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Microinvasion: A Diagnostic Dilemma.

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ABSTRACT

Microinvasive oral squamous cell carcinoma is a malignant tumour with invasion beyond basement membrane extending into superficial lamina propria without invasion into deeper structures. Such lesions are generally challenging to surgeon and pathologist in relation to clinical presentation, metastatic ability, therapeutic intervention and prognosis. There are no predefined histopathological criteria for identification of microinvasion and therefore, newer studies like immunohistochemistry for p53 expression and in situ hybridization have come up. The purpose of defining microinvasive oral squamous cell carcinoma is to identify these group of lesions which have minimal risk for lymph node metastasis and recurrence and treat them conservatively. Microinvasive lesions have got better prognosis if they are diagnosed and treated early. The aim of this paper is to stress on the importance of identifying microinvasive squamous cell carcinoma as a distinct entity for appropriate communication to the clinician regarding its nature , behaviour and treatment planning.

Keywords: microinvasion, oral squamous cell carcinoma

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INTRODUCTION

Oral and pharyngeal cancer are grouped together as the sixth most common cancer in the world. The annual incidence rate of oral and pharyngeal cancers is around 275,000 and 130,300 respectively [1, 2]. Two thirds of Oral squamous cell carcinoma (OSCC) occurs in developing countries. The incidence rate of oral cancer in India is high i.e., 20 per 100,000 population and accounts for over 30% of all cancers in the country. [1, 3]

Microinvasive oral squamous cell carcinoma (miOSCC) is a SCC with invasion beyond the epithelial basement membrane, extending into the superficial stroma [4] without invasion of deeper tissues. [5, 6] It is also defined as invasion with an irregular infiltrative border which is often accompanied by a reactive desmoplasia and not by the pushing type expansion of hyperplastic epithelium. [5, 7] The lesion is called microinvasion only if, the tumour is confined to papillary lamina propria, as defined by the depth of rete processes [5, 8]. The maximum depth of invasion in miOSCCs ranges from 0.5 mm to 2 mm when measured from the basement membrane of the adjacent non-neoplastic surface epithelium. This is attributed to the variations in epithelial thickness. [4]

Unlike microinvasive cervical cancer, there are no pre-defined classification system for miOSCC. [5, 8] Based on several studies it has been proposed that a modified pathological Tumour, Node, Metastasis (pTNM) staging system, in which three cut-off points for tumour thickness (5, 10 and 20 mm) should be combined with the largest tumour dimension to obtain the pT stage. A common point of disagreement exists among the pathologists when the epithelium is destroyed and a hypothetical surface line is reconstructed from the surface to measure the depth of invasion from the base of epithelium and tumour thickness, referred to as the entire tumour mass. [6, 9]

miOSCC is capable of metastasis. [4, 5] Therefore it is more accurate to consider the actual mass present beneath the theoretical reconstruction of basement membrane. [6] However the prognosis is good. [4, 10].

The aim of this review is to stress on the importance of identifying microinvasive oral squamous cell carcinoma as a distinct entity which in turn will facilitate appropriate communication with the clinician regarding its nature, behaviour and help in establishing appropriate treatment planning.

CLASSIFICATION:

Various classification systems have been proposed for microinvasive SCC of cervix and oesophagus. One classification of cervical cancer was given by FIGO Cancer Committee Meeting in 1985.

Stage IA—Preclinical carcinomas of the cervix (*i.e.*,those diagnosed only by microscopy)
StageIA1—Minimal microscopically evident stromal invasion
Stage IA2—Lesions detected microscopically that can be measured.

a) The upper limit of the measurement should not show a depth of invasion of more than 5 mm taken from the base of the epithelium, either surface or glandular, from which it originates
b) A second dimension, the horizontal spread, must not exceed 7 mm
c) Larger lesions should be staged as IB.

The choice of 5 mm and 7 mm as the maximum depth and lateral spread, respectively, is based on the following:

1. A three dimensional volumetric analysis of cervical carcinomas by Burghardt revealed that tumor volumes of less than 400 mm^3 were unassociated with lymph node metastasis.

2. The third dimension (length), although not measured, usually does not exceed the lateral diameter (width) by more than 50%. Thus, for a lesion that is 5 mm deep and 7 mm wide, the assumed maximum length would be 10.5 mm. The volume would thus equal 5 mm x 7 mm x 10.5 mm = 367.5 mm^3. [11-13]

Classification of microinvasive squamous cell carcinoma of oesophagus was given by Rubio CA, Liu FS, Zhao HZ (1989)

a) Grade I - characterized by regular epithelial buds of the same size.
b) Grade II - regular buds that varied in size.
c) Grade III - irregular buds (i.e., buds of varying length and width with irregular contours).
They proposed that in the esophageal mucosa, there is a close relationship among the degree of squamous cellular atypia, the formation of epithelial buds and the progression toward invasive carcinoma. [14]

Considering the above two classifications as a basis and based on degree of invasion, Kanno.N. (1990), in his histological study of early invasive oral squamous cell carcinoma, observed two types of invasion:

1) Primary invasion
2) Secondary invasion

1) Primary invasion

- Seen as microinvasion from the basal layer as budding, drop, and diffuse infiltration of atypical cells from the dysplastic epithelium or carcinoma-in-situ
- Downward growth of the dysplastic epithelium characterized by the structural atypia
- Unclearness of the basement membrane, round cell infiltration, proliferation of the blood vessels, and loose connective tissue around the early invasion

2) Secondary invasion

- Seen near the muscle layer or periosteum as a drop and diffuse infiltration, morphologically similar to the invasive patterns of developmental carcinoma. [15]

DIAGNOSIS:

Clinically miOSCC lesions present as patches, plaques or erosions similar to the clinical features of premalignant disorders. Therefore an accurate clinical examination is essential to avoid misdiagnosis [6, 16-20]. Non invasive diagnostic aids like autoflouresence can also be used for screening of normal looking microinvasive lesions. [21-23]

Histologically miOSCC lesions show presence of scattered malignant cells in the submucosa, just below basement membrane or within 1-2 mm of basement membrane. Tongues of discrete foci of malignant epithelium invading through the basement membrane can also be seen. Histologically, miOSCC occurs in two phases. The first as development from and as a continuum of carcinoma in situ (CIS). The second as invasion from an epithelium demonstrating no evidence of CIS. In the upper aerodigestive tract, severe dysplasia (i.e., carcinoma in situ) is not a prerequisite for the development of an invasive squamous cell carcinoma. Such invasive carcinomas ‘‘drop off’’ or ‘‘drop down’’ from the basal cell layer with the overlying mucosa showing no evidence of dysplasia. The invasive nests must be cytologically malignant showing dysplastic changes, dyskeratosis, mitotic figures with an irregular outline with infiltrative borders. The presence of invasion results in a desmoplastic host response exhibiting edematous change around the tumor nests with granulation tissue and fibrosis. [24]

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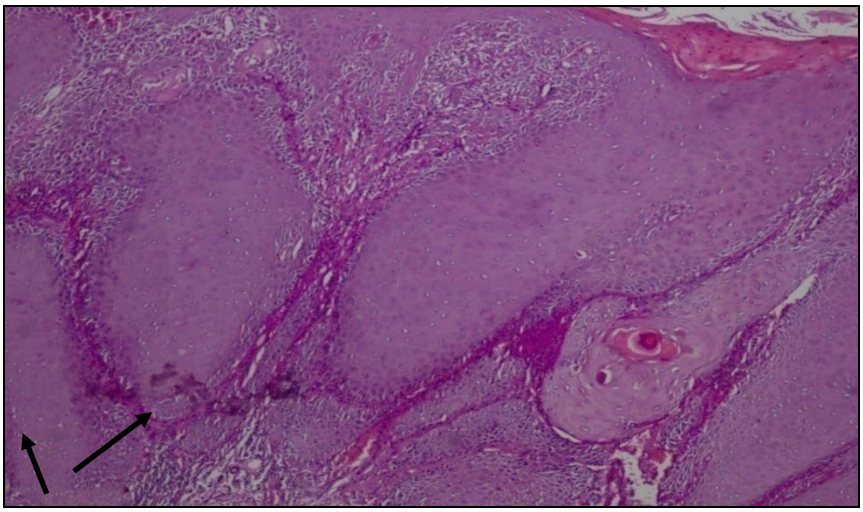

Fig 1: miOSCC showing drop off or drop down pattern of rete pegs and the overlying mucosa showing no evidence of dysplasia.

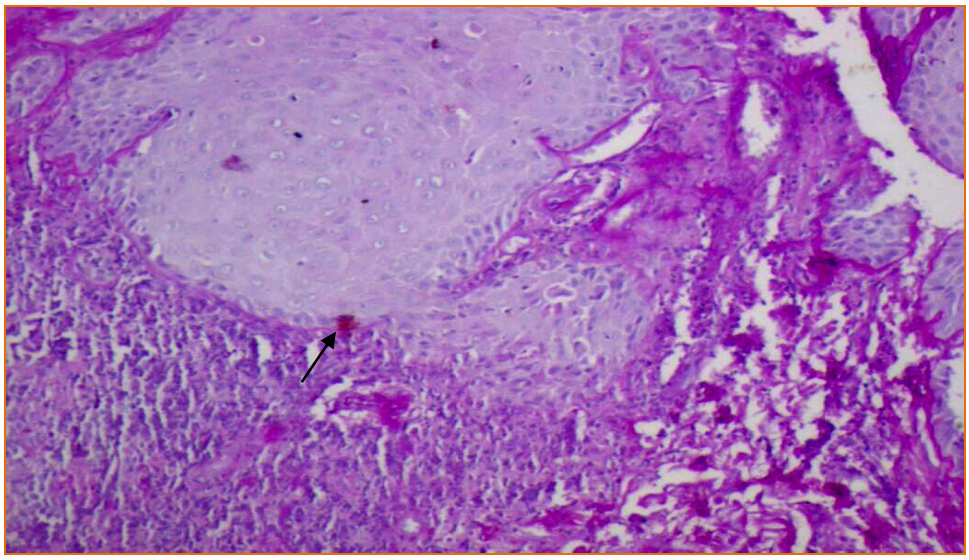

Fig 2: Photomicrograph of miOSCC showing a break in the epithelial basement membrane and infiltration into underlying connective tissue.

Non invasive diagnostic procedures like brush biopsy along with DNA image cytometry detects malignant nature of suspicious abnormal epithelial cells months prior to histology and increases the diagnostic accuracy

Special stains like PAS stain can be used for the assessment of basement membrane more vividly. [5] of brush biopsies.. Aneuploidy in the presence of an abnormal stemline is considered. [25] Examination of serial sections and assessment of keratinocytic atypia would also be helpful. Immunohistochemical markers like Pancytokeratins, E- cadherin, Laminin, collagen IV, can be used for the diagnosis of miSCC. Pancytokeratins help in the identification of keratinocytes in the stroma. [5] E-cadherin which is a glycoprotein maintaining the intercellular adhesions shows underexpression in miOSCC lesions which increases as it progresses towards invasive carcinoma. [26-33] Discontinuity in the expression of basement membrane markers like laminin and collagen IV is also seen (Fig 3 A, B & C). [26, 34-37]

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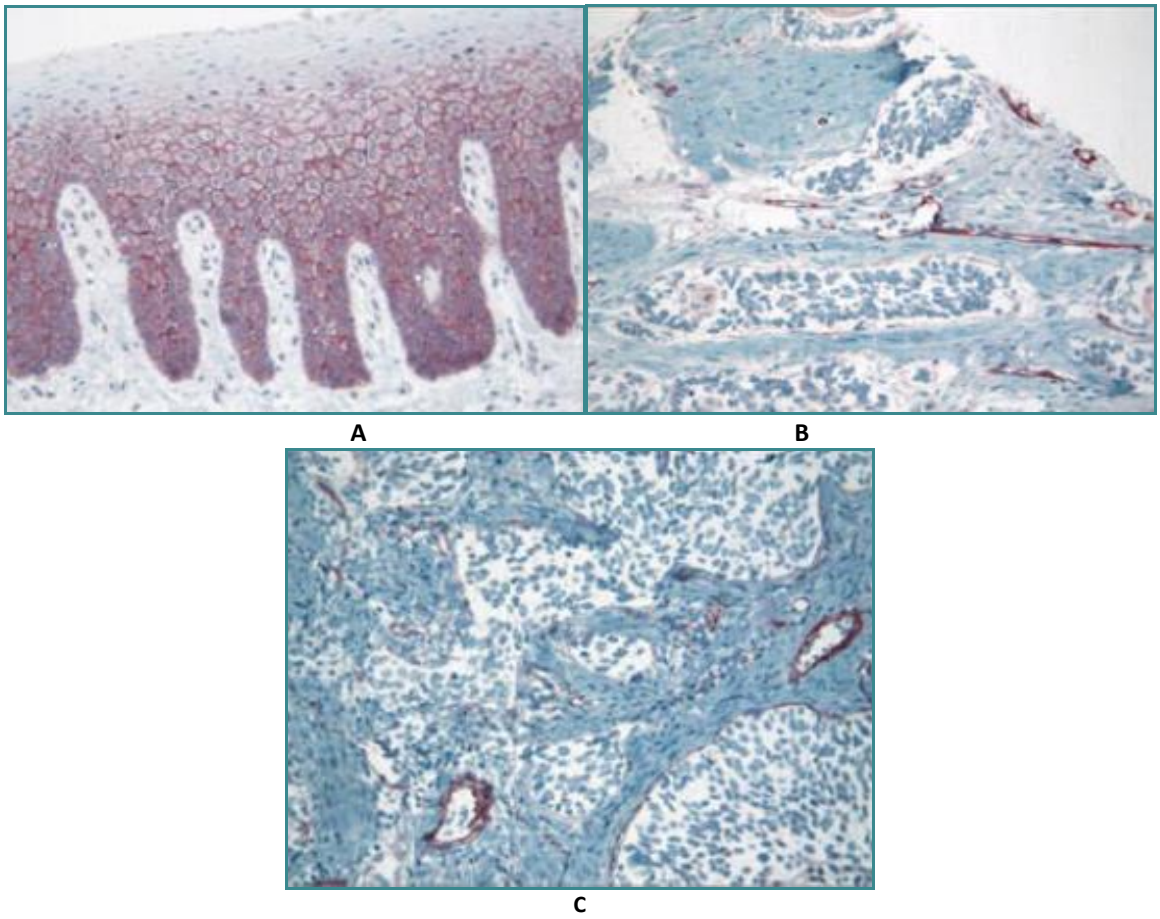

Fig 3 – A) Photomicrograph showing underexpression of E-Cadherin, B) & C) photomicrograph showing discontinuity in the expression of laminin and collagen IV

DISCUSSION

The diagnosis of OSCC is usually straightforward when there is unequivocal invasion together with cytological atypia which is detected by presence of islands, cords and other arrangements of squamoid epithelial cells. This criterion is particularly helpful: (1) when epithelial islands or cords are detected in submucosa below merely dysplastic surface epithelium (2) in the recognition of carcinoma cuniculatum which is characterised by tortuous centrally-keratinising columns of proliferated squamous epithelium with minimal cytologic atypia. [8, 38]

When unequivocal/submucosal invasion cannot be established, the question of 'early SCC' arises. The problem here would be to know whether frank invasion of the lamina propria is present or absent. Difficulty in identifying increases in the incisional biopsies showing proliferative, moderate or severe squamous epithelial dysplasia.

'Islands' of epithelium within the lamina propria should be regarded as suspicious, but it is also important to exclude, whether they represent sectioned rete processes, especially if these are long and bulbous which are seen in some reactive conditions or odontogenic residues. [8, 39] Examination of serial sections and assessment of keratinocytic atypia would be helpful. The integrity of the basement membrane could also be assessed in PAS-stained sections. Caution should be exerted when there is subepithelial brisk and infiltrative inflammatory reaction because such reaction could affect the disruption of basement membrane resulting in compromised assessment. When presence of early invasion is confirmed, it can be categorised as microinvasive OSCC if, tumour is confined to the papillary lamina propria as defined by the depth of the rete processes and superficially invasive if the tumour is confined to the reticular (deep) lamina propria but not yet involving the submucosal tissues. In case of uncertainity of microinvasion, the histology would be reported as

lacking unequivocal evidence of invasion or progressing to microinvasive OSCC. In such cases, a re-biopsy will have to be considered since an incisional biopsy may not contain the most advanced part of the lesion. [8]

For treatment, procedures influencing pathological staging and prognosis should be focussed on. Information provided by surgical staff such as illustrations or photographs showing the limits of the resection and also marking, by ink or sutures, the areas of special interest would be helpful. Care should be taken by the pathologist when inking the surgical margins – both peripheral and deep. It should be borne in mind that the deep aspect of large resections of the floor of mouth, may have been anatomically in contact with the tissues of nodal level I of the Radical Neck Dissection (RND). Failure to recognise this anatomical relationship can lead to misinterpretation of the margin of clearance and extent of direct spread of the primary tumour and extracapsular spread of metastatic tumour. [8]

Microinvasive OSCC is capable of gaining an access to lymphatics and blood vessels resulting in metastasis, even though it may be rare. [4, 5] Metastasis is governed by the nature of invasion. There are higher chances of metastasis if the invasion is in clusters and lesser chances if invasion is in single cell pattern. [5] In case of nodal metastases, it is debatable if radical approach like neck dissection should be uptaken. However surgical excision of lesions with 1 to 2 mm margins at the periphery and deep margins is recommended. [5, 40] There is no universally accepted treatment protocol for microinvasive OSCC with clinically negative nodes. [5, 40] In reported cases of mi SCC of lip, vermilionectomy combined with local wedge resection has shown to effectively resolve the carcinoma although, the cosmetic results of such combined treatment are poor. [41-43]

CONCLUSION

The purpose of defining microinvasive OSCC is to identify groups of lesions with minimal risk for lymph node metastases and recurrence. Such diagnosis can help the clinician perform appropriate treatment and avoid the morbidity associated with a more radical approach. Histopathological assessment of formalin-fixed biopsy tissue and surgical resection specimens remains the cornerstone of cancer diagnosis and pathological staging in routine clinical practice.

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