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).

Demographics

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...
<table>
<thead>
<tr>
<th>articles</th>
<th>sex</th>
<th>age</th>
<th>history</th>
<th>clinical exam</th>
<th>associated diseases</th>
<th>treatment</th>
<th>risk factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subramaniam et al</td>
<td>M</td>
<td>52</td>
<td>Hoarseness, Cough, Weight loss, Fatigue, Sore throat</td>
<td>Irregular left vocal cord mass extending to the anterior commissure</td>
<td>None</td>
<td>Amphotericin then ketoconazole for 1 month</td>
<td>DM Smoker</td>
</tr>
<tr>
<td>Ghosh et al</td>
<td>M</td>
<td>50</td>
<td>Dysphonia, Dysphagia, General, Symptom</td>
<td>General laryngeal inflammation, Right vocal cord ulcerated nodules</td>
<td>Disseminated</td>
<td>Amphotericin then itraconazole for 8 weeks</td>
<td>Smoker</td>
</tr>
<tr>
<td>Robayo et al</td>
<td>M</td>
<td>7</td>
<td>Diarrhea, Sore throat, Fever, Headache, Stridor</td>
<td>Granulomatous supraglottic mucosa which deforms the epiglottis and partially obstructs the airway</td>
<td>None</td>
<td>Amphotericin then changed to itraconazole for 12 months</td>
<td>Immunosuppressant medication</td>
</tr>
<tr>
<td>Pervez Katoch et al</td>
<td>M</td>
<td>20</td>
<td>Dysphagia</td>
<td>Fibrinous growth in the cricoid region subglottic</td>
<td>Pharyngeal</td>
<td>Fluconazole with complete remission</td>
<td>Endemic</td>
</tr>
<tr>
<td>John et al</td>
<td>M</td>
<td>53</td>
<td>Fever, Cough, Weakness, Hoarseness</td>
<td>Multiple ulcers on the laryngeal surface of the epiglottis and the vocal cords</td>
<td>Pulmonary</td>
<td>Adrenal gland treatment for 1 year</td>
<td>Endemic</td>
</tr>
<tr>
<td>Carter et al</td>
<td>F</td>
<td>73</td>
<td>Weight loss, Hoarseness, Dysphagia, Stridor</td>
<td>Multiple exophytic ulcer nodular lesions across the laryngeal epiglottis and vocal folds</td>
<td>None</td>
<td>Gastrostomy, Tracheostomy, Itraconazole for 2 months</td>
<td>Seropositive RA</td>
</tr>
<tr>
<td>Giménez et al</td>
<td>M</td>
<td>55</td>
<td>Fever</td>
<td>Erythematous keratinizing mass in both vocal cord</td>
<td>None</td>
<td>Itraconazole</td>
<td>Smoker Cirrhosis</td>
</tr>
<tr>
<td>O'Hara et al</td>
<td>M</td>
<td>78</td>
<td>Weight loss, Dysphagia, Night sweats</td>
<td>The superior right free edge of the epiglottis showed an irregular mass with focal ulceration</td>
<td>Pulmonary</td>
<td>Itraconazole for 9 months</td>
<td>Travel</td>
</tr>
<tr>
<td>Bist et al</td>
<td>M</td>
<td>62</td>
<td>Mouth swelling, Hoarseness</td>
<td>Multiple exophytic nodular lesions across the oropharynx, endolarynx and hypopharynx</td>
<td>Oral lesions</td>
<td>Pharyngeal Amphotericin then oral itraconazole for 3 weeks</td>
<td>Endemic Smoker</td>
</tr>
<tr>
<td>Teoh et al</td>
<td>M</td>
<td>70</td>
<td>Weight loss, Hoarseness, Dysphagia</td>
<td>Showed that the mucosa at the posterior one-third of both vocal folds were irregular</td>
<td>Pulmonary</td>
<td>Amphotericin then oral itraconazole for 5 months</td>
<td>DM Smoker</td>
</tr>
<tr>
<td>Masoud et al</td>
<td>M</td>
<td>60</td>
<td>Hoarseness</td>
<td>Ulcerative growth in the left vocal cord</td>
<td>None</td>
<td>Amphotericin then oral itraconazole for 12 weeks</td>
<td>TB Endemic</td>
</tr>
<tr>
<td>Solari et al</td>
<td>M</td>
<td>48</td>
<td>Weight loss, Hoarseness, Dysphagia, Stridor, Dyspnea, Cough, Weight loss</td>
<td>Epiglottitis, enlargement and mobile vocal cords with granulomatous lesions deforming and infiltrating the glottis and subglottis</td>
<td>Disseminated</td>
<td>Histoplasmosis Amphotericin then oral itraconazole with clinical improvement in 1 month</td>
<td>AIDS</td>
</tr>
<tr>
<td>Ahumadau et al</td>
<td>M</td>
<td>70</td>
<td>Dyspnea, Hoarseness, Dysphagia, Odynophagia, Fatigue, Anorexia, Weight loss</td>
<td>Vegetative lesion on the lingual surface of the epiglottis</td>
<td>Pharyngeal</td>
<td>amphotericin B then itraconazole for 12 months</td>
<td>Smoking Immunosuppressant drugs</td>
</tr>
<tr>
<td>Smeets et al</td>
<td>M</td>
<td>58</td>
<td>Weight loss, Hoarseness, Dysphagia</td>
<td>The vocal process was thickened, granulation tissue on right ventricular area</td>
<td>None</td>
<td>Itraconazole for 4 week</td>
<td>Travel</td>
</tr>
<tr>
<td>Boulouy et al</td>
<td>M</td>
<td>65</td>
<td>Hoarseness</td>
<td>Non-specific inflammatory changes in right vocal cord, edema and hypertrophic vocal cord</td>
<td>Pulmonary</td>
<td>Itraconazole for 6 months</td>
<td>Travel TB smoking</td>
</tr>
<tr>
<td>Authors</td>
<td>Gender</td>
<td>Age</td>
<td>Symptoms</td>
<td>Findings</td>
<td>Treatment</td>
<td>Disease(s)</td>
<td></td>
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<tr>
<td>Mackowiak et al</td>
<td>M</td>
<td>55</td>
<td>Weight loss, Hoarseness, Dysphagia</td>
<td>Yellowish, edematous mucosal changes in the inter-arytenoid region involving the posterior part of the vocal cords</td>
<td>Disseminated histoplasmosis, itraconazole for 2 months</td>
<td>Addison’s disease DM</td>
<td></td>
</tr>
<tr>
<td>Fechner et al</td>
<td>M</td>
<td>44</td>
<td>Sore throat, Hoarseness, Dysphagia</td>
<td>The vocal cords were swollen and covered with a thin white exudate.</td>
<td>None, Amphotericin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Donegan et al</td>
<td>M</td>
<td>69</td>
<td>Weight loss, Hoarseness, Dysphagia</td>
<td>Left large epiglottic and glottis mass</td>
<td>None, Amphotericin for 6 weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sonkhya et al</td>
<td>M/F</td>
<td>8M 2F</td>
<td>Weight loss, Hoarseness, Dysphagia</td>
<td>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 postcrioid and subglottic lesion.</td>
<td>One case pharyngeal, There were no signs of pulmonary or systemic involvement, Amphotericin in 3 cases, Itraconazole in 7 cases. for 6 months</td>
<td>10 patients from endemic area</td>
<td></td>
</tr>
<tr>
<td>Cairi et al</td>
<td>F</td>
<td>35</td>
<td>Hoarseness and sore throat</td>
<td>Whittish nodular lesions in the arytenoid cartilage and vocal cords</td>
<td>Paranasalsinus pulmonary, amphotericin followed by Itraconazole for 8 months, SLE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Larbcharoensub et al</td>
<td>F</td>
<td>39</td>
<td>Hoarseness for eleven months</td>
<td>Glotic mass</td>
<td>Pharyngeal oral cavity, Amphotericin B dead</td>
<td>SLE</td>
<td></td>
</tr>
<tr>
<td>Gulati, et al</td>
<td>M</td>
<td>47</td>
<td>Hoarseness, Painful ulcer tongue</td>
<td>Exophytic lesion (epiglottis and glottis)</td>
<td>Oral lesion, Itraconazole for 6 weeks</td>
<td>Endemic</td>
<td></td>
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<tr>
<td></td>
<td>M</td>
<td>45</td>
<td>Hoarseness</td>
<td>Exophytic lesion was noted on the anterior aspect of both vocal cords</td>
<td>Oral cavity, Itraconazole for 6 week</td>
<td>Endemic</td>
<td></td>
</tr>
<tr>
<td>Troncoso et al</td>
<td>M</td>
<td>30</td>
<td>Dysphagia, Dyspnea, Stridor, Fever</td>
<td>Indurated Glottis, supraglottic And Subglottic mass</td>
<td>Heptospleno-megaly, Amphotericin followed by Itraconazole for 12 months, AIDS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Le et al</td>
<td>M</td>
<td>58</td>
<td>Hoarseness, Dysphagia, Weightloss</td>
<td>Ulcerated mass that involved the left pyriform sinus and supraglottic space</td>
<td>Pharyngeal, Amphotericin then Itraconazole</td>
<td>Smoking Diabetes</td>
<td></td>
</tr>
<tr>
<td>Sane et al</td>
<td>M/F</td>
<td>55</td>
<td>Weight loss, Anorexia, Fever</td>
<td>Vocal cord paresis and edema with small irregular nodule on the right vocal cord</td>
<td>Disseminated, Amphotericin B for 1 year</td>
<td>Endemic</td>
<td></td>
</tr>
<tr>
<td>Larsen et al</td>
<td>M</td>
<td>63</td>
<td>SOB Sore throat, Fever weight loss stridor Hoarseness</td>
<td>Ulcerative mass supraglottic edema glottic</td>
<td>Pulmonary, Tracheostomy gastrostomy tube amphotericin patients was decanulated</td>
<td>Smoking Rheumatoid arthritis</td>
<td></td>
</tr>
<tr>
<td>Sataloff et al</td>
<td>F</td>
<td>44</td>
<td>Hoarseness</td>
<td>Laryngitis, non-specific changes in all larynx</td>
<td>None, Treatment with oral ketoconazole was instituted</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ragah et al</td>
<td>M</td>
<td>55</td>
<td>Hoarseness, Dysphagia, General symptom</td>
<td>Supraglottic glottis ulcer</td>
<td>Oral cavity, Pharyngeal, Treatment with amphotericin B resulted in a rapid recovery</td>
<td>Endemic TB</td>
<td></td>
</tr>
<tr>
<td>Klein et al</td>
<td>M</td>
<td>37</td>
<td>Hoarseness, Vague throat pain, Weightloss, SOB stridor</td>
<td>Destructive supraglottic lesion. The lesion was exophytic, extending down to the true vocal folds</td>
<td>Oral cavity, Tracheostomy, Itraconazole for 13 week</td>
<td>Smoking</td>
<td></td>
</tr>
<tr>
<td>Fernández Liesa et al</td>
<td>M</td>
<td>-</td>
<td>Hoarseness</td>
<td>Edema, erythema and leukoplaikia of the right vocal cord</td>
<td>None, Itraconazole treatment was successful</td>
<td>Smoker Travel</td>
<td></td>
</tr>
<tr>
<td>Yen et al</td>
<td>F</td>
<td>46</td>
<td>Dysphonia</td>
<td>Epiglottic mass</td>
<td>Disseminated, Amphotericin then Itraconazole death</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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 Verrucous mass anterior third left vocal cord Esophagus Pharyngeal Itraconazole 1 year

Alcurra et al 61 M Oral ulcer Weightloss Fever Multiple laryngeal, glottis ulcer Oral cavity Esophagus Itraconazole 2 months Smoker

Samuel et al 36 M 60 Sore throat Supraglottic ulcer Pharyngeal Pulmonary Micronazole 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 63 M Hoarseness, Dysphagia, Weightloss 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 glottic 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.

<table>
<thead>
<tr>
<th>Risk Factors</th>
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</thead>
<tbody>
<tr>
<td>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).</td>
</tr>
</tbody>
</table>

**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, leukoplasia and inflammation) in 6 patients (Chart 4).

**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...
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 reveal 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-

<table>
<thead>
<tr>
<th>Endemic</th>
<th>Travel</th>
<th>Smoking</th>
<th>AIDS</th>
<th>TB</th>
<th>Endocrinology diseases</th>
<th>Rheumatology diseases</th>
<th>Medications</th>
<th>Cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>5</td>
<td>12</td>
<td>3</td>
<td>5</td>
<td>3</td>
<td>4</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

Some patients had multiple risk factors

*Table 2: Number of patients having risk factors.*

**Chart 4:** Clinical exam presentation.

**Chart 5:** Histoplasmosis associated with other areas.
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 hematogenous spread to other organs. Primary pulmonary histoplasmosis is usually asymptomatic but chronic pulmonary histoplasmosis is clinically similar to pulmonary tuberculosis.

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 hematogenous 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.

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.

Laryngeal involvement is usually observed in disseminated histoplasmosis. Goodwin et al. 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.

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

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

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 take place in patients with CD4 T-cell counts lower than 200 cells/μl.

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 technique 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.

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.

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.  

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.

ACKNOWLEDGEMENTS

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CONFLICTS OF INTEREST

The author declare that he have no conflicts of interest.

REFERENCES


29. Klein AM, Tiu C, Lafreniere D. Malignant mimickers:

