

CASE REPORT

Histoplasmosis in nasopharynx clinically mistaken for nasopharyngeal malignancy

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Histoplasmosis is a rare type of fungal infection which may manifest as a respiratory disease or as a disseminated infection. It is common in immunocompromised patients and, in recent times, seen in association with COVID-19. On histopathological examination, many intracellular and extracellular yeast forms are seen, which can be confirmed by fungal stains. Histoplasmosis involving the nasopharyngeal region is quite rare. Till date, only less than 100 cases of pharyngo-laryngeal histoplasmosis have been reported. Such cases are clinico-radiologically easily and frequently mistaken for malignancy. Here, we report a case that initially had COVID-19-like symptoms and later presented with a nasopharyngeal mass clinico-radiologically mistaken as a nasopharyngeal malignancy. The diagnosis was established on histopathological examination and the patient recovered completely with anti-fungal treatment. A high grade of suspicion and thorough histopathological examination, especially in immunocompromised patients, complimented by fungal special stains is quite rewarding as even a disseminated disease is curable.

KEYWORDS: histoplasma, nasopharynx, malignancy, fungus.**INTRODUCTION**

Histoplasmosis is a rare and non-contagious fungal infection caused by thermotolerant fungi commonly found in soil. The fungus thrives at soil temperature in mycelial form and switches to yeast form at body temperatures of 37°C¹. *Histoplasma capsulatum* is known to be harmless in immunocompetent individuals; however, its occurrence is reported in immunocompetent individuals as well as in immunocompromised individuals². It is deadly in immunocompromised patients, such as HIV cases and those on steroids, due to their impaired immune system. T lymphocyte-macrophage response against *Histoplasma* is impaired in these cases³. Recently, histoplasmosis has been associated with COVID-19 and has been reported on a large scale. The disease manifestation is either immediate or latent and the affected individuals exhibit the disease as acute primary, chronic cavity and progressive disseminated. Disseminated and systemic mycosis occurs less commonly than the other two types of

histoplasmosis¹⁻⁴. The microconidia, moulds and hyphal fragments of histoplasma existing in the soil are introduced in the host through inhalation or mouth. The fungus then switches to yeast form, reaches lung alveoli and intestines, and ultimately disseminates through the bloodstream and lymphatics to the distant organs.

The disease caused by *Histoplasma capsulatum* var. *Capsulatum* is Histoplasmosis Capsulati, also known as Darling's Disease, American Histoplasmosis, Classical Histoplasmosis, small form Histoplasmosis, and that caused by *Histoplasma capsulatum* var. *Duboisii* is Histoplasmosis Duboisii commonly called African Histoplasmosis or large form Histoplasmosis⁵. Histoplasmosis is found worldwide and is endemic in regions of Latin America and North America, Europe and few regions of Asia. In India, Histoplasmosis is endemic in Gangetic Delta of West Bengal and Assam^{1,6}.

Symptoms of Histoplasmosis are similar to any other acute respiratory distress syndromes (ARDS) including COVID-19. The association of COVID-19 with secondary

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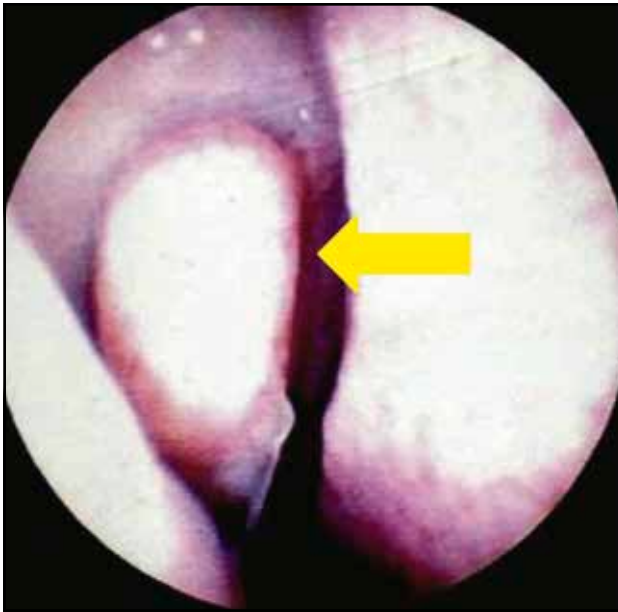
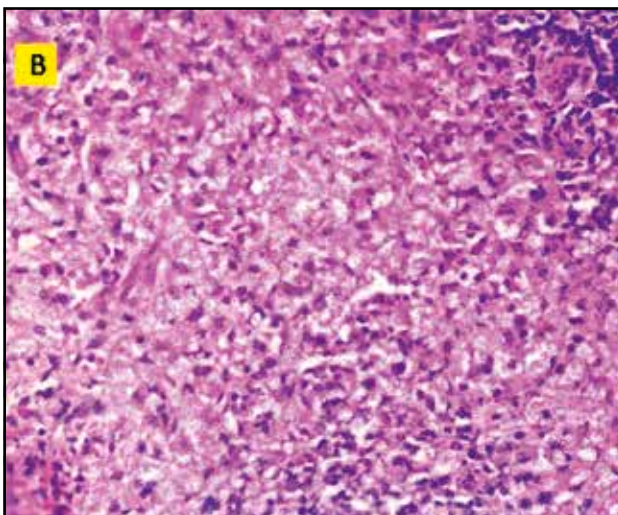
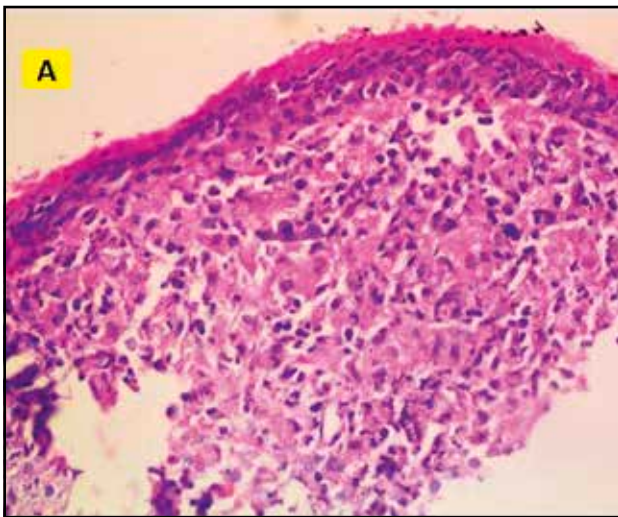


Figure 1. Endoscopy image of the nasopharynx showing a nodular mass with intact overlying mucosa.



infection of Histoplasmosis makes the treatment difficult. Hospital admission with impaired immune system in COVID-19 increases the risk of opportunistic infections including fungal diseases or consideration of reactivation of latent *Histoplasma* cannot be denied³.

Here we report a case of a 65-year-old male who presented with dysphagia post COVID-19-like symptoms, primarily suspected as a case of nasopharyngeal malignancy. The patient, after relevant investigations and histopathological examination, was finally diagnosed with disseminated Histoplasmosis.

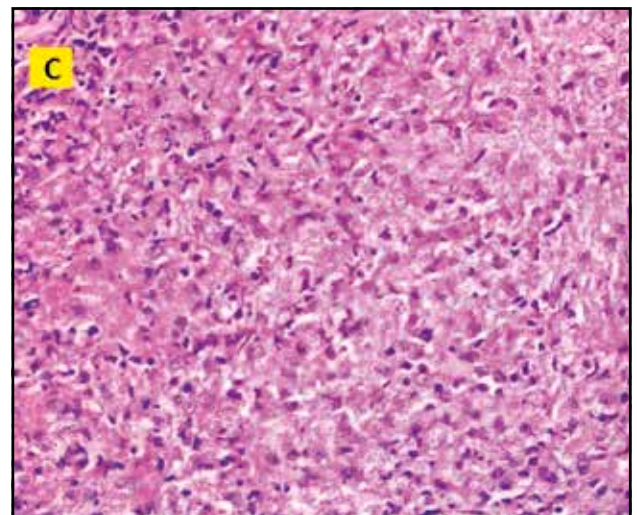
CASE REPORT

A 65-year-old male, a lawyer by occupation, visited our hospital with the complaint of dysphagia and high-grade fever, weakness and weight loss of 6 kg in one month along with loss of appetite and occasional vomiting. The patient had previous history of hypertension and transient ischemic attack (TIA) and was on medication for TIA. He gave history of COVID-19-like symptoms with fever, cough and dyspnoea. Although his RT-PCR for COVID-19 was negative, he underwent treatment with then the prevalent COVID-19 protocol with administration of oral steroids, remdesivir and oxygen up to 5 litres on dyspnoea for 7 days. The patient partially recovered after the treatment for COVID-19 and subsequently reported with complaint of dysphagia and fever.

On examination, the patient was febrile and presented with small nodular lesions over face and neck causing umbilicated look, bilateral grade III pedal edema, scrotal edema and palatal granularity.

On routine blood investigations, he had mild iron deficiency anaemia with pancytopenia. His computer tomogra-

Figure 2. Microphotographs showing: **A**], a lesion covered by intact respiratory mucosa with subepithelial tissue showing submucosal inflammatory infiltrate; **B**], the infiltrate is rich in histiocytes and macrophages; **C**], with focal areas showing epithelioid granulomas (H&E - A] x100; B] and C] x400).



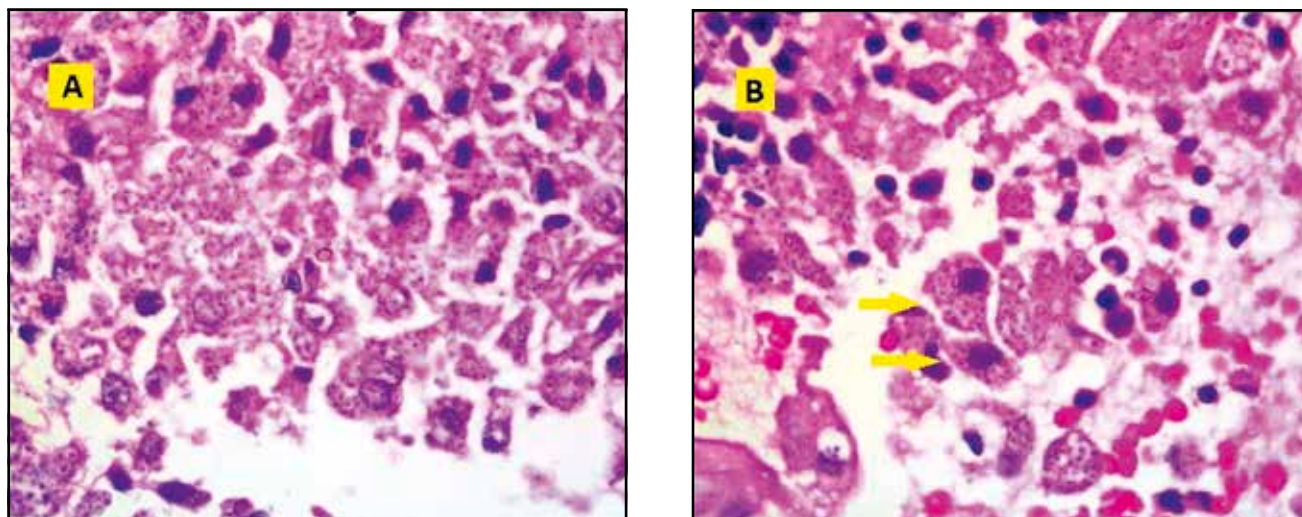


Figure 3. Oil immersion images showing: **A**], both intra- and extra-cellular budding yeast forms of *Histoplasma* surrounded by clear halo; **B**], intracellular yeast forms in macrophages (marked by yellow arrows); **C**], predominantly extracellular yeast forms (H&E).

phy (CT) scan revealed precarinal and paratracheal lymphadenopathy, multiple patchy ground glass opacities in bilateral lung parenchyma, hypodense lesions in the right adrenal gland, and hepato-splenomegaly. The gastroscopy revealed extrinsic compression on the stomach causing gastro-esophageal reflux. Mild medico-renal disease, mild left pleural effusion with basal compressive atelectasis and resolving changes of previous lung changes of atypical viral infection were other radiological findings.

An eccentric nodular thickening was noted in the right nasopharynx mimicking a malignant neoplasm. Nasopharyngeal endoscopy showed a nodular mass measuring 2.0x1.0 cm (Figure 1). The mucosa overlying the mass was unremarkable.

With these radiological and endoscopic findings, he was clinically diagnosed with a disseminated nasopharyngeal malignancy.

The mass was then biopsied and submitted for histopathological examination. The Hematoxylin and Eosin (H&E) stained slides revealed tissue partly lined by respiratory type of epithelium. The subepithelial connective tissue showed granulation tissue and necrotic tissue with diffuse infiltration of inflammatory cells such as histiocytes, macrophages and lymphocytes (Figure 2). Numerous intracellular (within macrophages) and extracellular budding yeast forms of *Histoplasma* were noted. These yeast forms appeared as small round to oval structures surrounded by a clear halo (Figure 3). Fungal stains – Grocott's Methenamine Silver (GMNS) stain and Periodic Acid-Schiff (PAS) stain – confirmed the yeast forms of *Histoplasma* (Figure 4) and thus, he was finally diagnosed with progressive disseminated *Histoplasmosis* based on the histopathological examination and the CT scan.

He was treated for *Histoplasmosis* with 3mg per kg dose of injection Amphotericin for 3 weeks, following which all the

symptoms including the skin lesions, fever and pedal edema were resolved. Later, the patient was shifted to oral Posaconazole after discharge (300 mg BID on day 1, followed by 300 mg QD for 6 weeks).

On regular follow-up examination, all the signs and symptoms were resolved post treatment for *Histoplasmosis*.

He is symptom-free 2 years after completing the anti-fungal treatment and he has resumed his regular duties.

DISCUSSIONS

Histoplasmosis was first described by Samuel Taylor Darling in 1906. Dodd and Tompkins detected *Histoplasmosis* for the first time in living infants in 1934, and the first *histoplasmosis* case in India was detected by Panja and Sen⁷. Pharyngo-laryngeal *histoplasmosis* was first reported by Brown and colleagues in 1940. Till date, there are fewer than 100 cases of *histoplasmosis* detected in the pharyngo-laryngeal region and it is quite easily and frequently misdiagnosed as malignancy⁸.

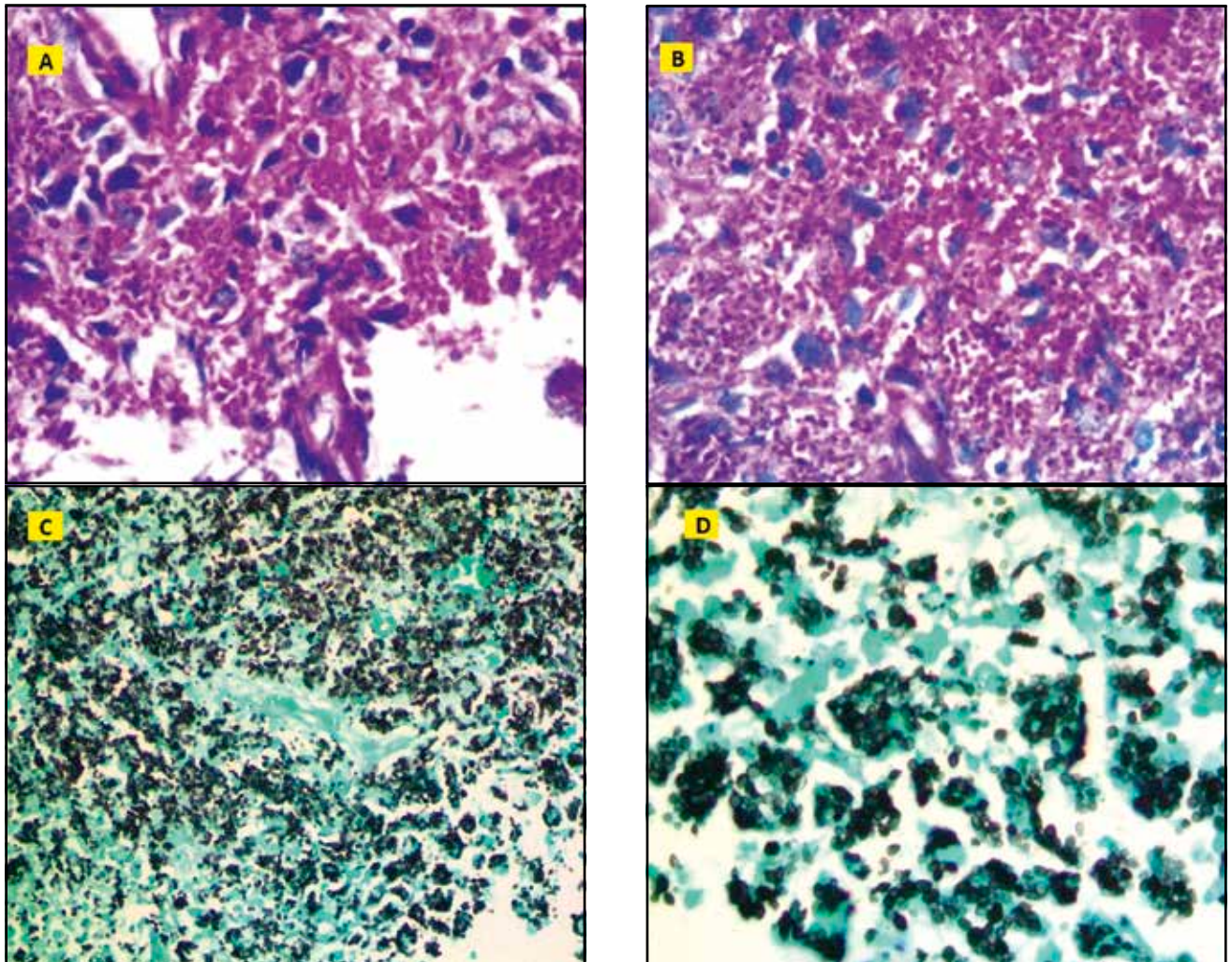


Figure 4. A) and B) PAS stained sections showing both intra- and extracellular yeast forms of Histoplasma (PAS - oil immersion); C) and D) GMNS stained sections showing intra- and extra-cellular yeast forms of Histoplasma (GMNS – C] x400; D] Oil immersion).

Histoplasmosis is caused by dimorphic, rare and non-contagious fungi, commonly found in bird faeces, which settles in soil. The fungus exists in mycelial form at the soil temperature, in the form of conidia as macroconidia (8 to 15 μm in diameter) and microconidia (2 to 4 μm in diameter). It transforms in yeast form when introduced to body temperature of 37°C. Histoplasma is commonly found in soil with large amount of bird or bat guano. The soil yields the organisms for many years⁹.

Histoplasmosis may manifest as acute pulmonary, chronic cavitory pulmonary or disseminated histoplasmosis. Pulmonary manifestations of histoplasmosis are similar to any other respiratory distress syndrome, including COVID-19. Thus, exclusion of all other causes is necessary before suspecting histoplasmosis as a diagnosis. A large number of immunocompetent individuals remain asymptomatic. However, in immunocompromised cases, the inoculation of Histoplasma through inhalation may cause the infection. The disease may be associated with immunocompromised individuals with

conditions such as AIDS (the most common), corticosteroid consumption, hematologic malignancies, organ transplant cases and, in recent times, COVID-19-affected individuals due to reduced T cell immunity against histoplasmosis^{3,9}. In the current report, we present the case of a 65-year-old male who was admitted in ICU for COVID-19-like symptoms followed by the development of dysphagia and a nasopharyngeal mass. Clinico-radiologically, he was diagnosed with a disseminated nasopharyngeal malignancy. It was only after the histopathology examination that malignancy was excluded and he was diagnosed with histoplasmosis.

The current situation of COVID-19 infection has a proven effect on reduced immune response, causing various superimposed infections in the affected individuals, worsening the condition. These include various bacterial, fungal and parasitic infections further worsening the individual's condition. Fungal infections commonly affecting the COVID-19 patients include Aspergillosis, Mucormycosis, Candidiasis and Histoplasmosis^{3,10}. In the presented case,

the patient may have been exposed to COVID-19 followed by disseminated histoplasmosis.

Similar reports are published in the literature by authors who encountered COVID-19 infected individuals with superimposed histoplasmosis¹¹⁻¹³. These cases had all the signs and symptoms of respiratory syndrome similar to those other ARDS cases. All the patients were recovered after prolonged treatment with anti-fungal drugs. The symptoms are similar to those experienced by people with COVID-19 and thus histoplasmosis may remain undiagnosed many times. Considering the other possibility of reactivation of *H. capsulatum* in COVID-19-affected individuals, María A. Toscanini et al.³ carried out a study for the detection of anti-*H. capsulatum* antibodies from serum samples in COVID-19 patients with moderate to severe symptoms. 8 out of 39 COVID-19 patients showed antibodies in serum against *Histoplasma*. Thus, they concluded the need for an accurate diagnosis to improve the prognosis of these patients³. In 2020, Fernando A. Messina et al.¹⁴ published a case of COVID-19 with superimposed infection of histoplasmosis in a patient who presented with advanced HIV infection. The patient presented with fever and multiple skin lesions, with a history of HIV for the last 10 years. The patient improved after treatment with anti-fungal drugs, including Amphotericin B and Itraconazole. The authors highlighted the importance of an accurate diagnosis, as antifungal treatment resulted in significant improvement of the disease process¹⁴. Reduced immunity resulting from COVID-19 infection coupled with immunosuppression resulting from steroid treatment for COVID-19 might be the other possible etiological factors in such cases. In the current case, the RT-PCR for COVID-19 was negative. So, apart from COVID-19, the other probability we suggest is of de novo histoplasmosis, which partially responded initially and flared with disseminated infection subsequently.

Although rare, histoplasmosis can at times be fatal and thus, a proper diagnosis and accurate treatment is necessary. It is usually unsuspected and underdiagnosed or misdiagnosed as a malignancy, as in our case with the nasopharyngeal mass that was mistaken for malignancy based on clinical and radiological findings. A clinicopathological study was conducted by Bhattacharya et al.¹⁵, in 2015, to look for the aetiology of various masses arising from the sinonasal tract and nasopharynx. The study concluded that a large number of cases turned out to be malignant. Only a single case (2.04 %) of nasopharyngeal masses was diagnosed as histoplasmosis¹⁵. Claudia Miranda et al.⁶, in 2018, reported a case of a 79-year-old male presenting with odynophagia, dysphagia, fever and weight loss. The CT scan showed diffuse thickening of the oropharynx, supraglottic larynx, extending up to the vocal cords. Suspecting an oropharyngeal malignancy, biopsy was done and the histopathological examination revealed the diagnosis of Histoplasmosis⁶. Our case was almost similar, with a clinico-radiological diagnosis of nasopharyngeal malignancy with widespread dissemination. It was only after biopsy and histopathological examination that a proper diagnosis was established.

Nasopharyngeal involvement of histoplasmosis is very rare. We noticed only two other reported cases of histoplasmosis in the Indian literature, that presented with nasal masses. A case presented by Jano Roy et al.⁷ in 2021 reported a 12-year-old girl with complaint of dysphagia and nasal obstruction. The patient had a past history of tuberculosis and was treated for the same. The nasal mucosa showed punched-out lesions in the right philtrum, ala, vestibule and anterior septum⁷. Another report of a 55-year-old male, with complaints similar to our case, presented with a nasal mass primarily diagnosed as rhinoscleroma⁴. Both these cases were diagnosed on histopathological examination and recovered after treatment with antifungal therapy.

Our case too was diagnosed with histoplasmosis after histopathological examination aided with fungal special stains of PAS and GMNS that highlighted the features of yeast forms of the fungus. The patient was treated by antifungal drugs, including Amphotericin B and Itraconazole, for a prolonged period of time. The patient was recovered completely to a functional state after 4 months of treatment with restoration of all the symptoms to normal.

Amphotericin B was the only drug till 1990s used for the treatment of fungal diseases. Untreated cases had higher (83%) mortality rate over the cases treated with anti-fungal drugs (23%). Later on, the azole group of drugs were introduced, improving the success rate up to 85%, with following 6-month-long treatment. Itraconazole is known to be more effective, with fewer side effects as compared to other Azole drugs⁹.

CONCLUSIONS

Histoplasmosis is known to manifest as respiratory disease or in disseminated form. Nasopharyngeal involvement of histoplasmosis is extremely rare and such cases mimic malignancy. Histoplasmosis is encountered most commonly in immunosuppressed cases but, also, should be suspected in immunocompetent individuals. Recent surge in COVID-19 cases has resulted in overlap of the symptoms and, thus, negligence of such cases. A high degree of suspicion coupled with thorough histopathological examination complimented with fungal special stains is quite rewarding, as even the disseminated disease is curable.

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