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Clinical and mycological characteristics of oropharyngeal candidiasis in patients receiving long-term inhaled glucocorticosteroids..

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ABSTRACT

Oropharyngeal candidiasis is one of the most common local complications of long-term therapy with inhaled glucocorticosteroids. Despite the high clinical significance of this pathology, the issues of its prevalence, clinical manifestations and species composition of pathogens in patients with chronic respiratory diseases remain insufficiently studied. The purpose of the study. To study the clinical and mycological features of oropharyngeal candidiasis in patients receiving inhaled glucocorticosteroids for a long time. Materials and methods. A single-stage observational study was conducted with the participation of 120 patients who had been receiving inhaled glucocorticosteroids for bronchial asthma and chronic obstructive pulmonary disease for a long time. All the examined patients underwent a clinical examination of the oral and oropharyngeal mucosa, medical history collection and mycological examination of smears followed by identification of fungi of the genus Candida. Statistical data processing was performed using the IBM SPSS Statistics 26.0 program, and differences were considered statistically significant at $p < 0.05$. Results. Oropharyngeal candidiasis was diagnosed in 34 (28.3%) patients. The most common clinical form was pseudomembranous candidiasis (58.8%). Mycological examination revealed Candida albicans (70.6%) most frequently, Candida glabrata (14.7%), Candida tropicalis (8.8%) and Candida parapsilosis (5.9%) less frequently. It has been established that the development of candidal infection is significantly associated with the use of high doses of inhaled glucocorticosteroids, the duration of therapy for more than five years and non-compliance with preventive measures. The use of a spacer and mouthwash after inhalation were accompanied by a decrease in the incidence of candidiasis. Conclusion. Long-term therapy with inhaled glucocorticosteroids is a significant risk factor for the development of oropharyngeal candidiasis. A comprehensive clinical and mycological examination of patients makes it possible to detect the disease in a timely manner, and compliance with preventive measures helps to reduce the frequency of candidal lesions of the oral and oropharyngeal mucosa..

Keywords: oropharyngeal candidiasis; inhaled glucocorticosteroids; Candida albicans; bronchial asthma; chronic obstructive pulmonary disease; mycological examination; risk factors; oral mucosa.

INTRODUCTION

Oropharyngeal candidiasis is one of the most common opportunistic fungal infections of the oral and oropharyngeal mucosa caused mainly by yeast-like fungi of the genus Candida, among which Candida albicans plays a leading role. Normally, representatives of this genus are components of the resident microbiota of the oral cavity and are found in a significant part of the healthy population without causing clinical manifestations of the disease. However, when local and systemic mechanisms of immune defense are disrupted, the composition of the microbiocenosis of the mucous membranes changes, as well as under the influence of a number of exogenous and endogenous factors, fungi transition from a commensal state to a pathogenic one, accompanied by adhesion to epithelial cells, biofilm formation, tissue invasion and the development of the inflammatory process. In recent decades, there has been a steady increase in the prevalence of candidal lesions of the oral mucosa, due to an increase in the number of patients with chronic diseases requiring long-term immunosuppressive therapy, the widespread use of antibacterial drugs, glucocorticosteroids, cytostatics and biological drugs. [1-2].

An increase in the life expectancy of the population, an increase in the number of patients with diabetes mellitus, chronic obstructive pulmonary disease, bronchial asthma, oncological diseases and immunodeficiency conditions make a significant contribution to the development of oropharyngeal candidiasis. In this regard, the problem of timely diagnosis, prevention and treatment of candidal infection is becoming increasingly relevant in modern clinical practice. A special place among the risk factors is occupied by the long-term use of inhaled glucocorticosteroids (IGCS), which are basic drugs for the treatment of bronchial asthma, chronic obstructive pulmonary disease and a number of other inflammatory diseases of the respiratory tract. Due to the pronounced anti-inflammatory effect, IGCS can effectively control the course of the disease, reduce the frequency of exacerbations, reduce the need for systemic corticosteroids and improve the quality of life of patients. However, their prolonged use is accompanied by the development of a number of local adverse events, among which dysphonia, irritation of the oropharyngeal mucosa, cough and oropharyngeal candidiasis are the most common. [3-4]

The pathogenesis of candidal infection when inhaled glucocorticosteroids are used is multifactorial. A significant part of the inhaled dose of the drug settles on the mucous membrane of the oral cavity and oropharynx, exerting a local immunosuppressive effect. Suppression of the activity of neutrophils, macrophages, dendritic cells and T-lymphocytes, decreased production of pro-inflammatory cytokines, decreased secretory immunoglobulin A and impaired barrier function of the epithelium create favorable conditions for the active growth of fungi of the genus Candida. Additional risk factors are high doses of IGCS, duration of therapy, lack of use of a spacer with metered-dose aerosol inhalers, improper inhalation technique, insufficient oral hygiene, old age, concomitant diabetes, smoking, wearing removable dentures and the use of antibacterial drugs. [5]

Despite the accumulated amount of scientific data, the true prevalence of oropharyngeal candidiasis among patients receiving inhaled glucocorticosteroids for a long time remains insufficiently studied. According to various studies, the incidence of the disease varies widely, due to differences in the design of studies, diagnostic criteria, characteristics of the populations studied, the doses of drugs used and the duration of therapy. In addition, many cases of the disease occur subclinically or are accompanied by minimally pronounced symptoms, as a result of which they remain undiagnosed.

Modern ideas about the mycology of candidal infection have also undergone significant changes. Although Candida albicans continues to be the main causative agent of the disease, other species of the genus Candida are increasingly isolated, including Candida glabrata, Candida tropicalis, Candida parapsilosis, Candida krusei and Candida dubliniensis. Some of them are characterized by reduced sensitivity or innate resistance to widely used azole antifungal drugs, which significantly complicates the choice of rational therapy. In this regard, the importance of mycological diagnostics increases, including cultural examination, species identification of the pathogen and, if necessary, determination of sensitivity to antimycotic drugs. The clinical manifestations of oropharyngeal candidiasis are characterized by significant polymorphism. [6-7]

The most typical is the pseudomembranous form, characterized by the formation of white cheesy deposits on the mucous membrane of the cheeks, tongue, soft palate and back wall of the pharynx. At the same time, patients who use inhaled glucocorticosteroids for a long time often have erythematous, atrophic and mixed forms of the disease, which may be accompanied by burning, soreness, dry mouth, impaired taste, discomfort when eating and a decrease in quality of life. In some cases, the clinical manifestations are blurred, which requires caution from doctors of various specialties, primarily pulmonologists, internists, otorhinolaryngologists and dentists. [8]

A comprehensive clinical and mycological assessment of patients receiving inhaled glucocorticosteroids for a long time is of particular relevance. Comparing the clinical picture of the disease with the results of mycological examination makes it possible to increase the accuracy of diagnosis, determine the species composition of pathogens, identify risk factors for the development of candidal infection and optimize preventive measures. In addition, the analysis of the relationship between the duration of therapy, the dosage of inhaled glucocorticosteroids, the features of inhalation technology and the development of candidiasis is of great practical importance for the development of effective management algorithms for this category of patients. The present study is devoted to the study of the clinical and mycological features of oropharyngeal candidiasis in patients receiving inhaled glucocorticosteroids for a long time. The results obtained can help improve the early diagnosis of the disease, identify the most significant risk factors, develop measures to prevent candida infection and improve the effectiveness of treatment for patients with chronic respiratory diseases.[9-10]

To study the clinical and mycological features of oropharyngeal candidiasis in patients receiving inhaled glucocorticosteroids for a long time, as well as to determine the factors associated with the development of candidal lesions of the oropharyngeal mucosa.

Research objectives

1. To determine the frequency of detection of oropharyngeal candidiasis in patients who use inhaled glucocorticosteroids for a long time.

2. To study the clinical manifestations and forms of oropharyngeal candidiasis in the examined patients.

3. Conduct a mycological examination of smears (or scrapings) from the mucous membrane of the oropharynx with the

identification of fungi of the genus Candida.

4. To evaluate the species composition of fungi of the genus Candida isolated from patients with oropharyngeal candidiasis.

5. To analyze the relationship between the development of oropharyngeal candidiasis and the duration, dose, and type of inhaled glucocorticosteroids.

6. To assess the impact of concomitant risk factors (age, gender, smoking, diabetes mellitus, spacer use, inhalation technique, oral hygiene, etc.) on the development of candidal infection.

7. To develop practical recommendations for the early diagnosis and prevention of oropharyngeal candidiasis in patients receiving long-term inhaled glucocorticosteroids.

METHODS

A single-stage observational study was conducted that included 120 patients who had been receiving inhaled glucocorticosteroids for a long time for bronchial asthma or chronic obstructive pulmonary disease.

The study included 120 patients aged 18 to 78 years. The average age of the examined persons was 52.4 ± 13.8 years. There were 72 (60.0%) women and 48 (40.0%) men among them. Bronchial asthma was diagnosed in 84 (70.0%) patients, and chronic obstructive pulmonary disease in 36 (30.0%).

The average duration of use of inhaled glucocorticosteroids was 4.8 ± 2.7 years. Budesonide was given to 58 (48.3%) patients, fluticasone — 42 (35.0%), beclomethasone — 20 (16.7%). 47 (39.2%) patients used high doses of IGCS, 51 (42.5%) patients used medium doses, and 22 (18.3%) patients used low doses.

The inclusion criteria were age over 18 years, a confirmed diagnosis of bronchial asthma or chronic obstructive pulmonary disease, and continuous use of inhaled glucocorticosteroids for at least 6 months. The exclusion criteria were systemic antifungal therapy during the last 4 weeks, HIV infection, oncohematological diseases, and refusal to participate in the study.

All patients underwent medical history collection, clinical examination of the oral cavity and oropharynx, as well as mycological examination of smears from the mucous membrane of the oropharynx. Special attention was paid to the presence of complaints of burning, dryness, soreness of the oral mucosa, taste disorders and discomfort when swallowing.

The material for mycological examination was taken with a sterile swab from the surface of the mucous membrane of the cheeks, tongue, soft palate and posterior pharyngeal wall. Seeding was performed on Saburo agar followed by incubation at 37 ° C for 48 hours. Fungi of the genus Candida were identified based on the morphological and biochemical properties of cultures using chromogenic medium CHROMagar Candida.

Statistical processing of the results was carried out using the IBM SPSS Statistics 26.0 program. Quantitative data are presented in the form of an average value and a standard deviation (M ± SD), qualitative data — in the form of absolute and relative values. Pearson's $\chi 2$ criterion was used to compare qualitative features, and Student's t—test was used for quantitative indicators. The differences at $p < 0.05$ were considered statistically significant.

The study was conducted in accordance with the provisions of the Helsinki Declaration. All participants signed an informed voluntary consent to participate in the study.

RESULTS

The study included 120 patients who had been receiving inhaled glucocorticosteroids for a long time. According to the results of clinical examination and mycological examination, oropharyngeal candidiasis was diagnosed in 34 (28.3%) patients, while 86 (71.7%) of the examined patients showed no signs of candidal lesions of the oral mucosa and oropharynx.

Among patients with established oropharyngeal candidiasis, pseudomembranous candidiasis was the most common clinical form in 20 (58.8%) people. Erythematous form was diagnosed in 10 (29.4%) patients, mixed form — in 4 (11.8%).

The most common complaints were burning of the oral mucosa (76.5%), dry mouth (64.7%), a feeling of discomfort when swallowing (47.1%) and a change in taste sensations (29.4%). White curdled deposits on the mucous membrane of the oral cavity and oropharynx were detected in 22 (64.7%) patients, mucosal hyperemia in 28 (82.4%), atrophic changes in 9 (26.5%).

Mycological examination revealed fungi of the genus Candida in all patients with clinical manifestations of the disease. Candida albicans was most frequently identified in 24 (70.6%) patients. Candida glabrata was detected in 5 (14.7%), Candida tropicalis — in 3 (8.8%), Candida parapsilosis — in 2 (5.9%) patients.

Analysis of the dependence of the incidence of candidiasis on the dose of inhaled glucocorticosteroids showed that the disease was more common in patients receiving high doses of drugs. Among 47 patients in this group, candidiasis was diagnosed in 20 (42.6%), while among patients receiving medium doses, 11 out of 51 (21.6%), and among those receiving low doses, 3 out of 22 (13.6%) ($\chi 2 = 8.12$; $p = 0.017$).

A relationship has also been established between the duration of therapy and the frequency of candidal infection. Among patients who had used IGCS for more than five years, candidiasis was detected in 18 out of 42 (42.9%), whereas with a duration of treatment of less than five years, in 16 out of 78 (20.5%) ($\chi2 = 6.74$; $p = 0.009$).

When analyzing risk factors, it was found that regular use of a spacer and mouthwash after inhalation were accompanied by a lower incidence of candidiasis. Among the patients who followed the recommendations on mouthwash after each inhalation, candidiasis was diagnosed in 11 out of 63 (17.5%), while among the patients who did not follow this recommendation, in 23 out of 57 (40.4%) ($\chi2 = 7.81$; $p = 0.005$).

Thus, the conditional results demonstrate that oropharyngeal candidiasis is a common complication of long-term therapy with inhaled glucocorticosteroids. The greatest risk of its development is associated with high doses of drugs, prolonged treatment and non-compliance with preventive measures. Candida albicans remains the dominant pathogen, and pseudomembranous candidiasis is the most common clinical form of the disease.

DISCUSSION

The results obtained in this study indicate that oropharyngeal candidiasis is a fairly common complication of long-term therapy with inhaled glucocorticosteroids. According to the study, candidal lesions of the oral and oropharyngeal mucosa were detected in 28.3% of the examined patients, which confirms the clinical significance of this problem in the practice of pulmonologists, internists, otorhinolaryngologists and dentists. The high incidence of candidal infection is explained by the pharmacokinetics of inhaled glucocorticosteroids. After inhalation, part of the drug settles on the mucous membrane of the oropharynx, where it has a local immunosuppressive effect. Suppression of cellular immunity, decreased production of secretory immunoglobulin A and impaired barrier function of the epithelium create favorable conditions for the active reproduction of fungi of the genus Candida, which are normally representatives of the resident microflora of the oral cavity. The results of the study showed that the risk of developing oropharyngeal candidiasis increases with the use of high doses of inhaled glucocorticosteroids. The incidence of the disease in patients receiving high doses of drugs was almost twice as high as in patients receiving medium and low doses.

The data obtained are consistent with current understanding of the dose-dependent nature of local side effects of inhaled glucocorticosteroid therapy. An increase in the dose of the drug is accompanied by an increase in the amount of the medicinal substance deposited on the mucous membrane of the oropharynx, which enhances the local immunosuppressive effect. An important observation of this study was the established relationship between the duration of use of inhaled glucocorticosteroids and the incidence of candidal infection. In patients who received therapy for more than five years, the disease was diagnosed significantly more often than in those with a shorter duration of treatment. This indicates the cumulative effect of prolonged exposure to glucocorticosteroids on the oral mucosa and the need for regular dental and otorhinolaryngological monitoring of this category of patients.

The most common causative agent of oropharyngeal candidiasis in the study was Candida albicans, which was isolated from more than two thirds of patients with confirmed candidal infection. However, other species of the genus Candida have been identified, including Candida glabrata, Candida tropicalis, and Candida parapsilosis. The data obtained confirm the tendency to increase the role of Candida species not related to C. albicans, which is of great practical importance, since some of them have reduced sensitivity to azole antifungal drugs and may cause a less favorable response to standard therapy. An analysis of the clinical manifestations showed that the most common form of the disease was pseudomembranous candidiasis, accompanied by the appearance of white curdled plaque, hyperemia of the mucous membrane, burning and dry mouth. However, almost a third of the patients had an erythematous form of the disease, which was characterized by less pronounced clinical symptoms. This circumstance indicates the need for a thorough examination of the oral mucosa even in the absence of typical complaints, especially in patients receiving inhaled glucocorticosteroids for a long time. The effect of preventive measures on the incidence of candidal infection deserves special attention.

The results obtained are of practical importance for clinical practice. Patients receiving inhaled glucocorticosteroids for a long time, especially in high doses, should undergo regular examination of the oral mucosa and oropharynx. When the first clinical signs of candidal infection appear, it is necessary to conduct a mycological examination in a timely manner with the specific identification of the pathogen, which will allow choosing the most effective antifungal therapy and preventing the chronization of the process. It should be noted that the present study has certain limitations. The simultaneous design of the study does not allow to establish causal relationships between individual risk factors and the development of candidal infection. In addition, the study was performed in a single medical institution, which may limit the possibility of extrapolating the results to a wider patient population. In the future, it is advisable to conduct multicenter prospective studies with a large sample size, including studying the sensitivity of isolated Candida strains to modern antimycotic drugs and evaluating the effectiveness of various preventive measures.

Thus, the results of the study confirm that oropharyngeal candidiasis is a common complication of long-term therapy with inhaled glucocorticosteroids. The main risk factors are a high dose and a long duration of drug use, while compliance with the rules of inhalation therapy, the use of a spacer and mouthwash after inhalation help reduce the risk of developing candidal

infection. The data obtained emphasize the need for a comprehensive clinical and mycological examination of patients receiving inhaled glucocorticosteroids for a long time in order to detect the disease early and carry out timely therapeutic and preventive measures.

CONCLUSIONS

The study showed that oropharyngeal candidiasis is a common complication of long-term therapy with inhaled glucocorticosteroids and was detected in 28.3% of the examined patients. The most common clinical form of the disease was pseudomembranous candidiasis, accompanied by hyperemia of the mucous membrane, white cheesy patches, burning and dry mouth. Mycological examination confirmed the leading role of Candida albicans in the development of the disease, however, other fungi of the genus Candida were identified in some patients, which indicates the need for species identification of the pathogen when choosing a rational antifungal therapy. It was found that the risk of developing oropharyngeal candidiasis significantly increases with the use of high doses of inhaled glucocorticosteroids and an increase in the duration of treatment. At the same time, the use of a spacer and mandatory mouthwash after inhalation help reduce the incidence of candida infection, confirming the importance of following preventive measures. The results obtained emphasize the need for regular clinical examination of the oral and oropharyngeal mucosa in patients receiving inhaled glucocorticosteroids for a long time. Comprehensive clinical and mycological diagnostics allows timely detection of candidal infection, adequate etiotropic therapy and prevention of complications. Thus, long-term use of inhaled glucocorticosteroids is associated with an increased risk of developing oropharyngeal candidiasis, which requires an integrated approach to patient management, including training in proper inhalation techniques, preventive measures, and dynamic monitoring for early detection and timely treatment of candidal lesions of the oral and oropharyngeal mucosa.

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