CASE REPORT

PRIMARY LARYNGEAL *CRYPTOCOCCOSIS* ASSOCIATED WITH PROLONGED INHALED STEROID USE. A CASE REPORT AND LITERATURE REVIEW

Beenish Syed

Sindh Infectious Diseases Hospital and Research Center, Karachi Pakistan

ABSTRACT

Primary Laryngeal Cryptococcosis is a rare clinical entity. Prolonged use of inhaled corticosteroids has been reported in previous literature as a significant risk factor in the pathogenesis of the disease. We report here a case of biopsy proven isolated laryngeal cryptococcosis without pulmonary ` in an elderly male. Our patient had a history of Asthma with prolonged use of inhaled corticosteroids for >15 years. Serum *Cryptococcal* Antigen titers were also raised. Managed medically with oral Fluconazole with reduction in dose of inhaled steroids, for 6 months duration with complete resolution of symptoms and improvement in titers. We also present a review of literature of cases reported in the last 22 years. A total of 25 cases have been reported and all of them presented with hoarseness of voice, had varied macroscopic and histopathological appearances, often mimicking malignancy. Sensitivity of serum *Cryptococcal* antigen remained low (39%). Majority (>60%) patient had long term exposure to high-dose inhaled steroids for varied duration. Anti-fungal therapy (Fluconazole) was instituted in most cases with good outcomes and only few cases required surgical excision or laser therapy for residual lesions. Reduction in dose of inhaled steroids for risk factor modification along with anti- fungal therapy can be effective in treatment of *Cryptococcal* Laryngitis.

Keywords: *Cryptococcus neoformans*, Laryngeal *Cryptococcosis*, Inhaled corticosteroids

BACKGROUND

Cryptococcus sp. is an encapsulated yeast, found mostly in bird excrement and soil.[1,2] Among the species, *Cryptococcus neoformans* is considered pathologically significant.[2] *Cryptococcal* infections are more commonly seen in immunocompromised hosts with conditions like HIV, post-transplantation, and with use of prolonged systemic steroids and immunosuppressive therapies, but can also be seen in otherwise healthy individuals. Defect in T-cell mediated immunity is the most important pathogenic factor.[2] Most infections involve the lungs and can disseminate to the brain causing meningitis or encephalitis in immunocompromised individuals.[1,2] *Cryptococcal* infection of the larynx without pulmonary involvement has been reported in literature previously in both immunocompetent as well as immunocompromised patients, predominantly those with a history of prolonged inhaled steroids use.[2,3] It is an important clinical entity because diagnosis can often be delayed due to low clinical suspicion as symptoms develop insidiously and closely mimic those of a laryngeal mass.[3,4]

We present here a case of an elderly male with Asthma and prolonged Inhaled steroid use with isolated Laryngeal *Cryptococcosis*. Extensive work-up ruled out any other risk factor and patient responded well to medical management with anti-fungal treatment and reduction in the dose of inhaled steroids.

Correspondence: Dr Beenish Syed, Sindh Infectious Diseases Hospital and Research Center, Karachi Pakistan

Email: bnishsyed@yahoo.com

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CASE HISTORY

This is a case of 71 years old male, resident of Karachi and shopkeeper by profession. He is a known case of asthma (15 years) and hypertension for 12 years and treated for HCV in the past. He was taking inhaled steroids and bronchodilators for 15 years. Referred to infectious diseases clinic with H/O of progressively increasing hoarseness of voice for 5 months along with dysphonia. There was no history of throat pain, dysphagia or odynophagia, fever, increased cough and shortness of breath. No weight loss was reported. He was an occasional pipe smoker but had left the habit 30-35 years back. He had been on inhaled corticosteroids and beta-agonists for last 15 years for his Asthma. Dose of inhaled steroids could not be ascertained from the history as no prescriptions were available. He was prescribed short courses of systemic steroids occasionally in the past. There was no H/O

TB or TB contact. Physical examination of the neck showed no swelling or enlarged lymph nodes. Oropharynx was also normal on gross examination. Rest of the systemic examination was also unremarkable except for bilateral occasional wheeze. All hematological and biochemical workup was normal. Chest X-Ray was also found to be normal. No other imaging was done initially. Fibreoptic laryngoscopy (FOL) showed bilateral irregular thickened and swollen vocal cords and granulation tissue present posteriorly. Biopsy was taken and histopathology showed: Tissue covered with benign mucosa exhibiting surface ulceration with underlying moderate to severe acute and chronic inflammation with vaguely formed granulomas showing collection of epitheloid cells and scattered foreign body giant cells. Narrow based, spherical, budding yeast cells with thick capsule were seen on PASD staining, suggestive of *Cryptococcus sp*. (Figures-1 and 2). Cryptococcal antigen titers were elevated at 1:4. HIV serology came out to be negative. Further evaluation with chest and brain imaging (CT and MRI) was done and were found to be un- remarkable with no evidence of dissemination. Oral Fluconazole 400 mg once per day was started and dose of inhaled steroids were reduced. Patient responded well in 4 weeks with improvement in his voice. CRAG titers reduced to 1:1 after 6 weeks of treatment. Patient was continued on anti-fungal for a prolonged period (6 months) and followed up in ID clinic for one year. He remained stable on all subsequent follow up visits.

Table 1: Literature Review (From year 2000 onwards).

S. No	Reference	Age/Sex	Risk factors	Cryptococcal Antigen	Treatment & Outcome
1.	McGregor *et al* (2003)[12]	60/M	Diabetes, Ex – smoker, Tobacco chewer	No data	Oral Fluconazole for 6 weeks with complete resolution of symptoms
2.	Nardous *et al* (2003)[13]	55/M	Asthma, allergic and fungal sinusitis, sinus surgery, inhaled corticosteroids	No data	Itraconazole 200mg twice daily for 6 weeks followed by 400 mg Fluconazole daily for 10 weeks. Patient became disease free at the end of treatment.
3.	Bamba *et al* (2005)[14]	68/F	Smoking (50 pack years)	No data	Surgical excision Resolution of symptoms post-surgery
4.	Zeglaoui *et al* (2005)[15]	65/F	HIV +	Positive	Amphotericin (0.7mg/kg/day) for 3 weeks then Fluconazole 400 mg/day for 6 months
5.	Joo *et al* (2009)[16]	82/F	Inhaled and systemic corticosteroid for COPD	Positive	Itraconazole for 6 weeks. Fluconazole for further 2 months. 585 nm pulse dyed laser. Incomplete pathological resolution at 4 months. Biopsy done twice. Final pathological resolution at 7 months with improvement of symptoms
6.	Gordon *et al* (2010)[17]	64/M	ICS	No data	Daily Fluconazole 400 mg for 10 months Pathological resolution
7.	Gordon *et al* (2010)[17]	44/M	HIV + Hepatitis C + Smoker	No data	Symptomatic resolution after 3 months of oral Fluconazole
8.	Gordon *et al* (2010)[17]	79/F	ICS	Negative	Oral Fluconazole 400 mg daily for 6 months with complete resolution
9.	Chang *et al* (2013)[8]	53/M	Exposure to pigeons	No data	Fluconazole 400 mg OD for 6 weeks with complete resolution of symptoms
10.	Mittal *et al* (2013)[18]	58/M	Inhaled steroids, h/o sleeping under eucalyptus tree 1 year back	Negative	Fluconazole for 8 weeks. Outcome not reported.
11.	Bergeron *et al* (2015)[19]	78/F	Asthma – ICS Active gardener	Negative	Fluconazole 400mg daily. Decreased dose of inhaled steroids, with resolution of symptoms in 15 weeks
12.	Tamagawa *et al* (2015) [20]	82/F	COPD Rheumatoid	High titers	Resolution of pharyngeal lesion after 3 months of oral Fluconazole

			Arthritis Prolonged steroids		
13.	Atiya *et al* (2015) [21]	38/F	HIV +	No data	IV Fluconazole 400mg for 14 days followed by 4 weeks of oral therapy with symptomatic improvement
14.	Jeng *et al* (2016)[9]	71/F	Exposure to bird droppings ICS	No data	Fluconazole 100 gm OD for 6 months. Debulking. Symptomatic resolution at 4 and pathological resolution at 11 months
15.	Menon *et al* (2016)[22]	80/F	High dose ICS. Asthma/COPD	No data	No data
16.	Wong DJ *et al* (2017)[2]	66/F	Asthma, ICS. Congenital, pulmonary stenosis and lifelong allergic rhino sinusitis	Undetectable	6 months of oral fluconazole 200 mg twice daily with reduction in inhaled corticosteroid dose by half
17.	Wong DJ *et al* (2017)[2]	69/F	Asthma. Oral and inhaled corticosteroids	Cryptococcal serum antigen recorded a very low positive of 2 *via* the latex agglutination test.	8 months of treatment with oral Fluconazole. Asymptomatic at lower dose of fluticasone.
18.	Sandhu J *et al* (2017)[23]	30/M	ESRD. Renal allograft. Oral prednisolone. HIV -ve	No data	Oral fluconazole 400mg per day for 6 months with complete recovery.
19.	Casillas *et al* (2019)[24]	52/M	Chronic smoker	No data	IV Amphotericin for 4weeks with improvement in voice.
20.	Quintero *et al* (2019)[10]	80/M	Ex-smoker, COPD, prolonged ICS. Exposure to pigeon droppings	Positive	Oral fluconazole 400 mg PO daily and switching to B agonist inhaler for 5 months with complete resolution of lesion and symptoms
21.	Morse *et al* (2019)[4]	68/F	COPD. H/O colorectal cancer	Positive	Presence of cryptococcoma. Oral fluconazole 400mg/day for 12 months. Complete resolution after 6 months
22.	Schimmel *et al* (2019)[7]	80/F	COPD	Positive	Laryngeotracheobronchitis. Oral fluconazole with rigid bronchoscopy and tracheal stenting. Complete resolution of symptoms but later developed tracheal involvement and stenosis
23.	Winters JR *et al* (2020)[1]	51/F	ICS/Asthma	No data	Oral anti-fungal therapy for 5 months. Surgical excision. No recurrence for 3 years on active surveillance
24.	Mallany *et al* (2021)[3]	83/M	Asthma/COPD. ICS	Positive	Oral fluconazole 400mg/day for 3 months with complete clinical resolution
25.	Yoshimine *et al* (2020)[6]	68/M	Asthma/ Lomg standing ICS. Smoking	Positive	Involvement of trachea, bronchi and vocal cords. Fluconazole 400mg/day for 6 months with complete resolution of lesions

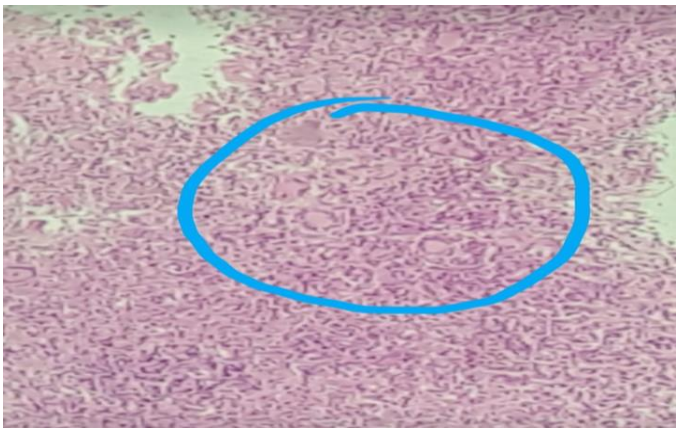

Figure-1: Slide 1 showing moderate to severe acute and chronic granulomatous inflammation.

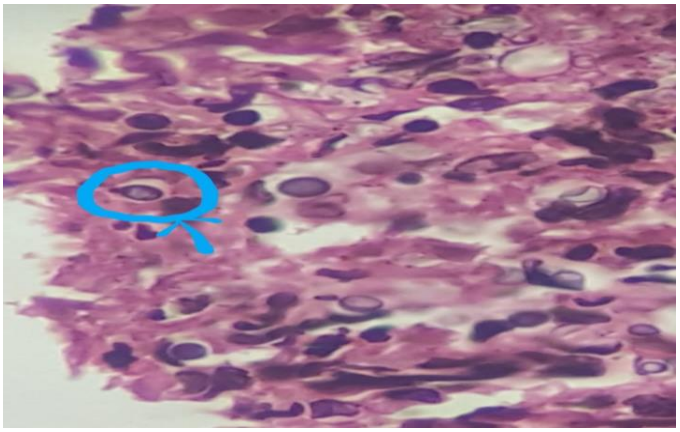

Figure-1: Slide 2 showing Vaguely formed granulomas showing collection of epithelioid cells with scattered foreign body giant cells.

DISCUSSION

Primary Laryngeal *Cryptococcosis* is a rare clinical condition. To the best of our knowledge, 32 cases have been reported in the literature so far since 1975, with a slight male preponderance (17:15).[2,3] Median age at presentation was 65 years.[5] A few of the recent case reports have also shown involvement of trachea and bronchi. It is a cause of hoarseness of voice.[6,7] Dysphonia was the most common presenting symptom seen in 100% of patients reported similar to our patient.[2,5] According to the cases reported, inhaled corticosteroid use is the most common risk factor seen in localized *Cryptococcosis* of the larynx.[2,5] Only 3 cases reported possible *Cryptococcal* exposure related to bird droppings.[8-10] Worrall *et al* in their literature review pointed out that only a minority of patients (28%) had history of immunosuppression in the form of HIV/AIDS, Post-transplant or treatment for autoimmune disorders like Rheumatoid Arthritis. Remaining 67% were immunocompetent with history of taking inhaled corticosteroids only, and remaining 5% had exposure to bird droppings or had no definitive risk factor.[3,5] This suggests that inhaled corticosteroids, particularly in high doses, are a potential risk factor for developing isolated laryngeal *Cryptococcosis* in otherwise immunocompetent patients.[2]

Inhaled corticosteroids cause localized immunosuppression and disruption of laryngeal mucosal barrier. Smoking, gastro-esophageal reflux and radiation are other factors that can cause disruption of the laryngeal mucosal barrier. Six of the previously reported cases also had history of smoking as well.[2,12,14,16,17] A combination of smoking and prolonged use of Inhaled steroids augments the mucosal injury and predisposes for localized infection of the larynx. Up to 90% of inhaled drug is deposited in the upper airway of patients which allows the ubiquitous *Cryptococcus* to colonize and infect via direct inoculation.[2] Similar to these case reports the only significant risk factor that can be established in our patient was prolonged use of inhaled steroids.

Macroscopically Laryngeal *Cryptococcosis* can mimic malignancies like squamous cell carcinoma and other fungal lesions, therefore fiberoptic larnygoscopy (FOL) and biopsy with appropriate staining are essential for diagnosis.[1,2,8] The spectrum of endoscopic findings in the case reports ranged from limited local erythema with or without leukoplakia, local swelling or verrucous to polypoid lesions.[1,2,8)] Histopathological findings included: granulomatous inflammation, inflammation without granuloma, pseudo-epitheliomatous hyperplasia, squamous cell hyperplasia and spherical budding yeast cells with thin capsule.[2,3] Majority specimen (55%) stained positive with Gomori methenamine silver and/or Mucicarmine stain.[5] Similar histopathological findings can be seen in other mycotic infections like *Candida* and *Histoplasma* as well as Squamous cell carcinoma, therefore it is important to specifically look for *Cryptococcus* if clinically suspected.

Positive serum cryptococcal antigen (CRAG) was seen only in few (39%) patients with localized disease.[5] Titers were also found to be generally low. It has been reportedly used as an adjunct for diagnostic and monitoring purposes in disseminated disease but not validated for use in localized laryngeal disease.[1] Serum CRAG titers were elevated in our patient which helped in the initial diagnosis and were subsequently used to monitor response as well.

Similar to our patient most cases were medically treated with oral antifungal agents. Most common regimen was high dose oral fluconazole (400 mg/day).[1,5] Treatment duration was minimum 6-8 weeks. Duration varied from 6 weeks to 1 year. Longer duration of 6-12 months is needed for marked immunosuppression and disseminated disease.[1] No current guidelines exist for treatment of localized laryngeal *cryptococcosis.* Reduction in dose of inhaled steroids is a useful adjunct to medical treatment. However, dose reduction of inhaled corticosteroids should be done on an individual basis depending on the patient's pulmonary status.[2] In previous case reports a few patients with residual disease required surgical excision after medical treatment and at least 3 out of the 25 reported patients responded to surgical excision alone.[2] Pulse-dye laser is also good therapeutic option for patients with residual disease who are unable to undergo surgical treatment.[11] Majority of the patients reported in literature showed complete resolution of their symptoms with very few recurrences or residual disease.[2,3] An overview of existing literature from year 2000 onwards is presented in Table-1.

CONCLUSION

Laryngeal *Cryptococcal* infection is a rare clinical entity. Use of inhaled steroids for prolonged periods is a significant risk factor even in immunocompetent persons. Histopathological examination with appropriate staining enables accurate diagnosis. Oral fluconazole 400 mg once daily is recommended for a maximum 6-12 months as the first line treatment along with reduction in the dose of inhaled steroids according to the patient's requirements. Surgical treatment may be necessary if indicated. No guidelines exist in literature whether these patients should be followed clinically or with repeat FOL to document resolution of lesions.

REFERENCES

1. Winters JR, Manosalva RE, Morrison MP. Laryngeal cryptococcal infection. Ear, Nose Throat J. 2020; 99(1): 13-4.
2. Wong DJY, Stanley P, Paddle P. Laryngeal cryptococcosis associated with inhaled corticosteroid use: case reports and literature review. Front Surg 2017; 4: 63. DOI: doi.org/10.3389/fsurg.2017.00063
3. Mallany HP, Curcin N, Borgia S, Belchetz G. Squamous cell proliferation as a reactive mechanism to laryngeal cryptococcus infection: A case report. Cureus 2021; 13(1). E12587. DOI: 10.7759/cureus.12587
4. Morse JC, Gelbard A. Laryngeal cryptococcoma resulting in airway compromise in an immunocompetent patient: A case report. Laryngoscope 2019; 129(4): 926-29. DOI: 10.1002/lary.27456.
5. Worrall DM, Lerner DK, Naunheim MR, Woo P. Laryngeal cryptococcosis: An evolving rare clinical entity. Ann Otol Rhinol Laryngol. 2019; 128(5): 472-9. DOI: 10.1177/0003489419826131
6. Yoshimine K, Tobino K, Sakabe M, Ooi R. Cryptococcosis in the vocal cords, trachea, and bronchi. Intern Med 2021; 60(18): 3003-3008. DOI: 10.2169/internalmedicine.6559-20
7. Schimmel M, Villari C, Van Nostrand K. Cryptococcal laryngotracheitis: A rare cause of tracheal stenosis in immunocompetent host. Am J Respiratory Critical Care Med 2019; 199: A4657. DOI: doi.org/10.1164/ajrccm-conference.2019.199.1
8. Chang YL, Hung SH, Liu CH, Hsu HT, Chao PZ, Lee FP, *et al*. Cryptococcal infection of the vocal folds. Southeast Asian J Trop Med Public Health. 2013; 44(6): 1043-6.
9. Jeng JY, Tomblinson CM, Ocal IT, Vikram HR, Lott DG. Laryngeal cryptococcosis: Literature review and guidelines for laser ablation of fungal lesions. The Laryngoscope. 2016; 126(7): 1625-29. DOI: doi: 10.1002/lary.25749.
10. Quintero O, Trachuk P, Lerner MZ, Sarungbam J, Pirofski LA, Park SO. Risk factors of laryngeal cryptococcosis: A case report. Med Mycol Case Rep. 2019; 24 : 82-5. DOI: 10.1016/j.mmcr.2019.04.009
11. Ihenachor EJ, Dewan K, Chhetri D. Pulsed dye laser treatment of primary cryptococcal laryngitis: A novel approach to an uncommon disease. Am J Otolaryngol. 2016; 37(6): 572-4. DOI: 10.1016/j.amjoto.2016.08.007
12. McGregor DK, Citron D, Shahab I. Cryptococcal infection of the larynx simulating laryngeal carcinoma. South Med J 2003; 96(1): 74-8. DOI: 10.1097/01.SMJ.0000047976.06958.D6.
13. Nadrous HF, Ryu JH, Lewis J, Sabri AN. Cryptococcal laryngitis. Chest 2003; 124(4): 307.
14. Bamba H, Tatemoto K, Inoue M, Uno T, Hisa Y. A case of vocal cord cyst with cryptococcal infection. Otolaryngol Head Neck Sur 2005; 133(1): 150-2. DOI: 10.1016/j.otohns.2005.01.003
15. Zeglaoui I, Belcadhi M, Mani R, Sriha B, Bouzouita K. Laryngeal cryptococcosis revealing AIDS: A case report. Rev de Laryngolo Otol Rhinol 2009; 130(4-5): 307-11.
16. Joo D, Bhuta SM, Chhetri DK. Primary cryptococcal infection of the larynx in a patient with severe chronic obstructive pulmonary disease: A case report. The Laryngoscope. 2009; 119 (S1 S1): 169-S. DOI: https://doi.org/10.1002/lary.20447
17. Gordon DH, Stow NW, Yapa HM, Bova R, Marriott D. Laryngeal cryptococcosis: Clinical presentation and treatment of a rare cause of hoarseness. Otolaryngol Head Neck Surg. 2010; 142(3): 7-9. DOI: 10.1016/j.otohns.2009.08.030.
18. Mittal N, Collignon P, Pham T, Robbie M. Cryptococcal infection of the larynx: case report. J Laryngol Otol. 2013; 127(S2): 54-S6.
19. Bergeron M, Gagné A-A, Côté M, Chênevert J, Dubé R, Pelletier R, editors. Primary larynx Cryptococcus neoformans infection: a distinctive clinical entity. Open forum infectious diseases; 2015 Dec 1;2(4): 160. Oxford University Press.
20. Tamagawa S, Hotomi M, Yuasa J, Tuchihashi S, Yamauchi K, Togawa A, *et al*. Primary laryngeal cryptococcosis resembling laryngeal carcinoma. Auris Nasus Larynx. 2015;42(4): 337-40.

DOI: 10.1016/j.anl.2015.01.003.
21. Atiya Y, Masege SD. Cryptococcal laryngitis: An uncommon presentation of a common pathogen. South Afr Med J. 2015; 105(10): 875.
DOI: 10.7196/samjnew.8779
22. Menon V, Jo H, Corte P, Lee A, Wignall A, Reddel H. An unusual cause of laryngotracheobronchitis. Clin Microbiol Newsletter. 2016; 38(10): 79-86.
23. Sandhu J, Sandhu JS, Puri HK, Munjal M. Laryngeal cryptococcus: a rare cause of hoarseness in renal allograft recipient. J Nephropharmacol. 2017; 6(1): 27-29.
24. Casillas E, Lee M. A case of cryptococcal laryngitis. Chest 2019; 156(4): A647.
DOI: doi.org/10.1016/j.chest.2019.08.630