Brief Communication

Calcifications in oral carcinomas: Depicts diversity of calcium in cancer biology!

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Abstract

Calcifications in the soft tissues can be accidental findings during diagnostic procedures. Oral squamous cell carcinoma (OSCC) forms the major percentage of oral malignancies; calcifications are rare findings in OSCC. Calcifications are seen as a result of necrosis, chronic inflammations as well as degenerative changes and imbalances of the local calcium and phosphorous environment. The presence of calcifications can be a prognostic marker, hypothesizing that the influx of calcium from hard tissues into the soft tissues, can probably determine the invasive nature and the destructive characteristics of the carcinoma; hence, detecting calcifications can help us in predicting the prognosis and spread of the malignancy.

Keywords: Calcified keratin pearl, dystrophic calcification, oral cancer, prognostic marker

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INTRODUCTION

Oral squamous cell carcinoma (OSCC) is the most common malignancy in the oral cavity and has a survival rate of about 50%.[1] Clinical staging and histologic grading of OSCC are prognostic indicators as they dictate the treatment plan which involves multi-disciplinary treatment modalities.[2] Keratin pearls are the characteristic feature of well-differentiated OSCC which are easily identifiable and commonly observed phenomena considered as predictors of the biological behaviour of the tumour.[3] A rarely observed phenomenon is the presence of calcifications in the keratin pearls. The scientific literature search revealed only a single article 'Calcified keratin pearls in oral squamous cell carcinoma' by Sarode *et al*.[4] The authors speculated four reasons for the presence of calcifications present in the keratin pearls. High calcium concentration in the malignant epithelial cells, a higher concentration of apoptotic cells in well-differentiated OSCC initiating calcification, hypercalcaemia in the tumour environment and keratin calcification initiated at an intra-cellular level were designated as the probable aetiology.[4]

The formation of keratin is considered to favour a good prognosis as keratin is an end product of the squamous cells, but calcifications within the keratin pearls may have a diverse story to tell [Figure 1]. Calcium acts as a critical regulator of various cellular mechanisms and in many aspects, this role gets intersected in the progression and

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pathogenesis of cancer. The role of calcium is crucial in the cell cycle where it induces important genes like *FOS, JUN, MYC* and helps in the developmental process.[5] Similarly, it is very important in cancer cell migration and cancer progression. It induces the matrix metalloproteinases and helps in the phosphorylation of the contractile proteins, which in turn leads to the remodelling of stromal components and helps in cancer cell migration. Calcium signalling also induces cell death and plays a role in cell apoptosis.[6]

In the progression of cancer, the role of calcium signalling pathways is very evident. There are expressions of calcium pumps in some types of cancers.[7] Some studies have shown that overexpression of definite calcium channels resulted in reduced cell proliferation and promoted cancer cell death.[7,8] Cancer cells use calcium channels and pumps for various cellular level mechanisms, with aberrant expressions of a few calcium regulatory proteins in a few types of cancer.[8] Targeting definite regulatory proteins can aid in cancer therapy. The pharmacological modulation of calcium channels and calcium signalling can alter cell proliferation and migration or induce cell death which can bring hope to cancer therapies.[9] The activation of calcium ion permeable gates in the cells can lead to cell death and this has been demonstrated by various breast cancer cell models.[10]

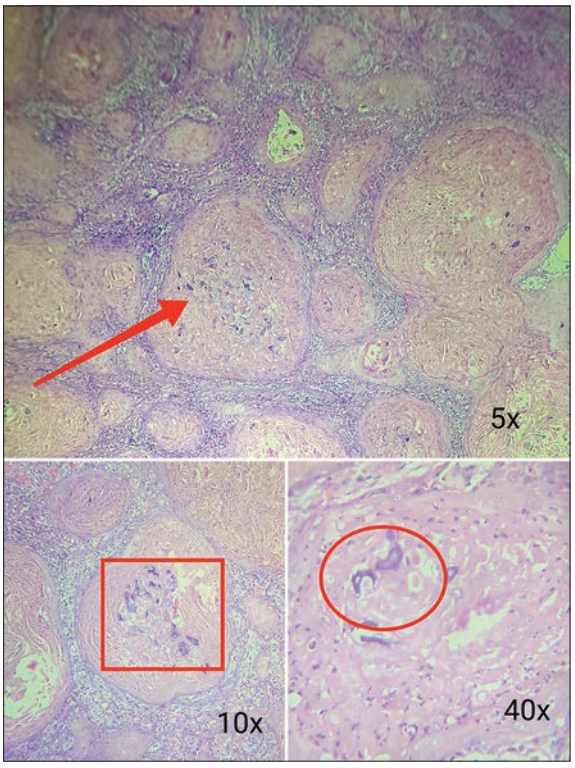

Figure 1: Well-differentiated squamous cell carcinoma showing calcifications in keratin pearls (5x, 10x, 40x, H and E stain)

Tumour microenvironment and calcium signalling do play a role in cancer therapies. The contribution of the tumour microenvironment is one of the key elements in cancer progression. Metastasis and micrometastasis depend on the tumour microenvironment.[11] Mipsagargin (calcium channel agent) is a prodrug that works in line with the tumour microenvironment to induce cell death. This prodrug linker is an enzyme-substrate for prostate-specific membrane antigen (PSMA), which when expressed higher on the tumour cell surface results in the localized accumulation of thapsigargin (an anticancer drug) inducing cancer cell death.[12]

Calcium ion signalling plays a bidirectional role in cancer progression along with the immune system. The immune system may either promote cancer through attenuation of prometastatic pathways or it may lead to the destruction of the cancer cells.[13] Cancer-associated-macrophage-released cytokine promotes invasiveness with the help of calcium signals in breast cancers. However, there are many opportunities to explore on the possible role of immune response along with calcium signalling pathways in cancer progression. Epidermal growth factor and hypoxia in the tumour (hypoxia-induced epithelial to mesenchymal transition) environment may lead to cancer invasiveness; however, an influx of calcium induces chelation and hence progression of cancer regresses.

Calcifications in metastatic colorectal cancer treated with chemotherapy were studied retrospectively and it was found that tumours with calcification showed longer median survival free progression and better outcomes.[14] Tumour calcification is a very rare and interesting phenomenon denoting different intra-cellular biologic phases. Firstly, due to the progression of cancer cells in the form of islands into the stroma leading to a compact microenvironment, and the lack of nutrition of the central cells disturbs the cellular environment causing calcium accumulation. Secondly, necrosis can happen, activating the immune cells, which causes dystrophic calcifications due to the inactivation of calcium signalling pathways.

Hypercalcaemia in malignancy due to increased levels of osteoclastic bone resorption can occur with or without metastasis to bone. The main humoral factor that is associated with this mechanism is parathyroid hormone (PTH) related protein. There can be increased extrarenal-activated vitamin D and PTH secretion. There is a new wing to the thought that because of the release of local cytokines from the tumour, it results in excess osteoclast activation and enhanced bone resorption, often through *RANK/RANKL* pathways.[15]

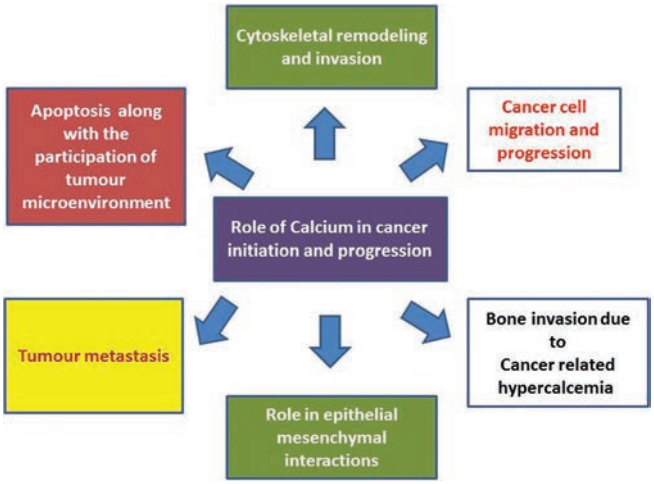

Figure 2: Role of calcium in cancer initiation and progression

Dystrophic calcification results from local or systemic injury to the epithelium. There can be connective tissue diseases (characterized by abnormal fibres), inflammation and trauma.[16,17] The pathogenesis of calcification in basal cell carcinoma is contributed by calcium-binding proteins found in poorly differentiated keratinocytes that may contribute to the aetiology of basal cell carcinoma with calcification.[18]

Hence, the presence of calcifications in the tumours suggests a significant role of calcium; whether it leads to the progression of cancer or regression of cancer is a long debatable issue providing a wide opportunity for the researchers to think about the diverse role of calcium in cancer biology [Figure 2].

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Conflicts of interest
There are no conflicts of interest.

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