



NESTED LIVES"- UNVEILING THE MYSTERIES OF CELL IN CELL PHENOMENON

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ABSTRACT

Introduction: Cell in cell structure refers to a phenomenon in which one viable or dying cell is completely enclosed within another living cell. Cell in cell structures are most commonly described in tumors particularly melanoma, aggressive carcinomas, immune interactions and developmental processes. They arise through mechanism such as entosis, emperipolesis and cell cannibalism, each involving distinct cellular and molecular pathways.

Aims & Objectives: To study the different cell in cell phenomenon in various disease process, it's mechanism and the pathological significance of cell in cell structures.

Materials and Methods: This is retrospective study of 22 cases of cell in cell structures is studied 3 years from April 2023 to March 2026.

Results: Our study shows female predominance with ratio of 1.2:1(F:M). Among 22 cases nine cases (40.91%) were found in 41 to 50 years of age. Out of 22 cases 12 (54.5%) cases were malignant and 10 (45.5%) benign cases were noted. Out of 22 cases 9 (40.91%) were cell cannibalism, 7 (31.82%) were phagocytosis, 6 (27.27%) were emperipolesis.

Discussion and Conclusion: Cell in cell structures should be identified during routine reporting in both benign and malignant diseases, as advances in microscopy and molecular profiling of these fascinating phenomenon provide insights to their diagnostic, prognostic and therapeutic importance.

Keywords: Emperipolesis, Phagocytosis, Cell Cannibalism and Metastatic Deposits of Squamous Cell Carcinoma.

INTRODUCTION

Cell in cell structure refers to a phenomenon in which one viable or dying cell is completely enclosed within another living cell⁽¹⁾. It is observed in both physiological and pathological contexts. Cell in cell structures are most commonly described in **physiological conditions**- 1.Immune interactions, 2. Fetal liver development and 3.Megakaryocytes in bone marrow and also in pathological conditions like 1. Primary and metastatic squamous cell carcinoma, 2.Melanoma and 3.Other aggressive carcinomas.

They arise through mechanism such as **cell cannibalism, phagocytosis, entosis, emperipolesis and enclysis**, each involving distinct cellular and molecular pathways. Cell in cell structure formation influences tumour progression, immune modulation and tissue homeostasis by regulatory cell survival, competition and clearance⁽²⁾. In this study recognition of cell in cell structure on routine H&E sections by morphology of cells was performed and supplemented by IHC where ever necessary for potential diagnostic and prognostic purpose.

Aims and Objectives

1. To study the different cell in cell phenomenon in various disease process.
2. To study the mechanism for the basis of different types of cell in cell phenomenon.
3. The pathological significance of cell in cell structures.

MATERIALS & METHODS

Study design and settings: This is a retrospective study of 3 year from March 2023 to April 2026, conducted at the Narayana Medical College, Nellore

Methods



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Routine histopathological processing was done. Sections were cut and stained with H&E stain. All the data was divided in different categories, analysed and summarized as percentage. This was a 3 years study of 22 cases seen during routine reporting. The study include different types of cell in cell structure in the various disease processes.

Sample and data collection: H&E sections of 22 cases of cell in cell structures were collected including both benign and malignant diseases of various organ system. All the data was divided in

different categories, analysed and summarized as percentage. These cases were supplemented with suitable IHC markers where ever necessary.

RESULT

Distribution of cases in relation to age

Considering occurrence of cell in cell phenomenon in relation to age the commonest age group of presentation is 41-50 yrs (40.91%) followed by 31-40yrs (27.27%), followed by 51-60yrs (18.18%), followed by 21-30yrs (13.64%)

Table 1: Distribution of Cases in Relation to Age

Age	No of cases	Percentage
21-30	3	13.64%
31-40	6	27.27%
41-50	9	40.91%
51-60	4	18.18%

Distribution of cases in relation to sex

Among total of 22 cases female predominance was noted in relation to occurrence of cell in cell phenomenon. Female 12 cases (54.5%) followed by male 10 cases (45.5%)

Distribution of cases based on benign and malignant conditions

Among total of 22 cases, malignant lesions are most commonest 12 cases (54.5%) followed by benign lesions 10 cases (45.5%)

Table 2: Based on Cell in Cell Structure

Cell in cell structure	No of cases	Percentage
Cell cannibalism	9	40.91%
Phagocytosis	7	31.82%
Emperipolesis	6	27.27%
Enclysis	0	0
Entosis	0	0

Cell cannibalism (9 out of 22 cases), 4 cases of malignant fluid cytology (primary malignant mesothelioma), 2 case is amelanotic melanoma and 2 case is metastatic deposits of squamous cell carcinoma, 1 case is invasive **breast carcinoma**

Phagocytosis (7 out of 22 cases), 7 cases were showing Reactive lymphadenitis.

Emperipolesis (6 out of 22 cases)- 3 cases were Rosai Dorfman Disease (RDD), 2 cases were thymic cell carcinoma and 1 case of emperipolesis in maltoma.

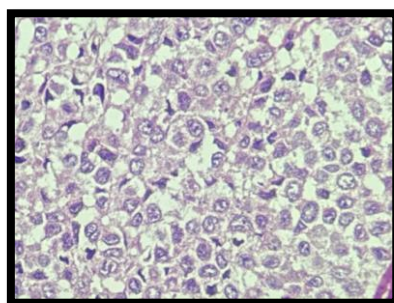


FIGURE 1: X400 H&E Cell cannibalism in amelanotic melanoma

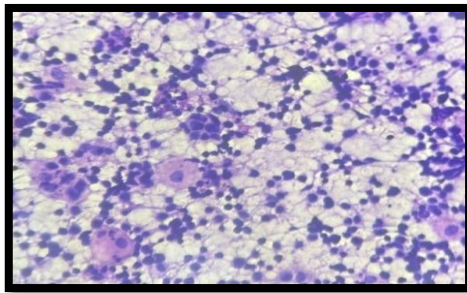


FIGURE 2: X400 H&E Cell cannibalism in cytology of SCC metastasis to lymphnode

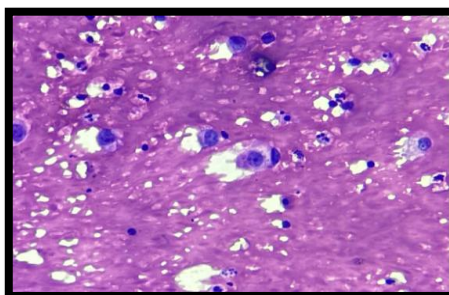


FIGURE 3: X400 H&E Cell cannibalism in malignant fluid cytology

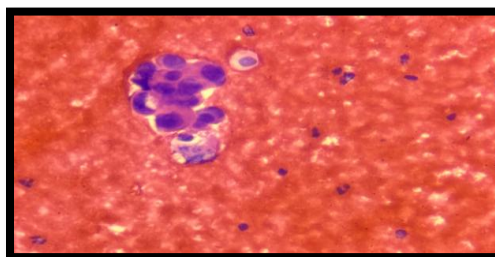


FIGURE 4: X400 H&E Cell cannibalism in malignant fluid cytology

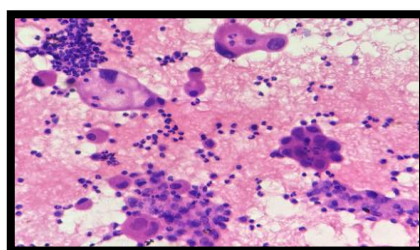


FIGURE 5: X400 H&E Tumour cell cannibalistic cell (below) and neutrophil tumour cell cannibalism in malignant mesothelioma

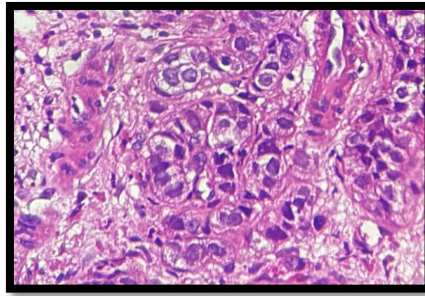


FIGURE 6: X400 H&E Cell cannibalism in moderately differentiated SCC

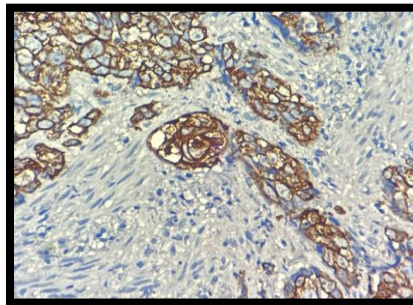


FIGURE 7: X400 H&E Cytokeratin marker positive in squamous cell carcinoma showing cell cannibalism

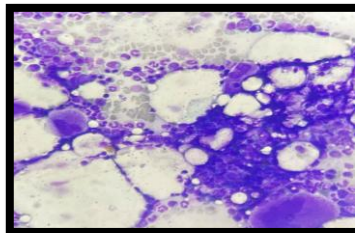


FIGURE 8: X100 H&E Physiological Emperipolesis in bone marrow by megakaryocyte

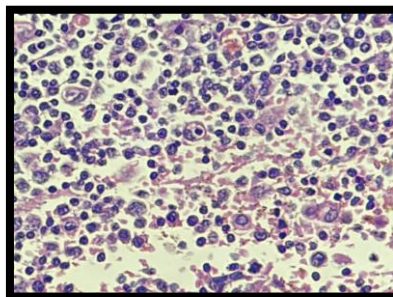


FIGURE 9: X400 Emperipolesis in H&E sections of maltoma

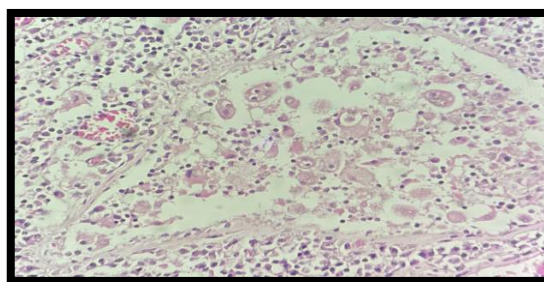


FIGURE 10: X400 Emperipolesis showing in H&E section of RDD

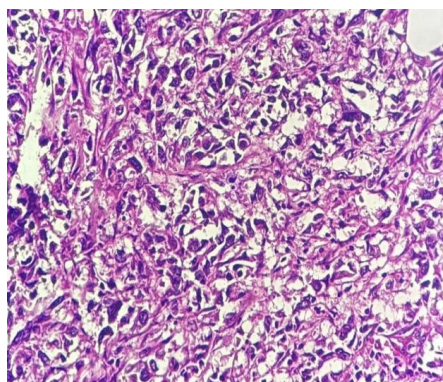


FIGURE 11: X400 Emperipolesis showing in H&E section of invasive breast carcinoma

DISCUSSION

This was a 3 years study of 22 cases seen during routine reporting. The study include different types of cell in cell structure in the various disease processes. There are many classification of these cell in cell structures but broadly they are divided based on the initiation of mechanism into 2 types. They are Endocytic cell in cell structure (initiated by outer cell) and Invasive cell in cell structure (initiated by inner cell)⁽³⁾. Endocytic CICs are further subdivided depending upon the molecular mechanism into following

1. Phagocytosis like mechanism (includes **cell cannibalism** and **phagocytosis**)
 2. Pinocytosis like mechanism (includes **enclysis**)
- Invasive CICs are subdivided into following
1. Homotypic (includes **Entosis**)
 - Heterotypic (includes **Emperipolesis**)
- Enclysis is initiated by the hepatocyte, which actively extends lamellipodia or blebs and surrounds the T cell. CD8+ T cells and B cells spontaneously migrate between hepatocytes
- Entosis is defined as the invasion of an epithelial cell's cytoplasm by another epithelial cell.

Table 3: Cell in Cell Structure with Other Studies

Study	Conclusion
Borensztejn et al., ⁽⁴⁾	Cell in cell structures are related to both physiological and pathological conditions and also their presence can relate to tumour aggressiveness(1).
Wang X et al., ⁽⁵⁾	cell cannibalism it is associated with tumour aggressiveness and tumour progression in pancreatic ductal carcinoma (2)
Jaafari et al., ⁽⁶⁾	Cell cannibalism in premalignant conditions and squamous cell carcinoma. Presence of tumour cell cannibalism is observed more in SCC than in premalignant lesions(3).
Cherry Bansal et al., ⁽⁷⁾	Study suggest presence of cell cannibalism in fluid cytology help in evaluation of the tumour staging and tumour aggressiveness. (4)

Other studies proposed that this phenomenon occur in unfavourable condition for their feeding activity, particularly under starvation, low nutrient supply and aggressive tumours. In fluid cytology cannibalistic cells should be distinguished from the macrophages, macrophages have the vesicular

nuclei but cannibalistic cells have the hyperchromatic nuclei and increased N:C ratio. Because of the limited cases included in this study the CIC association with tumour aggressiveness cannot be commented, but the cases included under

cell cannibalism were all high grade malignancies and associated with metastasis.

Table 4: Proteins Involved in Cell in Cell Structure

Cell in cell structure	Proteins involved
Cell cannibalism	ezrin and caveolin-1 are commonly involved another protein involved TM9SF4
Phagocytosis	Phosphatidylserine most commonly involved, other proteins are PD-L1 and β 2 microglobulin
Emperipolesis	ezrin, F-actin, ICAM-2, E-cadherin and CD44

Limitations:

1. Sample size is small
2. The proteins involved in different mechanism of cell in cell structures are assessed by molecular study, which was not possible in our setup.
3. No enclysis and entosis were reported.

CONCLUSION

Cell in cell structures should be identified during routine reporting in both benign and malignant diseases, as advances in microscopy and molecular profiling of these fascinating phenomenon provide insights to their diagnostic, prognostic and therapeutic importance.

1. Cell in cell phenomenon should be correctly identified in routine histopathological reporting as each denote specific morphological and prognostic values.
2. Cell cannibalism has proved to the important morphological parameter well allied with anaplasia, tumour aggressiveness and higher grade on increased metastatic potential.
3. Hence, it is recommended to screen each cancer specimen for identification of cell cannibalism to validate its role as morphological predictor and prognosticator.

Declaration by Authors

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Conflict of Interest: No conflicts of interest declared.

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