RESEARCH COMMUNICATION

Risk of the Contralateral Mucosa in Patients with Oral Potentially Malignant Disorders

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Abstract

Background: It is known that abnormal changes may occur in any part of the oral mucous membrane exposed to a carcinogen. Therefore patients with oral potentially malignant disorders (PMDs) are at risk of developing similar lesions at multiple sites. Objectives: To determine the risk of the contralateral mucosa in patients presenting with oral PMDs. Materials and methods: Sixty individuals with PMDs were selected for this study. These comprised 32 (53.3%) Indians, 23 (38.3%) Chinese, four (6.7%) Malays and one (1.7%) Nepalese. All selected cases had histopathological confirmation of their primary existing lesion as inclusion criteria. Cases that subsequently presented with a lesion in the corresponding anatomical site also underwent scalpel incisional biopsy on this second lesion to verify its diagnosis. The remaining cases that presented with unilateral PMDs at the time of study were subjected to a cytobrush biopsy on the normal looking contralateral mucosa. Results: A total of 70 primary PMDs were detected in 60 patients. The most common PMD found was oral lichen planus (n=40, 57.1%). Of the 60 patients studied, 28 (46.6%) exhibited bilateral lesions either synchronously (n=21, 35.0%) or metachronously (n=7, 11.6%). The remaining cases that had undergone cytobrush biopsy on the corresponding anatomical site yielded normal cytological results. Conclusions: Present findings demonstrated that patients presenting with PMDs in the upper aerodigestive tract are at a greater risk of developing a second lesion most probably in the contralateral anatomical site.

Keywords: Oral potentially malignant disorder - oral mucosa - clinical study - screening

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Introduction

In 2005, the World Health Organization Collaborating Centre for Oral Cancer and Precancer Working Group advocated abolishing the distinction between oral potentially malignant lesions and conditions, and proposed the term 'potentially malignant disorder' (PMD) to encompass both these entities (Warnakulasuriya et al., 2008). PMD was recommended in preference to precancer as it conveys that not all lesions described under this term may transform into cancer. The two most common PMDs are leukoplakia and erythroplakia (van der Waal, 2008). Early detection of PMD is aimed at improving survival rates as carcinogenesis is a multistep process and prevention is possible if these lesions are detected at an early and reversible stage of the disease (Reibel, 2003; Ram and Siar, 2005; Tamamura et al., 2006; Lim et al., 2009; Siar et al., 2009).

The concept of 'field cancerization' was first introduced by Slaughter et al. in 1953. According to this theory, premalignant change may occur in any area of the oral mucosa when exposed to a carcinogen. This in turn would increase the risk for patients with oral cancer in developing multiple primary tumours and secondary tumour recurrence following complete excision of the primary tumour. A recent study has shown that abnormal histological changes could occur in clinically normal looking mucosa of patients with oral cancer and PMDs (Thomson, 2002).

Oral cancer ranked as the sixth most common malignancy worldwide (Silverman 2001). In Malaysia, according to the Third National Cancer Registry Report (Lim et al., 2008), oral cancer ranked twenty-first among cancers in males and sixteenth in females with an incidence being highest among Malaysian Indians. Local retrospective studies based on archival oral pathology tissue records found that oral squamous cell carcinoma (OSCC) accounted for more than 90% of all oral cancers in Malaysia and more than 70% of these cases are diagnosed at an advanced stage, T3 or T4 (Siar et al, 1990; Ng and Siar 1992). However much less is known about PMD locally. One major study based on a nationwide survey of oral mucosal lesions found a low prevalence rate for oral leukoplakia and oral lichen planus (Zain et al., 1997). It is known that most oral cancers arise from long-standing pre-existing PMD including oral leukoplakia (Reibel, 2003). It is also known that PMD may occur as solitary or multifocal lesions. Approximately 3-24% of PMD

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patients have multifocal lesions (Thomson, 2002). These multifocal lesions purportedly arose as a consequence of field cancer change. It has been shown that distinct clinicopathological differences exist between single and multiple dysplastic lesions (Hamadah et al., 2010).

The present prospective clinical study on PMDs was initiated by two dental undergraduates (MCM and PPG) as part of their Fourth Year elective project. Their primary objective was to determine the risk of the contralateral mucosa in patients presenting with oral PMD. In their initial study, only 15 patients were examined. This project was later expanded to involve a further 45 cases.

Materials and Methods

Sample

Medical ethics approval [Ethics approval No. DF OP411/0033/(U)] was obtained prior to the commencement of this study. All examiners were trained and calibrated. Sixty individuals presenting with PMDs were selected. These were patients attending the Oral Medicine Clinic at the Faculty of Dentistry, University of Malaya, Kuala Lumpur, Malaysia, and were under the care of one of the Oral Medicine specialists (SCH).

They consisted of 32 (53.3%) Indians, 23 (38.3%) Chinese, four (6.7%) Malays and one (1.7%) Nepalese. There were 34(56.7%) females and 26 (43.3%) males, with an overall mean age of 50.0 years (Range: 24 –71 years). All patients gave their consent to participate in this study. Clinical examinations were carried out to assess the status of the oral mucosa in the corresponding anatomical site. At least two trained examiners were present to determine the clinical diagnosis of the oral mucosal lesion. In the event of a difference in opinion, the final diagnosis was made based on consensus after consultation with their Supervisor (SCH).

Histopathological examination

All 60 selected cases underwent scalpel incisional biopsies for histopathological verification of their primary existing lesion(s) as inclusion criteria in this study. Cases that subsequently presented with a lesion in the corresponding anatomical site were also subjected to incisional biopsy on this second lesion to verify their diagnoses. These procedures were performed by the Supervisor (SCH). The criteria for diagnosis of PMD were based on those in current use (Reibel, 2003; Warnakulasuriya et al., 2008).

Cytobrush examination

For ethical reasons, the remaining cases that presented with a unilateral PMD lesion at the time of the clinical study were only subjected to a cytobrush biopsy of the normal looking mucosa in the corresponding anatomical site. From the collected data, the types of lesions in the primary and contralateral anatomical sites, number of synchronous versus metachronous lesions, their anatomical locations and time interval between the primary lesion and onset of the metachronous lesions were analyzed.

Results

Data on 60 patients with oral PMDs are summarized in Table 1. Majority of patients presented with single PMD in the primary anatomical mucosal site while in five patients two or more PMDs were encountered. A total of 70 primary PMDs were detected. The most common PMD found was oral lichen planus (OLP) (n=40, 57.1%) and the most prevalent site was the buccal mucosa. In the miscellaneous group of primary PMDs (n=10) detected, there were four proliferative verrucous leukoplakia (PVL) lesions, two lesions each for candidal leukoplakia and chronic discoid lupus erythematosus (DLE), and one lesion each for oral submucous fibrosis (OSF) and carcinoma in-situ.

Examination of the contralateral oral mucosa in the study sample revealed that 28 (46.6%) patients exhibited PMDs either synchronously (n= 21, 35.0%) or metachronously (n=7, 11.6%). Their data are detailed in Table 2. The time interval for these contralateral lesions to appear ranged from three months to 11/2 years. A total of 42 PMDs from the contralateral sites were detected. All these lesions were subjected to incisional biopsies and histopathological examination. OLP (n=30, 71.4%) was the most prevalent PMD found. In the miscellaneous group, the two synchronous lesions were PVLs whereas the metachronous lesion was not a true bilateral lesion. It was an OSCC that developed in the same site as the primary PMD (right ventral tongue). The left ventral tongue of the said patient was normal and also cytobrushed. In the remaining cases that presented with normal-looking contralateral mucosa, their cytobrush findings were normal.

Table 1. Patients with Potentially Malignant Disorders at Primary Oral Mucosal Sites

Variables	Male	Female	Ratio
Total cases (n=60)	26 (43.3 %)	34 (56.7%)	1:1.3
Mean age (Range) (yr)	49.0 (28-71)	50.8 (24-68)	-
Ethnicity (n=60)			
Malays (4, 6.7%)	0 (0.0%)	4 (6.7%)	-
Chinese (23, 38.3%)	8 (13.3%)	15 (25.0 %)	1:1.9
Indians (32, 53.3%)	15 (25.0%)	17 (28.3%)	1:1.1
Others (1, 1.7%)	1 (1.7%)	0 (0%)	-
Habits (n=60)			
Betel (1, 1.7%)	0 (0.0%)	1 (1.7%)	-
Smoking (6, 10.0%)	5 (8.3%)	1 (1.7%)	5:1
Alcohol (2, 3.3%)	1 (1.7%)	1 (1.7%)	1:1
None (51, 85.0%)	20 (33.3%)	31 (51.7%)	1:1.6
Site distribution (n=70)			
Buccal M (26, 37.1%)	9 (12.8%)	17 (24.3%)	1:1.9
Ventral T (13, 18.6%)	2 (2.9%)	11 (15.7%)	1:5.5
Dorsum T (10, 14.3%)	2 (2.9%)	8 (11.4%)	1:4
Commissur M (3, 4.3%)	1 (1.4%)	2 (2.9%)	1:2
Floor of mouth (2, 2.9%)	0 (0.0%)	2 (2.9%)	-
Others (16, 22.8%)	7 (10.0%)	9 (12.8%)	1:3
Types of PMD (n=70)			
OLP (40, 57.1%)	18 (25.7%)	22 (31.4%)	1:1.2
Mild ED (16, 22.9%)	6 (8.6%)	10 (14.3%)	1:1.7
Moderate ED (4, 5.7%)	0 (0.0%)	4 (5.7%)	-
Others (10, 14.3%)	6 (8.6%)	4 (5.7%)	1.5:1

M, mucosa; T, tongue; PMD, potentially malignant disorders; OLP, Oral lichen planus; ED, epithelial dysplasia

Table 2. PMD Patients with Synchronous and Metachronous Lesions in the Contralateral Oral Mucosa

Variables	Synchronous	Metachronous
No. of patients (28, 46.6%)	21 (35.0%)	7 (11.6%)
Mean age (Range) (yr)	49.5 (24-67)	47 (36-66)
Males/Female (M:F)	8/13 (1:1.6)	3/6 (1:2)
Ethnicity (n=28) (46.6%)		
Malays (n=3) (5.0%)	2 (3.3%)	1(1.7%)
Chinese (n=11) (18.3%)	8 (13.3%)	3 (5.0%)
Indians (n=14) (23.3%)	11 (18.3%)	3 (5.0%)
Others (0)	0	0
Mean time interval (Range) (m)-		7 (3 -18)
Site distribution (n=42))		
Buccal M (18, 42.9%)	15 (35.7%)	3 (7.2%)
Dorsum T (7, 16.7%)	7 (16.7%)	0 (0.0%)
Ventral T (8, 19.0%)	2 (4.8%)	6 (14.2%)
Others (9, 21.4%)	8 (19.0%)	1 (2.4%)
Types of PMD (n=42)		
OLP (30, 71.4%)	26 (61.9%)	4 (9.5%)
Mild ED (7, 16.7%)	3 (7.2%)	4 (9.5%)
C leukoplakia (2, 4.8%)	1 (2.4%)	1 (2.4%)
Others (n=3) (7.2%)	2 (4.8%)	1 (2.4%)

M, mucosa; T, tongue; PMD, potentially malignant disorders; OLP, oral lichen planus; ED, epithelial dysplasia; C, candidal

Discussion

One of the earliest studies to evaluate the incidence of field change observable in oral mucosa was by Thomson (2002). His sample consisted of 26 consecutive new (untreated) patients that presented with a unilateral OSCC (18) or a PMD (eight), and all these cases underwent 'mirror image' biopsies from clinically normal-looking mucosa at corresponding anatomical sites. Our study differed from Thomson's work (2002) in two main aspects. We have limited our current investigation into determining the risk in the corresponding anatomical mucosal site of patients with primary PMD. No attempt was made to assess the status of the contralateral mucosa in patients with OSCC. Secondly, for ethical reasons, we did not perform any incisional biopsies of the clinically normal-looking contralateral mucosa in those cases presenting with unilateral PMD in the primary mucosal sites.

In his study, Thomson (2002) found that 15 patients (58%) demonstrated histologically abnormal tissue upon microscopic examination of the clinically normal-looking mucosa at corresponding anatomical sites. Of these patients, six (23%) showed reactive change/cellular atypia associated with chronic irritation, seven (27%) exhibited frank dysplasia, whilst two (8%) displayed carcinoma-in-situ (CIS) or microinvasive SCC. In the present study, the cytobrush samples from the clinically normal-looking mucosa at corresponding anatomical sites of 32 patients (53.3%) yielded normal cytological results. There are limitations with this technique as an investigative tool for the detection of abnormal changes in the oral mucosa (Potter et al., 2003). However these issues are not within the scope of discussion here. Given that false negative reports are possible with this noninvasive method (Potter et al., 2003), all our PMD cases including those with clinically normal-looking contralateral mucosa were placed on a regular follow-up basis. Those cases with unilateral PMD involving the ventro-lateral tongue and floor of mouth were monitored very closely because the risk of malignant transformation is known to be significantly higher at these sites (Napier and Speight, 2008). To date no clinically observable changes were found in these cases. The single case of OSCC arising in the primary PMD site (right ventral tongue) was detected during the duration of the project. His previous biopsy was diagnosed as mild epithelial dysplasia. Whether this first biopsy was representative remains arguable.

OLP is relatively uncommon in Malaysia, affecting 0.38% of the general population (Zain et al., 1997). In the present study, OLP formed the most prevalent PMD found at both the primary and contralateral anatomical mucosa sites of our study sample. This finding is not unexpected because a substantial number of patients attending the Oral Medicine Clinic here presented with OLP. There could be an institutional bias because our Oral Medicine Clinic is one of the main tertiary referral centres for oral diseases including screening for PMD in Malaysia. Furthermore, as OLP lesions run a chronic protracted course and that 50% of lichen planus patients tend to present with oral lesions, many of our OLP patients were long-term review cases (Rad et al., 2009).

In the current study, OLP and oral lichenoid lesions (OLL) were considered as one and the same, and no attempt was made to distinguish them clinically or histologically. Many of the patients in our series also presented with significant medical histories related to systemic therapy for treatment of diabetes mellitus and hypertension but these details were not included for analysis here. It is known that both OLP and OLL carry comparable risk of malignant transformation, with increased risk in the atrophic/erosive/ulcerative forms. At our Oral Medicine Clinic all OLP and OLL patients alike are placed on a recall programme (Lim et al., 2009). There is a large body of evidence that favours the need for recall of these OLP patients to screen for possible malignant transformation (Lo Muzio et al., 1998; Mattsson et al., 2002; Mignogna et al., 2006; Rad et al., 2009; van der Meij et al., 2003). A previous study disclosed that the risk in Malaysians is about 1.2% (Yaacob et al., 2002). To date, none of the cases on active follow-up in this study sample exhibited this change.

Dysplasia is the term used to describe the occurrence of architectural disturbance and cytological atypia in the abnormal or disturbed oral epithelium (Warnakulasuriya et al., 2008). It is believed that the presence of dysplasia in the oral epithelium signifies a likely progression to cancer. The general consensus is that the more severe the degree of dysplasia the greater the likelihood of progression to malignancy. In the present study, most of our primary PMDs and PMDs at the corresponding anatomical sites demonstrated mild dysplasia. The subjectivity of grading dysplasia and the wide inter- as well as intra-observer's variations are well-known and have been discussed elsewhere. Generally, mild dysplasia is associated with a low risk of malignant transformation (less than 5%). Although not statistically significant, in this study, there was an observable trend for the lateral/ventral tongue

and floor of mouth to display increased vulnerability to dysplastic change.

The less common cases examined in our study sample included OSF, candidal leukoplakia and PVL. OSF is a chronic insiduous PMD characterized by burning sensation, pallor and stiffening of the oral mucosa due to irreversible progressive fibrosis of the underlying connective tissues. The malignant transformation rate is 7.6% over a 17-year period (van Wyk et al, 1990). In the present series only one case of OSF was registered. This was a 34-year-old female, an Indian national who came to Malaysia as a newly-wed bride. Her progress is unknown as she apparently left Malaysia and returned to India for treatment. Candidal leukoplakia (chronic hyperplastic candidiasis) is a distinct form of candida-associated leukoplakia that tends to affect the commissural mucosa and dorsum tongue (Sitheeque and Samaranayake, 2003). The reported risk of malignant transformation is about 10%. Two cases of candidal leukoplakia were encountered in our series and both presented with lesions that characteristically involved the commissural mucosa. In both cases, no malignant change was recorded. PVL is a distinct and aggressive form of leukoplakia characterized by multifocal extension of these lesions and its invariable progression to carcinoma (Cabay et al., 2007). Only one such case was seen in this study. The patient was an elderly Indian female who underwent multiple biopsies from different sites. During the study period, the histopathological diagnoses of the primary and contralateral PVL lesions ranged from mild to moderate dysplasia. The outcome of her PVL lesions remained unknown as she was lost to follow-up.

In summary, our findings suggest that patients presenting with PMDs in the upper aerodigestive tract are at greater risk of developing a second lesion most probably on the contralateral site. An overwhelming number of OLP patients in the study sample and poor follow-up compliance were the key limitations of this study.

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