Short Communication

Factor associated with oral candidiasis caused by co-infection of Candida albicans and Candida glabrata: A retrospective study

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Abstract This study aimed to determine the factors associated with the co-infection of Candida albicans and Candida glabrata. This retrospective study conducted between January 2015 and 2020 comprised 131 patients who were diagnosed with oral candidiasis. The factors associated with this condition were analyzed by univariate and multivariate logistic regression. Age and denture use were identified as significant risk factors in the univariate analysis. The multivariate logistic regression analysis revealed that denture use (odds ratio [OR], 8.44; 95% confidence interval [CI], 1.99–28.3) and immunosuppressive therapy (OR, 9.20; 95% CI, 1.19–62.0) had significant effects on co-infection with the two Candida species. These findings suggest that immunosuppressive therapy using and dentures is significantly associated with oral candidiasis caused by co-infection of C. albicans and C. glabrata.

Introduction

Oral candidiasis is an opportunistic mucosal infection caused by the Candida species. Candida species are commensal fungi located in the oral cavity and do not cause any harm under normal conditions; however, changes in the oral environment can alter their balance, leading to infection. This study aimed to determine the factors associated with the co-infection of Candida albicans and Candida glabrata.
environment can allow it to overgrow and lead to the development of clinical symptoms. The predisposing factors for oral candidiasis include immunocompromised conditions, diabetes, presence of a dental prosthesis, xerostomia, history of radiation therapy (RT) to the head and neck region, and long-term use of antibiotics and immunosuppressive drugs. Patients with oral candidiasis complain of symptoms such as tongue pain, burning sensation, and taste abnormalities, which often affect their quality of life.

*Candida albicans* remains the main etiological agent in oral candidiasis, and the normal oral carriage of this particular species among the healthy adult population ranges from 30% to 50%. In recent years, the pathogenesis of oral candidiasis has changed with the use of medications, such as broad-spectrum antimicrobials and immunosuppressive agents, and an increase in non-albicans *Candida* species, particularly *Candida glabrata*, has been reported. The incidence of oral candidiasis caused by *C. glabrata* has increased by more than 17% in recent years. *C. glabrata* is rarely isolated alone and is often identified along with *C. albicans*. Oral candidiasis caused by co-infection of *C. albicans* and *C. glabrata* was found to be more severe and difficult to treat because *C. glabrata* is naturally resistant to azole antifungal agents. Therefore, an increase in the dosage of antifungal drugs might aid in curing this clinical condition. Nonetheless, it is important to assess the risk of developing oral candidiasis due to co-infection with the two *Candida* species.

Although some studies on co-infection of *C. albicans* and *C. glabrata* have been conducted in vitro, the clinical characteristics of patients with this condition remain unclear. The aim of this study was to evaluate the risk factors for the development of *C. albicans* and *C. glabrata* co-infection by comparing patients who developed the co-infection with those who were affected by any one of the *Candida* species. The objective was to subsequently assist in decision making associated with the treatment and prevention of patients from developing co-infection.

Materials and methods

Patients

One hundred and ninety-four patients who were diagnosed with oral candidiasis, based on their signs, symptoms, and results of a swab test at the Department of Oral Medicine, Hokkaido University Hospital, between January 2015 and December 2020, were recruited. Among them, 45 patients were excluded because of insufficient examinations such as blood tests and periodontal pocket examination, and 18 were excluded because of edentulous jaws. Subsequently, 131 patients who presented with the clinical manifestations in the oral cavity, were positive for oral candidiasis in the swab test, and did not receive antifungal treatment before the swab test, were enrolled in this study.

This retrospective study was conducted with the approval of the Hokkaido University Hospital Independent Clinical Research Review Committee (Approval No. 021-0085). All the study procedures were performed in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from all the participants. This article does not disclose identifiable information of any of the participants in any form. Hence, consent for publication is not applicable here.

Diagnosis of oral candidiasis and fungal identification

The lesions, which presented as white plaques and erythematous patches, were swabbed (Eiken Chemical Co., Ltd., Tokyo, Japan), and the specimens were promptly transported to the laboratory at our hospital. The swabs were directly inoculated onto CHROMagar medium (Kanto Chemical, Tokyo, Japan) and incubated at 36 °C. After 48 h, the samples that demonstrated colony formation were considered positive for oral candidiasis. The *Candida* species were identified by the color of the colony formed on the medium.

Study variables

Various factors such as patient characteristics (age, sex, smoking habit, diabetes mellitus [DM], use of a denture, immunosuppressive therapy, and history of cancer) and clinical parameters (periodontal pocket depth [PPD], serum albumin level, RT to the head and neck region, classification of oral candidiasis, and types of *Candida* species) were retrospectively examined from the medical record. PPD examination was performed using a periodontal probe. Oral candidiasis was classified according to the conventional criteria established by Lehner.

Statistical analysis

Statistical analyses were performed using JMP Pro for Windows (Version 14.0, SAS Institute, Cary, NC, USA) and included Fisher’s exact test and logistic regression analysis. The factors associated with co-infection were tested using univariate and multivariate logistic regression analysis. A *P* value of <0.05 was considered statistically significant.

Results

As shown in Table 1, 131 (52 men and 79 women; mean age, 65 years; median age, 66 years; age range, 28–89 years) were included in this study. The number of patients having different types of oral candidiasis was as follows: 69 with pseudomembranous candidiasis, 50 with acute erythematous candidiasis, and 12 with chronic erythematous candidiasis. A total of 23 patients were infected with a mixture of *C. albicans* and *C. glabrata*, 107 patients were infected by *C. albicans* alone, and 1 patient was infected with *C. glabrata* alone.

The univariate analysis demonstrated age (odds ratio [OR], 3.34; 95% confidence interval [CI], 1.16–9.65) and use of dentures (OR, 6.16; 95% CI, 1.97–19.3) as significant risk factors. Based on the *P* values in the univariate analysis and the factors conventionally regarded as risk factors for oral candidiasis, we decided to enter the following four factors into the multivariate analysis: age, sex (OR, 0.42; 95% CI, 0.16–1.07), use of a denture, history of immunosuppressive therapy (OR, 3.90; 95% CI, 0.81–18.8). As shown in Table 2, significant associations were observed for the use of a
denture (OR, 8.44; 95% CI, 1.99–28.3) and a history of immunosuppressive therapy (OR, 9.20; 95% CI, 1.19–62.0).

Discussion

To the best of our knowledge, this is the first study to evaluate the risk of developing a co-infection with C. albicans and C. glabrata among patients who infected with both or either of these species. In the multivariate logistic analysis, using dentures and immunosuppressive therapy were found to be significantly associated with co-infection; alternatively, age, which was identified as a significant risk factor in the univariate analysis, did not demonstrate any significant association in the multivariate analysis. Thus, age might be considered as a confounding factor in co-infection.

It is conceivable that oral candidiasis caused by C. glabrata alone is rare, and only two patients with this condition were observed in the present study. C. glabrata cannot form true hyphae, which is crucial for its adherence to the surface; moreover, in contrast to C. albicans, it generally occurs in the yeast form within the oral cavity. However, C. glabrata has been reported to adhere more readily to dentures than C. albicans because its cell surface is four times more hydrophobic and its ability to adhere to acrylic resin is two times higher than that of C. albicans. Dental prostheses have often been reported as a risk factor for the development of oral candidiasis. In addition, the hyphae produced by C. albicans may serve as a scaffold for the attachment of C. glabrata. Therefore, the presence of dentures and C. albicans may promote the colonization of C. glabrata, which in turn could promote co-infection. Furthermore, as indicated in the current study, co-infection is further aggravated by immunosuppressive therapy.

The risk of onset of oral candidiasis has been reported previously, and age has been identified as a typical factor. Nonetheless, the present study suggests that age may be a confounding factor in co-infections. Many factors change with age, and the volume of the resting saliva is a typical example. Saliva contains many components that inhibit the growth of Candida species. The volume of resting saliva decreases with age; therefore, a decrease in saliva flow increases the risk of developing oral candidiasis. Likewise, the number of teeth lost and the use of dentures increases with age. Alternatively, DM and smoking, which are known to be the risk factors for oral candidiasis, were not detected as risk factors in the present study. The risk factors for developing co-infections might be different from the conventional factors identified for oral candidiasis.

This study has several limitations. The time factor for the development of the co-infection was not determined in this study. Oral candidiasis was diagnosed based on swab examination alone; hence, the results may differ if additional tests are performed. Furthermore, we did not consider the findings of xerostomia and the oral hygiene status of the patient. Additional studies using an increased number of cases and test items are warranted.

In summary, the results of this study suggest that denture use and immunosuppressive therapy is significantly associated with oral candidiasis caused by co-infection of C. albicans and C. glabrata.

Declaration of competing interest

The authors have no conflicts of interest relevant to this article.

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