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Between-Lesion Discrepancies in Terms of Dysplasia, Cell Turnover and Diagnosis in Patients with Multiple Potentially Malignant Oral Lesions

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Abstract: *Objective:* The present study assessed patients with multiple oral lesions to evaluate the mis-estimation rate in terms of diagnosis and risk of malignant transformation when only one biopsy is performed.

Study Design: Thirty-five patients presenting at least two white and/or red lesions in different oral mucosa sites with a final diagnosis of leuko/erythroplakias or lichenoid lesions were included, for a total of 70 biopsies.

Results: Nineteen patients (54%) had at least one between-lesion discrepancy considering the presence/absence of dysplasia (10 patients), normal/high cell turnover (13 patients) or diagnosis (5 patients). Discrepancies were not related to clinical aspect or within-patient similarity of lesions.

Conclusions: Multiple oral lesions in the same patient can significantly differ in terms of dysplasia, high cell turnover and, even diagnosis. Multiple biopsies are imperative and diagnosis as well as risk of malignant transformation should be formulated for each single lesion rather than for each individual patient.

Keywords: Leukoplakia, lichenoid lesion, dysplasia, cell turnover, diagnosis.

INTRODUCTION

Oral squamous cell carcinoma (OSCC) is frequently preceded by lesions named "potentially malignant disorders" of which leuko/erythroplakia and lichenoid lesions are the most common [1].

Leuko/erythroplakia is defined as a white/red patch or plaque that cannot be characterized clinically or pathologically as any other disease [1]. It has been postulated that leuko/erythroplakia is the clinical expression of genetic alterations within the oral mucosa epithelium whose accumulation can facilitate the development of OSCC [2].

Lichenoid lesion is the consequence of a chronic cell-mediated immune condition of unknown etiology, in which T lymphocytes accumulate beneath the epithelium of the oral mucosa and increase the differentiation rate of the stratified squamous epithelium [3]. Unlike leuko/erythroplakia, the diagnosis of lichenoid lesion is specifically formulated by histological disclosure of a band-like lymphocytic infiltrate filling the lamina propria, and liquefactive degeneration of basal keratinocytes [4].

There is currently no unique reliable parameter to identify lesions predictive of malignant transformation. Risk assessment is usually based on clinical, pathological and more recently on bio-molecular evaluations [5,6]. The diagnosis is a good parameter to discriminate lesions at higher risk of malignant transformation. The malignant potential of lichenoid lesions is still a matter of debate, but it is widely accepted that the frequency of malignant transformation is low [7]. By contrast, leuko/erythroplakia is associated with an increased likelihood of malignant transformation with a risk of OSCC development ranging from 6% up to 36% [8].

The clinical aspect is another prognostic factor; white and uniformly flat and thin leuko/erythroplakias are usually associated with a relatively lower risk of malignant transformation as compared to non-homogeneous lesions [2,9], while the association between clinical aspect and malignant potential is of very limited value when we consider lichenoid lesions [7].

At present, dysplasia is the strongest predictive parameter associated with malignant transformation, and it is generally accepted that the risk increases with dysplasia severity, presumably due to the accumulation of genomic alterations [5,10]. However, if a lesion showing signs of dysplasia should be considered at high risk, the absence of this parameter does not allow the clinician to consider the lesion at low risk. The high variability of results may be due to the limitations of the incisional biopsy technique that may reveal different histological patterns in a single lesion, depending on the surgical site [11-13]. Additionally, a key factor that may misestimate the overall risk of a patient developing OSCC is the presence of multiple lesions in the same oral cavity. To this point, it is widely accepted that all lesions in the same oral cavity must be evaluated, but it is not unusual in clinical practice for both diagnosis and prognosis to be formulated on the basis of a single biopsy from a single lesion that is thought to be the most representative.

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No literature studies have hitherto quantified the rate of between-lesion discrepancies in terms of presence/absence of dysplasia or other biomolecular markers when patients with multiple oral lesions undergo only one biopsy.

The present study undertook histological evaluation of all lesions in patients with multiple oral lesions belonging to the group of potentially malignant lesions. Our aim was to quantify the between-lesion mis-estimation rate in terms of diagnosis, presence/absence of dysplasia and high/normal cell turnover.

PATIENTS AND METHODS

The study population was selected among 158 patients with white or red plaques who referred to the University of Bologna Department of Oral Sciences from 2005 and 2011. To be initially considered, each patient must have at least two lesions (white and/or red plaques) in different oral mucosa sites at least 2 cm away from each other; 64 patients complied with this criteria.

The study design was in accord with the IRB standards of our institution and was in accordance with the Helsinki declaration of 2008.

Each subject underwent incisional biopsy of both lesions at different oral sites. Incisional biopsies were carried out under local anaesthesia by well-experienced oral surgeons unaware that they would be part of a study, but following a standard protocol for the treatment of multiple oral lesions. Selection of biopsy site was based on the clinical features, focusing on the area of non-homogeneous appearance when present or tissue indurations [13]. The specimen was taken with a biopsy punch to a depth of at least 5 mm and a 3-5 mm margin of clinically normal mucosa was also included. All tissues were fixed in 10% formalin and paraffin-embedded as routine. Serial sections were cut from each block and stained with hematoxylin and eosin for histological evaluation. Histological examination and immunohistochemical stainings were performed blindly at the Section of Anatomic Pathology of the Department of Hematology and Oncology, Bologna University at Bellaria Hospital. All cases were examined by the same pathologist. Histological diagnoses were performed following the WHO book criteria [10,14].

After the clinical and histological evaluation, only lesions with a final diagnosis of leuko/erythroplakia or lichenoid lesion were considered.

Leuko/erythroplakia was clinically defined as a white/red patch or plaque that could neither be rubbed off nor diagnosed as any specific disease [1], and diagnosed histologically following the criteria proposed in the World Health Organization's blue book [14].

Lichenoid lesion was diagnosed histologically following histological features that included irregular acanthosis, degeneration of the basal layer of the epithelium and a band of lymphohistiocytic infiltrate in the upper chorion composed almost exclusively of mature lymphocytes [4].

The final population consisted of 35 patients (14 males and 21 females aged 49-82 years, mean 65.1 ± 8.9) who presented two lesions (white and/or red plaques) in different oral mucosa sites at least 2 cm away from each other, with a final diagnosis of leuko/erythroplakia or lichenoid lesion, for a total of 70 lesions.

Lesions were classified into two groups according to their clinical aspect: 40 homogeneous white lesions (uniformly flat, thin with shallow cracks of the surface keratin, plaque type); 30 mixed lesions (white and red associated appearance) [1].

Patients were divided into two groups considering the similarity of the two lesions: 19 patients presented similar lesions (12 patients with both homogeneous white lesions, and 7 patients with both mixed lesions), whereas 16 patients showed different lesions (white and mixed lesions).

The following parameters were considered as prognostic markers for malignant transformation:

-Moderate/severe dysplasia (atypical hyperplasia according to the Ljubljana classification) was characterized by increasing atypia, loss of polarity, and frequent mitoses, involving more than two-thirds of the epithelium while lacking infiltrative growth. Squamous cell hyperplasia (simple hyperplasia, according to the Ljubljana classification) was characterized by increased basal-parabasal layers, acanthosis, in the absence of architectural alterations [14]. The rationale behind selecting only lesions with high grades of dysplasia was to be sure about the effective presence of dysplasia, thereby reducing the subjectivity of its assessment and the well-established relative high rate of malignant transformation [15,16] and hence well-differentiate the group of lesions with dysplasia from that of hyperplastic lesions.

-Cell turnover was evaluated by measuring Ki67 expression of Ki67 protein which is a protein expressed in proliferating cells (G1, S, G2, and M phases), but not in resting cells (G0 phase), and is a useful marker for the simple and rapid evaluation of proliferating cells in a tumour or pre-neoplastic lesion [17]. A monoclonal anti-Ki67 antibody (Dako, Denmark, clone MIB-1, diluted 1:200) was used to measure protein expression. All tissues were fixed in 10% buffered formalin and paraffin-embedded using a routine protocol. Sections (2 μm) were serially cut from selected blocks and immunostained using an automatic stainer (Autostainer, Ventana, USA). The percentage of positive nuclei in 400 consecutive epithelial cells in areas representative of the lesion provided a semi-quantitative immunohistochemical evaluation. The cut-off value for high Ki67 expression was established at 20% of stained nuclei because no sample from normal mucosa showed higher values in the present series or in previous studies [18-20].

STATISTICAL ANALYSIS

Chi square analysis was used to evaluate any significant relationship between within-patient discrepancies in terms of dysplasia, cell turnover or diagnosis and clinical aspect or similarity of the lesions.

RESULTS

Table **1** summarizes the clinical and histological features of the population.

Table 1. Clinical and Histological Features of the Entire Population

Cases	Sex/Age	Clinical Aspect	Diagnosis	Dysplasia	Cell Turnover	Discrepancies
		First/Second Lesion	First/Second Lesion	First/Second Lesion	First/Second Lesion	
1	F/75	W/W	LEUK/LEUK	No/No	High/High	None
2	M/58	W/W	LEUK/LEUK	No/No	Normal/Normal	None
3	M/57	W/W	OLL/OLL	Yes/No	High/Normal	Dysplasia Cell turnover
4	F/57	W/W	OLL/OLL	No/No	Normal/Normal	None
5	F/66	W/W	OLL/OLL	No/No	High/High	None
6	M/55	W/W	OLL/OLL	No/No	Normal/Normal	None
7	M/59	W/W	OLL/OLL	No/No	Normal/Normal	None
8	F/65	W/W	LEUK/OLL	No/No	Normal/Normal	Diagnosis
9	M/59	W/W	LEUK/LEUK	No/No	High/High	None
10	F/78	WR/WR	LEUK/LEUK	No/Yes	Normal/High	Dysplasia Cell turnover
11	F/68	WR/WR	OLL/OLL	No/No	High/Normal	Cell turnover
12	F/69	WR/WR	OLL/OLL	No/No	Normal/Normal	None
13	F/62	WR/WR	OLL/OLL	No/No	Normal/Normal	None
14	F/59	W/W	LEUK/LEUK	No/No	High/Normal	Cell turnover
15	F/57	WR/WR	OLL/OLL	No/No	Normal/High	Cell turnover
16	F/67	WR/W	OLL/LEUK	Yes/No	High/Normal	Dysplasia Cell turnover Diagnosis
17	F/68	W/WR	LEUK/LEUK	No/No	High/Normal	Cell turnover
18	F/75	WR/W	OLL/OLL	Yes/No	High/Normal	Dysplasia Cell turnover
19	F/71	WR/W	OLL/OLL	No/No	Normal/Normal	None
20	M/49	WR/W	OLL/OLL	No/No	High/Normal	Cell turnover
21	M/66	W/WR	OLL/OLL	No/No	Normal/Normal	None
22	F/56	W/WR	OLL/OLL	No/No	Normal/Normal	None
23	F/57	W/WR	OLL/OLL	No/No	Normal/Normal	None
24	M/51	WR/W	OLL/OLL	Yes/No	Normal/Normal	Dysplasia
25	M/77	W/WR	LEUK/OLL	Yes/No	High/High	Dysplasia Diagnosis
26	F/66	W/WR	LEUK/LEUK	No/Yes	High/High	Dysplasia
27	M/75	W/W	LEUK/LEUK	No/No	High/Normal	Cell turnover
28	F/64	W/W	LEUK/LEUK	No/Yes	Normal/High	Dysplasia Cell turnover
29	M/60	WR/WR	OLL/OLL	No/No	High/High	None
30	F/64	WR/W	OLL/OLL	No/No	Normal/High	Cell turnover

Table 1. contd…

Cases	Sex/Age	Clinical Aspect	Diagnosis	Dysplasia	Cell Turnover	Discrepancies
		First/Second Lesion	First/Second Lesion	First/Second Lesion	First/Second Lesion	
31	M/77	WR/W	LEUK/LEUK	No/No	High/Normal	Cell turnover
32	F/71	W/WR	LEUK/OLL	Yes/No	Normal/Normal	Dysplasia Diagnosis
33	M/72	WR/W	LEUK/LEUK	No/No	Normal/Normal	None
34	F/77	WR/WR	LEUK/OLL	Yes/No	Normal/Normal	Dysplasia Diagnosis
35	M/82	WR/W	LEUK/LEUK	No/No	Normal/Normal	None

Clinical aspect: W: white lesion; WR: white and red lesion;
Diagnosis: LEUK: erythro/leukoplakia; OLL: lichenoid lesion
Dysplasia: Yes; No
Cell turnover: High; Normal

Single lesions (70 lesions from 35 patients): 29 lesions had a final diagnosis of leuko/erythroplakias (21 presented as white lesions and eight as mixed lesions), and 41 lesions were diagnosed as lichenoid lesions (19 presented as white lesions, and 22 as mixed lesions).

Dysplasia: hystological evidence of dysplasia was found in 6 leuco/erythroplakias (3 among the 21 homogenous white lesions and 3 among the 8 mixed lesions) and in 4 lichenoid lesions (one among the 19 homogenous white lesions and 3 among the 22 mixed lesions).

Cell turnover: high ki67 values were found in 13 leuco/erythroplakias (10 lesions in the group of 21 homogeneous white lesions and three among the eight mixed), and in 12 lichenoid lesions (4 lesions in the group of 19 homogeneous white lesions and 8 among the 22 mixed lesions).

Single patients (35 patients with two lesions each): 19 patients (54%) showed at least one between-lesion discrepancy (in terms of presence/absence of dysplasia, low/high ki67 values or even in terms of diagnosis).

Discrepancy in terms of dysplasia: 10 patient showed a between-lesions mis-estimation rate in terms of dysplasia (presence of dysplasia in one lesion and absence in the other): 4 discrepancies were found among the 19 patients with clinically similar lesions (both white or both white/red), and 6 discrepancies among the 16 patients with clinically different lesions (one lesion white and the other mixed) (chi square 1.15; ns).

Discrepancy in terms of cell turnover: 13 patients showed a between-lesions mis-estimation rate in terms of cell turnover (one lesion with high cell turnover and normal cell turnover in the other): 7 discrepancies were found among patients with clinically similar lesions, and 6 discrepancies among patients with clinically different lesions (chi square .03; ns).

Discrepancy in terms of final diagnosis: surprisingly, 5 patients showed a between-lesions mis-estimation rate in terms of diagnosis (one lesion diagnosed as leuco/erythroplakia and the other as lichenoid lesion): 2 discrepancies were found among patients with clinically similar lesions, and 3 discrepancies among patients with clinically different lesions (chi square .51; ns).

DISCUSSION

Leuko/erythroplakias and lichenoid lesions are the potentially malignant lesions that most frequently turn into OSCC. Despite a similar clinical aspect they differ in aetiology and above all in their risk of developing into OSCC. Quantifying the risk of malignant transformation in a single lesion is challenging and often based on the clinical aspect, and the histological or bio-molecular features of the lesion in addition to the diagnosis [9,21].

The matter is further complicated by the presence of multiple lesions in the same oral cavity. Multiple oral lesions in the same oral cavity are not unusual and can be found in 27% of patients with oral premalignant lesions [22]. It is well known that most authors recommend that all lesions in the same patient be histologically evaluated to address the dentist to the most correct therapeutic approach [11-13], but it is not unusual in clinical practice for both diagnosis and prognosis to be formulated on the basis of a single biopsy from a single lesion that is thought to be the most representative.

Our purpose was to obtain information on the rate of misestimating the risk of each patient developing OSCC when only one lesion is evaluated in patients with multiple lesions.

To the best of our knowledge, this is the first study to quantify the error that may derive from the biopsy of a single lesion in a patient with multiple lesions. The results show that when only one lesion is studied in a patient with multiple potentially malignant lesions, the probability of misestimating the real risk of OSCC is high. If we consider the presence/absence of dysplasia as a predictive marker, ten patients (29%) had at least one between-lesion discrepancy, while the rate of discrepancy rose to 54% when low/high Ki67 values or different diagnosis were also taken into consideration.

It follows that if only one biopsy was performed in each patient and the biopsied lesion showed dysplasia or altered turnover, the absence of dysplasia or altered turnover in the other lesion would have neither changed the risk assessment nor the therapeutic approach to the patient. On the other hand, if the only biopsied lesion lacked dysplastic features, a significant underestimation of the overall risk would have occurred in that patient. Additionally, our results showed that the clinical aspect of the lesions was not a useful index to predict a between-lesion discrepancy because discrepancies were found both in the group of patients with clinically similar lesions and in the group of patients with clinically different lesions.

These findings emphasize that the risk assessment in a patient with multiple lesions must be the result of the evaluation of each single oral lesion, in agreement with Thomson et al. and Saito et al. who reported discrepancies in the grade of dysplasia in patients with multiple lesions [22,23].

Very interesting and surprising results came from the discrepancy in terms of diagnosis when only one lesion was considered. Five patients (14%) would have been misdiagnosed if only one lesion had been biopsied. This would have led to a different approach to therapy and follow up considering that the management of lichenoid lesions significantly differs from that of leukoplakias [24-26].

The unexpected finding of lesions with a different diagnosis in the same patient has not been widely discussed in the literature. To the best of our knowledge, only a few case reports have described concomitant lichenoid lesions and leukoplakias in the same patient [27-31]. Different hypothesis may be formulated to explain the existence of different lesions with a different diagnosis in the same patient. Some cases may represent the casual coexistence of two different diseases. The finding of lesions diagnosed as lichen together with leukoplakias has been reported in the literature, even though these are clinical studies lacking a histological diagnosis of oral lichen planus [27,32]; so that a misdiagnosis may have occurred.

Different histological diagnosis may also result from poorly representative samples that might not harbor the essential features for a correct diagnosis, depending on the site chosen by the practitioner or the between-pathologists interpretation [12,13,33]. However, a lack of signs of lichenoid reactions within a lichenoid lesion is quite unlikely since features suggestive of lichen may be found even distant from the lesion in an apparently healthy mucosa [34].

Other suggestive hypotheses postulate that cases of different diagnosis in the same patient may represent specific diseases with multiple lesions at different degrees of development. Lichenoid inflammatory infiltrate acting chronically on oral mucosa may generate genetic aberrations in keratinocytes which, in case of clonal expansion, may spread in altered fields in which a leukoplakia could arise. A field effect in oral lichen planus is suggested by the tendency of multiple and multifocal OSCCs in OLP patients to undergo malignant transformation [35, 36].

Our results do not confirm any of these hypotheses, but they do show that concomitant leukoplakias and lesions diagnosed as lichenoid are not unusual when all lesions are histologically studied in patients with multiple lesions. The ongoing follow-up of these patients will shed more light on this issue.

CONCLUSIONS

When treating patients with multiple potentially malignant oral lesions a single biopsy procedure may greatly misestimate the overall risk of developing OSCC and above all may even lead to a final misdiagnosis in the individual patient.

The similarity of clinical aspects cannot be used as a reliable index to choose the most representative lesion, since many discrepancies in terms of dysplasia or altered cell turnover and above all in the histological diagnosis have also been found between lesions with a very similar clinical aspect. Multiple biopsies are thus recommended to reduce the possibility of underdiagnosis or misdiagnosis and the overall risk of developing an OSCC should be expressed on each single lesion rather than on each individual patient.

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CONFLICT OF INTEREST

None declared.

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