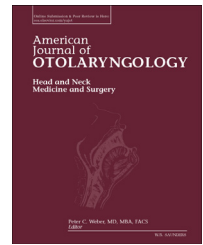


Available online at www.sciencedirect.com

ScienceDirect

www.elsevier.com/locate/amjoto

Intranasal fungal (*Alternaria*) infection related to nasal steroid spray☆☆☆

Geng-He Chang, MD^a, Wen-Hung Wang, MD, PhD^{b,c,d,*}

^a Department of Otolaryngology-Head and Neck Surgery, Chang Gung Memorial Hospital, Chiayi, Taiwan

^b Department of Otolaryngology, Cathay General Hospital, Taipei, Taiwan

^c Department of Otolaryngology, Sijih Cathay General Hospital, New Taipei City, Taiwan

^d Fu-Jen Catholic University School of Medicine, New Taipei City, Taiwan

ARTICLE INFO

Article history:

Received 1 July 2013

ABSTRACT

During the past three decades intranasal corticosteroid sprays have been proven to be efficient and reasonably safe for the treatment of rhinitis, sinusitis and nasal polyposis. The adverse effects are generally localized and self-limited and rarely systemic or significant. We report an immunocompetent female treated with triamcinolone acetate nasal spray for chronic rhinitis in whom an intranasal fungal infection with *Alternaria* species developed three months later. The infection was refractory to topical therapies alone, and was resolved with a combination of systemic and topical antifungal therapy. We also described the clinical manifestations of this rare infection and our therapeutic experience. In addition, we reviewed previous literature of fungal infections related to nasal corticosteroid sprays and compared them with our report.

© 2013 Elsevier Inc. All rights reserved.

1. Introduction

Intranasal corticosteroid (INC) sprays are universally prescribed for treatment of allergic rhinitis [1], rhinosinusitis [2] and nasal polyposis [3] with excellent therapeutic effects. In general, the administration of INC sprays is reasonably safe, and significant or systemic adverse effects have rarely been reported. Some local adverse effects such as epistaxis, nasal irritation, sneezing, nasal dryness, burning sensation, cough, throat discomfort and pharyngitis have been reported in a few patients, however these complications were transient and self-limited [4]. A rare but significant local complication of septum perforation was reported in one patient, although it was considered to be the consequence of mechanical trauma to the nasal septum [5]. The potential adverse effect of intranasal candidiasis is included on the safety labels of marketable INC sprays approved by the United

States Food and Drug Administration (USFDA), however few reports have demonstrated the clinical manifestations, appropriate treatment and therapeutic results of intranasal fungal infections. To the best of our knowledge, no previous reports have described an INC spray-related *Alternaria* infection. We first present a case with this rare adverse effect, and then describe the clinical presentation, local findings and therapeutic efficiency.

2. Case report

A 50-year-old woman presented with obstructive sleeping apnea (respiratory disturbance index: 29.0 per hour) and essential hypertension with no medical treatment. She was otherwise healthy, although she had suffered from perennial nasal obstruction and post-nasal dripping for years, for which

☆ Financial Disclosures: None.

☆☆ Conflicts of Interest: None.

* Corresponding author. Department of Otolaryngology, Cathay General Hospital, Taipei, and Fu-Jen Catholic University School of Medicine, New Taipei City, Taiwan. Tel.: +886 2 27082121.

E-mail address: ent.taiwan@gmail.com (W.-H. Wang).

she had never taken any medication or undergone sinonasal surgery. On examination, pale and hypertrophic turbinates, a deviated nasal septum and serous postnasal drips were observed with no nasal polyps, purulent drainage or other anatomical abnormalities. The serum total immunoglobulin E (IgE) level was 90.2 kU/L and no predominant allergens were detected by allergen-specific IgE tests. Triamcinolone acetate nasal spray (Nasacort AQ, 55 mcg/ds, 120 ds/bot) with a dose of 110 mcg for each naris per day at bedtime was prescribed for treatment of the chronic rhinitis, and she used the INC spray regularly without overdosing or taking other medications. However, she complained of bilateral intermittent intranasal irritation and even pain lasting for a few days at an outpatient follow-up visit three months later. Detailed nasal endoscopy disclosed multiple white powdery patches on bilateral sides of the nasal septum and the caudal surfaces of the bilateral inferior and middle turbinates (see Fig. 1). The oral cavity, nasopharynx, oropharynx, hypopharynx and larynx were unremarkable without lesions or erythematous mucosa. Under the impression of an INC spray-related intranasal fungal infection, we discontinued the triamcinolone acetate nasal spray. We then encouraged nasal douching with warm salted water and prescribed ketoconazole ointment (2%, 10 g/tube) to be applied to the infected turbinates and septum twice per day as topical therapy. A fungal infection with *Alternaria* species was subsequently confirmed by the results of cultures from swabs of the infected turbinates.

A workup to survey the underlying disease was initiated. The complete blood count was unremarkable with normal distribution of white blood cells and no immature cells. The

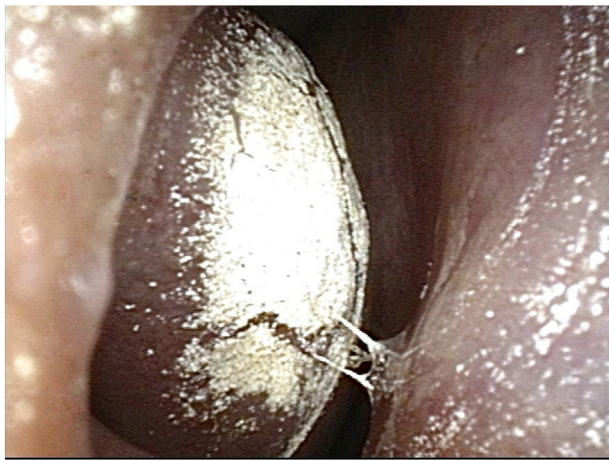


Fig. 1 – Nasal endoscopy showed multiple white powdery patches on the right side of the septum and the caudal surface of the right inferior turbinate. [Original: Fig. 1 – Nasal endoscopy showed multiple white powdery patches on bilateral sides of the septum and the caudal surfaces of the bilateral inferior turbinates (A and B) and the left middle turbinate (C) but not on the right middle turbinate (D). => We modified the “bilateral sides of the septum” to “the right side of the septum”, “the caudal surfaces of the bilateral inferior turbinates” to “the caudal surface of the right inferior turbinate”, and deleted the “(A and B) and the left middle turbinate (C) but not on the right middle turbinate (D)”].

fasting blood glucose level, creatinine level, liver enzymes, anti-nuclear antibodies, rheumatoid factor, and erythrocyte sedimentation rate were all within normal ranges. The quantitative immunoglobulin (Ig) blood test for IgG and IgA revealed antibody levels within normal range including the IgG subtypes. Chest radiography and abdominal echography did not reveal any significantly abnormal findings. In general, the patient was immunocompetent.

The turbinate lesions and nasal symptoms could be suppressed temporarily for days to weeks but easily relapsed, and consequently the congested infected turbinates resulted in intolerable nasal obstruction, irritation and pain. Therefore, we prescribed oral fluconazole (200 mg once per day) and enhanced the topical therapies with diluted fluconazole solution (50 mg fluconazole dissolved in 500 ml of warm salted water) for nasal douching followed by ketoconazole ointment applied to the infected turbinates and septum twice per day. After two weeks of treatment the nasal symptoms greatly improved, and the infection was eventually resolved with no further recurrence after one year of follow-up. The patient subsequently accepted submucosal resection of the deviated septum and hypertrophic turbinates to facilitate nasal breathing.

3. Discussion

INC sprays have been extensively prescribed for the treatment of rhinitis, rhinosinusitis and nasal polyposis with efficient and safe therapeutic results over the past three decades. Intranasal candidiasis, a potential adverse effect, is warned of on the drug safety labels of the marketable INC sprays approved by the USFDA, however few reports have demonstrated the clinical manifestations, adequate treatment and prognosis. To the best of our knowledge, INC spray-related fungal infections have been reported in the nasal cavity [6], oro-hypopharynx [7], oral cavity and esophagus [8] (see Table 1). In the majority of cases, beclomethasone dipropionate (BDP) nasal spray was responsible for the adverse effects except for one oro-hypopharyngeal infection which was related to budesonide. The duration of usage ranged from 7 months to 2 years and all of the cases were immunocompetent except for one patient with chronic lymphocytic leukemia diagnosed after a BDP-related intranasal candidiasis infection. The species was uniformly *Candida albicans*; however, the clinical manifestations were variable. As in our case, intranasal candidiasis presented as multiple intranasal white patches and caused nasal irritation. However, oro-pharyngeal candidiasis manifested as erythematous mucosa with sore throat, odynophagia and even dysphagia. Some of these cases were initially misdiagnosed as bacterial pharyngitis and inefficiently treated with antibiotic until throat swabs for smears revealed fungal hyphae leading to the diagnosis of candidiasis. Discontinuing the INC spray was the initial management for all of these cases. Buccal/esophageal candidiasis was treated with only sodium gualenate hydrate (an anti-inflammatory agent) for gargling and nasal douching without antifungal agents, and achieved symptomatic improvement after two weeks. Oro-hypopharyngeal candidiasis was treated with oral miconazole or clotrimazole for two weeks, and rapid symptomatic relief was achieved in a few days. In contrast, intranasal candidiasis was treated with saline douches and oral

Table 1 – A collection of case reports about intranasal corticosteroid spray-related fungal infection.

Author (year)	Age (y/o)	Sex	DM/ID	INC sprays	Duration (months)	Fungus	Location	Treatment	Results
Our report	50	F	No	Triamcinolone acetonide	3	<i>Alternaria</i> species	Nasal cavities	Fluconazole (oral + nasal douche)	CR
Shuto H (2007) [8]	69	F	No	BDP	24	<i>C. albicans</i>	Buccal/esophagus	Sodium guaiacolate hydrate (gargling + nasal douche)	CR
Kyrmizakis DE (1999) [7]	37	M	No	BDP	7	<i>C. albicans</i>	Oro-hypopharynx	Oral miconazole	CR
	55	F	No	Budesonide	12	<i>C. albicans</i>	Oro-hypopharynx	Oral clotrimazole	CR
	30	M	No	BDP	18	<i>C. albicans</i>	Oro-hypopharynx	Oral miconazole	CR
Webb EL (1993) [6]	62	F	CLL	BDP	18	<i>C. albicans</i>	Nasal cavities	Oral ketoconazole	CR

Abbreviations: F: female, M: Male, DM: diabetes mellitus, ID: immune deficiency, INC: intranasal corticosteroid, BDP: beclomethasone dipropionate, *C. albicans*: *Candida albicans*, CLL: chronic lymphocytic leukemia, CR: complete remission.

ketoconazole (400 mg twice per day) for eight weeks before eradicating the infection. Compared with these INC spray-related cases of candidiasis, the triamcinolone acetonide was first advised to cause the intranasal fungal infection with a shorter duration of usage in an immunocompetent patient. In addition, the intranasal fungal infections appeared to be more refractory to treatment compared with the buccal/esophageal and oro-hypopharyngeal cases.

Alternaria, a genus of ascomycete fungi, is a common allergen for allergic rhinitis and asthma [9], although the allergen-specific IgE tests showed no response to *Alternaria* in our case. Several clinical studies have demonstrated the topical therapeutic efficiency of INC sprays with very low systemic bioavailability [10]. The *Alternaria* distribution in the infected turbinates and septum was at the interface between the route of the INC aerosol and intranasal mucosa. Therefore, INC spray-induced topical immune suppression resulting in the intranasal fungal infection was assumed to be the pathological mechanism.

In the current case, the intranasal *Alternaria* infection was refractory to topical therapies alone until a combination of systemic and topical antifungal therapies resolved the infection with no further recurrence. We hypothesize that the congested turbinates supported a humid dead space in the nasal cavities leading to incomplete topical therapy, thereby causing the consequent relapses.

4. Conclusion

INC sprays carry the risk of complications with fungal infections along the route of the aerosol including the nasal cavities, oral cavity, pharynx and esophagus. Since INC sprays are prescribed for the treatment of rhinitis, rhinosinusitis and nasal polyposis, a follow-up examination should be arranged if symptoms of nasal irritation, pain, sore throat, odynophagia or dysphagia develop based on an awareness of an INC spray-related fungal infection. Once a fungal infection is suspected, detailed examinations with smears and cultures should be performed to establish a definite diagnosis. The INC spray

should be discontinued immediately and a combined therapy of topical and systemic antifungal agents may be necessary for a refractory condition.

REFERENCES

- [1] Sardana N, Santos C, Lehman E, et al. A comparison of intranasal corticosteroid, leukotriene receptor antagonist, and topical antihistamine in reducing symptoms of perennial allergic rhinitis as assessed through the Rhinitis Severity Score. *Allergy Asthma Proc* 2010;31:5–9.
- [2] Joe SA, Thambi R, Huang J. A systematic review of the use of intranasal steroids in the treatment of chronic rhinosinusitis. *Otolaryngol Head Neck Surg* 2008;139:340–7.
- [3] Bachert C. Evidence-based management of nasal polyposis by intranasal corticosteroids: from the cause to the clinic. *Int Arch Allergy Immunol* 2011;155:309–21.
- [4] Klossek JM, Laliberté F, Laliberté MF, et al. Local safety of intranasal triamcinolone acetonide: clinical and histological aspects of nasal mucosa in the long-term treatment of perennial allergic rhinitis. *Rhinology* 2001;39:17–22.
- [5] Cervin A, Andersson M. Intranasal steroids and septum perforation—an overlooked complication? A description of the course of events and a discussion of the causes. *Rhinology* 1998;36:128–32.
- [6] Webb EL. Nasal candidiasis in a patient on long-term topical intranasal corticosteroid therapy. *J Allergy Clin Immunol* 1993;91:680–1.
- [7] Kyrmizakis DE, Papadakis CE, Lohuis PJ, et al. Acute candidiasis of the oro- and hypopharynx as the result of topical intranasal steroids administration. *Rhinology* 2000;38: 87–9.
- [8] Shuto H, Noguchi H, Nishikata H, et al. A case of the esophageal candidiasis supposedly caused by rhinencysis steroid chronic administration before sleep. *Arerugi* 2007;56: 714–20.
- [9] Mokhtari Amirmajdi M, Mokhtari Amirmajdi NA, Eftekharzadeh Mashhadi I, et al. *Alternaria* in patients with allergic rhinitis. *Iran J Allergy Asthma Immunol* 2011;10: 221–6.
- [10] Daley-Yates PT, Kunka RL, Yin Y, et al. Bioavailability of fluticasone propionate and mometasone furoate aqueous nasal sprays. *Eur J Clin Pharmacol* 2004;60:265–8.