Isolated Laryngeal Coccidioidomycosis - A Case Report and Review of the Literature

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Introduction

Coccidioidomycosis involving the larynx is a rare occurrence which seems to present with non-specific upper airway symptoms. The diagnosis is made by tissue biopsy and the treatment is usually fluconazole for 6-12 months depending on the clinical presentation. In unusual presentations of laryngeal problems clinicians should consider Coccidioidomycosis, especially in endemic regions.

Case Presentation

We present a 59-year-old Hispanic female resident of West Texas who presented with symptoms of hoarseness, sore throat, and low-grade fevers for 2-3 months. She had been evaluated by her primary care physician who had treated her with several courses of antibiotics including quinolones, azithromycin, and cephalosporins. Because of the persistence of her symptoms she was sent to an ENT specialist. She had a persistent cough, low-grade fevers for 2-3 months. She had been evaluated by her primary care physician who had treated her with several courses of antibiotics including quinolones, azithromycin, and cephalosporins. Because of the persistence of her symptoms she was sent to an ENT specialist.

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A biopsy of the lesion revealed spherules with endospores and accompanying granulomas; fungal cultures were consistent with Coccidiodes immitis. Chest x-ray was unremarkable. Computed tomography (CT) scan of the chest revealed two pulmonary nodules at the superior segment of the left lower lobe. Other relevant labs included hemoglobin and hematocrit of 13.9 g/dL and 40.6% respectively, normal range 11.5-15 and 34-44. White blood count was 11,000 per µL (4-10.5) with 58% neutrophils, 31% lymphocytes, 8% monocytes, 2% eosinophils, and 1% basophils. The C. immitis complement fixation titer (CFT) was negative at <1:1 and enzyme immunoassay (EIA) was unavailable. The patient was placed on fluconazole 400 mg per day for 6 months. Serial follow-ups revealed a decreasing size of the laryngeal mass with complete resolution of the lesion by the end of 3 months and repeat chest x-ray demonstrated some resolution in the size of the lung nodules. Repeat serum Coccidioidomycosis CFT level remained negative.

Discussion

Coccidioidomycosis spp. is a dimorphic fungus endemic to the southwestern United States and Northern Mexico [1]. Infection occurs through inhalation of the Coccidioidomycosis arthroconidium from the soil. The areas with the highest endemic sources of infection are in California and Arizona which together make up more than 50% of all cases [2]. The incidences in high-risk locations have risen from 5.3 cases per 100,000 in 1998 to 42.6 per 100,000 cases in 2011 [3]. This rise in reported cases has been in part hypothesized to the increased sensitivity of Coccidioidomycosis serological tests and industrialization into endemic areas [3,4]. The most common presentation of Coccidioidomycosis includes symptoms of chronic fatigue, malaise, and productive cough. Episodes of occasional arthralgias are common with a primary pulmonary source as well [5]. The risk factors associated with severe disseminated infection are immunosuppression such as, AIDS, solid organ transplant recipients, lymphomas, or prolonged steroid use [6]. While the vast majority of Coccidioidomycosis infections have a primary pulmonary source, primary Coccidioidomycosis of the larynx is a very rare and unusual presentation.

A review of the literature was done using Medline and PubMed and was simplified into a table (Table 1). The following characteristics seemed consistent with patients with laryngeal Coccidioidomycosis. First, the most common complaint appeared to be vocal changes, primarily hoarseness of the voice in 50% of cases. Other presenting symptoms were cough, malaise, and a non-specific flu-like presentation. Secondly, 50% of the patients demonstrated evidence of possible pulmonary involvement with chest imaging, however only 23% of patients underwent bronchoscopies or pulmonary biopsies. In a majority of cases, the diagnosis was confirmed with a biopsy of the larynx or sputum cultures. And thirdly, in 58% of cases the CFTs were equal or greater than 1:16. Any positive CFT is considered clinically relevant; IgG will diminish over a period of 6 months after treatment. It is for this reason that it is used as a marker of successful therapy along with clinical resolution of the initial symptoms. In addition, PCR for Coccidioidomycosis spp has been developed which has shown very high sensitivity and specificity in infected patients [7]. As well,
use of enzyme immunoassay (EIA) for patients infected with *Coccidioidomycosis* can assist with a definite diagnosis in presence of an inconclusive or inconsistent CFT [8]. Sensitivity for patients with symptomatic infections is very high, however in immunocompromised or asymptomatic patients results should be interpreted with caution [8].

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Age/ Sex</th>
<th>Presentation</th>
<th>Diagnosis</th>
<th>Pulmonary Cocci</th>
<th>Serology</th>
<th>Therapy</th>
<th>Outcome</th>
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</thead>
<tbody>
<tr>
<td>Allen et al.</td>
<td>2011</td>
<td>52/F</td>
<td>1 year history of dysphonia and cough with prior history of treated pulmonary coccidioidomycosis</td>
<td>Videolaryngoscopy positive for erythema and pseudomembranous exudate over epiglottis and periform fossa. Chest CT demonstrated large peumomocles and lung damage. Biopsy of vocal cords and sputum cultures grew <em>C. immitis</em>.</td>
<td>No</td>
<td>Complement fixation titer (CFT) was 1:32</td>
<td>Fluconazole</td>
<td>After 6 weeks of antifungal therapy, laryngoscopy noted complete resolution of infection.</td>
</tr>
<tr>
<td>Patel et al.</td>
<td>2009</td>
<td>28/M</td>
<td>1 week history of sore throat, hoarseness, dry cough, and dysphagia</td>
<td>Contrast computed tomography scan of neck and chest positive for abscess on false vocal cord with lymphadenopathy and pulmonary nodules; culture positive for <em>C. immitis</em>.</td>
<td>Yes</td>
<td>Undetectable IgG &amp; IgM</td>
<td>I&amp;D; oral fluconazole</td>
<td>Clinically improved</td>
</tr>
<tr>
<td>Crum et al.</td>
<td>2004</td>
<td>47/M</td>
<td>Hoarseness, neck adenopathy and increasing CF titer, history of pulmonary coccidioidomycosis</td>
<td>FNA of neck LN was negative, laryngoscopy noted 3 nodules on vocal cords which yielded a positive diagnosis</td>
<td>No</td>
<td>CFT was 1:8, increased from 1:2</td>
<td>Fluconazole 600mg QD for 2 months</td>
<td>Adenopathy and hoarseness resolved over 2 months. No relapses over 11 month follow-up period.</td>
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<td>Rosen et al.</td>
<td>2001</td>
<td>14/M</td>
<td>3 week history of worsening hoarseness and dyspnea; history of disseminated coccio as a child</td>
<td>Chest X-ray noted calcified granulomas consistent with previously treated pulmonary coccidioidomycosis. Laryngoscopy with biopsy grew <em>C. immitis</em>.</td>
<td>No</td>
<td>IgG was positive, CFT was 1:16</td>
<td>IV fluconazole for 3 days, switched to PO 200mg Q6hr</td>
<td>Unknown</td>
</tr>
<tr>
<td>Boyle et al.</td>
<td>1991</td>
<td>40/F</td>
<td>6 week history of moderate hoarseness, lymphadenopathy of the rt side of the neck, fever, night sweats, moderate dry cough, and fatigue</td>
<td>Contrast computed tomography scan of neck positive for supraglottic edema and near total compromise of the airway as well as bilateral lymphadenopathy and a nodule on right perijugular lymph node; biopsy and histological examination positive for caseating granulomas and multinucleated giant cells, double walled spherules with endospores indicated <em>C. immitis</em>.</td>
<td>Yes</td>
<td>IgG; CFT was 1:32</td>
<td>Fluconazole</td>
<td>Clinically improved</td>
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<td>Hajare et al.</td>
<td>1989</td>
<td>31 mo/M</td>
<td>2 day history of respiratory distress and stridor, history of steroid-dependent nephrotic syndrome</td>
<td>Chest X-ray was unremarkable. Laryngoscope revealed epiglottic and subglottic edema. Tracheal aspirate grew C. immitis.</td>
<td>No</td>
<td>CFT was 1:32</td>
<td>Amphotericin B for 4 weeks however d/c due to worsening renal function. Switched to fluconazole PO 6.6mg/kg/day for 1 year</td>
<td>Compliment fixation was negative 6 months after hospital discharge</td>
</tr>
<tr>
<td>Dudley</td>
<td>1987</td>
<td>21F</td>
<td>3 month history of gradually increasing neck mass and reports of not feeling “up to par”</td>
<td>Mass excised and histologic evidence of caseating granulomas.</td>
<td>No</td>
<td>CFT was 1:2</td>
<td>Excised; no antbx</td>
<td>3 year follow up showed no evidence of infection</td>
</tr>
<tr>
<td>Dudley</td>
<td>1987</td>
<td>13/F</td>
<td>Neck mass and lethargy; 1 year later neck nodes developed again, bilaterally</td>
<td>Biopsy/ histology confirmation; Biopsy showed caseating granulomas with endospore-packed spherules</td>
<td>No</td>
<td>CFT 1:32; CFT 1:32</td>
<td>Ketoconazole 6mo; ketoconazole (600mg) daily for 3mo.</td>
<td>Cervical adenopathy disappeared; Cervical adenopathy disappeared with no signs of return over 3 year follow up</td>
</tr>
<tr>
<td>Benitz et al.</td>
<td>1983</td>
<td>5/M</td>
<td>5 week history of right-sided pleuritic chest pain, cough, fever, occasional night sweats; increasing stridor and intercostal retractions.</td>
<td>Chest X-ray showed infiltrates in the middle and lower lobes of the right lung as well as mediastinal lymphadenopathy on the right. Cocciidiodin skin test positive. Laryngoscopy and biopsy was performed and histologic examination showed granulomatous lymphadenitis and spherules consistent with C. immitis.</td>
<td>No</td>
<td>CFT 1:8 initially, but up to 1:32</td>
<td>Amphotericin B for 10 wk (total dose of 60mg/kg)</td>
<td>After 14 month there was no further recurrence of respiratory distress or stridor</td>
</tr>
<tr>
<td>Gardener et al.</td>
<td>1980</td>
<td>1/M</td>
<td>3 month history of rhinitis, stridor, and cough. Also noted were lethargy and dysphonia.</td>
<td>Bronchoscopy/ biopsy; sample obtained showed histologic evidence of granulomas and spherules suggestive of endospores consistent with C. immitis. The pathogen was also isolated from the sample; a skin C. immitis skin test showed 5mm of induration and erythema.</td>
<td>Yes</td>
<td>CFT was 1:8</td>
<td>Amphotericin B (IV) for 4 mo (total dose 65mg/kg) and tracheostomy</td>
<td>Although CFT remined unchanged and skin test positive, no symptoms or growth recorded at 5 month follow up</td>
</tr>
<tr>
<td>Ward et al.</td>
<td>1977</td>
<td>4.5 mo/M</td>
<td>3 month history of upper respiratory tract infection associated with wheezes and cough; subglottic stenosis with granular lesions</td>
<td>Laryngoscope and biopsy were taken; upon histopathologic examination fibrous stroma and spherules consistent with C. immitis were found.</td>
<td>No</td>
<td>CFT ranged from 1:32 to 1:128</td>
<td>Amphotericin B until CFT returned to 1:32 (total dose 271mg)</td>
<td>At 6 month post-treatment follow up, patient had no signs of infection and healthy</td>
</tr>
</tbody>
</table>
The current treatment of laryngeal Coccidioidomycosis is amphotericin B or fluconazole, however the drug of choice is fluconazole [1,9-19]. To date, there have been no cases of laryngeal Coccidioidomycosis being treated with the newer azoles such as voriconazole or posaconazole. Relapse rates in isolated laryngeal infections are not known due to the scarcity of documented cases.

In this case, the usual features included multiple repeat negative CFT’s, no definite evidence of pulmonary disease, and an isolated infection in an otherwise healthy female. At this point it would be difficult to speculate as to whether she would have had a positive EIA in the presence of a localized infection. However, given the laboratory and clinical data available, it would indicate the primary source of the patient’s Coccidioidomycosis infection was limited only to her larynx. Due to her lack of pulmonary symptoms and negative CFT, a bronchoalveolar lavage was unnecessary and would add unneeded risks to the patient. There have been many proposed hypotheses of isolated laryngeal involvement however no proven theory has emerged as yet [20]. The most likely etiology of laryngeal involvement is from hematogenous spread of a primary pulmonary focus or dissemination from a high fungal burden in the host [20]. However, the etiology of our patient’s laryngeal Coccidioidomycosis is not clear.

Due to the sporadicity of cases of laryngeal involvement of Coccidioidomycosis, morbidity and mortality is difficult to determine. With ease and mobility of travel it is very feasible for patients who live outside the expected area of infectivity to develop this illness. While cases of isolated laryngeal C. immitis are exceedingly rare, one should consider uncommon fungal etiologies like Coccidioidomycosis in patients with difficult to treat upper respiratory tract or pneumonia-like symptoms.

In summary, laryngeal Coccidioidomycosis is an unusual presentation of a common illness endemic to the southwestern United States. The diagnosis is made on the biopsy of the larynx and treatment is with fluconazole for 6-12 months.

Acknowledgement
Dr. Suresh J. Antony for his input and assistance in developing this manuscript.

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<td>Platt</td>
<td>1977</td>
<td>45/M</td>
<td>Hoarseness for 1 year with associated fever, malaise, hemoptysis and weight loss; history of pulmonary coccidioidomycosis s/p lobectomy</td>
<td>Chest X-ray showed extensive bilateral infiltration with cavitation. \textit{C. immitis} was isolated in the sputum cultures.</td>
<td>No</td>
<td>CFT was 1:28-1:256</td>
<td>Amphotericin B for 2 year intermitently, however sputum was still positive. Switched to miconazole nitrate for 10 weeks for resolution.</td>
<td>Acute infection was resolved however bone marrow aspirate to assess anemia noted spherules of \textit{C. immitis}.</td>
</tr>
<tr>
<td>Singh et al.</td>
<td>1956</td>
<td>34/M</td>
<td>Productive cough for 3 month with dysphagia and hoarseness for 1 month</td>
<td>Tracheostomy with biopsy of tracheal cartilage grew \textit{C. immitis}. Biopsies from cutaneous lesions also grew the fungus.</td>
<td>No</td>
<td>CFT was positive</td>
<td>Dihydroxystilbamidine (IV) Q4hrs, total of 20 doses.</td>
<td>3 month after therapy, cutaneous lesions were healing and patient no longer required tracheostomy</td>
</tr>
</tbody>
</table>

Table 1: Review Literature of Coccidioidomycosis

With ease and mobility of travel it is very feasible for patients who live outside the expected area of infectivity to develop this illness. Due to the sporadicity of cases of laryngeal involvement of Coccidioidomycosis, morbidity and mortality is difficult to determine. With ease and mobility of travel it is very feasible for patients who live outside the expected area of infectivity to develop this illness. While cases of isolated laryngeal C. immitis are exceedingly rare, one should consider uncommon fungal etiologies like Coccidioidomycosis in patients with difficult to treat upper respiratory tract or pneumonia-like symptoms.

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