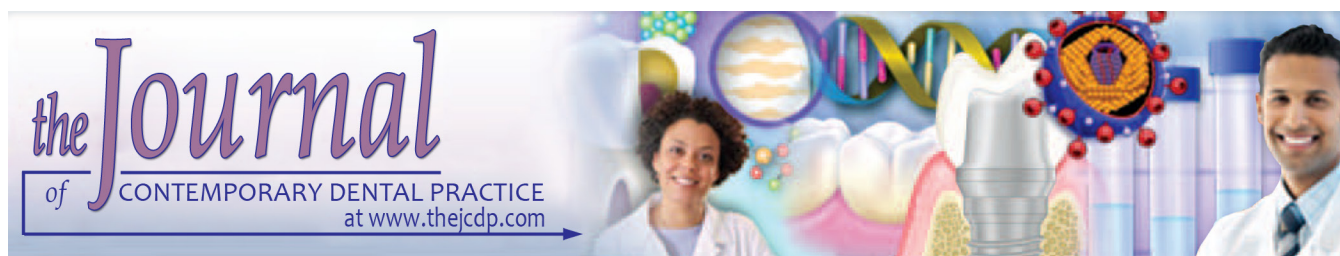


SHORT COMMUNICATION



Emperipolesis: An Unreported Novel Phenomenon in Oral Squamous Cell Carcinoma

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ABSTRACT

Emperipolesis is a phenomenon characterized by engulfment of hematopoietic cells by megakaryocytes, monocytes, fibroblasts, and malignant cells within their cytoplasm. This phenomenon has been reported in various physiological and pathological conditions including malignancies. However, emperipolesis has never been reported in oral squamous cell carcinoma (OSCC) till date. We have analyzed histopathological slides of 56 cases of OSCC to see lymphocyte engulfment by tumor cells. Five cases showing features of this phenomenon were observed. Lymphocytes were typically identified as small round cells with oval nuclei and scanty cytoplasm. Both partial and complete engulfment of lymphocytes by tumor cells was appreciated. Nuclei of the host tumor cells were crescent shaped and illustrated small concave indentation, so as to accommodate the internalized lymphocyte. The intercellular bridges were not seen between the internalized cell and the host cell. There were no signs of degeneration appreciable in either cell, thus ruling out the possibility of cannibalism phenomenon. Although emperipolesis is a well-known phenomenon in pathology, this is the first report showing its evidence in OSCC.

Keywords: Emperipolesis, Histopathology, Oral cancer, Oral squamous cell carcinoma.

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INTRODUCTION

Oral squamous cell carcinoma (OSCC) is the most common malignant neoplasm of oral cavity, which is usually preceded by premalignant disorders.^{1,2} Unpredictable behavior, such as tumor cell cannibalism³⁻⁵ and microbial interactions with signaling pathways⁶ baffle us in understanding the tumor biology. One of such behavioural patterns is emperipolesis, which is not yet reported and explored in OSCC till date.

Emperipolesis has been reported in various physiological and pathological conditions (Table 1). It is the movement of viable cells after getting internalized, and is often used as a general term to refer to the process of cells entering, moving within, and exiting the host cell. Megakaryocytes, monocytes, fibroblasts, and malignant cells can be involved in this phenomenon by exhibiting viable hematopoietic cells in their cytoplasm.⁷

Wang et al,⁸ revealed that the internalization of hematopoietic cells is an active process and only involves incursion by live cells, which is unique and dissimilar to cellular cannibalism. Other differences between emperipolesis and cannibalism are listed in Table 2. Although both emperipolesis and cannibalism are exclusively seen in malignancy, they are also reported in benign lesion.⁹ Lymphocytes may practice this alternative cell-in-cell phenomenon to abolish target tumor cells in addition to the usual target cell eradication

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Table 1: Diseases showing emperipolesis

Sl. no.	Diseases showing emperipolesis
1	Rosai–Dorfman disease
2	Autoimmune hemolytic anemia
3	Carcinoma
4	Neuroblastoma
5	Multiple myeloma
6	Leukemia
7	Malignant lymphomas

Table 2: Differences between emperipolesis and cellular cannibalism

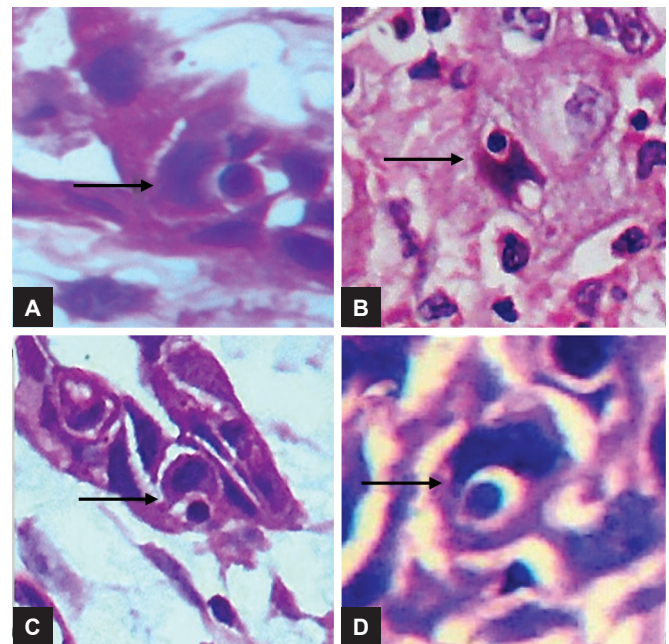
Feature	Emperipolesis	Cannibalism
Cell engulfment	Homogeneous	Homogeneous/ Heterogeneous
Fate of internalized cell	No damage	Degradation
Host cells	Megakaryocytes, dendritic cells, fibroblasts, or tumor cells	Tumor cells
Fate of host cell	Live or dead	Live
Purpose	Unknown, defense (?)	Nutrition
Mechanism	Invasion by internalized cell	Engulfment by host cell

through the cytolytic effects. The disintegration of host tumor cells via lysosome-mediated degradation pathway after emperipolesis of natural killer (NK) cells has been demonstrated at an ultrastructural level. Okuyama et al¹⁰ spotted that cancer cells in stomach were exterminated by lymphocytes that had penetrated in their cytoplasm. Takeuchi et al¹¹ reported dead or dying cancer cells that had incorporated T cells, and suggested that the cytotoxic granules dispersed in the cytoplasm of target cancer cells are responsible for intervening in the degradation activity. However, another perspective dictates that internalization of NK cells by target tumor cells could be a measure for survival as a mean to escape immune surveillance, which is analogous to the related process of cannibalism. It was discovered that some NK cells themselves were disintegrated by tumor cells via a lysosome-mediated mechanism, similar to the process of entosis.⁸ However, there are reports showing that the internalized NK cells ultimately commit to apoptotic cell death via activation of caspase 3 and deoxyribonucleic acid fragmentation, which is in contrast to the process of entosis.¹¹ These findings propose that emperipolesis of NK cells could be a mechanism of tumor progression, perhaps through nutrient recycling during metabolic stress conditions.

Emperipolesis of functionally normal lymphocytes may ensue as a retaliation activity by the cytotoxicity interceded by these cells or offer a benefit through recycling of nutrients to the host tumor cell, but the significance of emperipolesis of neoplastic lymphocytes is ambiguous. The phenomenon may relate to specific features of those T lymphocytes that intrude epithelial cells.¹²

EMPERIPOLESIS IN OSCC

We have analyzed histopathological slides of 56 cases of OSCC to see lymphocyte engulfment by tumor cells. Five cases showing features of this phenomenon were observed, demographic data of which are given in Table 3. Lymphocytes were typically identified as small round cells with oval nuclei and scanty cytoplasm. Both partial and complete engulfment of lymphocytes by tumor cells were appreciated (Figs 1A to D and Figs 2A to D). Nuclei of the

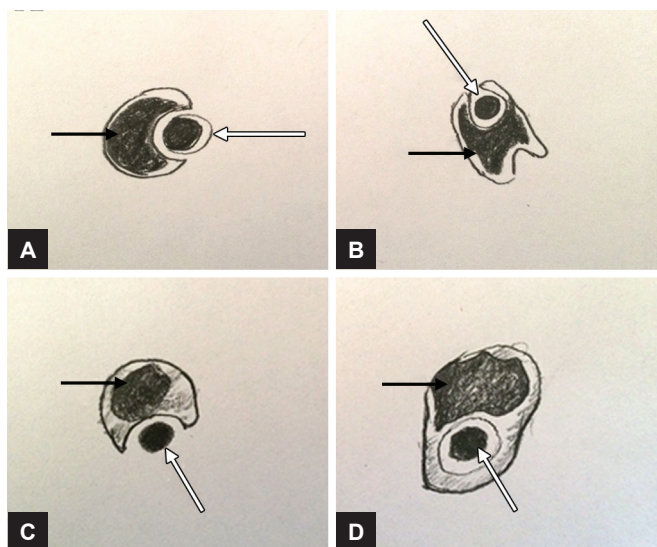


Figs 1A to D: Photomicrograph showing partial (A–C) and complete (D) engulfment of lymphocyte by tumor cells (black arrow) (Hematoxylin and eosin stain; magnification 400×)

Table 3: Demographic and clinical data of OSCC cases showing emperipolesis

Sl. no.	Age	Sex	Habit	Site	T	N	M	TNM stage	Grade	Emperipolesis/HPF	Treatment	Follow-up
1	65	M	Tobacco chewing	Buccal vestibule	T3	N ₂ b	M ₀	IVa	Moderate	3	Excision radiotherapy	Local recurrence (6 months)
2	58	F	Mishri	Tongue	T2	N ₂ a	M ₀	IVc	Well	2	Excision radiotherapy	No recurrence (2 years)
3	38	M	Ghutka chewing	Buccal mucosa	T3	N ₁	M ₀	III	Moderate	4	Excision radiotherapy	Regional recurrence (1 year)
4	59	M	Tobacco chewing	Alveolar mucosa	T4	N ₂ b	M ₀	IVa	Moderate	3	Excision radiotherapy	No recurrence (2 years)
5	65	M	Smoking	Gingiva	T4	N ₂ b	M ₀	IVa	Moderate	2	Excision radiotherapy	Follow-up lost

HPF: High-power field



Figs 2A to D: Schematic representation of photomicrograph showing emperipolesis phenomenon with lymphocyte (white arrow) and host tumor cell (black arrow)

host tumor cells were crescent shaped and illustrated small concave indentation so as to accommodate the internalized lymphocyte. The intercellular bridges were not seen in between the internalized cell and the host cell. There were no signs of degeneration appreciable in either cell, thus ruling out the possibility of cannibalism phenomenon.

In conclusion, this is the first ever evidence of emperipolesis in OSCC. Careful distinction of emperipolesis from other forms of cell-in-cell phenomenon is needed for their identification. We recommend future studies on emperipolesis in OSCC on larger sample size with clinicopathological correlation, which could show some interesting conclusions. Moreover, molecular analysis of this enigmatic phenomenon in OSCC will unveil the future therapeutic opportunities for targeted therapy.

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