ORIGINAL ARTICLE

Clinicopathological correlation of oral candidiasis – Our experience in a tertiary centre over two decades

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Abstract

Introduction: Oral candidiasis is one of the most common fungal infections that has been widely reported around the world. In Malaysia, the available studies for this infection are scarce. *Materials and Methods:* This is a 20-year retrospective study aimed to investigate the prevalence, demographic characteristics, clinical presentations, and the association of oral candidiasis with clinical parameters in oral candidiasis cases reported in the Faculty of Dentistry, Universiti Malaya from 1999 until 2019. A total of 12,964 histopathological records from the Oral Pathology Diagnostic and Research Laboratory (OPDRL) between 1999 to 2019 were retrieved. Oral candidiasis cases were selected according to the inclusion and exclusion criteria. Information of interest was obtained and analysed. *Results:* From the total records retrieved, 378 oral candidiasis cases were recorded and 82.8% were diagnosed from smear test. This study showed that oral candidiasis was predominantly reported in female (64.2%) and Indian population (64.2%). The peak incidence was in the sixth decades of life (27.0%). The most commonly affected site was tongue and coated tongue was the most common clinical presentation. More than 50% of the cases had comorbidity and 10.6% were associated with dentures. Ethnicity and site of occurrence were significantly associated (p<0.05) with oral candidiasis. *Conclusion:* This is the first large-scale study of oral candidiasis cases in Malaysia. The findings of this study are useful for clinical assessment of patients suspected of oral candidiasis.

Keywords: Demography, Malaysia, oral candidiasis, prevalence

INTRODUCTION

Oral candidiasis is the most common opportunistic mycotic infection in humans. Compared to 200 different types of Candida genus, such as *Candida tropicalis*, *Candida parapsilosis* and *Candida krusei*. *Candida albicans* is the main pathogen isolated from oral candidiasis, while the other rarely cause diseases. *Candida albicans* is considered to have a dimorphic property, having the capacity to change itself morphologically from yeast to hyphae forms.[1] The relatively innocuous yeast form is characterised by having a single oval cell with a diameter of 2-4μm, while the pseudohyphae form is in elongated ellipsoid cell shape with constricted septa or as parallel-walled true hyphae. Hyphae form shows a more invasive nature compared to yeast form.[2] The transition from yeast form to pseudohypahe

form is facilitated by the host temperature (37°C), which is the ideal temperature for *Candida albicans* to grow.[3] *Candida albicans* is part of normal oral commensal, harboured by 30-50% of normal population without any clinical manifestations.

There are several characteristics that encourage the growth of *Candida albicans* within the host cells, such as the morphological transformation between the forms of yeast and hyphae, the adhesins and invasins expression on the cell surface, and the biofilms buildup.[4] *Candida albicans* adheres to host cell surfaces by the expression of adhesin.[5] By inducing its own endocytosis with adhesins and invasins, it then invades the oral epithelial cells. The secretion of fungal hydrolases helps inactive penetration of the host cell by breaking down barriers. Upon the

contact of *Candida albicans* to the host cell, it triggers the formation of hyphae cell from yeast cell.[6] *Candida albicans* is capable to construct a biofilm on a denture (abiotic) or host cell (biotic) with yeast cells in the lower part and hyphae cells in the upper part of the biofilm.[7]

Oral candidiasis can be categorised into primary and secondary oral candidiasis based on the site involved.[8] Primary oral candidiasis can be further classified into three categories which are acute (pseudomembranous, erythematous), chronic (hyperplastic, pseudomembranous, erythematous), and candida-associated lesions (denture stomatitis, angular cheilitis and median rhomboid glossitis). Secondary candidiasis is described as a chronic candidiasis of the mucocutaneous, which occurs as recurrent superficial infections of the mouth, skin, and nail beds.[9] Secondary infection of candidiasis for oral mucocutaneous lesions treated with topical steroids, such as oral lichen planus has been reported.[10] Improper monitoring and evaluation of topical steroids use may lead to many adverse effects, including oral candidiasis that often presents as burning sensation of the oral cavity.[10]

Pseudomembranous candidiasis (thrush) presents clinically as extensive white patches involving buccal and labial mucosa, tongue, hard and soft palate, oropharynx, and periodontal tissue. These white patches can be easily scraped off leaving an erythematous base. Patients with extremes of age, diabetes mellitus, acquired immunodeficiency syndrome (AIDS), leukaemia, corticosteroid use, prolong broad-spectrum antibiotics use and psychotropic drugs users are more susceptible to pseudomembranous candidiasis.[11]

Erythematous candidiasis, previously known as 'antibiotic sore mouth' because it could be manifested in patients with long-term broad-spectrum antibiotics use.[12] This form of candidiasis has also been associated with HIV patients. Patients would often complain of soreness at the localised erythematous area. The lesions are usually presented as depapillated area on the dorsum surface of the tongue or palatal lesion in HIV patients.[13]

The hyperplastic candidiasis or previously referred as 'candidal leukoplakia' is typically presented in chronic form. Clinically, it appears as well demarcated, slightly elevated, adherent homogeneous or nodular white plaques that cannot be wiped away. The lesion is primarily seen at the commissural region of buccal mucosa

and may be presented on the lateral border of the tongue and palate. This condition is commonly encountered among smokers and may demonstrate dysplastic changes histologically.[14]

Chronic atrophic candidiasis also called 'denture stomatitis', is commonly seen on the palate but it may also be found on mandibular mucosa. It manifests as chronic mucosal inflammation in 50-65% of denture wearers, typically restricted to the denture-bearing area.[15] Although the lesions are usually asymptomatic, some patients might complain of burning sensation and soreness. Poor oral hygiene practice, ill-fitting prosthesis, xerostomia, and nocturnal denture-wearer are the contributing factors of this condition.[15]

Angular cheilitis is associated with intraoral candidal infection where oral commissure (unilaterally or bilaterally) becomes erythematous, swollen, cracking, bleeding and crusty. Angular cheilitis can develop spontaneously but more often affecting elderly with wrinkled face particularly in between the nasolabial fold and at the angle of the mouth when the environment is moist.[16]

Median rhomboid glossitis can usually be seen on the central dorsum of the tongue and palate. It presents clinically as well-demarcated erythematous area with smooth or lobulated surface and papillary atrophy. However, most of the cases are clinically asymptomatic and only some may complain of irritating painful lesions. It tends to be associated with corticosteroids use and smoking.[17] Increasing candidal carrier rate by smoking activity especially amongst diabetic patients were found to be significantly higher.

Diagnosis of oral candidiasis is established through thorough clinical examination and supported by laboratory investigations namely smear, culture and sensitivity, histology staining with Periodic Acid-Schiff (PAS) or polymerase chain reaction (PCR). A stained smear and histology staining with PAS enable identification of blastospores and pseudophyphae morphologically compatible with *Candida albicans*. Culture of Candida species is usually performed on Sabouraud or dextrose Sabouraud medium. PCR studies are mainly used for detection of invasive candidiasis.[18]

Oral candidiasis has a wide variety of treatment options depending on the different aetiologies. The treatments for oral candidiasis include attention to local predisposing causes, oral hygiene education and antifungal treatment. Correction of local predisposing causes aids

in avoiding the need for prolonged courses of treatment. The use of topical antifungal agents which are available in gel, tablet, suspension, and cream are beneficial for lesions which are confined to oral cavity. Systemic antifungal treatment is indicated for lesions that are poorly responsive to the topical antifungal agents.[18]

The complex host and organism interaction exhibit a variety of clinical presentations that affect the oral mucosa. However, our understanding on this fungal disease in Malaysia population is limited. We aimed to investigate the prevalence, demographic characteristics and clinical characteristic of oral candidiasis and the association between oral candidiasis with clinical parameters in oral candidiasis cases diagnosed in the Oral Pathology Diagnostic and Research Laboratory, Faculty of Dentistry, Universiti Malaya from year 1999 to 2019. This epidemiologic study is hoped to shed light to the patterns of pathologies and give better insight in diagnosis of disease and appropriate choice of treatment.

MATERIALS AND METHODS

This was a record-based retrospective study of oral candidiasis cases diagnosed in the Faculty of Dentistry, Universiti Malaya, Malaysia. The ethical approval (DF OS2003/0008 (U)) was granted by the Faculty of Dentistry Medical Ethics Committee (FDMEC), University Malaya.

Histopathology reports from January 1999 to December 2019 were retrieved from the archive of Oral Pathology Diagnostic and Research Laboratory (OPDRL), Faculty of Dentistry, Universiti Malaya. A total of 12,964 reports were reviewed and 378 cases were included in this study.

The inclusion criteria were smear reports with diagnosis of oral candidiasis, incisional or excisional biopsy reports with evidence of candidal infection. In the cases of recurrent oral candidiasis, primary and recurrent reports were reviewed and considered as one case. The recurrent lesions that were diagnosed for the first time in this institution, of which the original diagnosis was made in other healthcare centres were included and considered as one case. Smear reports with inadequate samples for definitive diagnosis and unidentifiable fungal infection were excluded in this study.

Information obtained from these reports were gender, age, ethnicity, clinical presentation of the cases, presence of comorbidity, site of lesion(s), duration since lesion first noticed, types of investigation (smear/biopsy), co-existence of other oral lesions and the presence of any removable prosthesis. Comorbidity other than HIV, diabetes mellitus, malignancy, asthma, and systemic lupus erythematosus (SLE) was coded as "others".

The data collection was recorded in Microsoft Excel. Parameters of interest were analysed using SPSS version 12.0.1 (IBM Corp., Armonk, N.Y., USA). Descriptive statistics were illustrated in the form of tables, bar charts and pie charts for better data projection and comparison. Association between oral candidiasis and parameters of interest were tested using Chi square test. For all the statistical analysis, P value <0.05 was considered to denote statistical significance.

RESULTS

Prevalence of oral candidiasis
A total of 12,964 histopathology reports were retrieved from January 1999 to December 2019and 378 cases (2.92%) were oral candidiasis. The majority of oral candidiasis cases (82.8%) were diagnosed with PAS-stained smear tests. 11.9% of these oral candidiasis cases were found associated with other oral lesions such as oral lichen planus and oral epithelial dysplasia. Cases of oral candidiasis associated with other oral lesions were diagnosed through biopsy specimens. The biopsy specimens which showed features of candida infestation would be further stained with PAS special stain to confirm the diagnosis of candidiasis.

Demographic characteristics of oral candidiasis
The demographic characteristics namely gender, ethnicity and age distributions are summarised in Table 1. Oral candidiasis demonstrated a gender predilection for woman (64.2%) in this study. The prevalence of oral candidiasis was highest in Indian population, followed by Chinese and Malay. Oral candidiasis was mostly diagnosed in the sixth decades of life, with the mean age of 58.1-year-old and ranging from 2-month-old to 91-year-old.

Clinical characteristics of oral candidiasis
This study showed that 57% of the patients were presented with underlying medical problems. Figure 1 illustrates the breakdown of medical history. Social history analysis revealed that 12.7% of oral candidiasis cases from 48 cases of available data practiced high risk social habits and the most common habit was betel quid

Table 1: Demographic characteristic of oral candidiasis cases

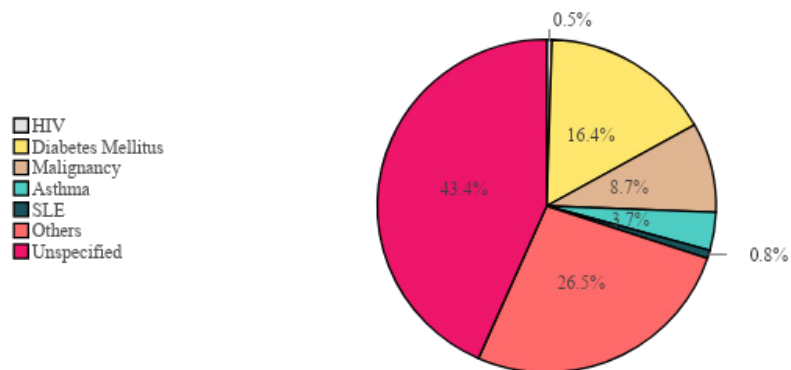| Variables	Oral candidiasis	
	Not associated with other oral lesion, n (%)	Associated with other oral lesion, n (%)
Total cases	333 (88.1)	45 (11.9)
Diagnostic Test		
Smear	310 (82.0)	3 (0.8)
Biopsy	22 (5.8)	40 (10.6)
Unspecified	1 (0.3)	2 (0.5)
Gender		
Male	111 (29.4)	21 (5.6)
Female	219 (57.9)	24 (6.3)
Unspecified	3 (0.8)	0 (0.0)
Race		
Malay	69 (18.3)	3 (0.7)
Chinese	137 (36.2)	7 (1.9)
Indian	113 (29.9)	33 (8.7)
Others	8 (2.1)	1 (0.3)
Unspecified	6 (1.6)	1 (0.3)
Age (Years)		
0 – 10	4 (1.1)	0 (0.0)
11 – 20	5 (1.3)	1 (0.3)
21 – 30	15 (4.0)	0 (0.0)
31 – 40	30 (7.9)	2 (0.5)
41 – 50	37 (9.7)	7 (1.85)
51 – 60	87 (23.0)	15 (4.0)
61 – 70	74 (19.6)	7 (1.85)
71 – 80	67 (17.7)	11 (2.9)
81 – 90	9 (2.4)	2 (0.5)
91 – 100	1 (0.3)	0 (0.0)
Unspecified	4 (1.1)	0 (0.0)

FIG. 1: Distribution of patient with medical history (n = 378).

chewing (Fig. 2). 10.6% of the oral candidiasis patients wore denture/dentures. Oral candidiasis was commonly seen on the tongue followed by buccal mucosa (Table 2). Duration analysis revealed more than one third of patients noticed the presence of lesion after a year duration. Majority of the patients presented with white coated tongue followed by white lesion and red lesion (Table 2). 8.2% of the patients suffered from burning sensation and presented with depapillated tongue. The other less common clinical presentations including ulceration, angular cheilitis and swelling.

Association of oral candidiasis with clinical parameters

Chi square tests were performed to evaluate the association of oral candidiasis with age, gender, ethnicity, site of occurrence, presence of comorbidity and denture wearers. Oral candidiasis was significantly associated with ethnicity and site of occurrence (p<0.05) (Table 3). The other clinical parameters showed no significant associations.

DISCUSSION

This study indicated that 378 out of 12,964 histopathological reports in the Faculty of Dentistry, Universiti Malaya were diagnosed as oral candidiasis in the past 20 years. On average, 19 cases of oral candidiasis were diagnosed yearly. The cases seen in our centre was relatively low compared to study by Sedgley

and Samaranayakewho reported 24% of Asian subjects having oral yeast infection with *Candida albicans* isolated in 77% of the cases.[19] The low incidence of cases seen in this centre is possibly due to the redistribution of cases to other dental healthcare centres in Malaysia. Unfortunately, no study specifically discussed the incidence of oral candidiasis in Malaysia. A multicenter study would be able to increase the generalisability of oral candidiasis cases in this country.

Our study showed PAS-stained smear test was the main diagnostic test to diagnose oral candidiasis cases. This diagnostic test is non-invasive and can be done by chairside with simple instruments needed. It is noteworthy to mention that errors during specimen collection, transportation and processing may lead to discrepancy in definitive diagnosis. An adequate smear from representative area is crucial for diagnosis making. Hence, well-trained health care and laboratory professionals are important for accuracy and precision of a diagnostic test. This diagnostic test can easily be carried out in patients who are suspected with oral candidiasis and enables clinician to construct treatment plan accordingly.

Isolation of Candida species can be done using smear, swab, an imprint culture, collection of whole saliva, concentrated oral rinse and mucosal biopsy. Quantitative estimation of fungal load can be obtained from imprints, concentrated oral rinse and culturing the oral rinse.[20] A quantitative estimation of fungal load can further acknowledge the severity of the
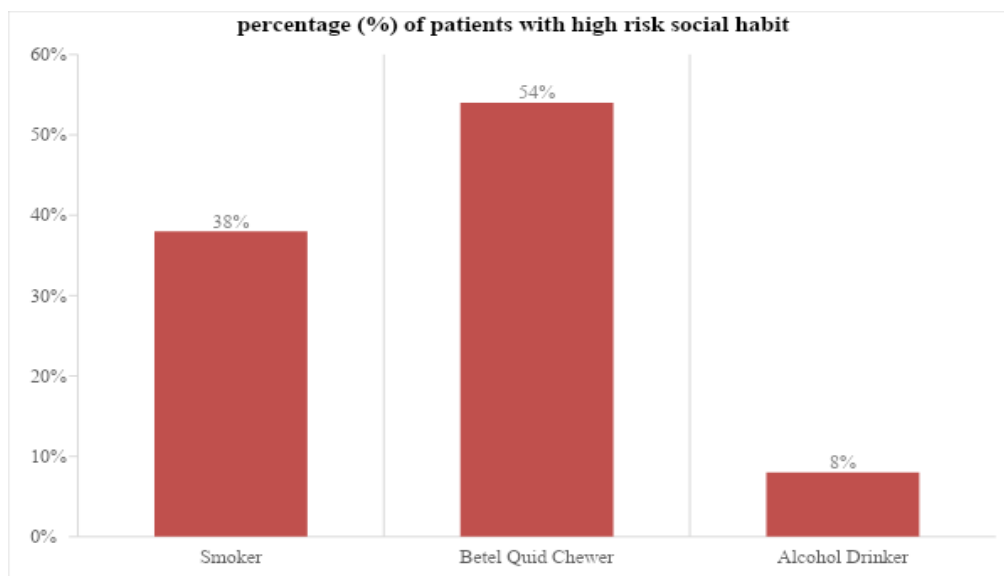

FIG. 2: High risk social habits (n = 48) (Missing data: 330).

Table 2: Site of occurrence and clinical presentation of oral candidiasis (n=378)

Variables	Frequency, n	Percentage %
Site		
Tongue	211	55.8
Buccal Mucosa	93	24.6
Hard Palate	23	6.1
Soft Palate	3	0.8
Denture Base	16	4.2
Gingiva	11	2.9
Lips	14	3.7
Others	5	1.3
Unspecified	2	0.5
Clinical Presentation		
White Coated Tongue	111	29.4
White Lesion	76	20.1
Red Lesion	42	11.1
Depapillated Tongue	31	8.2
Burning Sensation	31	8.2
Others	63	16.7
Unspecified	24	6.3
Duration from first notice		
Less than 6 months	129	34.1
6 months to 1 year	13	3.4
More than 1 year	40	10.6
Unspecified	196	51.9

infection according to the load of pathogenic candidiasis and aid in more effective treatment planning. However, smear test is the most common employed diagnostic technique for our centre due to the lack of laboratory infrastructure. Therefore, quantitative estimation of fungal load and fungal speciation were not carried out for colonies that are isolated.

Out of 378 cases, one-tenth was associated with other oral lesions which were oral lichen planus and oral epithelial dysplasia. These lesions are known as primary keratinized lesions which were superimposed by Candidal infection.[21] Biopsy specimens demonstrated features of fungal infestation were further sent for PAS staining for fungal identification. Oral lichen planus is one of the oral potentially malignant disorders (OPMD) recognised by WHO 2017 whereas oral epithelial dysplasia is the spectrum of architectural and cytological changes with an increased risk of squamous cell carcinoma transformation.[22] To date, there are no known studies that confirmed the direct association of oral candidiasis with oral malignancies.[12] However, Gall *et al*. suggested that there is a possibility some strains of *Candida albicans* have certain features to aid in the development of pathological conditions and precancerous changes.[23] Therefore, co-exist oral lesions should be evaluated after candidiasis therapy to investigate the relationship between candidiasis and the development of OPMD. According to the study by Sankari *et al*., leukoplakia with the presence of candida species is more likely to turn cancerous compared to the non-infected one.[24] *Candida albicans* produces carcinogenic compounds such as N-nitrosobenzylmethylamine and nitrosamine which are deposited in the inner layer of mucosa and combined with DNA, causing anomalies in the replication of DNA. These anomalies lead to production of oncogenes which can trigger malignant transformation.[24] However, our study did not have sufficient data to illustrate the relationship between OPMD with co-existence Candidal infection and malignant transformation.

Table 3: Association of oral candidiasis with clinical parameters

Clinical Parameters	Variables	n	SD	p-value
Age	≤ 50 y/o > 50 y/o Unspecified Total	101 273 4 378	1.745	0.689
Gender	Male Female Unspecified Total	132 243 3 378	0.489	0.185
Ethnicity	Malay Chinese Indian Others Unspecified Total	72 144 146 9 7 378	0.840	**0.000***
Sites	Tongue Buccal Mucosa Hard Palate Soft Palate Denture Base Gingiva Lips Others Unspecified Total	211 93 23 3 16 11 14 5 2 378	1.711	**0.000***
Comorbidity	Presence Absence Total	214 164 378	0.496	0.084
Denture Wearers	Yes No Total	40 338 378	0.308	0.363

Test performed: Chi square test; *p<0.05 = significant

Our data showed a slight female predominant which is in contrary to other similar studies where both genders were equally affected.[25] Lack of awareness amongst males' gender is also contributing to this result, which is supported by the study of Ghani *et al*. that men were less likely to pay attention to the intraoral changes whilst women are generally more concerned on their health and well-being.[26] Another study discussed on gender and age correlation with denture-induced stomatitis showed that females were more affected than males.[27] Our findings concurred with those reported by Loster *et al*., with 77.5% of denture wearers exhibiting stomatitis were female.

Oral candidiasis occurs in all age groups, our study found that people aged 50 and above demonstrated higher predilection compared to the younger age group. Previous research also portrayed the similar results.[28] We speculate that these results are due to presence of comorbidity and risk factors in the elderly. Aging causes physiological and/or pathological health problems that can disrupt the balance in the oral microbial environment or preservation of the oral health leading to higher prevalence of oral candidiasis in the aging group.[29]

Indian populations showed higher prevalence in comparison to other races. There is no study conducted in Malaysia that focused on race predilection in oral candidiasis. The study of Noor *et al*. has suggested that Indians have lower oral health literacy scores compared to Malays and Chinese due to a lack of oral health

education and knowledge among the Indian population. This might have contributed to the higher prevalence of oral candidiasis in this ethnic group.[30] Our data showed that the most common high-risk social habits among our patients were betel nut chewing and smoking. Smoking has been reported as the possible risk factors for oral candidiasis.[11] The association between high-risk factor and oral candidiasis is yet to be established. There are studies that were conducted to investigate the effect of the smoking and alcohol to oral candidiasis but there is no consensus been concluded yet.[11]

There is a lot of missing data for high-risk habits data collection in our study. We are unable to draw a firm conclusion for association between high-risk habits, especially betel quid chewing and the occurrence of oral candidiasis. This is one of the major limitations for our study as clinicians did not provide complete patients' history in the laboratory request form. It has been reported that betel quid chewing has no significant effect on oral colonization by Candida species.[31] Betel quid chewing is associated with a wide variety of oral mucosal lesions and carries risk of malignant transformation. An Asian consortium study in 2012 reported higher prevalence of oral potentially malignant disorders among betel quid chewers in South Asian communities.[32] Relationship between high prevalent in Indians ethnicity, betel quid chewing habits, oral candidiasis and oral potentially malignant disorders can be further investigated in a larger sample size and more complete data compilation.

In the present study, more than half of the patients have underlying medical conditions. Numerous previous studies have reported the risk factors such as diabetes mellitus, malignancies, asthmatic patients, and immunodeficiency were present in the oral candidiasis group.[8,33] In our samples, the most common encountered medical condition was diabetes mellitus. Excessive amount of glucose in the body may result in proliferation of *Candida albicans*, even with the presence of sufficient oral flora.[34] An uncontrolled amount of glucose also resulted in inhibiting the killing ability of neutrophils in the body that caused an increase in the colonization of the *Candida albicans*.[35] Oral candidiasis was reportedly common in asthmatic patients due to inhaled corticosteroids that can reduce salivary IgA.[36]

Usage of a removable prosthesis is one of the known risk factors of oral candidiasis. Based on a previous study, it was shown that 65% of complete denture wearers were predisposed to oral candidiasis and this was reflected in our study although the number of cases were small.[37] Removable prosthesis can serve as a conducive environment for the *Candida albicans* to grow as the environment underneath the prosthesis will be anaerobic, with low oxygen and pH level.[18] Together with low salivary rate flow, it will cause candida species to be more readily attached to the acrylic thus, a higher chance of developing candidiasis.[11] In comparison to the mucosa, the candida species can attach to the porous surface of acrylic more easily.[38]

In connection with the clinical presentation, the most frequent form of oral candidiasis in this study was pseudomembranous candidiasis. This is contrary to Neville *et al*. who documented that erythematous candidiasis was more frequently encountered than pseudomembranous candidiasis.[18] This might be due to the white lesions or patches that can be detected easily at chairside in comparison to red lesions. More than half of the recorded cases were medically complex patients who had higher propensity to develop pseudomembranous candidiasis due to their immune status. Our data collection has been challenging as the majority of the clinicians did not specify the types of candidiasis in the records. Recognition of various presentations of oral candidiasis is essential for clinicopathological correlation of oral candidiasis.

Further statistical analysis showed a significant association between oral candidiasis with ethnicity and site of occurrence. As for the site of occurrence, tongue, buccal mucosa and hard palate were among the sites with a high percentage where oral candidiasis was found in this study which is consistent with other previous studies.[26] We speculate that the reason for this is due to lack of proper hygiene in these areas, people usually neglected this area during tooth brushing. Besides that, it could be due to the anatomical structures of the tongue that serves as conducive environment for the growth of pathogen, such as Candida species.[18]

Due to the retrospective nature of this study, missing data was one of the major setbacks. This is due to the data was not collected in a standardized method or format. These missing data of potentially confounding factors may negatively impact on the outcome of the study. Since the data were collected based on convenience sampling, the outcome may not represent the general population and may subject to bias.

CONCLUSION

Oral candidiasis has always been the first probable diagnosis when it comes to yeast infection with the typical clinical presentations such as white scrapable patches and oral thrush in the oral cavity. Within the limitation of this study, we found that oral candidiasis was found to be significantly associated with Indian ethnicity, female predilection and the tongue was most affected. Early detection by primary health care personnel is encouraged to identify the signs of oral candidiasis and educate patients with a better oral hygiene and healthy lifestyle particularly with regard abstinence from betel nut chewing and smoking habits. Properly filled laboratory request form with patient's details and history would be beneficial for disease evaluation and review. A multicenter study should be carried out to identify a more definitive and representative correlation of clinicopathological features to oral candidiasis in Malaysian population.

Conflict of interest: The authors declare no conflict of interest.

Authors' contribution: YCG - conception and study design, manuscript writing; CCT & DL- review and edit manuscript; NQMH, NAE & ASA - Data collection, analysis and wrtie-up.

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