

Systematic Review

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Laryngeal Histoplasmosis Overview

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ABSTRACT

Objective: The objective of this study was to present a review article about laryngeal histoplasmosis.

Data Sources: Published English-language literatures in PubMed and Google scholar.

Review Methods: PubMed and Google scholar were systematically searched using search terms: laryngeal and histoplasmosis.

Study Selection: We included studies about laryngeal histoplasmosis.

Results: Forty studies were included in this study. The results showed that most patients are male over 40 years old, and most cases were reported from endemic areas. Hoarseness dysphagia and general symptoms were the common symptoms of laryngeal histoplasmosis. Laryngeal mass was the most common finding during laryngeal exam. Itracanzole was the most common medication used to treat this disease. Laryngeal histoplasmosis had a good prognosis, but some cases may need long-term treatment up to 1 year.

Conclusion: Histoplasmosis is a rare fungal granulomatous disease that may mimic laryngeal malignancy or tuberculosis.

INTRODUCTION

Primary laryngeal histoplasmosis is a rare disease. Less than 100 cases of laryngeal histoplasmosis have been reported in English literatures since it was first described in 1940 by Brown and colleagues. The clinical symptoms and signs may mimic tuberculosis or laryngeal malignancy.¹

MATERIAL AND METHODS

Literature review was conducted using PubMed (MEDLINE) and Google Scholar for English articles. The following keywords were used: laryngeal and histoplasmosis.

INCLUSION CRITERIA

All laryngeal histoplasmosis articles published after 1984 were included in the study.

RESULTS

Forty studies about laryngeal histoplasmosis were available in PubMed (MEDLINE) and Google scholar in English literature (Table 1).

Demographs

There were 51 patients of age ranged from 7 to 73 with majority of the patients over 40 years old. There were 43 males and 8 females in the study Chart 1 and 2.

Symptoms

Forty-two patients had hoarseness (82%), 33 patients had difficulty swallowing (64%) (odynophagia, dysphagia, sore throat or globus), 9 patients had difficulty in breathing (17%) (stridor or

Articles	Sex	Age	History	Clinical exam	Associated diseases	Treatment	Risk factor
Subramaniam et al ¹	M	52	Hoarseness, Cough, Weight loss, Fatigue, Sore throat	Irregular left vocal cord mass extending to the anterior commissure	None	Amphotericin then ketoconazole for 1 month	DM Smoker
Ghosh et al ²	M	50	Dysphonia, Dysphagia, General, Symptom	General laryngeal inflammation, Right vocal cord ulcerated nodules	Disseminated	Amphotericin then itraconazole for 8 weeks	Smoker
Robayo et al ³	M	7	Diarrhea, Sore throat, Fever, Headache, Stridor	Granulomatous supraglottic mucosa which deforms the epiglottis and partially obstructs the airway	None	Amphotericin then changed to Itraconazole for 12 months	Immunosuppressant medication
Pervez Katoch et al ⁴	M	20	Dysphagia	Friable growth in the cricoid region subglottic	Pharyngeal	Fluconazole with complete remission	Endemic
John et al ⁵	M	53	Fever, Cough, Weakness, Hoarseness	Multiple ulcers on the laryngeal surface of the epiglottis and the vocal cords	Pulmonary Adrenal gland	Voriconazole treatment for 1 year	Smoker Endemic
Carter et al ⁶	F	73	Weight loss, Hoarseness, Dysphagia, Stridor	Multiple exophytic ulcer nodular lesions across the laryngeal epiglottis and vocal folds	None	Gastrostomy, Tracheostomy, Itraconazole for 2 months	Seropositive RA
Giménez et al ⁷	M	55	Fever	Erythematous keratinizing mass In both vocal cord	None	itraconazole	Smoker Cirrhosis
O'Hara et al ⁸	M	78	Weightloss, Dysphagia, Night sweats	The superior right free edge of the epiglottis showed an irregular mass with focal ulceration	Pulmonary	Itraconazole for 9 months	Travel
Bist et al ⁹	M	62	Mouth swelling, Hoarseness	Multiple exophytic nodular lesions across the oropharynx, endolarynx and hypopharynx	Oral lesions Pharyngeal	Amphotericin then oral itraconazole for 3 weeks	Endemic Smoker
Teoh et al ¹⁰	M	70	Weightloss, Hoarseness, Dysphagia	Showed that the mucosae at the posterior one-third of both vocal folds were irregular	Pulmonary	Amphotericin then oral itraconazole for 5 months	DM Smoker
Masoud et al ¹¹	M	60	Hoarseness	Ulcerative growth in the left vocal cord	None	Amphotericin then oral itraconazole for 12 weeks	TB Endemic
Solari et al ¹²	M	48	Weightloss, Hoarseness, Dysphagia, Stridor, Dyspnea Cough, Weightloss,	Epiglottitis, enlargement and mobile vocal cords with granulomatous lesions deforming and infiltrating the glottis and subglottis	Disseminated histoplasmosis	Amphotericin then oral itraconazole with clinical improvement in 1 month	AIDS
Ahumadau et al ¹³	M	70	Dyspnea, Hoarseness, Dysphagia, Odynophagia, Fatigue, Anorexia, Weight loss	Vegetative lesion on the lingual surface of the epiglottis	Pharyngeal	amphotericin B then itraconazole for 12 months	Smoking Immunosuppressant drugs Travel
Smeets et al ¹⁴	M	58	Weightloss, Hoarseness, Dysphagia	The vocal process was thickened. granulation tissue on right ventricular area	None	Itraconazole for 4 week	Travel
Bouldouyre et al ¹⁵	M	65	Hoarseness	Non-specific inflammatory changes in right vocal cord, edema and hypertrophic vocal cord	Pulmonary	Itraconazole for 6 months	Travel TB smoking

Mackowiak et al ¹⁶	M	55	Weight loss Hoarseness Dysphagia	Yellowish, edematous mucosal changes in the inter-arytenoid region involving the posterior part of the vocal cords	Disseminated histoplasmosis	itraconazole for 2 months	Addison's disease DM
Fechner et al ¹⁷	M	44	Sore throat Hoarseness, Dysphagia	The vocal cords were swollen and covered with a thin white exudate.	None	Amphotericin	-
Donegan et al ¹⁸	M	69	Weight loss, Hoarseness, Dysphagia	Left large epiglottic and glottis mass	None	Amphotericin for 6 weeks	-
Sonkhya et al ¹⁹	8 M 2 F	2 (30) 4 (40) 4 (50)	Weightloss, Hoarseness, Dysphagia	Endophytic growth in 6 cases, exophytic growth in 2 cases and ulcerative lesion in 2 cases. False cord and aryepiglottic fold was the common site of involvement (6 cases). Epiglottis involvement was seen in 3 cases and only 1 case was with postcricoid and subglottic lesion.	One case pharyngeal	There were no signs of pulmonary or systemic involvement Amphotericin in 3 cases. Itraconazole in 7 cases. for 6 months	10 patients from endemic area
Cairolì et al ²⁰	F	35	Hoarseness and sore throat	Whitish nodular lesions in the arytenoid cartilage and vocal cords	Paranasalsinus pulmonary	amphotericin followed by itraconazole for 8 months.	SLE
Larbcharoensub et al ²¹	F	39	Hoarseness for eleven months	Glottic mass	Pharyngeal oral cavity	Amphotericin B dead	SLE
Gulati, et al ²²	M	47	Hoarseness Painful ulcer tongue	Exophytic lesion (epiglottis and glottis)	Oral lesion	Itraconazole for 6 weeks	Endemic
	M	45	Hoarseness	Exophytic lesion was noted on the anterior aspect of both vocal cords	Oral cavity	Itraconazole for 6 week	Endemic
Troncoso et al ²³	M	30	Dysphagia, Dyspnea, Stridor, Fever	Indurated Glottis, supraglottic And Subglottic mass	Heptosplenomegaly	Amphotericin followed by Itraconazole for 12 months	AIDS
Le et al ²⁴	M	58	Hoarseness, Dysphagia, Weightloss	Ulcerated mass that involved the left pyriform sinus and supraglottic space	Pharyngeal	Amphotericin then itraconazole	Smoking Diabetes
Sane et al ²⁵	M	55	Weight loss, Anorexia, Fever	Vocal cord paresis and edema with small irregular nodule on the right vocal cord	Disseminated	Amphotericin B for 1 year	Endemic
Larsen et al ²⁶	M	63	SOB Sore throat Fever weight loss stridor Hoarseness	Ulcerative mass supraglottic edema glottic	Pulmonary	Tracheostomy gastrostomy tube amphotericin patients was decanulated	Smoking Rheumatoid arthritis
Sataloff et al ²⁷	F	44	Hoarseness	Laryngitis. non-specific changes in all larynx	None	Treatment with oral ketoconazole was instituted	-
Ragah et al ²⁸	M	55	Hoarseness, Dysphagia, General symptom	Supraglottic glottis ulcer	Oral cavity Pharyngeal	Treatment with amphotericin B resulted in a rapid recovery	Endemic TB
Klein et al ²⁹	M	37	Hoarseness, Vague throat pain, Weightloss, SOB stridor	Destructive supraglottic lesion. The lesion was exophytic, extending down to the true vocal folds	Oral cavity	Tracheotomy, Itraconazole for 13 week	Smoking
Fernández Liesa et al ³⁰	M	-	Hoarseness	Edema, erythema and leukoplakia of the right vocal cord	None	Itraconazole treatment was successful	Smoker Travel
Yen et al ³¹	F	46	Dysphonia	Epiglottic mass	Disseminated	Amphotericin then Itraconazole death	-

Coiffier et al ³²	M	10	General symptoms	Ulcerated pharyngo-laryngeal lesions	Disseminated	Amphotericin B then oral itraconazole	Endemic
Postma et al ³³	M	54	SOB, Globus, Hoarsness	Verrcous mass anterior third left vocal cord	Esophagus Pharyngeal	Itraconazole 1 year	-
Alcurra et al ³⁴	M	61	Oral ulcer Weightloss Fever	Multiple laryngeal, glottis ulcer	Oral cavity Esophagus	Itraconazole 2 months	Smoker
Samuel et al ³⁵	M	60	Sore throat	Supraglottic ulcer	Pharyngeal Pulmonary	Miconazole for 1 month oral cavity	-
Rajagobal et al ³⁶	M	72	Dysphagia, Dysphonia, Weightloss	Supraglottic, glottic and subglottic mass	Pharyngeal	Intubated, 1 year itraconazole	Smoker
Zain et al ³⁷	M	63	Hoarseness, Dysphagia, General, Symptoms	Glottis and Supraglottic mass	Oral cavity	Amphotericin	Addison Disease
Wolf et al ³⁸	M	60	Hoarseness, Dyspnea	Glottic mass	Pulmonary	Amphotericin	-
César Garcia de Alencar et al ³⁹	F	25	Fever, Nausea, Weightloss, Hoarseness	Ulcerated mass in the glottis space	None	Amphotericin B patient died of cardiovascular complications	Larynx tuberculosis
Pochini Sobrinho et al ⁴⁰	M	44	Dysphonia, Dysphagia, Sore throat, Weightloss	White necrotic lesion spread throughout his larynx, exophytic lesion in the upper right border of the epiglottis	None	Amphotericin B then fluconazole	AIDS

Table 1: Articles included in the study.

Male Female

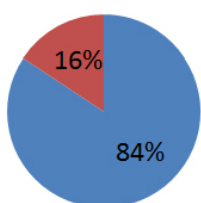


Chart 1: M/F rate.

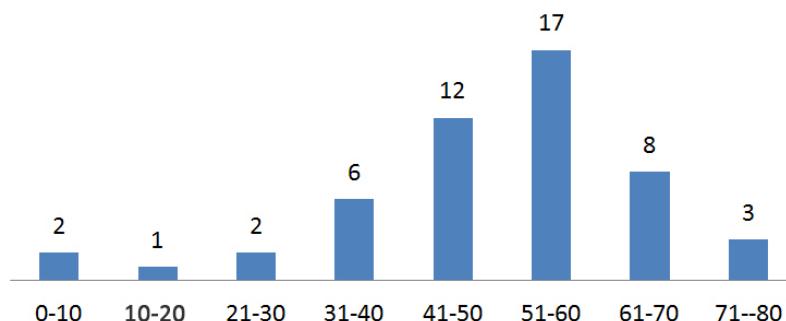


Chart 2: Age distribution.

dyspnea) and 36 patients had general symptoms (70%) (fever, night sweat and weight loss) Chart 3A.

Laryngeal Exam

Seventeen patients had laryngeal histoplasmosis in glottic area, 17 patients had laryngeal histoplasmosis in supraglottic area, and 2 patients had laryngeal histoplasmosis in subglottic area, while the other 15 patients had laryngeal histoplasmosis in multiple laryngeal areas Chart 3B.

Clinical laryngeal exam revealed the presence of a mass in 22 patients, ulcerated mass in 8 patients, nodule in 4 patients, granuloma in 4 patients, ulcer in 7 patients, ulcerated mass in 8 patients and other forms (keratosis, thickness and irregularity of vocal cord, leukoplakia and inflammation) in 6 patients (Chart 4).

RISK FACTORS

Twenty patients were living in endemic area, 6 patients had history of travelling to endemic area, 12 patients were smokers, 3 patients had AIDS, 5 patients had a history of Tuberculosis, 3 patients had endocrinology diseases (DM, Addison disease), 4 patients had rheumatology diseases, 2 patients were on immunosuppressant medications and one patient had hepatic cirrhosis (Table 2).

Associated Another Area Involvement

Eleven patients had histoplasmosis in pharynx (23%), 8 patients had histoplasmosis in pulmonary tract, 7 patients had histoplasmosis in oral cavity (17%), 4 patients had histoplasmosis in other organs (9%) (esophagus, nose, liver) and, 6 patients had

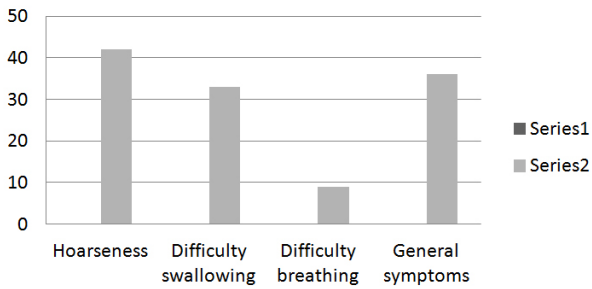


Chart 3A: Histoplasmosis laryngeal symptoms.

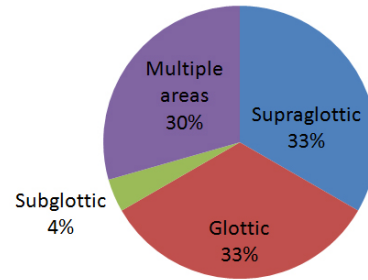


Chart 3B: Histoplasmosis laryngeal locations.

disseminated histoplasmosis disease (13%) Chart 5.

Treatment

Nine patients received only IV amphotericin, 15 patients received IV amphotericin followed by itraconazole, and 22 patients received only azole medications Table 3.

Only 36 articles reported treatment period that vary from 1 month to 12 months, the treatment should be continued until the symptoms improve and the physical exam did not re-

veal the presence of laryngeal histoplasmosis (Chart 6).

Prognosis

3 patients were dead, while the other 48 patients improved, no recurrence were reported.

DISCUSSION

Histoplasmosis is a worldwide distribution granulomatous disease that is caused *Histoplasma capsulatum* which is a dimor-

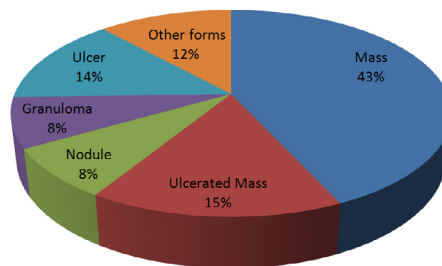


Chart 4: Clinical exam presentation.

Endemic	Travel	Smoking	AIDS	TB	Endocrinology diseases	Rheumatology diseases	Medications	Cirrhosis
20	5	12	3	5	3	4	2	1

Some patients had multiple risk factors

Table 2: Number of patients having risk factors.

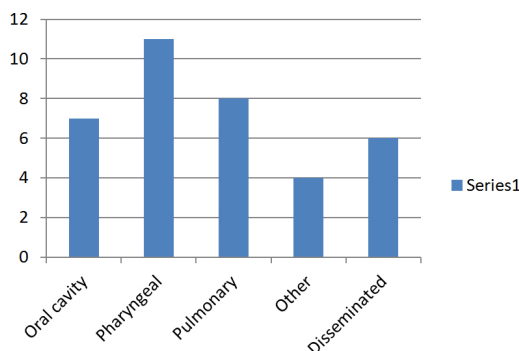


Chart 5: Histoplasmosis associated with other areas.

Amphotericin	Azole medications	Amphotericin+itraconazole	Dead
9/51	24/51	15/51	3/51

3 patients had a temporary tracheostomy, 2 patients had temporary gastrostomy tube. 3 patients were dead

Table 3: Treatment modalities.

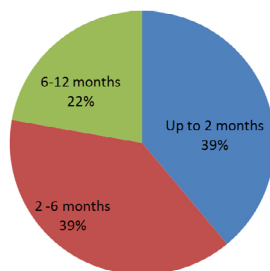


Chart 6: Treatment period.

phic intracellular fungus.¹

The fungus usually exists in the mycelial phase at room temperature. However once the spores are inhaled, the spores transform to the yeast phase which is responsible for the human infection and which leads to pulmonary infection that may be complicated by haematogenous spread to other organs. Primary pulmonary histoplasmosis is usually asymptomatic but chronic pulmonary histoplasmosis is clinically similar to pulmonary tuberculosis.¹

The clinical scenario of ranges from a mild infection localized to the gastrointestinal tract, skin, larynx or other extra pulmonary sites to severe disseminated multisystem disease that involve the bone marrow, liver, spleen and lungs.

The most common clinical presentation of laryngeal histoplasmosis is secondary to chronic disseminated histoplasmosis as a result of haematogenous spread. There are a few reports of sporadic primary laryngeal histoplasmosis cases.

The degree of infection is determined by the size of the inoculum and prior immune status of the host. It is often associated with general symptoms such low grade fever, weight loss and fatigue. Other symptoms of laryngeal histoplasmosis may include hoarseness, dysphagia, sore throat, cough and occasionally stridor.¹

It is known that macrophages are the major targets of *H. capsulatum*. The fungal surface heat shock protein 60 (hsp60) binds to alpha 2 integrins on macrophages surface. So macrophages are induced by this binding to secrete Tumor Necrosis Factor (TNF) which stimulates and recruits other macrophages to kill the histoplasma.⁴¹

Laryngeal involvement is usually observed in disseminated histoplasmosis. Goodwin et al⁴² observed that 66% of patients with chronic pulmonary histoplasmosis and 31% with sub-

acute pulmonary histoplasmosis developed laryngeal disease. Involvement of the larynx was observed in only 19% of patients with acute disseminated histoplasmosis.⁴³

Chest radiography, sputum and urine cultures and bone marrow aspiration biopsy should be done in any laryngeal histoplasmosis case to look for disseminated disease.³⁹

Clinical presentations of the laryngeal histoplasmosis include granulomas, ulceration, nodular ulcerative lesions, and verrucous and plaque-like lesions.³⁹

Histoplasmosis affects 4% to 5% of patients with AIDS, on whom it generally causes acute or subacute clinical disease with disseminated illness. These presentations of the infection takes place in patients with CD4 T-cell counts lower than 200 cells/ μ l.³⁹

In the biopsy, it can be observed with hematoxylin-eosin granulomatous tissue, necrosis, and infiltration of giant cells, lymphocytes, plasma cells and many macrophages. By using special stains such as coloring Gomorimethenamine-silver, coloring periodic acid-schiff (PAS) staining or Gridley technique⁴⁰ to identify macrophages and these cell containing hyphae.

Macroscopically, histoplasmosis should be differentiated from syphilis, tuberculosis, carcinoma, mid-line granuloma, mucormycosis, lymphoma, and other granulomatous diseases.⁴⁰

Anti-histoplasma serological tests using complement fixation and immune-diffusion methods are positive in about 90% of immune-competent patients and 70% of immune-compromised patients. Antibody tests may be false negative in immune-compromised patients. The antibodies usually start to appear during the second month after exposure in acute phase, and they may remain positive for several years.⁴⁴

The treatment of laryngeal histoplasmosis is similar to

the other forms of the disease. Although it is usually benign, histoplasmosis can be disseminated and cause severe fatal disease. Treatment of choice is IV amphotericin B, 0.3-0.6 mg/kg of body weight per day, with a maximum dose of 2-4 mg. Mucosal laryngeal lesions respond within 6-8 weeks, recurrences may occur. Itraconazole is an alternative treatment for laryngeal histoplasmosis. It is given orally 100 mg daily until clinical cures is achieved and then change the treatment regimen to 50 mg/day for 6 more months.⁴⁴

CONCLUSION

Laryngeal histoplasmosis is more common in male, most patients are over 40 year old and native or have a history of traveling to endemic area. It is usually associated with pharyngeal or pulmonary involvement. There is no specific laryngeal location for it, hoarseness is the most common symptom and mass (non-ulcerated or ulcerated) is the most common clinical finding during laryngeal exam. Treatment is by amphotericin, itraconazole or both. Some patients may need tracheostomy to relieve acute respiratory obstruction or gastrostomy tube for feeding. Prognosis is usually good with a few fatal cases in disseminated disease.

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CONFLICTS OF INTEREST

The author declare that he have no conflicts of interest.

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