complete shrinkage of all lesions with scarring

involve only the skin of the nose. The common differential diagnoses are lupus vulgaris, lepromatous leprosy, cutaneous leishmaniasis, rhinoscleroma, or malignancy. However, in our case, rhinoscleroma and other invasive molds like *Mucor* or *Aspergillus* were unlikely causes as nasal and paranasal mucosae were uninvolved. DH causing such lesions is very infrequent and a high index of clinical suspicion along with a thorough examination can help clinch the diagnosis. Moreover, PDH has a predilection for a reticuloendothelial system with less prominent pulmonary symptoms, as seen in our patient. It is commonly associated with HIV. Major risk factors include low CD4+ counts (<50 cells/μL), corticosteroids, immunosuppressives, and solid-organ transplants.[3-5]

Mucocutaneous involvement is a very important diagnostic clue (10–25%) and may, in fact, unmask PDH.[6,7] Characteristic skin lesions include umbilicated nodules, papules, plaques and ulcers; pustules, erosions, acneiform eruptions, keratotic plaques are less common.[6] Large fleshy growths as seen in our patients are unusual.

Diagnosis is established by cytology, histopathology, and fungal culture. Small intracellular yeast cells (2–4 micron) appear as basophilic dots with a pseudo capsule in macrophages. Culture from a clinical sample is the gold standard for the diagnosis of histoplasmosis but its sensitivity is low and utility is limited due to a longwaiting period.

PDH is fatal unless diagnosed and treated early. The various treatment options include amphotericin B (AMB), itraconazole, and other azoles, of which AMB is the drug of choice in disseminated cases.[1,2,8] HAART improves response to antifungals in patients of PDH with HIV/AIDS and decreases mortality. Immunocompromised patients need itraconazole prophylaxis for life, if immunosuppression cannot be reversed or if CD4 counts remain <150 cells/μL.

Histoplasmosis is uncommon in India, with relatively more cases being reported from the deltas of three major rivers—Ganga, Yamuna, and Brahmaputra in the north and north-east India.[8] The rest of the areas are considered nonendemic though there are no large-scale studies. The number of cases is on the rise, due to HIV and better detection rates. Most cases are DH, and the most common predisposing factor is HIV. Adrenal enlargement and lymphadenopathy have been reported in immunocompromised while oral lesions have been reported in both immunocompromised and immunocompetent individuals.[8,9] Few primary cutaneous cases have been reported from "nonendemic" areas in immunocompetent individuals.[10] AMB deoxycholate or liposomal AMB has been used in disseminated infections while primary cutaneous cases have been treated with itraconazole alone.

The possible differential diagnoses for growths on the nose are listed in Table 1. Clinicians must keep in mind that clinical manifestations may be atypical in

Table 1: Causes of chronic noduloulcerative growths on the nose

Disease	Salient clinical findings	Salient histopathological findings
Rhinoscleroma (granulomatous stage)	Dusky red stony hard, nontender rubbery intranasal and nasal nodules.	Russell bodies and pathognomonic large Mikulicz cells.
Lupus vulgaris	Slowly enlarging plaque with scarring at one end.	Tuberculoid granulomas with scanty or absent central caseation
Lepromatous leprosy	Nodular infiltration on nasal septum and turbinates, ulceration and nasal septum perforation leading to "saddle-nose" deformity.	Macrophage granuloma is large and expansile with sheets of foamy histiocytes.
Cutaneous and Mucocutaneous leishmaniasis	Single or multiple ulcers with raised, indurated margins and a sloughy base. Chronic local destruction of tissue may occur.	Histiocytes contain small oval amastigotes with para nuclear kinetoplast in the dermis.
Syphilitic gumma	Gumma (reniform ulcers with firm margins) on septum with central necrosis and surrounding granulation tissue. Both bony and cartilaginous nasal septum destroyed.	Dense perivascular or diffuse plasma cell infiltrate with marked endothelial swelling and proliferation in blood vessels.
Mucormycosis, Aspergillosis	Mostly involves paranasal sinuses and nose, rare on skin.	Mucormycosis - Large, aseptate hyphae with 90° branching and nonparallel walls. Aspergillosis- Branching septate hyphae.
Basal cell carcinoma (Nodulo ulcerative type)	Well defined lesions with rolled out border, indurated edge and ulcerated center with fleshy base and erosion or crusting on it. Central ulceration is characteristic.	Nests of basaloid cells in the dermis with scant cytoplasm and elongated hyperchromatic nuclei, peripheral palisading, peritumoral clefting, and mucinous stroma.
Squamous cell carcinoma	Slowly enlarging, firm, skin-colored to erythematous plaques or nodules which may show ulceration or infiltration.	Nests of squamous epithelial cells arise from the epidermis and extend into the dermis. Variable keratinization with keratin pearls is present.
Cutaneous metastasis	Rapidly enlarging nodular metastatic lesion on the nasal tip ("clown nose sign") (rare site).	According to the primary malignancy.

Contd...

Table 1: Contd...

Disease	Salient clinical findings	Salient histopathological findings
Mycosis fungoides (Type of Cutaneous T cell lymphoma	Erythematous to brownish confluent plaque and ulcerated lesions with purulent, hemorrhagic exudates and sharp elevated borders.	T cells in epidermis and dermis with cerebriform nuclei, Pautrier microabscesses, and epidermotropism.
Midline lethal granuloma (a type of NK/T cell lymphomas)	An extensive midfacial necrotizing lesion with perforated nasal septum and erosion of nasal bone, paranasal sinuses, and mutilated surrounding regions, aggressive course.	Diffuse lymphomatous infiltrate having an angiocentric and angiodestructive pattern.
Sarcoidosis (Lupus Pernio)	Chronic, persistent, indolent, indurated, reddish or violaceous painless nodules or plaques.	Epithelioid cell granulomas with Schaumann bodies and asteroid bodies +/-.
Wegener's granulomatosis (Granulomatosis with polyangiitis)	Nodular/papulonecrotic lesions develop in extremities, face, and scalp which may ulcerate. Saddle nose may form due to necrotizing granuloma of the nasal mucosa.	Leukocytoclastic vasculitis.

immunosuppressed individuals and, with the current pandemic of HIV, histoplasmosis should be kept as a differential diagnosis for such lesions.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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