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A clinico-pathological and cytological study of oral candidiasis

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ABSTRACT

Candidiasis of the oral mucosa arises chiefly as a result of infection with *Candida albicans*. Many clinico-pathological analyses of macroscopic findings have been described, although the clinical findings of oral candidiasis vary considerably and the conditions are complex. The present study analyzes the distribution, clinical, cytological and histological diagnoses of oral candidiasis, associated complex diseases and the diagnostic value of cytology. The ratio of *Candida* infection was 28.9% among 1551 study participants. Females were infected significantly more often than men ($p < 0.01$) and the affected age range was 60 - 79 years (61.0%, $p < 0.01$). The predominantly affected areas were the tongue (48.3%, $p < 0.01$) and gingiva (20.0%, $p < 0.01$), and occurrence at multiple loci was seen in 43 (9.6%) patients. The typical clinical findings of oral candidiasis were ulcerative/erythematous lesions (33.2%, $p < 0.01$) and pseudomembranous candidiasis (31.6%, $p < 0.01$). A histopathological diagnosis of candidiasis based on biopsy specimens from 26 lesions in patients with *Candida* infection indicated by cytology was confirmed from cultures. The breakdown of a cytological to a definite diagnosis was 6 positive (SCC 4, verrucous carcinoma 1, moderate to severe dysplasia 1), 6 suspected positive (mild dysplasia, 2; moderate to severe dysplasia, 2; papilloma, 1 and SCC, 1) and 14 negative (epulis, 3; papilloma, 3; granulation tissue, 2; fibrosis, 2 and others, 4). Exfoliative cytology can easily judge the presence of *Candida* species, although experience is necessary for the presumptive diagnosis of an oral mucosal disease. The application of exfoliative cytology using the Periodic acid-Schiff reaction is helpful for the earlier detection of oral candidiasis with various macroscopic findings.

Keywords: Candidiasis; Oral Exfoliative Cytology; Clinico-Pathology

1. INTRODUCTION

Candidiasis in the oral mucosa is usually caused by *Candida albicans*, which is an indigenous fungus in the oral cavity of healthy individuals. However, oral candidiasis can develop as a result of decreased host immunity, that is, as an opportunistic infection. The causes of oral candidiasis include being elderly or being an infant, having AIDS or diabetes, various drugs and local factors such as wearing dentures, steroid preparations and xerostomia. Many macroscopic findings of clinico-pathological analyses have been reported, although oral candidiasis has a variable clinical presentation and thus can be difficult to precisely diagnose. Exfoliative cytology to screen for oral mucosal disease has been performed for 30 years at our hospital and all specimens are checked for *Candida*. Additionally, the accuracy of detecting *Candida* by exfoliative cytology has already been proven by simultaneous culture testing [1].

The present study analyzes the distribution of oral candidiasis screened by exfoliative cytology according to sex, location, age and clinical findings. Clinical, cytological, histological diagnoses and complicated diseases associated with oral candidiasis and the effectiveness of cytology as a diagnostic tool are examined and discussed.

2. MATERIALS AND METHODS

We initially enrolled 1551 patients who presented mainly due to oral mucosal abnormalities, and who were diagnosed with a *Candida* infection by exfoliative cytology between April 2008 and March 2009 at the Department of Diagnostic Pathology at the Hospital of Nihon University School of Dentistry at Matsudo. All cytologi-

cal specimens were examined by Papanicolaou (Pap) staining and the Periodic acid-Schiff (PAS) reaction, and reconfirmed by an internationally qualified cytological screener and three specialists in oral cytopathology. *Candida* infection was diagnosed when spores, pseudohyphae and/or mycelia were confirmed by PAS reaction. *Candida* infection in those with only detectable spores was confirmed by colony formation and culture (Nissui Pharmaceutical Co. Ltd., Tokyo, Japan). Six cases performed biopsy immediately among 12 cases in which the malignant tumor was suspected, cytological and clinically. The 6 remaining cases transferred to another hospital at the patient's requests. The 437 cases except these 12 cases were performed intraoral re-examination after they had removed *Candida*. Biopsies were obtained from those with consistent macroscopic findings and diseases were histopathologically diagnosed by three oral pathologists using hematoxylin and eosin staining (H.E.) to determine more complex diseases. Histopathological diagnoses followed the diagnostic criteria of the World Health Organization WHO [2]. Data were analyzed according to the age, location, clinical diagnosis, cytological diagnosis, histopathological diagnosis and disease complexity. The Ethics committee of Hospital of Nihon University School of Dentistry at Matsudo approved this study, and all patients provided written, informed consent to participate in all procedures associated with the study. All data were statistically analyzed using the Chi-square test (SPSS).

3. RESULTS

3.1. *Candida* Infection Rate

Among 1551 (male 576, female 975) patients who presented at our hospital with an oral mucosa disorder as the chief concern, 449 (28.9%; male, 156 (34.7%); female 293 (65.3%)) of them were infected with *Candida.*

3.2. Distribution of Patients

Significantly more women than men ($p < 0.01$) were infected. The retrieval of information according to age excluded 2 men and 10 women of unknown age. **Table 1** shows the age distribution of individuals with oral candidiasis. Most of the infected individuals were aged 60 - 79 years (61.0%, $p < 0.01$). **Table 2** lists the locations of oral candidiasis. Most lesions were on the tongue (48.3%, $p < 0.01$), followed by the gingiva (20.0%, $p < 0.01$), cheek (11.1%), lips (5.3%), palate (4.2%) and oral floor (1.3%). The tongue was further sub-classified as the dorsum (43.8%, $p < 0.01$), margin (40.5%, $p < 0.01$), apex (7.4%), inferior aspect (4.6%), root (1.4%) and the entire tongue 5 (2.3%). Maxillo-mandibular infections were located in the gingiva (7.8%; 4/90), lip (8.3%; 2/24), right and left margin of the tongue (5.7%; 5/88), and cheek (22.0%; 11/50), and 43 (9.6%) patients had lesions at multiple loci.

3.3. Clinical Manifestations

The clinical manifestations of patients with oral candidiasis (**Table 3**) comprised ulcerative/erythematous lesions (33.2%, $p < 0.01$), pseudomembranous candidiasis (31.6%, $p < 0.01$), white patch/leukoplakia (12.2%), denture stomatitis (8.9%), erythema (7.1%), lichen planus (4.2%), nodules (2.2%) and angular cheilitis (0.4%).

Table 1. Distribution of the patients of oral candidiasis.

Age	No.	%	Male	%	Female	%
0 - 9	2	0.4	0	0.0	2	0.7
10 - 19	4	0.9	3	1.9	1	0.3
20 - 29	6	1.3	2	1.3	4	1.4
30 - 39	12	2.7	6	3.8	6	2.0
40 - 49	28	6.2	14	9.0	14	4.8
50 - 59	55	12.2	19	12.2	36	12.3
60 - 69	102	22.7**	30	19.2	72	24.6
70 - 79	172	38.3**	62	39.7	110	37.5
80 - 89	46	10.2	17	10.9	29	9.9
90 - 99	10	2.2	1	0.6	9	3.1
Unknown	12	2.7	2	1.3	10	3.4
Total No.	449	100.0	156	100.0	293	100.0

**: A significant difference ($p < 0.01$) was observed among all the age groups by chi-square test.

Table 2. The location of oral candidiasis.

Location	No.	%		No.	%
Gingiva	90	20.0	Lower	50	55.6**
			Upper	36	40.0**
			Upper & lower	4	4.4**
Palate	19	4.2	Hard	16	84.2**
			Soft	3	15.8*
Lip	24	5.3	Upper	12	50.0
			Lower	8	33.3
			Angle	2	8.3
			Upper & lower	2	8.3
Oral floor	6	1.3			
Tongue	217	48.3*	Dorsum	95	43.8**
			Margin	83	38.2**
			Apex	16	7.4
			Inferior aspect	10	4.6
			Root	3	1.4
			Right & left margin	5	2.3
			Entire tongue	5	2.3
Cheek	50	11.1*	Cheek	39	78.0*
			Right & left cheek	11	22.0*
Multiple	43	9.6			

Significant differences (**: $p < 0.01$,*: <0.05) was observed among all the age.

*Cytological study of oral candidiasis.

Table 3. Clinical diagnoses of oral candidiasis.

		No.	%
Acute forms	Pseudo membranous	142	31.6**
	Erythematous	32	7.1
Chronic forms	Leukoplakia	55	12.2
	Lichen planus	19	4.2
	Ulcerative/erythematous	149	33.2**
	Nodular	10	2.2
Candida-associated lesions	Denture stomatitis	40	8.9
	Angular cheilitis	2	0.4
	Median rhomboid glossitis	0	0.0
	Linear gingival erythema	0	0.0

**: A significant difference ($p < 0.01$) was observed among all the age groups by chi-square test.

3.4. Cytological and Histopathological Diagnoses

Cytology with the PAS reaction detected *Candida* infection with 100% precision. That is, *Candida* infection was confirmed by mycelia growth in all of the cultures that tested positive by PAS. **Table 4** shows the cytological and oral biopsy findings. Cytological diagnoses were negative in 395 (88.0%), suspected positive in 39 (8.7%) and positive in 15 (3.3%) cases. The estimated negative diagnoses comprised inflammatory lesions (67.9%; 305/395) and hyperkeratosis (20.0%; 90/395), and the estimated positive diagnoses were verrucous (0.2%; 1/15) and squamous cell carcinoma (SCC, 3.1%; 14/15). We histopathologically diagnosed 26 lesions from 24 patients in whom *Candida* infection was identified cytologically and confirmed by cultures. The breakdown of cytologically confirmed diagnoses is as follows. Six were confirmed as positive (SCC, (n = 4)); verrucous carcinoma, (n = 1); moderate to severe dysplasia, (n = 1), 6 suspected positive with mild (n = 2) and moderate to severe (n = 2) dysplasia; papilloma, (n = 1) and SCC (n = 1), and 14 were confirmed as negative, and having epulis (n = 3), papilloma (n = 3), granulation tissue (n = 2), fibrosis (n = 2) and others (n = 4). *Candida* infection was accompanied by benign and malignant diseases in 20 (76.9%) and 6 (23.1%) patients, respectively.

3.5. Treatment for *Candida* Infection

The 437 patients in whom *Candida* infection was cytologically diagnosed were treated with an antifungal drug. These strategies resulted in the disappearance of the fungal mycelia from 432 cases (98.9%).

4. DISCUSSION

Oral candidiasis is a common opportunistic infection in individuals with decreased immunity. Physiological factors

Table 4. Result of cytology, treatment and biopsy.

Cytological diagnosis	No.	%	Estimate diagnosis	No	%	No. of A.D.*	No. of C.C.**	No. of Biopsy	Definite diagnosis	No.
Negative	395	88.0	Inflammatory change	305	67.9	305	305	14	Epulis	3
			Hyperkeratosis	90	20.0	90	86		Papilloma	3
									Granulation tissue	2
									Fibrosis	2
									Fibro-epithelial polyp	1
									Pyogenic granuloma	1
									Capillry hemangioma	1
									Sjögren syndrom	1
Suspicious of positive	39	8.7	Dysplasia	39	8.7	39	38	5	Mild dysplasia	2
									Moderate to severe dysplasia	2
									Papilloma	1
									Squamous cell carcinoma	1
Positive	15	3.3	Verrucous carcinoa	1	0.2	0	0	7	Squamous cell carcinoma	4
			SCC***	14	3.1	3	3		Verrucous carcinoma	1
									Moderate to severe dysplasia	1

A.D.*: Antifungal drug; C.C.**: Cured Candidiasis; SCC***: Squamous cell carcinoma.

that predispose individuals to oral candidiasis comprise pregnancy, immune defects, drugs and malnutrition, and local factors including trauma, denture-associated problems and oral cancer [3]. Most reports have relied on macroscopic observation by dental clinicians, although many reports have described clinico-pathological studies of oral candidiasis. The present epidemiological study examined oral candidiasis detected by exfoliative cytology and by visible cultures. We also identified the value of oral exfoliative cytology for diagnosing oral candidiasis.

4.1. Ratio of Candidiasis

Candida species comprise the most common opportunistic fungal pathogens in humans, with *C. albicans* being the most prevalent cause of mucosal and systemic infection. *C. albicans* has been described as the most frequently encountered oral fungal commensal with detection rates of 40% to 65% in healthy adults [4]. The ratio of oral candidiasis in the present study was 28.9%, which was similar to the reported 24% of outpatients at a dental clinic [5] and 24.5% in a review of eight publications [6]. On the other hand, the rate of candidiasis was 14.09% in a large-scale Brazilian study of 1586 randomly selected individuals [7]. However, the detection rates were very low when *Candida* infection was determined only from interviews and macroscopic observations.

4.2. Epidemiological Features

Infection rates were influenced by age and removable prostheses in a Brazilian study [7]. Age-matched statistical analysis in the present study found a significantly higher infection rate among 60 - 79-year-olds than in any other age group. Many factors have been investigated, such as an impaired host defense causing deceased Salivary flow [8], an increase in the morbidity rate of diabetes [9], wearing dentures [10], and taking medicine to treat chronic [11] and auto-immune diseases such as Sjögren syndrome [8]. The prevalence rate of oral candidiasis among children with oral mucosal diseases was the highest among those aged 0 - 12 years (28.4%) [12], which was similar to findings from other countries [13-15]. The ratio of 0 - 19-year-olds was very small in the present study. Rare symptoms of oral candidiasis in children might have been one of the causes. The higher prevalence of candidiasis among women in the present study is in agreement with the findings of other studies [16, 17]. In fact, 62.9% of the patients who presented with the chief concern of oral mucosal abnormalities were female in the present study Furthermore, xerostomia and autoimmune diseases that cause oral candidiasis are prevalent among women. Half of our patients with a *Candida* infection had lesions that were concentrated mostly on the dorsum and edges of the tongue. The dorsal surface is the main ecological niche for *Candida* in the oral cavity [4,8,11,18]. Presumably, chronic contact with dentures [10] and relationships with oral mucosal diseases such as leukoplakia and injuries might explain the high frequency of infections being located on their edges. Moreover, since multiple symptoms were quite abundant (15.6%), we considered that factors such as age, drugs and immune defects were involved.

4.3. Clinical Manifestations

The clinical classification of candidiasis is highly complex because the findings are diverse. Therefore, we categorized candidiasis into acute, chronic and *Candida*-associated lesions based on Lakshman's classification [3]. We concentrated on the ulcerative/erythematous and pseudomembranous types. An inflammatory reaction was obvious in ulcerative/erythematous and *Candida*-associated lesions. The hyphae of *C. albicans* tightly adhere to epithelial cells, and proteinases secreted by the hyphae damage the oral mucosa [19]. Schaller *et al*. assert that *C. albicans* proteinase causes tissue damage and increasing vascular permeability leads to an inflammatory reaction and clinical symptoms [20]. Chronic erythematous candidiasis is associated with corticosteroids, antibiotics and HIV infection. Dentists often treat stomatitis with triamcinolone acetonide, which is routinely available at Japanese drugstores and prolonged use of this drug can become problematic [21]. In addition, candidiasis can be a side effect of the inhaled steroids that are used to treat asthma [22] and allergosis. Because erythematous candidiasis is similar to a non-specific inflammatory reaction, it should be cytologically diagnosed as soon as possible. The reported ratio of denture-related stomatitis (DRS) ranges from 11% to 67% [23]. A removable prosthesis is the most common cause of the growth and pathogenicity of *Candida* species [4,18,24]. Angular cheilitis is also associated with yeasts and bacteria in relation to wearing dentures [3]. *Candida* species proliferate by contact with the resin [10], and *Candida* counts significantly correlate with the intensity of denture plaque scores [25]. The rate of hyperplastic candidiasis that macroscopically presented like leukoplakia was 12.2% in the present study, and the malignant transformation rate was high [26]. Simultaneous *Candida* infection and several etiological factors seemed to play a role in malignant transformation [27]. *Candida* species were identified in 43.7% of the patients with lichen planus and leukoplakia in their oral cavities [28]. The reported prevalence of oral candidiasis varies between 8% and 94% in patients with advanced cancer, because of differences in diagnostic criteria, diagnostic methods and the study population [29]. Whether a condition depends only on a *Candida* infection or such infection with coexistent mucous membrane diseases should be determined as soon as possible. Macroscopic classification is

limited as most epidemiological surveillance concerning oral candidiasis considers the candidiasis, DRS and cheilitis as separate entities [17,30].

4.4. Accuracy of Exfoliative Cytology

Information about investigating *Candida* infection of the cervical area using Pap smears is very scarce [31]. *Candida* species have been detected based on the growth of hyphae on PAS smears [4,6]. The high accuracy of detecting oral candidiasis by exfoliative cytology was demonstrated here, as well as by others [1]. The cytological detection of candidiasis is simple, inexpensive, accurate and painless. As for oral candidiasis, it is clinically variegated to present the findings of leukoplakia or intractable ulcerative lesion, etc. In this result, the abbreviation half of oral candidiasis was occupied by these confusing clinical view. Therefore, discovery of candidiasis by cytology was useful for avoiding unnecessary biopsy. In addition, as a result of giving antifungal drug immediately, as for candidiasis detected by cytological diagnosis, the fungal mycelia disappeared with 98.9% of these cases. However, *Candida* can be over- and underdiagnosed when other mucosal diseases coexist, especially dysplasia and SCC. The size and shape of oral epithetlial cells infected with *Candida* significantly change [1,32]. Judgment of changes between atypia by *Candida* and dysplastic change should be required experience. In that case, judgment becomes possible by carrying out observation of a macro-scopic view, and exfoliative cytology after antifungal drug. In Japan, there is a custom which applies triamcinolone acetonide easily to stomatatis. Moreover, since triamcinolone acetonide is marketing, using it for a long period of time may be continued by a patient's judgment, and it tends to merge the side effects of the *Candidal* infection [33]. Cell atypia was observed in epithelial cells of the decubitus ulcer accompanied by the *Candidal* infection which uses triamcinolone acetonide for a long period of time, in this study. The observation of cytological specimen of intractable ulcer after the long-term application of triamcinolone acetonide should be carefully. The presence or absence of *Candida* species can be easily determined by exfoliative cytology, although experience is necessary for a presumptive diagnosis of oral mucosal disease. Exfoliative cytology using the PAS reaction enables earlier detection of oral candidiasis that presents with macroscopically variable symptoms.

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