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Candidal infection in oral leukoplakia: a clinicopathologic study of 396 patients from eastern China

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ABSTRACT

Previous studies have suggested a link between the presence of *Candida* invasion and oral premalignant lesion. The objective of the current study was to investigate the clinicopathologic features of candidal infection in biopsies of a large retrospective cohort of patients with premalignant oral leukoplakia (n = 396) from eastern China and assess the clinical implications. Candidal hyphae were detected with periodic acid-Schiff staining of the biopsy samples. The results showed that 59 patients (15.9%) with oral leukoplakia were infected by *Candida*. The average age of the patients with candidal leukoplakia was 60.7 years with equal sex ratio. The tongue was the predominant site (66.1%). Epithelial hyperplasia and dysplasia were involved in 44.1% and 55.9% of patients, respectively. Multivariate analysis revealed that patient older than 60 years (odd ratio [OR], 2.28; $P = .005$), lesion located at the tongue (OR, 1.89; $P = .038$), and presence of dysplasia (OR, 2.02; $P = .018$) were significant risk factors of candidal infection in oral leukoplakia. Collectively, clinicopathologic features of candidal leukoplakia in eastern China were elucidated. A point to highlight was that we identified a subpopulation that was more liable to candidal infection. Elderly patients with oral tongue leukoplakia with epithelial dysplasia had much higher risk of candidal infection. Antifungal therapy was further recommended to be routine treatment of this subpopulation.

1. Introduction

Oral *Candida* is a commensal colonizer of mucous membranes that can become an opportunistic pathogen. Epithelial changes of the oral mucosa, such as trauma, maceration, atrophy, hyperplasia, and dysplasia, may compromise the mucosal barrier and predispose to candidal infection [1,2]. Histopathologically, oral *Candida* presents epithelial hyperplasia, hyperparakeratosis, superficial microabscess formation, and various degrees of chronic inflammation in the lamina propria. Candidal hyphae may be seen invading the epithelium at right angles to the surface, which associated with the collections of polymorphonuclear leukocytes [3,4]. Histologically, detectable *Candida* invasion was best done by periodic acid-Schiff (PAS) reagent staining [4].

Oral leukoplakia is defined as "a white plaque of questionable risk having excluded (other) known diseases or disorders that carry no increased risk for cancer," which is the best-known potentially malignant lesion of the oral mucosa [5,6]. Epithelial hyperplasia and dysplasia are 2 of the key histologic features of leukoplakia. *Candida* invasion has been suggested to be a significant risk factor of malignant transformation of oral leukoplakia [7]. Histopathologically, candidal leukoplakia presents hyperorthokeratinized or hyperparakeratinized and various degrees of a chronic inflammatory cell infiltrate seen in the lamina propria; the parakeratinized surface epithelium may show irregular separation. Candidal hyphae may be seen invading the epithelium at right angles to the surface, which associated with the collections of polymorphonuclear leukocytes forming microabscesses [4].

Previous reports from the United Kingdom have determined the frequency of candidal infection in biopsies of oral mucosal diseases and shown that candidal infection correlated with the presence of oral dysplasia and neoplasia [8,9]. However, the issue of the prevalence and distribution of candidal infection in oral leukoplakia has seldom been addressed in China. We, therefore, retrospectively reviewed a large series of patients with oral leukoplakia (n = 396) from eastern China to investigate the epidemiological and clinicopathologic features of candidal infection in oral leukoplakia and to assess the clinical implications in the current hospital-based study.

2. Materials and methods

All the medical records of patients with the clinical and pathologic diagnosis of oral leukoplakia from January 2005 to December 2007

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were retrospectively reviewed in a standard computerized database of Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine. All the patients enrolled in this study underwent biopsy. The biopsy was fixed in formalin, embedded in paraffin, and processed for routine histopathologic examination. The World Health Organization criteria [10] for oral leukoplakia and epithelial dysplasia were used when examining the histopathology of the sections. The diagnosis of candidal leukoplakia was accorded to the Sitheeque-Samaranayake criteria [4]. Histopathologic diagnosis was given by the oral pathologists on duty from hematoxylin-eosin (HE)–stained slides, and candidal hyphae were detected with PAS staining of the biopsy samples.

Information regarding age, sex, lesion site, and histologic status at the time of the initial diagnosis of oral leukoplakia was all documented in detail. To analyze the candidal infection in oral leukoplakia, all the study participants were classified into group 1, general leukoplakia, which was not infected by *Candida*, and group 2, candidal leukoplakia, which was infected by *Candida*. This study was approved by the local institutional review board.

A descriptive analysis was performed on clinicopathologic parameters. Statistical analysis was carried out with the χ^2 test and Fisher exact test among qualitative variables and the Student *t* test among quantitative variables. Logistic regression was applied to evaluate odds ratios (ORs) for indicative of infection risk. Odds ratios with 95% confidence interval (CI) and *P* values were reported. All the tests were 2 sided, and $P < .05$ was considered statistically significant.

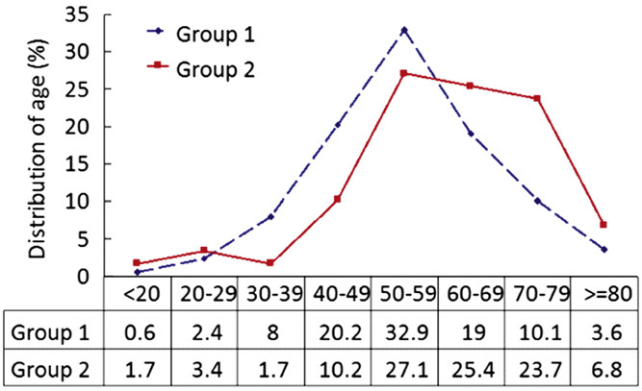
3. Results

3.1. Characteristics of candidal leukoplakia

The baseline characteristics of 396 patients with oral leukoplakia are summarized in Table 1. A total of 59 patients (15.9%) with candidal leukoplakia were identified for this study, ranging from 11 to 90 years with an average age of 60.7 years at the time of diagnosis. The percent distribution of the patient age was shown in Fig. 1. The peak incidence (27.1%) of the patients with candidal leukoplakia was the fifth decade of life. These patients with candidal leukoplakia were 29 females and 30 males. The tongue was affected in 39 patients (66.1%), followed by the buccal mucosa (20.3%). Epithelial hyperplasia and dysplasia were involved in 44.1% and 55.9% of patients, respectively. Representative histopathologic photographs of HE and PAS staining of candidal leukoplakia with epithelial hyperplasia and dysplasia were shown in Fig. 2.

Table 1
Baseline characteristics of 396 patients with oral leukoplakia

Characteristic, n (%)	General leukoplakia	Candidal leukoplakia
Total	337 (84.1)	59 (15.9)
Age (y)		
Mean (SD)	54.6 (13.3)	60.7 (15.4)
Range	7-87	11-90
Not available	11	–
Sex		
Female	170 (50.4)	29 (49.2)
Male	167 (49.6)	30 (50.8)
Site		
Tongue	162 (48.1)	39 (66.1)
Buccal mucosa	101 (30.0)	12 (20.3)
Gingiva	45 (13.4)	4 (6.8)
Palate	12 (3.6)	3 (5.1)
Mouth floor	10 (3.0)	–
Lip	6 (1.8)	–
Oropharynx	1 (0.3)	1 (1.7)
Histology		
Hyperplasia	224 (66.5)	26 (44.1)
Dysplasia	113 (33.5)	33 (55.9)



	<20	20-29	30-39	40-49	50-59	60-69	70-79	>=80
Group 1	0.6	2.4	8	20.2	32.9	19	10.1	3.6
Group 2	1.7	3.4	1.7	10.2	27.1	25.4	23.7	6.8

Fig. 1. Age distribution of patients with oral leukoplakia. Group 1, general leukoplakia. Group 2, candidal leukoplakia.

3.2. Comparison of general leukoplakia and candidal leukoplakia

To define the differences in clinicopathologic parameters between general leukoplakia and candidal leukoplakia, a comparative analysis was preformed (Table 2). The average age of the patients with general leukoplakia was 54.6 years compared with that of 60.7 years of the patients with candidal leukoplakia (Student *t* test, $P = .002$), with a difference in the age group (≤ 60, >60 years) (Fisher exact test, $P = .003$). Significant difference in lesion site (Fisher exact test, $P = .011$) was also observed, whereas differences in sex were not observed between the 2 groups.

To evaluate the candidal infection risk of patients with oral leukoplakia, clinicopathologic parameters were analyzed by using the logistic regression model (Table 2). On univariate analysis, sex was not associated significantly with infection risk. The elderly patient (>60 years) was associated with 2.43-fold (95% CI, 1.39-4.27; $P = .002$) increased infection risk compared with the nonelderly patient. The lesion located on the tongue was associated with 2.11-fold (95% CI, 1.18-3.76; $P = .012$) increased infection risk compared with that located on the other oral sites. The lesion had dysplasia was associated with 2.52-fold (95% CI, 1.44-4.41; $P = .001$) increased infection risk compared with the lesion had hyperplasia.

To further assess the influence of each factor, we did multivariate analysis. The 3 factors retained statistical significance. The infection risk of the elderly patient with oral leukoplakia (≥ 60 years) was higher than the nonelderly patient (adjusted OR, 2.28; 95% CI, 1.28-4.06; $P = .005$). The lesion located on the tongue was associated with increased infection risk compared with that located on the other oral sites (adjusted OR, 1.89; 95% CI, 1.04-3.46; $P = .038$). The infection risk of the lesion that had dysplasia was higher than the lesion that only had hyperplasia (adjusted OR, 2.02; 95% CI, 1.13-3.63; $P = .018$).

4. Discussion

Previous studies have suggested that the presence of *Candida* invasion was associated with the development of oral dysplasia and squamous cell carcinoma [11-16]. The current study attempts to elucidate the epidemiological and clinicopathologic features of candidal infection in biopsies of a large series of patients with premalignant oral leukoplakia (n = 396) from eastern China and assess the clinical implications of candidal infection in oral leukoplakia. Multivariate regression analysis revealed that old age, tongue lesion, and presence of dysplasia were significant risk factors of candidal infection in oral leukoplakia.

We found that the frequency of candidal infection in biopsies of oral leukoplakia was 15.9%, within the range reported in the literature [4,17]. We observed the average age at diagnosis of candidal leukoplakia was larger than that reported by Arendorf et al [18]. The sex ratio was equal