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ORIGINAL ARTICLE

Esophageal Candidiasis—An Adverse Effect of Inhaled Corticosteroids Therapy

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Over the last few decades, inhaled corticosteroids (ICs) became the cornerstone in the treatment of persistent asthma. Their use improved asthma control, decreased mortality and also minimized adverse reactions associated with systemic steroid. Esophageal candidiasis is a rare complication resulting from the use of ICs. Although, in recent years, as their prescriptions has increased, more cases have been reported, especially in Japan. Listed are 4 case reports regarding esophageal candidiasis in asthmatic patients associated with inhaled budesonide administration. In the cases reported herein, the use of a different device of dry powder budesonide might have favored esophageal drug deposition and *Candida* infection. Patients denied using systemic corticosteroids in the previous 6 months. Furthermore, none of the patients presented Diabetes mellitus, malignant disease, HIV infection, or other immunosuppressive conditions. We conclude that patients treated with high doses of ICs are at higher risk of developing esophageal candidiasis. These patients should undergo upper gastrointestinal endoscopy whenever they present symptoms. Nevertheless, we must keep in mind that infection might also be asymptomatic and esophageal candidiasis prevalence may be higher than that reported thus far.

Keywords Esophageal candidiasis, inhaled corticosteroid, budesonide, asthma, drug adverse reaction

INTRODUCTION

Over the last few decades, inhaled corticosteroids (ICs) became the cornerstone in the treatment of persistent asthma. The use of inhaled agents improved asthma control, decreased mortality and adverse reactions associated with systemic steroid treatment. However, oropharyngeal candidiasis and dysphonia are common adverse reactions of inhaled treatment and may lead to a lack of adherence with prescribed therapy (1).

On the other hand, esophageal candidiasis is a rare complication resulting from inhaled steroids' administration (2–4). In recent years, as the use of inhaled steroids has increased, more local adverse reactions have been reported, especially in Japan (5–7). A Japanese study reported that the prevalence of esophageal candidiasis was 37% in a population of asthmatic patients that had been treated with inhaled fluticasone (5).

Listed below are four case reports regarding esophageal candidiasis in asthmatic patients. As far as we know, in Latin America, these are the first reports of esophageal candidiasis associated with the use of inhaled budesonide.

Case Reports

The four patients herein reported suffered from moderate persistent asthma and were treated with a combination of inhaled budesonide and formoterol dry powder (Fig. 1). Regarding the dry powder device, three patients used the aeroliser and one the turbuhaler. Asthma was controlled in all patients, and they had each been instructed to rinse their mouth after corticosteroid inhalation.

Between 4 and 7 months following the last dose adjustment of inhaled corticosteroid, patients complained of epigastralgia and pyrosis (one patient). None of the patients reported fever and on clinical evaluation no evidence of moniliasis was noticed. Upper gastrointestinal endoscopy (UGE) of the patients revealed slightly raised white plaques, firmly adhered to the mucosa, suggestive of esophageal candidiasis. Histological examination of esophageal biopsies showed the presence of spores and septated hyphae, compatible with fungal infection.

Patients denied using systemic corticosteroids in the previous six months. Furthermore, none of the patients presented Diabetes Mellitus, malignant disease, HIV infection, or other immunosuppressive factors. Infections were treated and patients became free of symptoms.

DISCUSSION

Asthma, a chronic inflammatory disease of the airways, is associated with bronchial hyperresponsiveness and recurrent episodes of sibilus, dyspnea, mild chest pain, and coughing, especially at night and dawn (1). These episodes are associated with pulmonary airflow obstruction, which reverses spontaneously or with treatment (1).

Since asthma is an inflammatory disease, maintenance treatment is based on the use of inhaled corticosteroids (1). With the use of inhaled corticosteroids many patients were able to stop the use of systemic corticosteroids and thus, reduce their adverse effects. Adverse effects of inhaled steroid therapy include dry mouth and throat, hoarseness, oropharyngeal and laryngeal candidiasis (2, 3, 8). Nevertheless, esophageal candidiasis due to inhaled corticosteroids is rare. This is believed to be the first reported cases of esophageal candidiasis associated with inhaled corticosteroids in Latin America.

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	Case 1	Case 2	Case 3	Case 4
Sex	Female	Female	Male	Female
Age (years)	68	52	68	53
Asthma	Allergic	Non-Allergic	Allergic	Allergic
Esophageal symptoms	None	None	None	Present
Epigastric symptoms	Present	Present	Present	Present
Dose of budesonide	1200 mcg/day	1600 mcg/day	800 mcg/day	800 mcg/day
Equipment	Aeroliser (dry powder)	Aeroliser (dry powder)	Aeroliser (dry powder)	Turbuhaler (dry powder)
Co-morbidities	None	None	Hemochromatosis	None
Glycemia	Normal	Normal	Normal	Normal
Hemogram	Normal	Normal	Normal	Normal
HIV Serology	Negative	Negative	Negative	Negative
Immunoglobulins	Normal	Normal	Normal	Normal

FIGURE 1.—Relevant clinical and laboratory data of the four patients treated with inhaled budesonide and presented with esophageal candidiasis.

The first cases of esophageal candidiasis were reported in the late 1970's and were associated with beclomethasone (9, 10). However, the first case with lasting impact in medical literature was reported in 1988: a 23-year-old woman, treated with 400 mcg/day of inhaled beclomethasone (11). Yet, this patient also suffered from hypogammaglobulinemia with IgG 596 mg/dL, and normal levels of IgA and IgM. In 1992, 3 additional cases of esophageal candidiasis were reported in patients using inhaled corticosteroids; one of these patients had Diabetes Mellitus (DM) with no additional immunosuppression factors (12). Out of the 3 patients, 2 used 800 and 1600 mcg/day of budesonide with the turbuhaler. Out of the 4 patients herein reported, three used budesonide with a dry powder aeroliser device registered in Brazil.

In 1997, another case of esophageal candidiasis was reported in a 70-year-old woman, who was treated with 400 mcg/day of triamcinolone, and with no evidence of immunosuppression or DM (3).

Following the literature description of these seven cases of esophageal candidiasis secondary to inhaled steroids, in 2003, a Japanese research group published a study on the prevalence of esophageal candidiasis in patients under inhaled fluticasone treatment (5). A total of 49 patients underwent upper gastrointestinal endoscopy (UGE). Of the 49 patients, 36 were asthmatic and 13 suffered from chronic obstructive pulmonary disease (COPD). Patients were treated with 200 mcg to 1200 mcg per day of fluticasone, with a diskhaler device. Duration of treatment varied from 5 to 42 weeks. In order to prevent the development of oropharyngeal candidiasis, all patients had been instructed to rinse mouth immediately after inhalation therapy. Observation of white plaques in the esophagus was followed by biopsy and samples were sent to a laboratory to confirm the diagnosis.

In that study, the control group consisted of 700 patients with no immunosuppression or malignant disease, who underwent UGE because of upper gastrointestinal symptoms. In the control group prevalence of *Candida* colonization of the esophagus was 0.3%, whereas in the group treated with ICs, prevalence of *Candida* colonization was 36.1% (18 patients). None of the affected patients reported symptoms compatible with the disorder. Prevalence was significantly higher in the group treated with ICs ($p < 0.001$). Among patients with esophageal candidiasis, higher doses of ICs were

associated with a higher frequency of infection: esophageal candidiasis was present in 75% of patients treated with 1200 mcg of fluticasone per day. Patients treated with doses lower than 600 mcg per day did not develop esophageal candidiasis. Furthermore, prevalence of infection was significantly higher in patients with Diabetes mellitus ($p < 0.01$); all diabetic patients who participated in the study (5 patients) presented esophageal candidiasis. Finally, only one of 49 patients treated with fluticasone developed oropharyngeal candidiasis.

In the same year, another larger Japanese study was published which described a 35% prevalence of esophageal candidiasis in 20 patients who used fluticasone with a diskhaler device (6). This study also included a direct evaluation of the esophageal concentration of fluticasone after inhalation and results show that after 30 minutes fluticasone remained detectable in the esophagus. The authors decided to study one patient with grade III moniliasis, and changed the inhalation times to before breakfast and dinner, and obtained partial regression of the lesions to degree II. This study implies that the use of medication immediately before sleep increases the risk of developing active *Candida albicans* infection in the esophagus. Besides rinse mouth after corticosteroid inhalation, drinking and eating something may help to prevent esophageal candidiasis, because these procedures washout corticosteroids from the esophagus.

The same Japanese group that reported the first survey on the prevalence of esophageal candidiasis recently published a study that evaluated the effects of changing both the corticosteroid and the inhalation device while monitoring the evolution of patients with esophageal candidiasis due to ICs (7). Because of the risk of poor asthma control associated with the decreased dosage of ICs, fluticasone dry powder (diskhaler) was replaced with an equivalent dose of aerosol beclomethasone administered with a hydrofluoroalkane (HFA) pressurized metered-dose inhaler with a spacer device. Two to three months after the change in medication, a second UGE was performed to evaluate possible remaining lesions. Even without any antifungal treatment, lesions resolved in 9 of 10 patients and intensity of lesions decreased in the 10th patient (in the same period candidiasis reduced from degree III to degree II). This particular patient suffered from Diabetes mellitus (DM) and presented poor glycemia control

during this period, which might explain the non-resolution of lesions. None of the patients reported poor control of asthma symptoms. According to the results of that study, replacement of fluticasone diskhaler with beclametasone aerosol with a spacer device, without specific treatment, is enough to eliminate *Candida* infection (7). Other works had demonstrated that spacers reduce the incidence of colonization and clinical thrush (13, 14).

Another study disagreed with the prevalence rates described above. The results showed similar esophageal colonization rates between asthma patients taking corticosteroids and control group. This study emphasize that we must differentiate esophageal candidiasis from esophageal *Candida* colonization (15).

In order to inhibit local adverse effects of ICs, such as hoarseness and esophageal candidiasis, it is necessary to decrease the amount of ICs deposited on the oropharynx (7, 12). Studies have focused on the efficiency of inhalation devices (ID) regarding the proportion of the drug that reaches the lower airways (16, 17). The size of the drug particles, the flow rate (depending on characteristics of the ID, and of the patient), the size of the mouthpiece (outflow opening) and the internal geometry of the ID, and the type of flow (laminar or turbulent) will determine the amount of pulmonary and extra-thoracic deposition (mouth, pharynx, trachea and nasal fossae).

In the cases reported herein, the use of high doses of dry powder budesonide, the device features and possibly the size of the drug particle might have favored *Candida* infection.

We conclude that patients treated with high doses of ICs, especially patients with DM and other immunosuppressive factors, are at higher risk of developing esophageal candidiasis. We recommend that these patients undergo UGE whenever they present upper digestive symptoms that did not improve with treatment. Nevertheless, we must keep in mind that infection might also be asymptomatic and, in this case, prevalence may be higher than that reported thus far.

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