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## Brief Communication

# Primary aspergillosis of vocal cord: Long-term inhalational steroid use can be the miscreant



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## ABSTRACT

Primary laryngeal aspergillosis is extremely rare, especially in an immunocompetent host. It is commonly found as a part of systemic infection in immunocompromised patients. A case of vocal cord aspergillosis with no systemic extension in an immunocompetent patient on long-term steroid metered dose inhaler (MDI) is presented here, because of its rarity. The present case is a 28-year-old asthmatic female who was on inhalational steroid for 8 years, presented with sudden onset of severe dysphonia for 5 days. Fiberoptic laryngoscopy demonstrated whitish plaque involving right vocal cord, clinically suggestive of fungal laryngitis. Microlaryngeal laser surgery was performed with stripping of the plaque. Histopathology demonstrated ulcerated hyperplastic squamous epithelium with masses of fungal hyphae, which was confirmed to be *Aspergillus* species on fungal culture. This rare but serious adverse effect of long-term steroid MDI use must be kept in mind while treating an asthmatic patient. We also present a brief review of literature of laryngeal aspergillosis.

*Aspergillus*, an inherently nonpathogenic or weakly pathogenic fungus, produces a range of opportunistic infections. The term aspergillosis is used to describe all disease entities caused by any one of the ~35 pathogenic and allergenic species of *Aspergillus*. Only those species that grow at 37 °C can cause invasive aspergillosis. *Aspergillus fumigatus* is responsible for the most of the cases of invasive infections, almost all cases of chronic aspergillosis, and most allergic syndromes [1]. In the field of otorhinolaryngology, aspergillosis most commonly occurs in the external auditory canal or in the nasal sinuses, but its localization to the larynx is

rare, especially in nonimmunocompromised hosts [2]. Laryngeal aspergillosis is most often found in the immunocompromised people such as patients with advanced age, diabetes, long-term steroid use, COPD, low CD4 counts, leukemia, AIDS, or severe aplastic anemia [2,3]. To the best of author knowledge, only 22 cases of primary laryngeal aspergillosis in nonimmunocompromised patients have been reported so far. We report a rare case of primary vocal cord aspergillosis in an asthmatic patient on corticosteroid inhaler use and briefly review the etiological factors of laryngeal aspergillosis.

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## Case report

A 28-year-old female presented with a sudden onset of severe dysphonia for 5 days. She was an asthmatic and was on inhalational steroid (fluticasone 500 mcg bd) since 8 years. She also had a history of vocal abuse. She was treated with broad-spectrum antibiotics, repeatedly during the last 3 months due to recurrent episodes of lower respiratory tract infection. On presentation, fiberoptic laryngoscopy showed whitish plaque involving right vocal cord [Fig. 1A]. Fungal laryngitis was suspected though keratosis of the vocal cord was a differential. Videostroboscopy was done to document the mucosal wave formation. To establish the final diagnosis and to institute an appropriate treatment, histopathological confirmation was required. Micro-laryngeal laser surgery was performed, stripping of the slough under direct vision was done, and biopsy samples and fungal culture were taken. Microscopic examination showed [Fig. 1B and C] inflamed, ulcerated, hyperplastic squamous epithelium, abundant fibrinopurulent debris, granulation tissue, and colonies of fungal hyphae. Grocott Methenamine silver stain [Fig. 1D] revealed septate fungal hyphae in the white plaque, branching at acute angles, and morphologically resembling *Aspergillus* sp. *A. fumigatus* was isolated on fungal culture. The remainder of the head and neck examination was unremarkable. Her chest X-ray and computed tomography/paranasal sinuses showed no abnormality. She was seronegative for HIV, HBV and HCV. The patient had no history of immune deficiency, leukemia,

malignant diseases, and diabetes mellitus. Inhaled corticosteroid was discontinued and the patient was treated with voriconazole 200 mg bd for 8 days and instruction was given to maintain vocal hygiene. After 12 days of voice rest, her voice showed a significant improvement. A repeat videostroboscopic examination after 2 weeks showed apparently normal vocal cords. Since symptom of asthma persisted, inhalational fluticasone had to be started at a dose of 125 mcg bd with metered dose inhaler (MDI) using a spacer. Speech therapy was given for 2 months and her voice regained normalcy. She has been followed up for 3 years since the onset of vocal cord aspergillosis. Her voice was absolutely normal. Videostroboscopy was repeated at 6-month intervals, which showed normal mucosal wave formation in the vocal cords. There was no evidence of recurrence.

## Discussion

Laryngeal aspergillosis is most commonly seen as part of a broader spectrum of infection, involving the respiratory tract in immunocompromised people, but *Aspergillus* infection of the larynx of immunocompetent individuals have also been reported [4,5]. After extensive literature search, fewer than 50 cases of primary laryngeal aspergillosis have been reported; of these, 22 cases involving immunocompetent patients are summarized in Table 1 [6,7].

*Aspergillus* sp. is generally a nonpathogenic or weakly pathogenic fungus causing opportunistic infections.

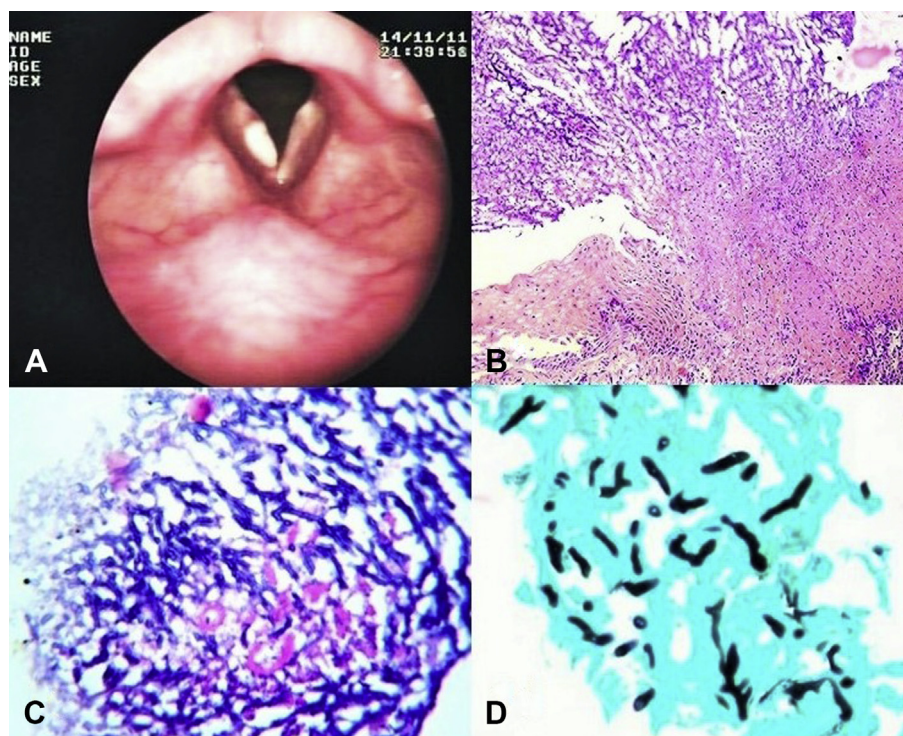


Fig. 1 – (A) Laryngoscopy showing thick white plaque involving a part of the right vocal cord. (B) Low power view of the plaque showing ulcerated squamous epithelium along with acute inflammatory exudate and fungal hyphae (H and E, ×100). (C and D) High power view of the above showing acute branching septate fungal hyphae in H and E and Grocott Methenamine silver stain, respectively (H and E and GMS, ×400).

Table 1 – Details of the cases of primary laryngeal aspergillosis in the immunocompetent patients.

Case	References	Age (year)/sex	Presenting features	Etiological factors
1	Liu et al. (2010)	30/female	Hoarseness of voice	Misuse of voice
2	Liu et al. (2010)	32/female	Hoarseness of voice	Extended spectrum antibiotic and misuse of voice
3	Wittkopf et al. (2006)	62/female	Hoarseness of voice	Cyst in vocal-fold
4–11	Nong et al. (1997)	30–40/4 males and 4 females	Hoarseness of voice	Unknown
12	Fairfax et al. (1999)	75/male	Hoarseness of voice	Prolonged use of inhalational steroid
13	Ogawa et al. (2002)	73/male	Hoarseness of voice	Therapeutic irradiation for the treatment of carcinoma of the larynx
14–15	Beust et al. (1998)	53/male and 54/male	Hoarseness of voice and dyspnea	Therapeutic irradiation for the treatment of carcinoma of the larynx
16	Dean et al. (2001)	17/female	Hoarseness of voice	Unknown
17	Benson-Mitchell et al. (1994)	62/male	Hoarseness of voice	Unknown
18	Kheir et al. (1983)	50/male	Hoarseness of voice	Unknown
19	Ferlito (1974)	76/male	Hoarseness of voice	Unknown
20	Rao (1969)	48/male	Hoarseness of voice	Unknown
21	Ran et al. (2008)	36/male	Hoarseness of voice	Broad spectrum antibiotic and inhaled corticosteroid
22	Ran et al. (2012)	30/male	Hoarseness of voice	?

Aspergillosis is thought to be caused due to host immunodeficiency rather than pathogenicity of the fungus itself [8]. Then how does healthy people become infected by *Aspergillus*? At present, the question still remains unanswered because there are only few case reports. There are a number of potential predisposing factors that may be associated with the development of primary laryngeal aspergillosis in the immunocompetent patients. The etiological factors include iatrogenic factors (including the long-term use of steroid MDI in high-dose), vocal abuse, vocal-fold cysts, fellatio and occupational factors [3,8–11].

Among iatrogenic factors, radiotherapy, steroid inhaler use, and laser treatment are important local factors that may predispose to the localized forms of aspergillosis [8,9]. Hoarseness of voice is a recognized complication of inhaled steroid therapy. Overall, it has been reported in 2% of patients receiving fluticasone and in 1% of patients on beclomethasone [9]. A significant proportion of inhaled corticosteroid is deposited in the larynx, especially on superior surface of the vocal cord, facilitating fungal colonization of the epithelial surfaces [11].

Systemic factor such as prolonged antibiotic therapy alters the local bacterial flora and disturbs the ecological balance between bacteria and fungi, thus allowing the overgrowth of *Aspergillus*. Several cases of invasive aspergillosis have been reported in patients receiving multiple antibiotics [10].

As a part of innate immunity, the intact epithelia of the respiratory tracts provide mechanical barrier to the entry of microbes from the external environment. Although vocal abuse may not be the direct cause, but by causing repeated frictions, it may cause local mucosal membrane barrier injury and edema, which may facilitate adhesion of the air suspended *Aspergillus* spores, followed by colonization, hyphae development, and invasion [10].

Laryngeal aspergillosis can complicate vocal fold cyst [6,11]. Wittkopf et al. reported a case of submucosal aspergilloma of the vocal cord developing in a preexisting vocal cord cyst [11]. The exact relationship between the cyst and laryngeal aspergillosis, however, is not clear.

*Aspergillus* is a saprophyte, inhabiting the soil. Thus, in certain otherwise healthy individuals engaged in farming and carpentry, occupation may be an etiological factor for the development of primary aspergillosis of larynx [10].

Though the history of oral sex was not present in our case, fellatio may be a highly suspected predisposing factor. By repeated friction, fellatio may cause local mucosal membrane barrier injury and may contribute to the causation of primary laryngeal aspergillosis in the immunocompetent individuals [3].

It is often seen that the diagnosis of fungal laryngitis is overlooked in the immunocompetent patients because it is generally considered as a disease of the immunocompromised patients, and because it often clinically mimics, more common and more serious conditions, for example, leukoplakia [5]. The laryngoscopic appearance of the vocal cord aspergillosis varies as with its histopathological appearance. Ulceration with or without hemorrhage, mass lesion with or without ulceration, white plaques on the vocal cords, and surrounding laryngeal structures are commonly described

laryngoscopic findings. Histologically, hyperkeratosis, edema, and erythema of the surface epithelium have been described as associated, nonspecific findings. Diffuse necrosis induced sloughing of epithelium has been reported in a small series by Ogawa et al. [8,11].

With the usual indolent clinical presentation and laryngoscopic appearances of laryngeal aspergillosis, the neoplastic lesion is often considered as a primary differential diagnosis. Equivocal clinical history and histopathological evidence of acanthosis and pseudoepitheliomatous hyperplasia often lead to a mistaken diagnosis of malignancy or premalignant condition. On the other hand, the presence of fungal hyphae and vascular emboli, with superimposed necrosis, may mask the underlying malignancy, especially in the setting of recurrent laryngeal cancer [8].

A high index of suspicion is required to reach the diagnosis and should be considered in any immunocompetent patient with persistent or refractory laryngitis when the above-mentioned predisposing factors are present. In these cases, demonstration of hyperkeratosis, particularly if associated with intraepithelial polymorphs, on histopathology, should trigger a search for fungal elements using specialized stains. Treatment by antifungal is required. The treatment should also be targeted toward the elimination of any predisposing factors, as failure to do so, may result in the persistence or recurrence of the condition.

### Conclusion

The occurrence of primary laryngeal aspergillosis in the immunocompetent patients and in patients with localized immunosuppression is an emerging trend. We suggest that asthmatic patients, while taking inhalational steroids if develop hoarseness of voice should be fully investigated by laryngoscopy and if required is to be followed by biopsy and fungal cultures. This case highlights a rare though possible serious adverse effect, which may result from the use of very high doses of inhaled corticosteroid therapy. Inhalational corticosteroids are available as over-the-counter drugs and people use it often without proper monitoring by pulmonologists. Hence, this rare but serious complication of the use of inhalational steroid must be kept in mind during the rampant use of the same.

### Source of support

Nil.

### Conflicts of interest

None declared.

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