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Microinvasive carcinoma: A Review and Case Report

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Running title: Invasion of squamous cell carcinoma

Clinical significance: Microinvasive carcinoma necessitates a more conservative surgical treatment as opposed to other forms of invasive carcinoma and therefore making a right diagnosis is essential.

ABSTRACT

Oral squamous cell carcinoma (OSCC} comprises95% of all forms of head and neck cancer, and in the last decade its' incidence has amplified by 50%. Carcinogenesis of the oral cavity is a multistage process, which concurrently involves precancerous lesions, invasion and metastasis. Microinvasive squamous cell carcinoma (SISCC) or the superficially invasive carcinomais a poorly defined terminology with regard to the oral cavity. Authors havedefined it as a horizontally spreading squamous cell carcinoma developing from a carcinoma in situ or severe dysplasia,exhibiting a focal and/or superficial invasion of > 2 mm and no further than the lamina propria.

INTRODUCTION

Oral squamous cell carcinoma (OSCC) is derived from the stratified squamous epithelium of the oral mucosa. It has been ascribed to multifactorial causes such as cigarette smoke, snuff, alcohol and the papilloma virus, among others. It is seen to occurcommonly at various sites of the oral cavity most frequentlythe lip, the lateralsurface of the tongue and the floor of the mouth. The OSCC increases with age, with the majority occurring in patients >40 years. Oral cancer initially presents as an epithelial dysplasia, which later degrades the subepithelial basement membrane (BM) leading to local destruction and distant invasion via metastasis. Invasion locally occurs through islets and cords of epithelial cells. [1]It is defined as the earliest stage in the genesis of oral cancer that can be observed histologically. The subject of microinvasion has been a subject of confusion since a long time.[2]

CASE REPORT

A 54-year-old male patient (**Figure 1 A**) complained of a burning sensation in the left back tooth region since 6 months. The burning sensation aggravated on consumtion of hot or spicy food and beverages. He had a history of chewing about 6-7 packets of tobacco for the past 15 years

Intraoral examination revealed a whitish verrucousleukoplakic lesion with erythema,on left buccalmucosa extending from 35-37 regions measuring around 4x 5 cm (**Figure 1B**). There was pain and bleeding andthe lesion was slightly tender onpalpation.

The left submandibular lymph node was palpable but not fixed and it was soft inconsistency. An OPG and a biopsy wereadviced.

No abnormality was detected on lesional site in the OPG.**(Figure 1D)** A clinical diagnosis of verrucousleucoplakia was given

One soft tissue bit from the retromolar region was taken for biopsy and another soft tissue from within the extraction socket of 38 (**Figure 1C**).

The Hematoxylin&Eosin stainedsofttissue section showedparakeratotic stratified squamous epithelium with severe dysplastic features like drop shape rete pegs,pleomorphism, basilar hyperplasia, acanthosis, highup mitoses, prominent nucleoli, interaepithelialkeratinization,with nuclear hyperchromatisim. Epithelium showed areas of pushing borders with slight breach in the basement membrane in some areas**(Figure 2b)** and epithelial pearls in the superficial lamina propria. (**Figure 2c)**and**(Figure 2d)**. Periodic acid Schiff stain (PAS) revealed a minute break in the basement membrane indicating a breach. (**Figure 2 b**)Focal areas of necrosis were also seen in the epitheliumwith papillary projections. The underlying connective tissue showed numerous chronic inflammatoryinfiltrate in the fibrovascularstroma.Tissue from the curetted socket showed severe dysplastic epithelium without invasion.

The above diagnosis suggested an early / microinvasive squamous cell carcinoma. Patient was referred to a higher cancer center where a wide marginal excision of the lesion was done and the patient showed complete recovery after a week.

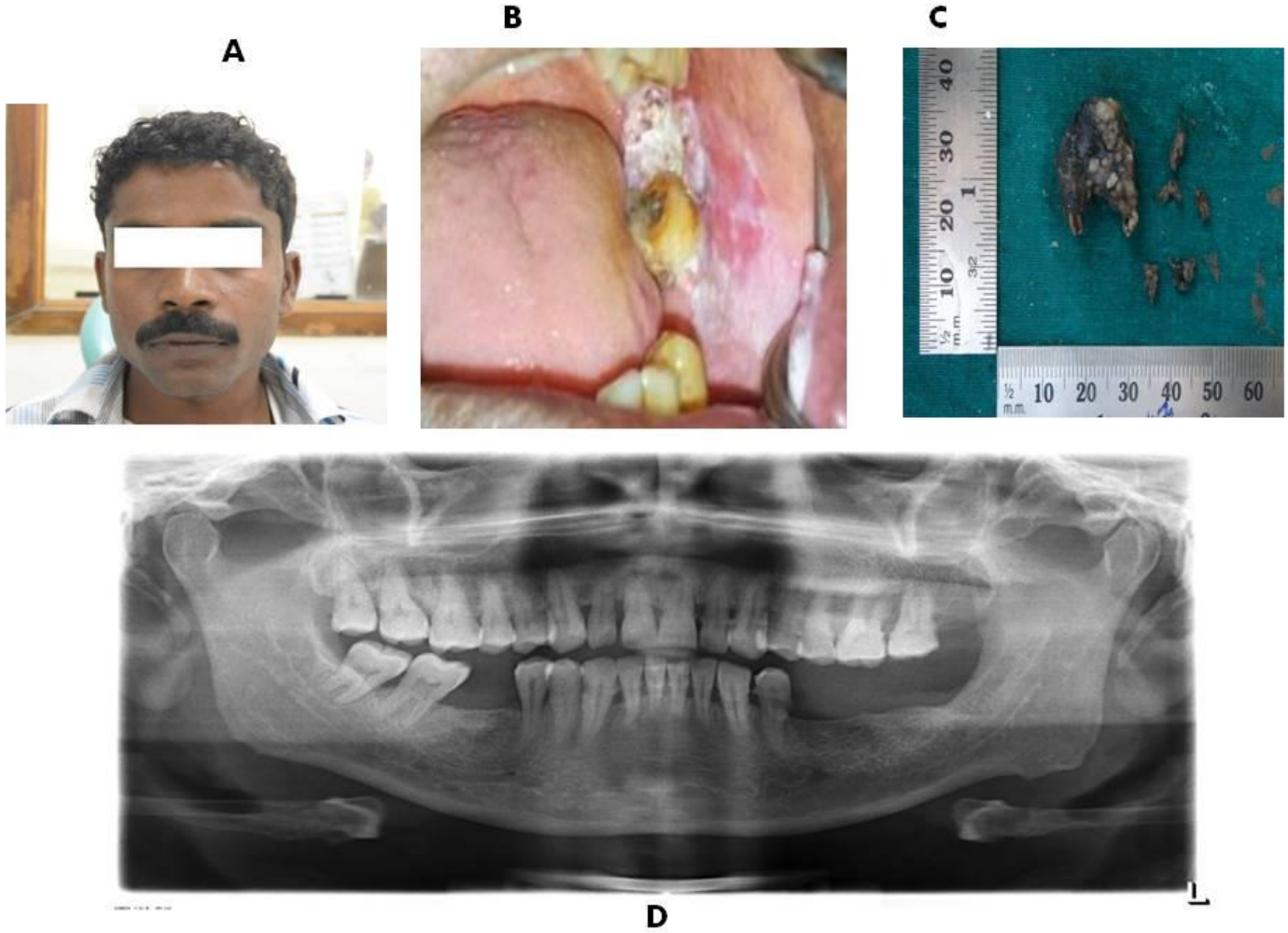


FIGURE 1

Figure 1 A: 54-year-old male patient

Figure 1 B: Intraorally, a whitish verrucousleukoplakic lesion with erythema on left buccal mucosa in 35-37 region measuring around 4x 5 centimeters in size

Figure 1 C: One soft tissue bit from the retromolar region was taken for biopsy and another soft tissue from within the extraction socket of 38

Figure 1 D: Healing extraction socket was detected on lesional side in the OPG

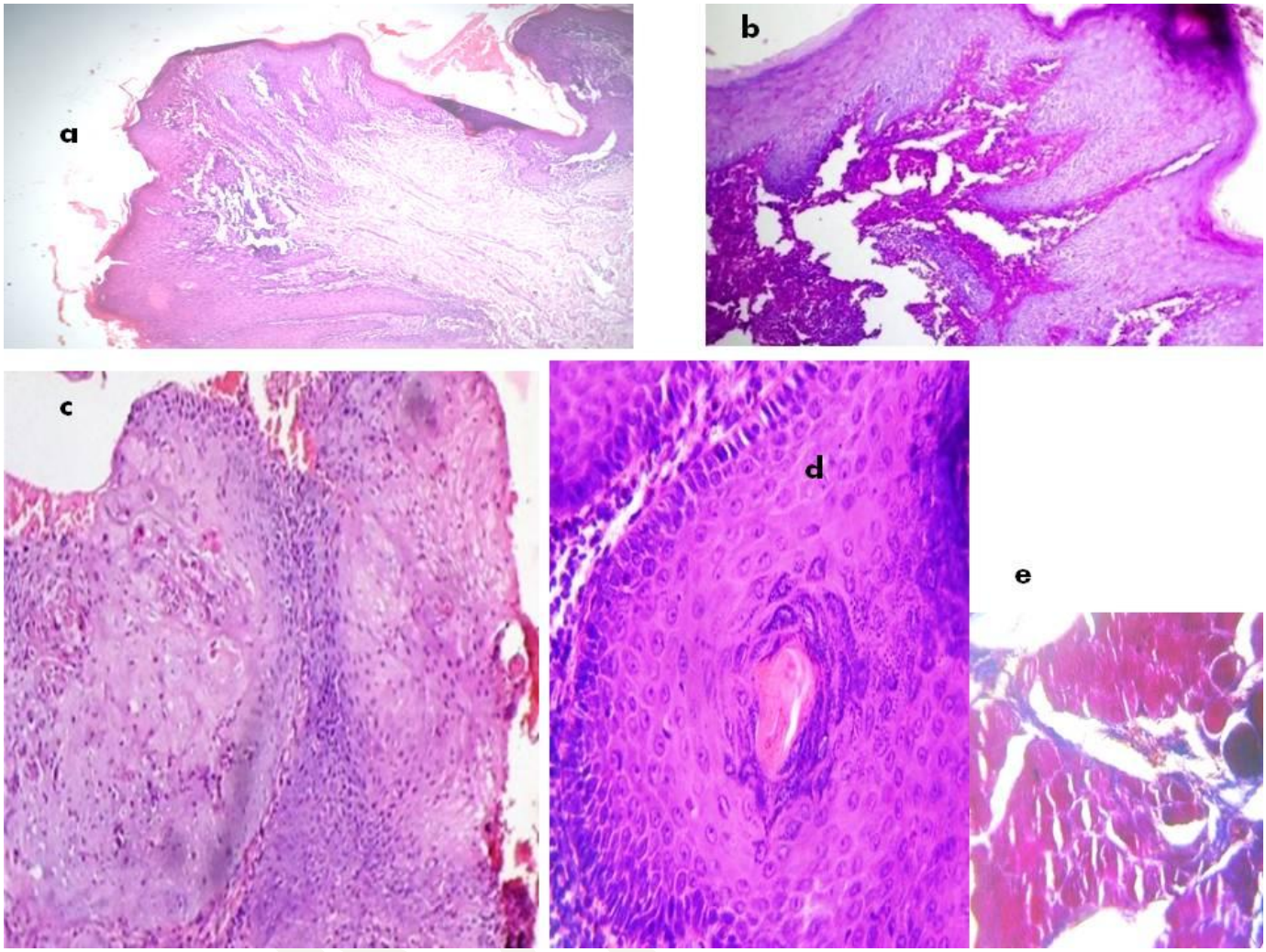
Figure 2 a:Parakeratotic stratified squamous epithelium with severe dysplastic features like drop shape rete pegs, pleomorphism, etc.

Figure 2b: PAS stained section showing a breach in the basement membrane

Figure 2c and Figure 2d: Epithelial pearls in the superficial lamina propria

Figure 2e: No invasion of the deeper tissues like the muscles

FIGURE 2



DISCUSSION

Two systems are used to histologically classify oral squamous cell carcinoma lesions;

- International Histological Classification of Tumors
- The pattern of the **Tumor Invasion Front** (TIF).

The first one is based on the type of differentiation such as the: well-differentiated, moderately differentiated and undifferentiated, which is essential to evaluate the tumor's growth rate and ability to metastasize. [1]

The TIF represents the area of the lesion with maximum depth of invasion and its progression into the surrounding tissues. The TIF is considered to be the most representative area of the tumor and is identified by four main features;

- ✓ the degree of keratinization,
- ✓ nuclear polymorphism,
- ✓ lymphocytic infiltration and
- ✓ pattern of invasion (PI):

Pattern of invasion includes:

i) Islet-infiltrating cells with wide fronts of invasion

ii) Thin infiltrating cords and

iii) Individual infiltrating cells. [1]

The prognosis is clearly dependent on the depth of the infiltration of the tumour as determined histopathologically and an infiltration of the tumor, more than 5millimeters intothe underlying tissue, indicates a metastasis to the lymphnodes and a poorer prognosis. [4]As per the Oncology committee of the International Federation of Gynaecology and Obstetrics (FIGO) in gynecological SCC, the depth of invasion should not be more than 5mm from the base of the epithelium (basement membrane of the neighbouring non-invasive epithelium) from which it develops and lateral spread (largest diameter) should not be more than 7mm. [2]

The survival factor in OSCC is based on

- the presence of regional lymphnode metastases,
- the size (surface dimension) and depth (extent of local infiltration) of the carcinoma,
- the oral anatomical site affected and
- the histopathological grade of the carcinoma [4]

The Terminology in context of other medical specialities

Microinvasive SCC shows the infiltration of the cancer into the superficial compartment of the lamina propria. However, the terminology is ambiguous and as such, though it sounds simple, the diagnosis of superficially invasive SCC can be subjective, with no common definition among pathologists. In case of the laryngeal lesions, theauthors consider includingthose lesions that show the presence of scattered malignant cells within the submucosa just below the basement membrane or within 1–2 mm of the basement membrane in the microinvasive category. Other authors however, consider the SCC as microinvasive, when discrete foci of malignant cells or a tongue, invades through the basement membrane. Barnes has definedmicroinvasive carcinoma as an invasive SCC that extends into the stroma by ≤0.5 mm, measured from the adjacent (nonneoplastic) epithelial basement membrane. Whatever may be the definition of microinvasive carcinoma,it has been accepted uniformly, to exclude lesions such as the Ca-in-situ(Tis) or those malignant lesions with islands that are limited to the surface epithelium at one end of the spectrum and at the other end,those carcinomas that invade deeply into muscle and cartilage and into extralaryngeal structures (T2 or greater tumors) in case of the laryngeal SCC.[4]Also, the presence of lymph-vascular space invasion excludes a diagnosis of microinvasive carcinoma. [5]The invading cells may gain access to the blood vessels and the lymphatics initiating metastasis; and although the possibility of metastasis exists, it is rare, and these tumors have excellent prognosis even if the site of the lesion was in the floor of the mouth.

Nevertheless, for a conclusive diagnosis to be made, the entire lesion needs to be studied, and not just a random tangentially cut specimen. [6]

Based on the histological evaluation of the tissue-removed, invasion has been divided into various stages namely:

- ✓ Stage 1A: which is further divided into
  - Stage 1A1 tumors, -lesions with minute foci of invasion observed microscopically
  - Stage 1A 2 that is observed macroscopically.
- ✓ Larger lesions staged as IB.

Histologically they can then be classified into

- Early stromal invasion
- Microinvasive carcinoma[3]

Microinvasivion SCC and stromal changes

In early stromal invasion, the cell nests protrude into the superficial stroma, or may show invasion of islands of epithelium into the stroma, about 1 mm from the epithelium.These invasions are very difficult to be identified microscopically and are identified only when they actually "drop off" into the underlying stroma from a surface epithelium that is severely abnormal and essentially non-invasive. The cells within this peg is said to be more differentiated (based on a higher eosinophillic cytoplasm and a lower N/C ratio), than the epithelium from which it has arisen. The invading cells is also found to be well demarcated in the stroma by a clear, edematous and cell free zone and peripherally with the plasma cells and lymphocytes. The highly eosinophillic cytoplasm is said to be due to dedifferention following the breaking free from the basement membrane. The high proliferationof epithelial cells is suggested to occur in a bid to ward off the inflammatory infiltration.[3]

For microinvasionto occur, not only the depth and volume of the tumorhas to be considered, but also the spread of the lesion parallel to the surface epithelium is important, and that too in multiple parallel sections. This observation enables the pathologist to guage the chances of vascular invasion by the tumor. The immune response of the individual and the growth pattern observed clinically is equally important to diagnose a tumor asmicroinvasive.

Connective tissue response to the MIC includes:

1. Keratin granuloma formation: in reaction to the keratin
2. Keratin may or may not be present and markers may be required to confirm presence of keratin [8]

Key features for histological confirmation of microinvasive cancer include.

- Round to oval cells arranged in a synctial manner.
- Eosinophillic cytoplasm occupying a large volume
- Round to oval nuclei with variation in size.
- Chromatin which is fine to coarsely granular with unequal distribution
- Micronuclei present but absence of macronuclei.
- N/C or the nuclear cytoplasmic ratio is lower in carcinoma-in-situ. [3]

Vascular alterations may help in diagnosing microinvasion, and therefore it should be recorded, as they may influence the treatment planning in the future.Vascular tissue within stroma without a lining negates microinvasion. And if they are found, they indicate the shrinkage of the stroma during fixation[7]

Pathogenesis of Microinvasive carcinoma

Microinvasive carcinoma can arise from two unrelated phases:

1. Development from, or in continuation of the Ca-in-situ: Seen in cases of laryngeal carcinoma and not commonly seen in the oral cavity.
2. Invasion that arises from the epithelium that shows dysplastic alterations with severe dysplasia, but lacking the full thickness ca-in-situ.Dropping off, of the epithelial cells, more than arising from a ca-in-situ is not a prerequisite for preceding the MIC.

Differential Diagnosis

1. **Pseudoepitheliomatous hyperplasia**
2. **Superficial extending carcinoma**where there is extensive extention into the lamina propria as opposed to MIC where the extent is limited.
3. Multifocal involvement. [8]

Treatment

- In cases of Ca-in-situ, the treatment includes a wide excision with adequate surgical margins. [9]

- In case of the MIC, a 1-2 cm margin on the peripheral and deep aspect is recommended. Frozen sections rather than biopsies need to be studied intraoperatively.[10]

CONCLUSION

Microinvasive squamous cell carcinoma of the oral cavity is not well represented in the grading system of oral cancer like the microinvasivetumors of other sites. This results in difficulty in assesing its prognosis and in its treatment planning. Therefore, an adequate representation of this lesion through a proper classification system is necessary.

Footnotes:

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