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Histoplasma: The Great Mimicker

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Abstract: ***We present a case of histoplasmosis that was initially misdiagnosed as malignancy and viral infection before being incidentally diagnosed. Histoplasmosis can mimic various diseases, making its diagnosis challenging. Key clues include the patient being from an endemic area, being immunocompromised, or having exposure to potential sources (e. g., bats in caves). In our case, none of these risk factors were present. The unique presentation as a cobblestone larynx further complicated the diagnosis. This case underscores the importance of recognizing histoplasmosis, even in atypical presentations, to enhance awareness and ensure timely treatment.***

Keywords: Histoplasma, Cobblestone larynx, biopsy

1. Introduction

Histoplasmosis, caused by the fungus Histoplasma capsulatum, is indeed an endemic mycosis. It's intriguing that it's considered rare in India, with only 144 cases between 1994 to 2017.[1] Our case presentation of histoplasmosis involves an elderly immunocompetent gentleman residing in a non - endemic region, with age being the only risk factor for disseminated histoplasmosis.[2] The manifestation as cobblestone larynx, initially misdiagnosed as laryngeal cancer and later as herpes, highlights the diagnostic challenges posed by this condition. In the background of a negative bronchoalveolar lavage, biopsy - proven diagnosis underscores the significance of histopathological examination in confirming such atypical presentations.

This case underscores the importance of considering histoplasmosis in the differential diagnosis of multisystem disease. Additionally, it emphasizes the need for a high index of suspicion, particularly when conventional treatments fail to yield expected results.

2. Case History

Our patient, a 58 - year - old farmer from Rampur, Uttar Pradesh, had no known comorbidities but had a history of smoking bidis for over 15 years, averaging 2 - 3 bidis per day. He presented to us with daily episodes of high - grade fever ranging from 99.5 to 104 degrees Fahrenheit, accompanied by chills and rigor and there was no diurnal variation. Additionally he had arthralgia in bilateral knee joints and pain in the shins eventually leading to difficulty in walking. Additionally, he experienced a persistent cough with minimal non - purulent sputum production for 3 months and mentioned unintentional weight loss of 6 kg over the past 6 months, initially maintaining a normal appetite but later appetite was reduced due to worsening odynophagia in the last 20 days. X - rays revealed no obvious abnormalities.

Despite multiple treatments at various medical establishments, including third - generation cephalosporins, macrolides, antivirals like acyclovir, and other symptomatic management, there was no significant improvement. He was admitted twice for intravenous antibiotics (piperacillin and tazobactam) without notable progress. A laryngoscopy done at a different medical center indicated a growth over the larynx suggestive of carcinoma, prompting him to seek a second opinion from us.

Upon admission, routine lab investigations revealed elevated CRP levels, ruling out comorbid conditions such as diabetes mellitus, hypertension, hyperlipidemia, and retroviral diseases. Oral swab culture and sensitivity showed no growth, while sputum culture revealed greater than 25 gram - positive cocci, considered normal commensals. Significantly raised liver enzymes, including GGT (>530) and ALP (>251), were noted.

To address odynophagia and ascertain its cause, we sought an opinion from the ENT team, who recommended a laryngoscopy. The examination revealed a severe cobblestone appearance of the larynx and diffuse petechial ulceration, typical of viral infections like herpes, prompting treatment with intravenous famciclovir. However, despite this treatment, the patient experienced no symptomatic relief, with continuous fever spikes and severe odynophagia persisting alongside the cough.

Given the severity of symptoms, including severe coughing and high - grade fevers, we conducted a CT scan of the chest and abdomen to rule out other sources of infection. The scan revealed multiple tiny bronchocentric nodules, mediastinal lymphadenopathy, air trapping, paraseptal emphysematous changes, and hepatosplenomegaly. A serum Beta D Glucan Assay was performed, indicating a value >500, suggestive of a fungal infection. Thus, urinary antigen for histoplasma was sent.

In light of these findings, we sought the opinion of a pulmonologist, who recommended bronchoalveolar lavage with sputum analysis. This procedure revealed a cobblestone appearance of the larynx and a white plaque on the medial wall of the bronchus intermedius. Subsequent biopsy of the white plaque identified histoplasma, despite the bronchoalveolar lavage failing to grow the organism.

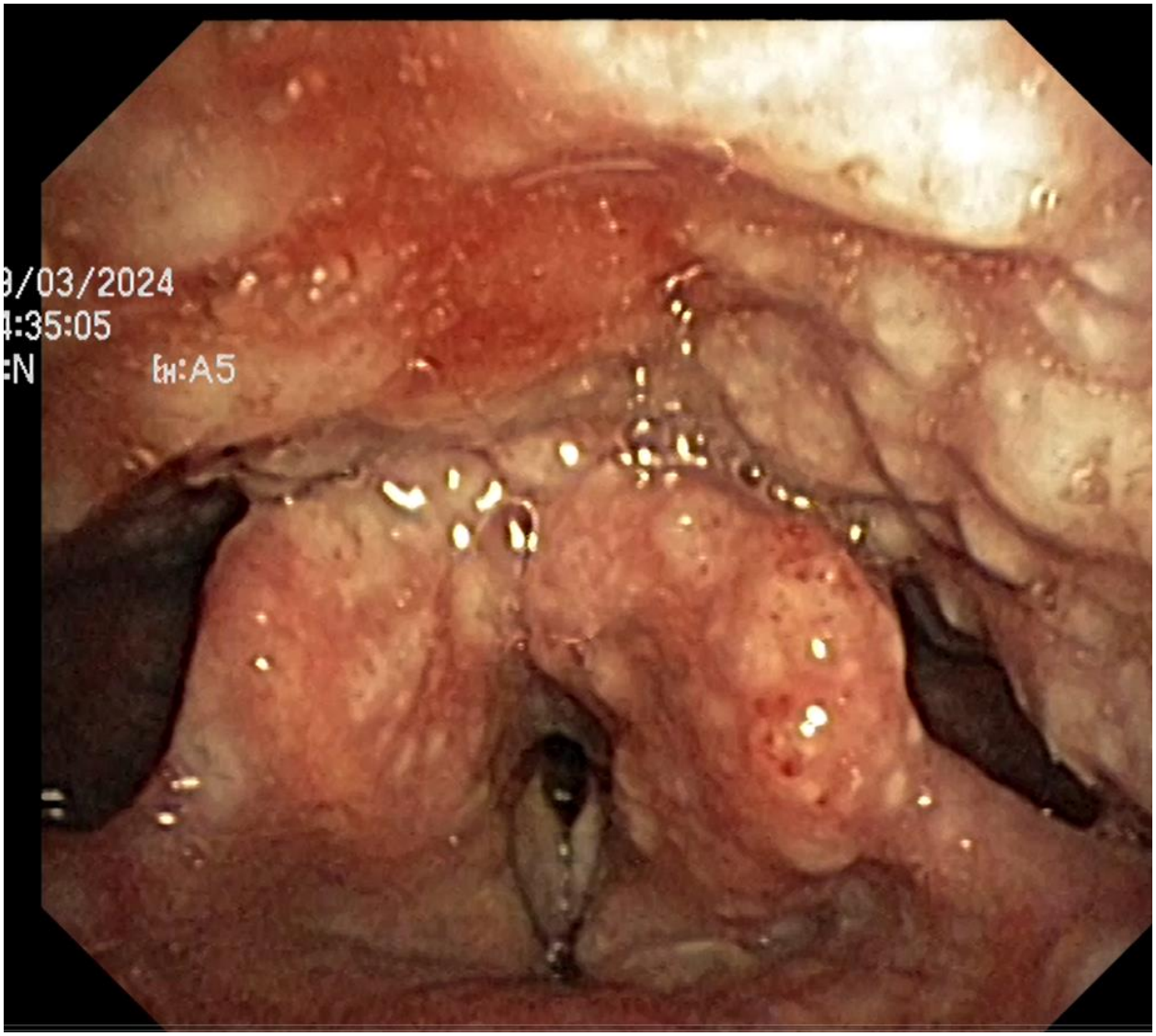

Figure 1: Cobblestone appearance of Larynx

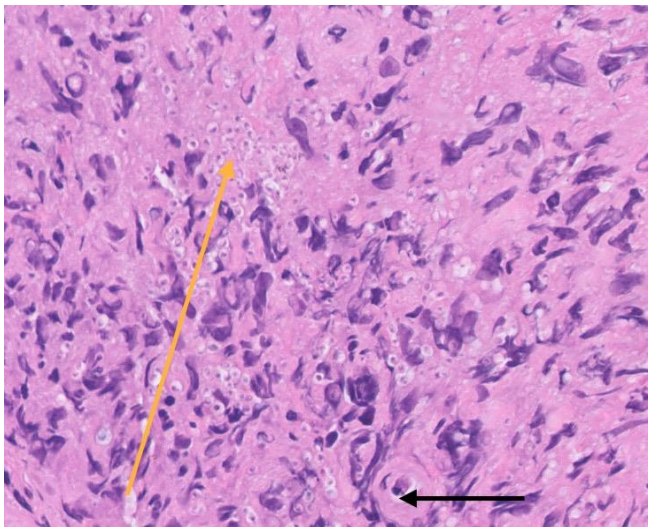

Figure 2: Histopathology indicating inflammation and Histoplasma

The above image indicates a fibrous tissue and mucinous glands with mixed inflammatory infiltrates (neutrophils and lymphocytes)

The yellow arrow indicates histiocytes with granulomas and Clusters of oval budding yeast cells with eccentric nuclei

Black arrow depicts perinuclear halo of histoplasma cell

Above image provides an impression of cobblestone appearance of hypopharynx and adjoining areas, pyriform sinuses, arytenoids, ventricles and vocal cords.

Following which patient was started on IV Liposomal Amphotericin B according to body weight for 7 days along with cover of itraconazole Patient was monitored with CRP and LFTs regularly.

On Further follow up patient on with oral itraconazole patient improved in febrile state with weight gain, relief in odynophagia and general well being.

Other relevant Initial Investigations were as follows:
HIV antibody IgM, HCV antibody IgM and HbsAg were negative HBA1C: 4.9%
Blood culture no growth Throat Swab: Gram positive cocci (non- pathogenic)
Sputum Culture No Growth only GPCs

BDG>523
Urine Histoplasma level 23.4 (positive if >1)

3. Discussion

The first recorded case of histoplasmosis in a human was identified by Samuel Darling in Panama.3 Histoplasmosis is caused by the fungus Histoplasma capsulatum, which has two variants that can infect humans: Histoplasma capsulatum var. capsulatum and Histoplasma capsulatum var. duboisii.4 The infection spreads through the inhalation of spores (microconidia) found in soil contaminated with bat or bird droppings.5 When these spores are inhaled, they convert to yeast forms at body temperature. The organism features heat shock protein 60 (HSP60), which binds to β2 integrins on macrophage surfaces.6 Once phagocytosed by macrophages, the release of tumor necrosis factor - alpha leads to inflammation in an immunocompetent host.7 In this case, prolonged inflammation likely resulted in a cobblestone appearance of the larynx.

Clinically, histoplasmosis manifests in three forms: (1) acute primary pulmonary, (2) chronic pulmonary, and (3) disseminated. Laryngeal involvement is typically associated with the disseminated form of histoplasmosis.

Disseminated variants of histoplasmosis/bronchoalveolar histoplasmosis are uncommon and typically occur in immunocompromised individuals and age extremes of under two years old and the elderly. In our case, advanced age was the only risk factor.8 Histoplasmosis is generally self - limiting in immunocompetent individuals and is unlikely to persist for six months. Symptoms such as fever, cough, joint pain, and weight loss are common in many chronic diseases, including lymphoma, tuberculosis, and sarcoidosis. The unusual feature in our case was multiple laryngeal growths, described as having a “cobblestone appearance,” which initially suggested a diagnosis of malignancy and herpes infection. Direct laryngoscopy in histoplasmosis can reveal a pearl - white appearance, granulomas, nodular ulcerative lesions, verrucous lesions, and plaque - like lesions on the laryngeal mucosa.[9]

In the demographic context of our patient, histoplasmosis more commonly presents with apical segment bullae, pleural thickening, and cavitations.[10] Our case exhibited nonspecific lung involvement with air trapping, multiple tiny lymph nodes, and paraseptal emphysematous changes, which were likely attributable to the patient's smoking history.

Beta - D - glucan levels, a component of the cell wall of various fungal pathogens including Histoplasma capsulatum, Candida species, Aspergillus species, and Pneumocystis species, are often elevated in fungal infections. Based on clinical findings, differential diagnoses should include carcinoma, tuberculosis, lymphoma, syphilis, papillomatosis, amyloidosis, and sarcoidosis.[9] However, a biopsy from the white plaque identified histoplasma, even though bronchoalveolar lavage did not yield the organism.

According to the European Organization for Research and Treatment of Cancer / Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) criteria, a proven diagnosis of invasive fungal infection requires confirmation by either histopathology or culture. A probable diagnosis relies on typical clinical presentation, predisposing conditions, and mycological evidence, such as antigenuria.1[1]Even though urinary antigen of histoplasma was positive, in atypical cases like this one, a biopsy, though invasive, is crucial for a definitive diagnosis.

In our patient, weightloss initially mislead to the diagnosis of malignancy and then tuberculosis. The erythematous cobblestone appearance of larynx with was indicating more towards a viral infection and he was treated for suspected herpes. After convincingly ruling these out, one should consider culturing the biopsy material for fungal identification such as histoplasma capsulatum. In such cases, a thorough clinical workup of the patient is necessary to rule out any underlying immunosuppressive condition such as HIV.

4. Conclusion

Histoplasmosis can be a diagnostic challenge, particularly in countries like India where tuberculosis is highly prevalent. Both diseases present with similar symptoms, including cough, fever, weight loss, joint pains, hepatosplenomegaly, and disseminated lymphadenopathy.[12] The rarity of histoplasmosis and its potential for atypical presentations underscore the need for clinicians to remain vigilant and consider this treatable disease as a differential diagnosis in relevant cases. This case adds to the existing literature on histoplasmosis, offering valuable insights into its diverse clinical manifestations and the diagnostic difficulties it presents.

Furthermore, we emphasize the importance of increased awareness about histoplasmosis among healthcare professionals. Recognizing histoplasmosis as a potential differential diagnosis, despite its rarity, is crucial for accurate diagnosis and effective treatment.

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