

CASE REPORT

Primary Laryngeal Histoplasmosis

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HOW TO CITE THIS ARTICLE:

Keshav Gupta. Primary Laryngeal Histoplasmosis. RFP J ENT Allied Sci 2025; 10(2): 43–48

ABSTRACT

Background: Histoplasma Capsulatum (HC) is a fungus known to infect the immunocompromised. It is present in bird droppings and soil. The fungus causes lung, eye and laryngeal infections in patients with poor immunity. Primary laryngeal histoplasmosis is a rare disease. Less than 100 cases have been recorded worldwide so far.

Methods: A 68-year-old male with an undiagnosed laryngeal mass came with stridor. He was managed with emergency tracheostomy and repeat histopathological evaluation. This was confirmed as a case of primary laryngeal histoplasmosis. He improved within a few weeks with antifungal therapy.

Discussion: The histopathological proof is necessary for its diagnosis. Once diagnosed, a few doses of the specific antifungal medicine do wonders. And that's where we want your attention.

Conclusion: A high degree of suspicion is required for its diagnosis. Treatment is quite simple. However, misdiagnosis and unnecessary interventions complicate its management.

KEYWORDS

• Primary Laryngeal • Histoplasmosis • Histoplasma Capsulatum

INTRODUCTION

Background: Histoplasma capsulatum (HC) is a saprophytic fungus known to cause infections in immunocompromised individuals. Pulmonary and ocular histoplasmosis have been extensively studied in HIV-positive patients, transplant recipients and diabetics.

Cases of laryngeal histoplasmosis (LP) are quite rare to encounter. Most of the cases of LP are called secondary laryngeal histoplasmosis, which occurs through the dissemination of fungus from the lungs to the larynx. However, there are still a few cases where HC involves the larynx alone. These

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➤ Received: 12-05-2025 ➤ Accepted: 02-06-2025



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cases are designated as primary laryngeal histoplasmosis. LP presents a granulomatous inflammation of the laryngeal lumen wall and the vocal cords. It may closely mimic tuberculosis and laryngeal malignancies. The suspicion of LP is still difficult in cases of primary laryngeal histoplasmosis. This may delay the diagnosis and the treatment.

Histoplasma Capsulatum

HC is a dimorphic fungus that exists as a mold and single-cell yeast. It grows as a mold in nature and a lab. It enters the human body through inhalation of microconidia, targets the host immune system, hampers cellular immunity, inhibits phagocytosis, and multiplies within the host alveoli in yeast form, triggering the granulomatous inflammation of the host tissues.

History

Dr Samuel Taylor Darling described *Histoplasma* in 1906. Histoplasmosis is also called Darling's disease for this reason. The other names are Ohio Valley Disease, Caver's Disease, Spelunker's Disease and Reticuloendotheliosis.

It was discovered in its yeast form and hence classified as a protozoan. Lima first identified it as a dimorphic fungus.¹

Epidemiology

HC is found throughout the world. In the United States, Histoplasmosis is the most prevalent endemic fungal infection, with an annual count of 50 million latent infections and 5 lakh new infections. It has the highest incidence in Ohio and Mississippi Valley in North America. The endemic region also includes parts of Northern Maryland, Southern Pennsylvania, Central New York and Texas. The lowest incidence is recorded in Antarctica, followed by Europe.

Histoplasma is divided into three taxonomic groups on a geographic and clinical basis.

Capsulatum-worldwide, *Duboisii*-Africa, *farcinosum*-non-human hosts, mainly horses.

On the genetic basis, there are eight clades. Kasuga's clade classification is more widely used nowadays.

Classification

Family-Ascomycetes

Morphology- Dimorphic. HC exists in mould form in the soil and yeast form in the host.

Natural Habitat-Soil in the natural habitat of HC where it is found in its fungal/ mould/ filamentous form with aerial hyphae. HC usually co-exists with 2 other fungi- *Blastomyces dermatitidis* and *Paracoccidioides brasiliensis*. This is the asexual form of HC which closely resembles *B. dermatitidis* in morphology. Hyphae of HC produce a globose macroconidia of size 8-15 micro-meters. These are seen as spherical bodies with finger like projections radiating from the cell wall like corona. HC also produces smaller ovoid microconidia of size 2-4 micro-meters. These spores exist as aerosols and are dispersed in air usually as bat droppings. Microconidia are the infectious forms present in soil and bird droppings. They enter the animal host body through inhalation.

Host-Warm-blooded animals serve as the host. In the host body, the fungus usually reaches the lungs where it transforms into its sexual/budding oval yeast form. These are small-sized yeasts of approximately 2-4 micro-meters. The cell walls of these yeasts express heat shock protein 60. This protein antigen binds to beta 2 integrins on the surface of macrophages. In response to this ligand-to-ligand binding, macrophages get activated and secrete tumour necrosis factor alpha which enhances recruitment of other macrophages. Within macrophages, fungal yeast further matures into blastospores. In histopathological sections of regional lymph nodes, it is seen in clusters within phagocytic cells like histiocytes and monocytes. From here, HC travels in the blood to the rest of the body.²

Clinical picture

Clinically, Histoplasmosis is divided into three forms

- 1) Acute Histoplasmosis
- 2) Disseminated Histoplasmosis
- 3) Chronic Histoplasmosis

1) Acute Histoplasmosis

Most of the patients are free of any symptoms. Presenting symptoms are flu-like symptoms such as high-grade fever, headache, non-productive cough, weakness, malaise and chest pain of less than 21 days duration.

Additionally, it may present with symptoms like joint pain, red-coloured multiple rounded swellings of the skin, and red-coloured multiple swellings of different shapes over the skin. Granulomas are not seen here. However, skin antigen tests for Histoplasma are positive. In blood, antibodies against HC are detected in one-fourth to three-fourth of cases. Urine and sputum antigens may be detected in less than one-fourth of cases. X-ray involvement is seen in 30-60% of cases with patchy diffuse pneumonitis with hilar lymphadenopathy.

Acute pericarditis is the feared sequel seen in 6 per cent of cases.

Chronic Histoplasmosis

Chronic histoplasmosis is characterised by caseous necrosis, granuloma formation and the presence of giant cells. Symptomatically, these cases closely mimic tuberculosis. On biopsy and histopathology, they give a tuberculosis like picture again. If a pathologist suspects a fungal infection, Methamine Silver Stain may confirm the diagnosis of LP.

Disseminated Histoplasmosis

It is characterised by multiple organ dysfunction (MOD) and is hence fatal.³

Other presentations of histoplasmosis

Presumed Ocular Histoplasmosis Syndrome (POHS)-In the orbit, Histoplasma may present with chorioretinitis, macular degeneration and loss of vision.

Laryngeal Histoplasmosis - LP is a rare disease entity. It is a disease of immunocompromised. Less than 100 cases of primary LP are documented in the literature.⁴

Diagnosis

Histoplasma urinary antigen - Galactomannan antigen may be detected in body fluids. In disseminated form, urinary antigen has a sensitivity of nearly 97%. However, in acute form, sensitivity ranges from 20-81%.

Serological testing - Immunodiffusion and complement fixation tests may be done. However, these have high cross-reactivity with other disseminated fungal infections.²

Histopathological analysis - Methamine silver stain is the stain of choice. Silver stains are good for intracellular small yeasts clustered and devoid of a capsule, seen well under a dark field microscope.

However, HC may also be detected by other stains such as:

Wright-Giemsa stain: HC peripheral spores may be seen as a halo-like circle.

PAS: Ovoid yeast may be stained within a macrophage.

H&E: It usually fails to detect HC except when large numbers of yeast are isolated in a sample.

Mucicarmine: It may differentiate HC from cryptococcus.

Fontana-Masson: It detects cryptococcus but not the HC.

Giemsa: It is capable of staining HC if the yield is good.

Calcuflour white: It stains chitin of the fungal cell wall and hence may detect fungus. But it fails to differentiate HC from other similar fungi.

Histological picture is morphologically similar to various other fungal yeast forms like *Candida glabrata* and *Sporothrix schenckii*.

Fungal culture: Fungal culture is the gold standard for confirmation of HC. Various culture medium may be used to isolate HC from clinical samples. These include Brain Heart Infusion (BHI), Ham's F-12 Nutrient Mixture, Roswell Park Memorial Institute (RPMI), Potato Dextrose Agar (PDA), Histoplasma-macrophage medium (HMM), Modified 3M medium.

Gene assays: These methods employ Polymerase Chain Reaction (PCR) for detection of HC. These include AccuProbe (Gen-Probe, Inc., San Diego, Calif.), exoantigen testing, and temperature-induced mycelium-to-yeast conversion.

Real-time PCR assay is also being used for the diagnosis of HC.⁵

2. Aim

The diagnosis and management of Laryngeal Histoplasmosis (LP).

3. Objectives

- I. Understanding the epidemiology, life cycle and the clinical picture of the involved micro-organism.
- II. Forming the differentials in a suspected case.
- III. Diagnosis of LP.

IV Treatment of LP.

Case Presentation

Here we present an interesting case of primary LP a 68-year-old male came in the Emergency Department of our Tertiary Care Hospital due to choking of breath. The patient had noisy breathing, and he was gasping for breath.

An urgent Laryngology call was sent. The Laryngologist decided to perform an emergency tracheostomy. The patient was admitted, consent was obtained, and the tracheostomy was performed. The breathing difficulty, noisy breathing, and gasping were immediately relieved. The patient became comfortable, and oxygen saturation levels were maintained.

Patient complaints

The patient had hoarseness of voice for the last 11 months. He had lost almost 12 kilograms in 11 months. He had difficulty in swallowing for the last 5 months. He started having breathing difficulty for the previous 3 months, which was associated with excessive sputum production. The sputum was occasionally blood-stained. The noisy breathing and the fight for breath appeared for the last 3 days. It worsened rapidly in the previous 3 days.

The history

The patient is a farmer by occupation. There was no neck swelling. There was no pain in the neck during the neck movements. The patient had difficulty in swallowing but there was no pain during swallowing.

The patient is a known diabetic for the last 10 years. He has been taking anti-diabetics for 10 years. There is no history of travel to endemic areas of common infective chronic laryngeal diseases. There is no history of endotracheal intubation. There is no history of Teflon exposure.

For the complaints of hoarseness of voice and difficulty in swallowing, he has undergone direct laryngoscopy and biopsy multiple times. Records show 3 laryngeal biopsy reports.

The first report is atypia with granuloma formation. Malignancy could not be confirmed. A repeat biopsy was advised.

The second report shows epithelioid cells, macrophages and Langerhans giant cells. Tuberculosis was suspected, but Ziehl-Neelsen staining was negative. Erythrocyte

Sedimentation Rate (ESR) was high. Mantoux was 19 cm. Exposure to mycobacterium could not be ruled out. The Patient also completed 6 months of ATT, but it did not afford any relief.

Another biopsy report shows a non-malignant, non-tubercular granuloma. Further workup was advised to achieve a conclusive diagnosis.

The routine investigations

All routine investigations were sent immediately after the tracheostomy. Here, significant findings were high blood sugar levels and anaemia of chronic illness. Endoscopy of the larynx showed a pinkish-white polypoidal fibrous mass completely blocking the supraglottic lumen. It was a firm mass and did not bleed on touching and suctioning. The endoscope could not be negotiated further. Contrast CT of the neck reveals a soft tissue density which did not take the contrast well. It had regular outlines and central necrosis. It was completely obstructing the supraglottis and the glottis.

The initial management

The endocrinologist puts the patient on baseline and mealtime insulin regimes with regular blood sugar monitoring. Blood sugars get regularised well. Direct laryngoscopy and biopsy were done in general anaesthesia.

Pathologists and microbiologists search for various clues presenting with granulomas such as intubation granuloma, Teflon granuloma, chronic granulomatous disease, sarcoidosis, tuberculosis, actinomyces, dimorphic fungi, syphilis, and granulomatosis with polyangiitis.

The diagnosis

Blood tests for autoimmune diseases were done. Rheumatoid Arthritis factor, anti-cyclic citrullinated peptide antibodies, anti-nuclear antibodies, cytoplasmic anti-neutrophil cytoplasmic antibodies, and perinuclear anti-neutrophil cytoplasmic antibodies were negative. ESR was high. The Mantoux test was positive. Sputum tests showed the presence of gram-positive cocci. Sputum acid-fast bacilli and sputum culture were negative for isolates. Contrast CT chest was normal. This ruled out most auto-immune conditions, tuberculosis, and sarcoidosis. Galactomannan was not detected in urine. So, Pulmonary histoplasmosis was also ruled out.

Hematoxylin and Eosin staining of the granuloma at the level of vocal cords showed stratified squamous epithelium with abundant mixed inflammatory infiltrate comprising of histiocytes, plasma cells, polymorphonuclear cells, and multinucleated giant cells without necrosis or vasculitis, mixed infiltrate, and multinucleated giant cells. Primary LP was a differential now. Accuprobe detected the presence of HC DNA using polymerase chain reaction (PCR).

Treatment

The patient was given IV conventional Amphotericin B in a dose of 0.7 mg/kg/day for 5 days. It offered great symptomatic relief to the patient. Also, it cleared granulomas to a great extent as evident in the Endoscopy Larynx. The patient was discharged on oral anti-fungal Itraconazole 200 mg twice a day for a period of 15 days. The patient was decannulated after 14 days and the tracheostomy was closed. He responded well at the time of decannulation. Follow-up period was uneventful.

DISCUSSION

Epidemiology

Involvement of the larynx is quite rare in histoplasmosis. 66% of chronic pulmonary histoplasmosis, 31% of acute pulmonary histoplasmosis and only 19% of disseminated histoplasmosis present with involvement of the larynx. Histoplasmosis with isolated laryngeal involvement is uncommon.⁶

Risk factors

The immunocompromised state is the major risk factor which favours laryngeal involvement. Hence, patients with AIDS, diabetes mellitus and those on immunosuppressants constitute the majority of patients of laryngeal histoplasmosis. Other risk factors include travel to endemic areas like Ohio Valley, smoking, tuberculosis and other endocrine disorders. This may be due to exposure to bats in this occupational group. A study has also reported exposure to pigeons as a risk factor.

Symptoms

Change of voice, difficulty in swallowing, painful swallowing, difficulty in breathing, sore throat, lethargy and weight loss are usual presenting symptoms.

Signs

Direct laryngoscopy may show the presence of whitish raised lesions and ulcerative or raised pinkish-white lesions of the laryngeal mucosa. Arye-epiglottic folds and false vocal cords are the common sites involved in Histoplasmosis.

Differential diagnosis

Laryngeal tuberculosis, laryngeal carcinoma, syphilis, papillomatosis, amyloidosis and sarcoidosis.⁷

Diagnosis

Direct laryngoscopy

Direct Laryngoscopy shows whitish nodules on laryngeal mucosa.

Biopsy

Biopsy is taken during Direct Laryngoscopy itself. The sample is sent for histopathology, fungal stains, fungal culture, nucleic acid amplification and gene assays.

Serology

Immunodiffusion and complement fixation are done to identify antibodies against fungal antigens but these have high cross-reactivity with other fungi.

Chest Radiography

This may show lung involvement. However, only 30-60 percent of cases of Pulmonary Histoplasmosis present with patchy diffuse pneumonitis and hilar lymphadenopathy. Cases of primary laryngeal histoplasmosis do not involve the lungs.

Bone marrow biopsy

It may show Histoplasma yeast in bone marrow aspirates.

Urine antigen detection

Urine Galactomannan may be positive in disseminated disease and a few acute cases.

Treatment

Conventional Intravenous Amphotericin B is administered in doses of 0.7-1 mg/kg/day until renal functions are maintained and patient shows symptomatic improvement.

Oral Itraconazole is given in the follow-up period-200 mg twice daily for 7-14 days.

Oral Fluconazole 200-400 mg once a day and Oral Ketoconazole 200-400 mg once a day are other alternatives for oral antifungals.⁸

Oral antifungals are given with meals to enhance their absorption.

CONCLUSION

It is rare for Otorhinolaryngologists to encounter diseases caused by *Histoplasma Capsulatum*, as the latter is more familiar to pulmonologists. Primary Laryngeal Histoplasmosis is a rare disease, and it is more common to present with laryngeal symptoms. There may not be any chest symptoms. It may not be a differential for the pathologist performing the histopathological evaluation. Once the diagnosis is missed, the unnecessary interventions will increase the financial burden and the patient's suffering. So, it is our part to be vigilant in the light of knowledge from the past.

Funding: None

Conflict of interest: As an author, I declare that there are no conflicts of interest.

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