Original paper

Morphology of cells undergoing epithelial mesenchymal transition in microinvasive and early invasive oral squamous cell carcinom a — a light microscopic study

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The present study focuses on identification of cancer attributes of epithelial mesenchymal transition (EMT) at the earliest possible stage (microinvasion) under a light microscope by using hematoxylin and eosin stains, making it feasible for researchers to investigate such cases with ease without the use of extensive setups. The present study is the first in the English literature to define EMT features in micro-invasive and early invasive oral squamous cell carcinoma (OSCC) under a light microscope. This is a retrospective study of histological sections of 43 cases of OSCC from the Department of Oral Pathology and Microbiology. The data collected were later statistically analyzed.

A total of 11 micro-invasive and 32 early invasive OSCC cases were assessed for core features of EMT.

The predominant feature defining EMT found was dense inflammatory infiltrate in both microinvasive (91%) and early invasive OSCC (88%) followed by cell individualization in 82% of microinvasive and 75% of early invasive OSCC, which was then followed by other features.

Reporting EMT in histopathological reports on a daily basis can aid in early diagnosis of OSCC as well as understanding carcinogenesis in early stages. Thereby, inclusion of EMT targeting therapeutics in early stages of OSCC can significantly alter the prognosis of cancer.

Key words: EMT, microinvasive OSCC, early invasive OSCC, loss of apical basal polarity, cell-to-cell adhesion weakening, cell individualization, established front back polarity, dense inflammatory cell infiltration.

Introduction

Oral squamous cell carcinoma (OSCC) is the most common form of head and neck cancer, associated with a high mortality rate, high recurrence rate, and less than 50% 5-year survival rate, suggestive of its aggressive and metastatic nature. The cataclysmic features of this malignancy are a consequence of its invasive nature [1, 2]. Cancer cell invasion across the basement membrane has been a well-studied phenomenon for years and the role played by protease dependent pathways that primarily involve matrix metalloproteinase

(MMPs) and streptokinase has been highlighted. However, many clinical trials have reported gross failure of both broad-ranging as well as specifically acting MMP inhibitors in reducing the mortality rates in cancer patients after the treatment [2]. The poor outcomes of MMP inhibitors thereby lead to the strong possibility that other mechanisms in addition to the MMP pathway which include physical as well as mechanisms related to tumor cell morphology and cell signaling, tumor microenvironment, etc., come into play [3]. One such mechanism which is the result of cross-talk between the malignant epithelial cells and the stromal cells is epithelial mesenchymal transition (EMT).

Epithelial mesenchymal transition is a phenomenon that enables epithelial cells to attain a mesenchymal phenotype. Epithelial cells whose hallmark characteristics include tight cell junctions (desmosomal attachments), apical-basal polarity, and polygonal shape transform into elongated loose and motile cells which resemble stromal fibroblasts [4]. Epithelial mesenchymal transition is known as a potential promoter of cancer progression in terms of invasiveness, metastasis, chemoresistance, recurrence, and finally poor survival outcomes in patients with established and advanced disease [2, 4]. However, in recent literature, it has been evident that EMT starts right at the inception of carcinogenesis and even on the infiltrative fronts in early disease. The best and worst part about the early transitory cells in head and neck cancers is that these cells are in hybrid states of partial EMT (pEMT) [5]. The best part is that if cells along the pEMT are therapeutically targeted we can have a potential treatment for cancer infiltration right at the early invasive level, and the worst is if they are not fixed at the hybrid state along the EMT axis they are going to be a major challenge for any therapy directed against EMT [2, 4, 5].

To the best of our knowledge the present study is the first research that focuses on the identification of histomorphological attributes of malignant cells undergoing EMT under light microscopy by using routine hematoxylin and eosin staining. This retrospective study also aims to provide microscopic criteria for diagnosis of cells undergoing EMT at the microinvasive and early invasive tumor fronts, making it feasible for pathologists and researchers to investigate such cases with ease without the use of extensive setups involving immunohistochemistry or electron microscopy. If its potential is extracted and studied further it can aid in the usual reporting of EMT in cancers which when therapeutically targeted can prevent its progression in the early stage itself.

Material and methods

In addition to the archives of the Department of Oral Pathology and Microbiology, VYWS Dental College and Hospital, Amravati, and Dent-O-Path Lab, Amravati was approached for retrieving 400 patient records from the previous four years. Discrete examination of each case paper was done via hematoxylin and eosin stained biopsies of clinically suspected cases of OSCC for the corresponding patients and retrospectively evaluated by three independent oral pathologists. Inclusion criteria to be considered included proper staining in which micro details were appreciated and the ones with poor staining, artefacts, and other maxillofacial lesions were excluded from the study. The 154 confirmed diagnosed OSCC cases were further subjected to histopathological examination for being diagnosed as microinvasive and early invasive OSCC. In the case of multiple histopathological slides for the same, the best representatives were chosen. In dire circumstances of unavailability of slides due to their return to the patients, new slides were prepared out of the remaining paraffin-embedded tissue samples.

Inclusion criteria

For diagnosing microinvasion the parameters considered were:

- a relatively thin tumor confined to the papillary lamina propria as defined by the depth of the rete process was considered,
- the depth varying 0.5–2 mm measured from the adjacent non-neoplastic surface epithelium because of greater variations in epithelial thickness was taken into account,

For diagnosing early invasion the parameters considered were in terms of depth of invasion, the cut-off considered was 2 mm for T1 and 4 mm for T2 in the 8th primary tumor, lymph nodes, metastases staging of OSCC.

On microscopic examination, 55 cases of OSCC were considered suspected cases of microinvasive and early invasive OSCC. Out of these 12 cases were factored out due to poor staining, inadequate expression of characteristics, and artefacts. The 43 histopathological slides secured (microinvasive OSCC; $n = 11$ and early invasive OSCC; $n = 32$) were further scanned under 40^{x} magnification and their microinvasive and tumor invading fronts were subjected to further analysis by the same three independent pathologists, to assess the cytological characteristics of EMT of cells at microinvasive and early invasive fronts.

The paramount parameters observed were recorded systematically.

The following are the core aspects of EMT observed in histopathological slides:

- loss of apical basal polarity,
- cell-to-cell adhesion weakening,
- cell individualization,
- established front back polarity,
- dense inflammatory cell infiltration.

Table I. Gender wise classification of microinvasive and early invasive carcinoma

Gender	No. of cases	Percentage
Male	35	88
Female	5	13

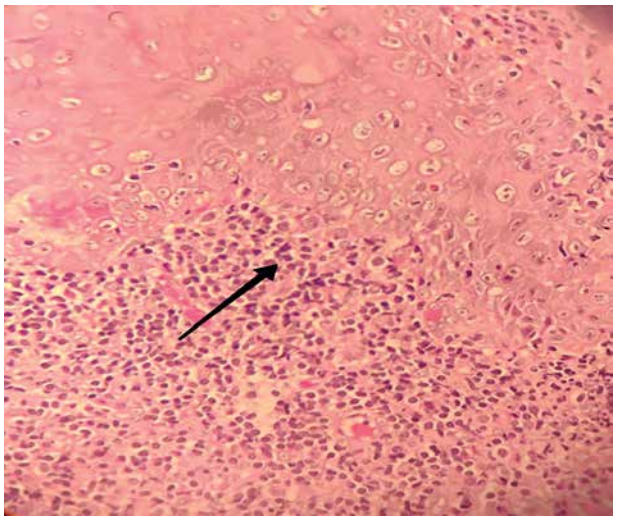

Fig. 1. Histological representation of dense inflammatory infiltration under light microscopy

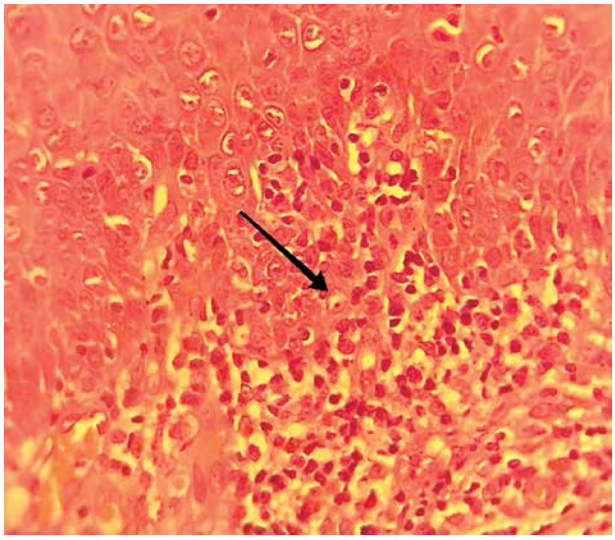

Fig. 2. Histological representation of cell individualization under light microscopy

Statistical analysis

Data were recorded and edited in MS Excel and analyzed using SPSS software version 21. Categorical variables are expressed as the number of slides and percentage of slides, while categorical data are expressed as proportions. Using the χ^2 test we analyzed the categorical data and the p-value was considered as statistically significant when the p-value < 0.05.

Future directions

We have evaluated the role of EMT in early and microinvasive OSCC. However, no studies to date have highlighted its role in potentially malignant pathologies (premalignancies). Incorporating EMT targeting therapeutics in the treatment of these lesions can prevent its transition to cancer. Hence, more studies are warranted in this direction.

Limitations of study

The prevalence rate of microinvasive and early invasive OSCC indicates substantially less reporting of this early stage of cancer in developing countries such as India. Hence, the sampling size available for study was limited, providing scope for more studies with greater sampling sizes.

Results

The data of 11 microinvasive OSCC patients and 32 early invasive OSCC patients were studied for obtaining the core histopathological parameters of EMT in microinvasive and early invasive OSCC along with its demographic correlation.

Patient characteristics

The median age of the patients at the time of the study was 53 $\pm$11.06 years.

The prevalence of microinvasive and early invasive OSCC is higher in the male population as compared to the females. Of the patients who met the inclusion criteria, 35 were male and 5 were female; hence, 88% were male. This stark contrast can be well appreciated in developing and developed South Asian countries. This is summarized in Table 1.

Comparison of histological parameters of epithelial mesenchymal transition in microinvasive oral squamous cell carcinoma and early invasive oral squamous cell carcinoma

Epithelial mesenchymal transition defining histopathological parameters to be analyzed in the microinvasive and early invasive OSCC fronts include: loss of apical basal polarity, cell-to-cell adhesion weakening, cell individualization, established front back polarity, and dense inflammatory cell infiltration.

A comparison of these features amongst the 11 hematoxylin and eosin stained histopathological slides of microinvasive OSCC which met the inclusion criteria revealed the results as the percentage of the dense inflammatory infiltrate accounting for 91% (n = 10), summarized in Figure 1. It was followed by cell individualization, being 82% (n = 9) (Fig. 2), loss of apical basal polarity and loss of cell-to-cell adhesion in 73% each (n = 8), illustrated in Figures 3, 4. Lastly, front back polarity accounted for 61%

($n = 7$) of cases (Fig. 5), whereas the evaluation of the 32 slides of early invasive OSCC which met the inclusion criteria affirmed the presence of dense inflammatory infiltration in 28 slides, cell individualization in 24 slides, front back polarity in 23 slides, cell-to-cell adhesion weakening in 22 slides, and loss of apical basal polarity in 20 slides.

This highlights the fact that the tendency of highest expression at both the microinvasive and early invasive tumor invading fronts lies with dense inflammatory infiltration whilst the least common is front back polarity in microinvasive OSCC and loss of apical basal polarity in early invasive OSCC.

The expression of these parameters along with the prevalence ratio in terms of probability index and other details is presented in Table 2.

For better understanding, this table is further simplified in Figure 6.

Comparison of demographic data according to their grading in early invasive oral squamous cell carcinoma

Early invasive OSCC can be further stratified according to their pattern of differentiation into three main grades: well differentiated, moderately differentiated, and poorly differentiated OSCC. This is summarized in Table 3.

The information collected was studied to analyze the correlation between grading of early invasive OSCC and gender predilection. But it revealed that there is no significant difference in the gender with the grading of early invasive carcinoma ($p = 0.82$). This can be better appreciated via Table 4.

Discussion

Oral squamous cell carcinoma has long been a cause of concern owing to its high morbidity and inadequate study on its pathogenesis factors other than those which are well known. Multiple kinds of research have been conducted in line with this and have led to the establishment of a definite conclusion that EMT is one of the key phenomena influencing carcinogenesis. The studies conducted by Ribatti *et al*. have long established a correlation between EMT and cancer progression [6].

Thus, diagnosing OSCC at early stages by targeting EMT can be of great aid in resolving the high mortality rates and the low survival rates in this complex scenario. Extensive research has been carried out over the immunohistochemical and molecular fronts of EMT but its applicability on a daily basis still poses certain limitations leaving opportunities to explore its histomorphological tendencies to address the gaps. This study is the first one to attempt to solve these problems at the light microscopic level [2, 4, 5].

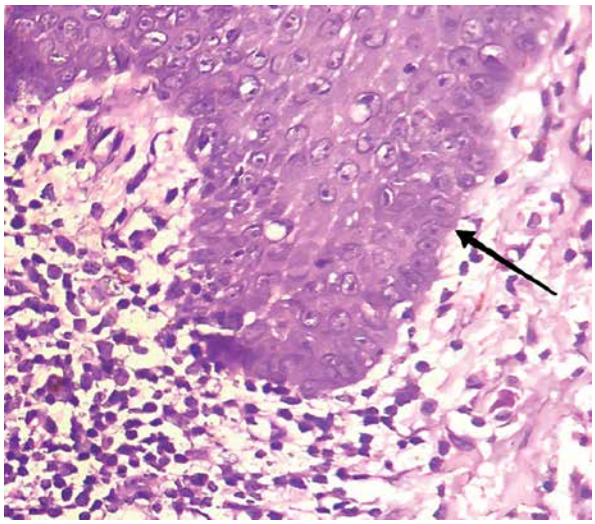

Fig. 3. Histological representation of loss apical basal polarity under high microscopy

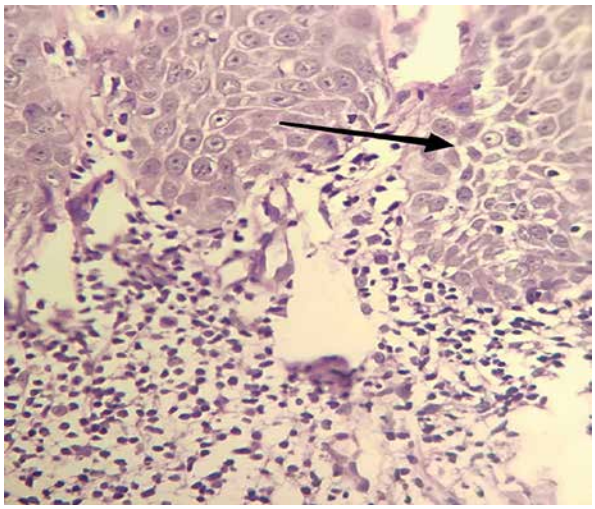

Fig. 4. Histological representation of loss of cell-to-cell adhesion under light microscopy

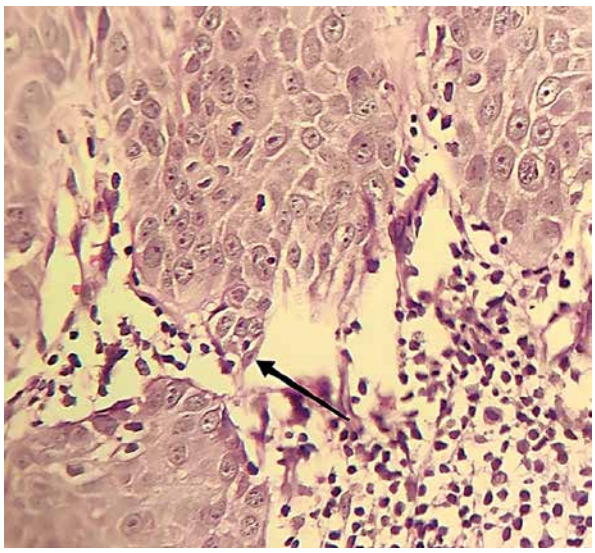

Fig. 5. Histological representation of gain of front back polarity under light microscope

Table II. Classification of microinvasive and early invasive oral squamous cell carcinoma

Parameters	Frequency		Percent of responses*		Percent of cases	
	Micro invasive	Early invasive	Micro invasive	Early invasive	Micro invasive	Early invasive
Dense inflammatory infiltration	10	28	24	24	91	88
Loss of apical basal polarity	8	20	19	17	73	63
Loss of cell-to-cell adhesion	8	22	19	19	73	69
Cell individualization	9	24	21	21	82	75
Front back polarity	7	23	17	20	64	72

**Here, percentage of responses signifies the probable frequency of occurrence of the feature in terms of 100. For example, the percentage of responses of front back polarity is 17%, which means that if in total 100 slides were to be considered then 17 slides would express this feature.*

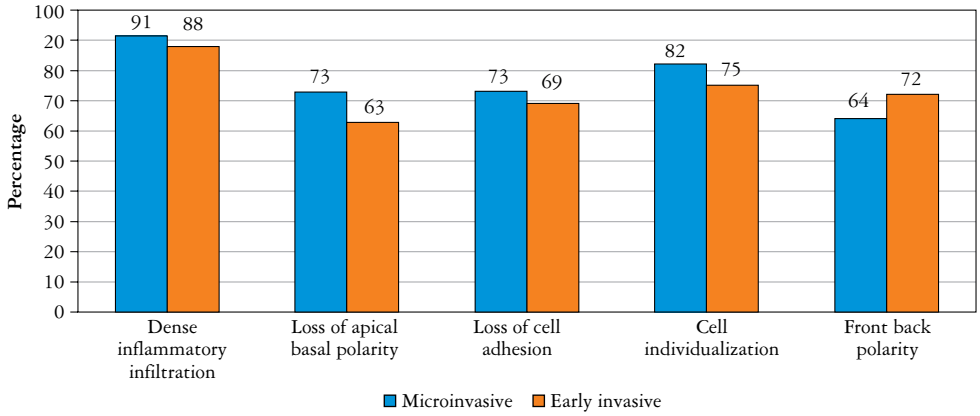

Fig. 6. Classification of microinvasive and early invasive oral squamous cell carcinoma

Table III. Classification of early invasive slides according to their grades

Grade	No. of cases	Percentage
Well	13	41
Moderate	17	53
Poor	2	6
Total	32	100

Table IV. Gender wise grading of early invasive oral squamous cell carcinoma

Gender	Moderate	Poor	Well	p-value
Female	2	0	2	0.82
Male	15	2	11	

The present study enlists the features of EMT visible under a light microscope in microinvasive and early invasive OSCC. The features observed were:
- loss of apical basal polarity,
- cell-to-cell adhesion weakening,
- cell individualization,
- established front back polarity,
- dense inflammatory cell infiltration.

The results obtained led to the conclusion of dense inflammatory infiltration being the predominant feature observed, followed by cell individualization, loss of cell-to-cell adhesion and loss of apical basal polarity, and lastly gain of front back polarity in microinvasive OSCC. On the other hand, the scenario of early invasive OSCC could be interpreted with dense inflammatory infiltrate being the most predominant feature, followed by cell individualization, front back polarity, loss of cell-to-cell adhesion, and the least frequent being loss of apical basal polarity.

As these features can be appreciated in the earliest stages of cancer with minimal setups, extracting its full potential could be a milestone in the diagnosis of cancer. This study is the first attempt at establishing guidelines for observing EMT.

Loss of cell-to-cell adhesion

Epithelial cells have multiple specialized interconnections in the form of subapical tight junctions and adherens junctions, as well as desmosomes and gap junctions at the lateral surfaces [6], all of which are crucial for cell-to-cell adhesion and communication, thereby maintaining the cell's integrity. Epithelial mesenchymal transition is accompanied by loss of cell-to-cell adhesion, which is a direct result of junctional proteins' breakdown. Apart from this, disassembly of the actin cytoskeleton may also compromise the adhesion and integrity of cells. The reduced expression of occludin levels and zonula occludens

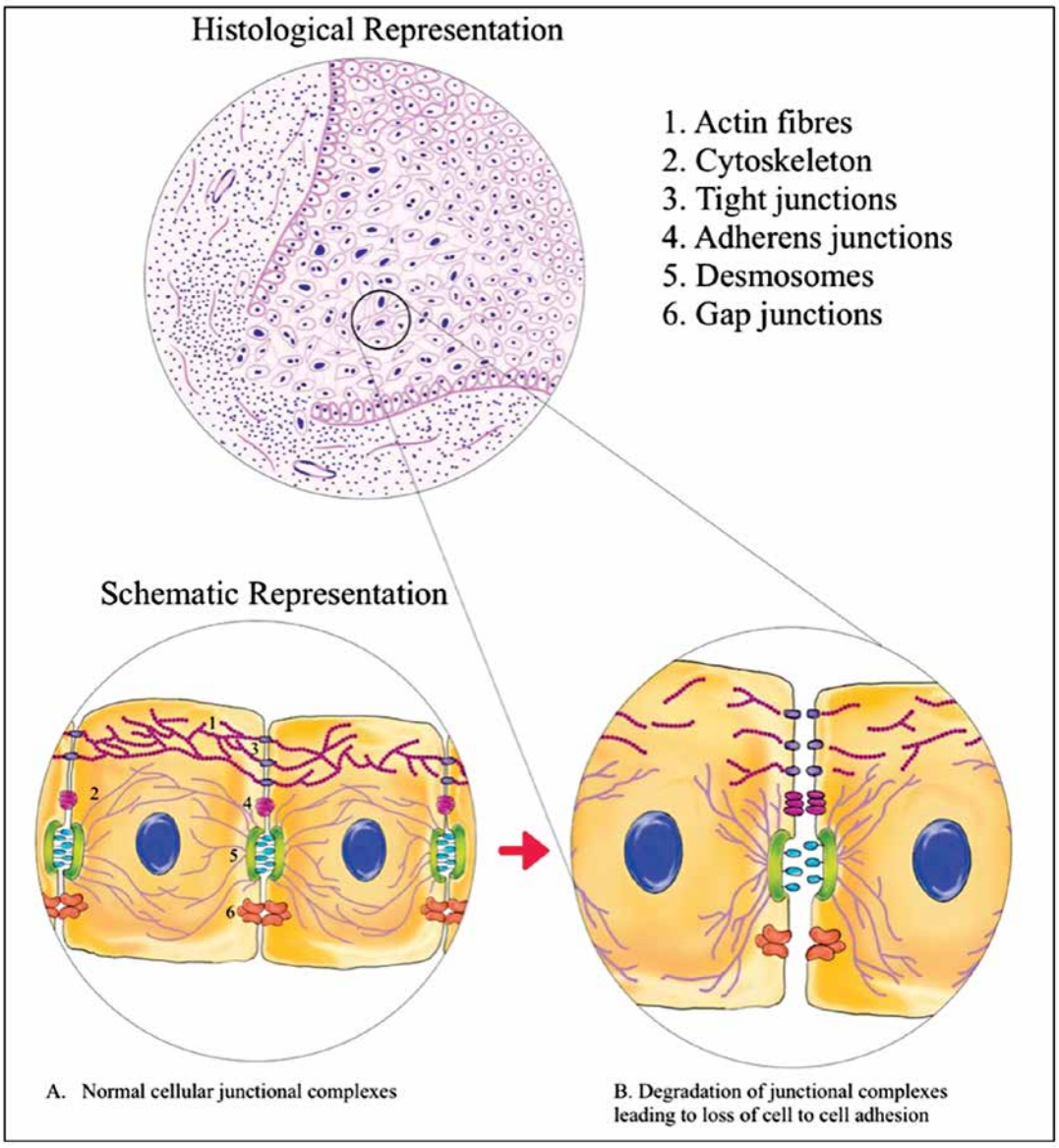

Fig. 7. Loss of cell-to-cell adhesion

[7, 8] and surprisingly enough overexpression of claudin [9] from these junctions are significant determinants of tight junction destabilization [7, 8]. Similarly, a decrease in the levels of E-cadherin, better known as epithelial cadherin, manifests in the form of disintegration of adherens junctions [9]. Degradation of desmosomal contacts is one of the significant alterations occurring in the process of EMT [7, 9]. Accompanying this is the dissolution of gap junctions, which is triggered by reduced connexin levels [10]. Histological apprehension of the cell-to-cell adhesion weakening at the invasive fronts can be appreciated under a light microscope by observing a large field of view. The intercellular junctional proteins can be visualized through the contrast generated by the absorption of light in dense areas, as in the case of desmosomes (Fig. 7) [11].

Loss of apical basal polarity

The specialized cellular junctions along with various protein complexes such as partitioning defective (PAR) complexes (comprising PAR6, PAR3, and atypical protein kinase C (aPKC)), Crumbs complexes (comprising Crumbs, protein associated with Lin-71 (PALS1) and PALS1 associated tight-junction protein) define the apical polarity whereas other complexes such as Scribble complexes (comprising Scribble, discs large (DLG) and lethal giant larvae (LGL)) and integrins localize to the basolateral compartment, hence defining the basolateral polarity of a cell [12]. As stated by Saintigy *et al*. it is dysregulation and degradation of these complexes along with catabolism of the above-mentioned junctional proteins that promote EMT and tumor progression [13]. The reason is a decrease in the levels of PAR complexes,

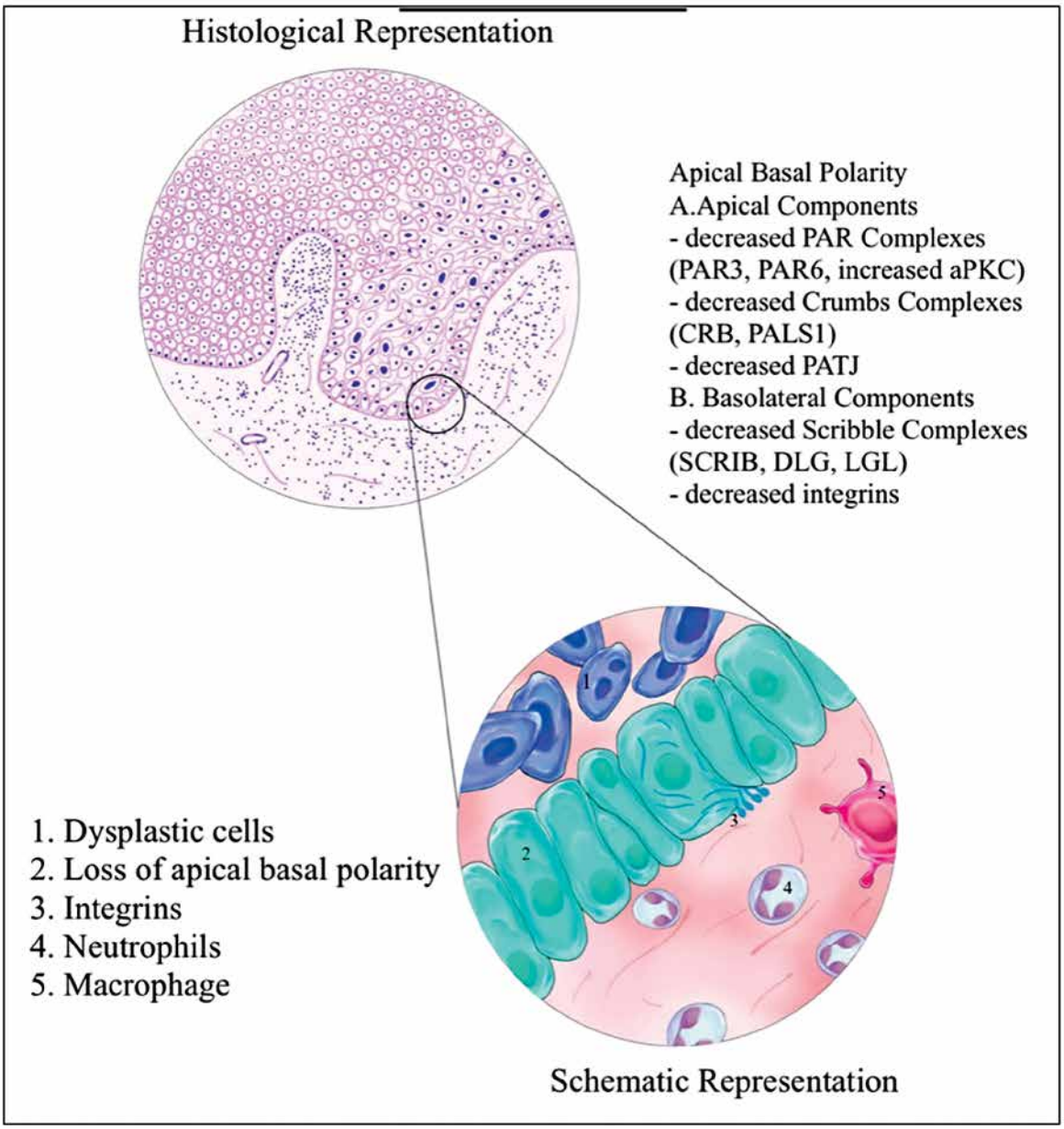

Fig. 8. Loss of apical basal polarity

Crumbs complexes, Scribble complexes, DLG, and LGL, which are one of the main oncosuppressors and play a pivotal role in the maintenance of polarity. When this is coupled with elevated levels of aPKC tumorigenesis ensues [8]. The histological proof of loss of apical basal polarity of cells is observed by taking note of the placement of the nucleus in the cellular matrix. The quantitative morphometric analysis of this attribute can be examined by measuring the distance between the upper pole of the nucleus and the basement membrane and the apical membrane of the cell and the basement membrane (Fig. 8) [14].

Cell individualization

As stated by Dissanayaka *et al*., the pattern of invasion in poorly differentiated OSCC is that of individual cells [15]. This presence of individual cell infiltration at the adjacent epithelial mesenchymal junction of the invasive front is termed cell individualization. Cell adhesion weakening following the loss of apical basal polarity leads to an indomitable consequence of the "breaking off" of cells. Once the forces binding the cells are lost, it is the tumor microenvironment that causes the cells to attain a phenotype that supports their movement to the adjacent mesenchyme. Due to this motility of cells, in the initial stages, the cells land up at the juncture of the epithelium and mesenchyme, hence promoting cell individualization and the individual cell invasion pattern of type 3 OSCC. Very few researchers have discussed this phenomenon, but the immunohistochemical and molecular studies of the cellular phenomena preceding it can be a reason for the substantiality of the

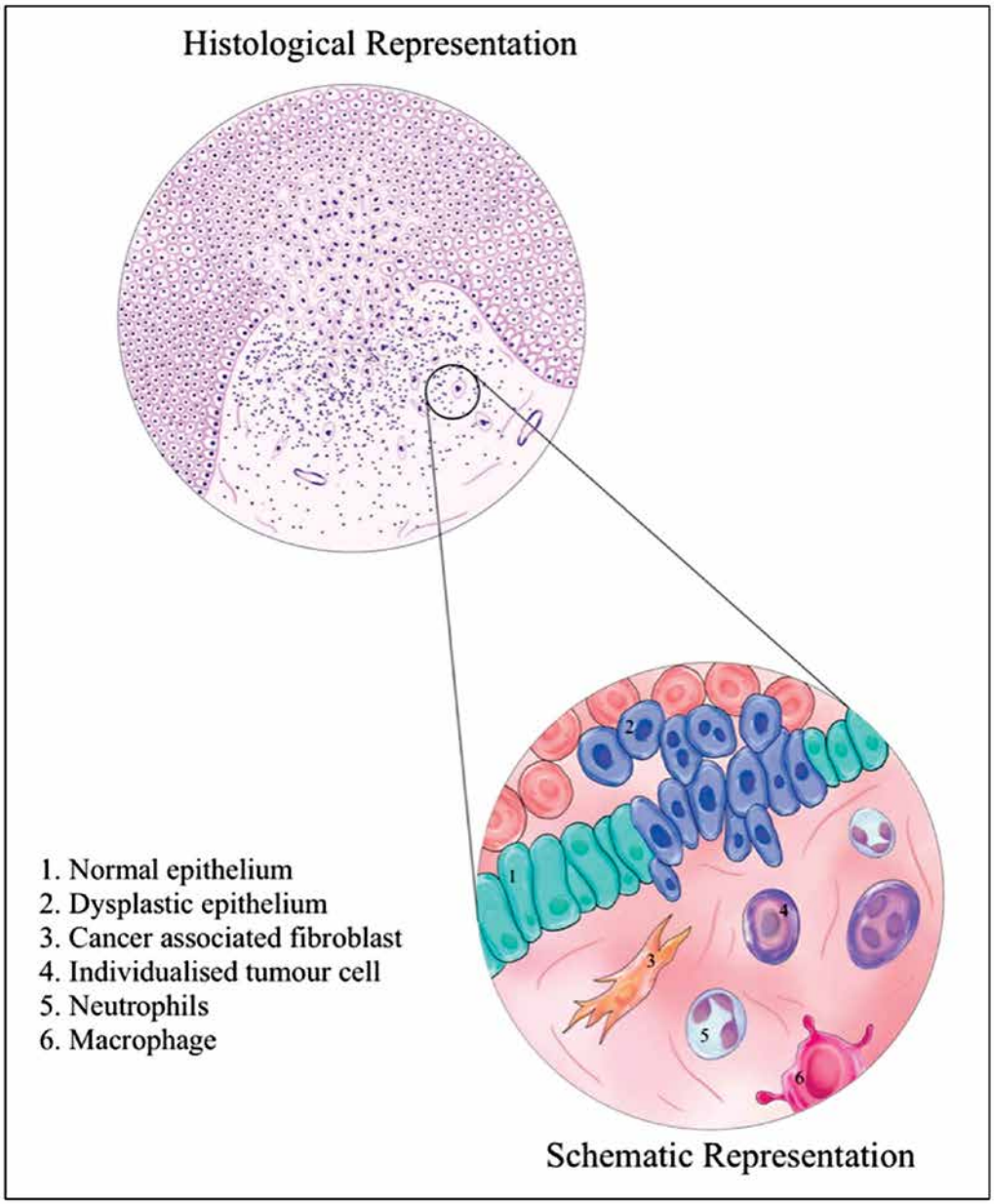

Fig. 9. Cell individualization

hypothesis of this cascade. The affirmation of epithelial invasion can be histomorphologically visualized as the presence of a single cell at the epithelial mesenchymal interface (Fig. 9) [15].

Dense inflammatory infiltration

Progression and metastasis of cancer have long been studied. However, links between cancer and inflammation have been explored only in recent times. As stated by Sven E. Niklander, it is the presence of inflammatory infiltrate in the mesenchyme that influences the process of EMT [16]. Cancer-induced inflammation is chronic in duration and is of non-resolving type, hence causing the observed long term aggressive effects in the patients. This attribute can be well appreciated in all stages of cancer ranging from the incipient stage to a full-blown invasion and hence it is termed as one of the hallmark features of cancer [17]. Proinflammatory mediators like cytokines, chemokines, reactive oxygen species, and other transcription factors cause the recruitment of inflammatory cells at the invasive fronts, which establish a link with the tumor cells and are responsible for the initiation of EMT via the establishment of the crosstalk hence established [18]. The unresolved presence of inflammation is maintained indefinitely due to a continuous cycle of inflammation induction by tumor cell signaling and tumor cell recruitment by the inflammatory cell signaling, resulting in the incessant flow of EMT altered cells [18]. The shift

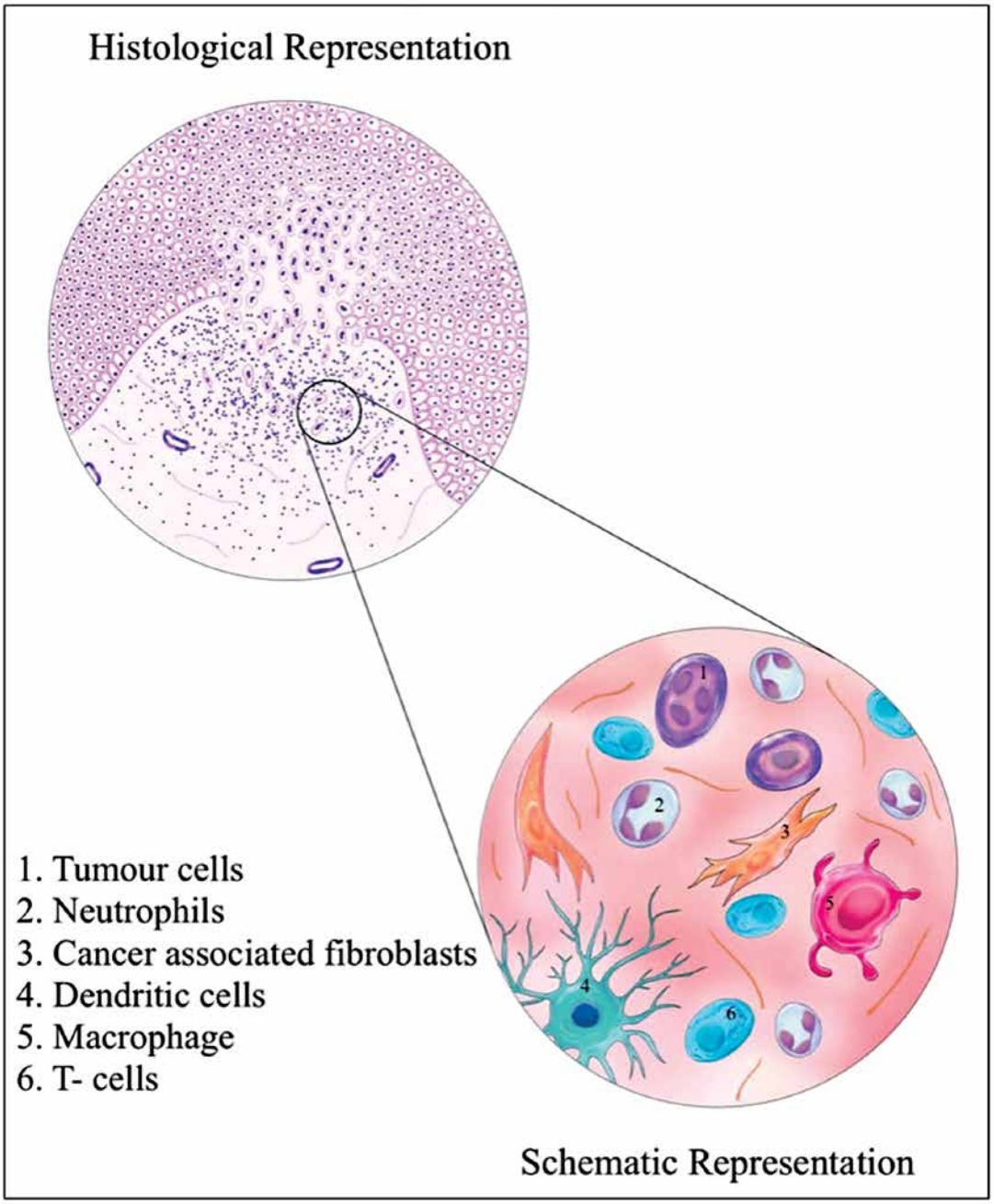

Fig. 10. Host response

of neutrophils, dendritic cells, macrophages, T cells, and activated resident cells such as cancer associated fibroblasts from pro-oncocytic to oncosuppressive is one of the main reasons for unwavering survival of cancer cells even in the presence of long standing inflammation [18]. The tumor microenvironment is considered to be conducive to EMT based on observation of gain of the front back polarity of epithelial cells [18], extracellular matrix degradation and invadopodia formation [16]. The histological sighting of the inflammation can be done by the criteria given by Klintrup *et al*. in the form of a band-like, cup-like zone or patchy appearance of inflammatory zones (Fig. 10) [19].

Not a lot has been explored regarding the following parameters at the histological front but the immunohistochemical as well as molecular studies done so far are suggestive of inflammation in the form of hematoxylin stained granules which appear to be denser at the tumor stroma interface than at the deeper levels.

Establishment of front back polarity

According to Leggett *et al*. [20] under the influence of EMT, cancer cells attain mesenchymal cell like phenotype better known as front back polarity. This well-known fact has several molecular and im-

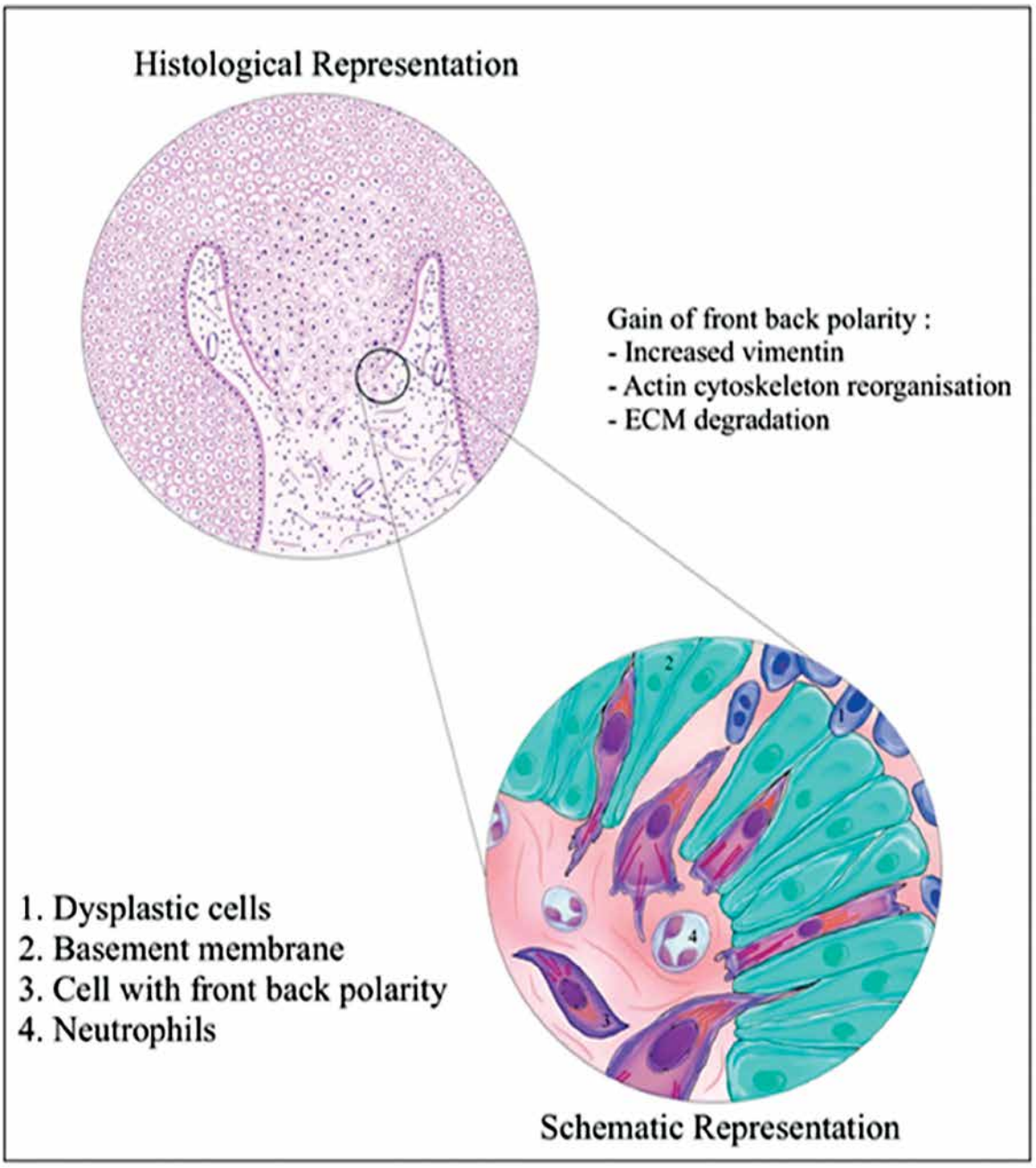

Fig. 11. Gain of front back polarity

munohistochemical studies supporting it. As stated by Lamouille *et al*. [21], the spindling of the epithelial cell as it tries to invade the adjacent mesenchyme is a result of actin cytoskeletal reorganization. Actin fibers within the epithelial cells maintain the structural integrity of the cell. When the cells undergo any change in shape actin fiber rearrangement is an instilled process that occurs. This process when coupled with vimentin expression provides motility to cells [22]. These cells invade the extracellular matrix by the formation of protrusions in the membrane in the form of sheets, spikes mimicking the lamellipodia or invadopodia [21]. These extensions perform the function of catabolism of the ECM by proteolysis, hence providing a medium for movement of EMT associated cells in the tumor microenvironment [21]. Overexpression of vimentin also accounts for cellular elongation morphologically noted to mimic the mesenchymal cell phenotype [22]. According to Friedl *et al*., the cells undergoing EMT are bound to have a phenotypic change ranging from a rounded appearance which signifies the absence of clear demarcation of polarity to a spindle shaped cell visible as a longitudinally elongated mesenchymal cell like appearance of an altered epithelial cell [23, 24]. Apart from this, the nomenclature of the cells undergoing EMT has a wide spectrum ranging from mesenchyme like cells, fibroblastoid phenotype [25] to spindle shaped

cells and front back or front rear polarized cells [20], all of which have a histomorphological bearing to it (Fig. 11).

Conclusions

The present study attempts to shed light on the fact that EMT is not an alternative but an integral part of initial stages of carcinogenesis and metastasis as observed in our study of early invasive and microinvasive OSCC. Hence, development of therapeutic protocols targeting EMT can prove to be a boon for arresting cancer spread. To date EMT has been visualized via molecular enzymes; however, this study demonstrates that it is possible to capture the phenomenon of EMT under a simple light microscope in routine histopathology. Hence, every histopathologist should include reporting of EMT features in day-to-day practice, providing an insight into the exact percentage of occurrence of EMT in various cancers.

The identification of histological features of EMT and preparation of slides from histological smears is technique sensitive. This can at times pose a limitation on observation by masking of these features by dense inflammatory infiltrate.

The authors declare no conflicts of interest.

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