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GHOST CELLS UNDER MICROSCOPE: A PERPLEXED HYPOTHESIS

Oral Pathology

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ABSTRACT

Cellular identities in the past have been based on the structural and functional aspects. Proper delineation of cellular structure occasionally could be ambiguous because of their varied existence either structurally similar or functionally dissimilar or vice versa. "Ghost cells"- is an area which is entailed by controversies allocated to their functionality and appearance. In odontogenic lesions they are considered as the enlarged epithelial cells with central space consequential to lost nucleus. Many authors have documented on the histogenesis and formation of ghost cells yet nothing relevant till date. This article is an attempt to concise the literature in precise manner to elaborate the ghost cell origin in histopathologic arena.

KEYWORDS

Ghost cells, aberrant keratin, degeneration, calcification

INTRODUCTION

The term "ghost" is used for the faint or shadowy figure deficient in usual substance of reality. The ghost cells (GC) in odontogenic lesions are the enlarged epithelial cells possessing lost nuclei, leaving a faint outline of the original nucleus [1]. These epithelial cells are documented as swollen, pale, eosinophilic, and seen either as isolated or in sheets with a clear preservation of basic cellular outline, usually with visible clear areas or remnants indicative of the pre-nuclear area [2]. These nucleated cells are termed in English literature as, *keratinized squamae* [3], *degenerated epithelium* [4], *epithelial pearls* [5], *enamel organ* [6], *concentric homogenous bodies* [7], *calcified globules resembling keratin* [8], *hyaline-like bodies* [9]. While in the German literature, *Rote Zellen* (red cells) is the name. This taxonomy was principally applied to undifferentiated epithelial cords of adamantinomatous craniopharyngiomas [10]. Later, Rywkind proposed the term *Verhornte epithelzellen* (keratinized epithelial cells), reflecting their origin and nature [11].

This article hypothesizes the origin and formation of GCs putting forth the various theories.

MOLECULAR PATHOGENESIS

Molecular basis of GCs is supported by the possible role played by Wnt and Notch signaling in pathogenesis. These two pathways act in close intertwined mode and simultaneously, uphold tissue homeostasis, control cell fate, patterning and morphogenesis through embryonic development. Also, studies showing positive immunostaining of Notch-1 and Jagged-1 in mineralized GCs concluded their calcification process linked to their upregulation [12, 13].

The accumulation of activated and mutated β-catenin in calcifying cystic odontogenic tumor (CCOT), pilomatricoma (PM) and craniopharyngioma (CP) point towards the Wnt-β catenin-Tcf⁄Lef activated pathway driving their tumorigenesis [14]. Also, aberrant Wnt pathways for the expression of similar enamel proteins in the GCs of CP and CCOT suggested the common stomatodeal ectoderm embryology and genetic alterations [15].

HYPOTHETICAL IMPLICATIONS

Over the years many experiments have been witnessed in the literature survey stating their areas of work for the GC origin and formation. Based on such historical evidences, several hypotheses were set forth towards GC origin.

Table 1: Hypothesis in ghost cells origin

INVESTIGATOR (S)	YEAR	HYPOTHESES
Highman and Ogden	1936	Described GCs as ***dyskeratotic cells*** with viable cellular outline in pilomatricoma [16]
Gorlin et al.	1962	GCs regarded as ***abnormal keratotic cells*** with mural cells distending towards cystic formation and transformation of viable odontogenic epithelial cells to GCs in calcifying odontogenic cyst (COC), PM, and CP [17]
Chaves	1968	GC formation considered as marked degeneration with ***aberrant keratinization*** [18]
Howells and Abrams	1968	Speculated unusual ***degenerative patterns*** related to GC formation. Transformation of large squamous mural cells to eosinophilic cells with intact nuclear outline. Stellate and basal cells enlargement with peripheral nuclear displacement suggested keratin. This caused breach in basement membrane with connective tissue herniation, and GC formation [19]
Levy et al.	1973	***Hypoxic metaplasia*** of odontogenic epithelium led to dissolution of surrounding hard tissue calcification causing apoptosis and keratinization in odontomas [20]
Sedano, Pindborg and Kerebel et al.	1975 and 1985	GCs represent different stages of ***keratinization*** (ortho, para- and aberrant) and are the by-product of metaplastic transformation of cells lacking developmental and inductive forces [21, 22]
Yamamoto et al.	1988	Epithelial cells undergoing ***abnormal terminal differentiation*** synthesize altered homogenous acellular products and degenerated GCs. Confirmed by involucrin and high molecular weight keratin staining [23]

Hong, Ellis and Hartman	1991	Gcs originated from ***coagulative necrosis*** in CCOT cases [24]
Gunhan et al.	1993	GCs derived from pre-programmed cells of amelogenesis through ***cytoskeleton re-organization*** [25]
Laba et al.	1997	***Epithelial origin*** of GCs with histochemical reaction for keratin and the immunohistochemical reaction for epithelial membrane antigen and cytokeratin (CK) [26]
Sissy and Rashad	1999	***Antigenic alterations*** resultant of coagulative necrosis of odontogenic epithelium staining negative or weak for CKs and positive in CPs [27]
Kim et al.	2000	Postulated ***apoptotic origin*** by associating GCs and apoptosis using apoptotic-related proteins (Bax +ve and Bcl-2 –ve) [28]
Takata et al.	2000	***Aberrant keratinization*** with faint/ -ve CKs by GCs in COC, while positive in adjacent epithelial cells [29]
Lan	2003	***Apoptotic process*** of basaloid cells with few transitional cells transforming into GCs [30]
Kusama et al.	2005	Differentiation of GCs into hair (positive for ***hard α-keratin antibodies*** (hair keratins) in PM, CCOT and CP) [31]
Praetorius and Shear	2007	***Abnormal keratinization*** in GCs with the potential to calcify. Keratin and GCs both showed yellow fluorescence with Rhodamine-B [32]

Whether related to odontogenic or non-odontogenic pathology, GCs always represent the epithelial derivation. Many [3, 17, 19, 33] believed that GCs can originate from any layer of epithelium, i.e., basal, intermediate, or superficial. Based on epithelial differentiation, they may take up the origin either from squamoid or stellate reticulum-like cells [34].

INSIGHT INTO GHOST CELLS PATHOLOGY

Some odontogenic and non-odontogenic tumors exhibit GCs as their characteristic feature. Many others have GCs as their occasional element. Sedano and Pindborg believed that such cells were also present in inner enamel epithelium of a normal developing human tooth and eruption cyst, respectively [21].

GC lesions with their histopathological features and differential diagnosis are summarized (table 2).

Table 2: Ghost cell lesions

Lesion	Histopathology	Stains/ IHC
Eruption cyst [35]	Reduced enamel epithelium	CK-10, 14 +ve/-ve, Tenascin and EGFR +ve/-ve
Type-1 Calcifying odontogenic cyst [24]	Columnar cells with overlying stellate reticulum-like cells with or without dentinoid material and dystrophic calcifications	Amelogenin +ve, Enamelin, Sheathlin and Enamelysin +ve/-ve
Ameloblastic fibro-odontoma [36]	Ameloblastic fibroma along with typical Composite odontome	CK-8, 13, 14, 16, 18, 19 +ve, PCNA +ve and BrdU +ve
Odontoameloblastoma [36]	Sheets of typical ameloblastoma with columnar, squamous and undifferentiated epithelial cells along with enamel, dentin, osteodentin, dentinoid, osteoid, cementum and bone	CK-8, CK-13, CK-14, CK-16, CK-18, CK-19 +ve, PCNA +ve and BrdU +ve
Odontoma [21, 36]	Enamel, dentin, pulp, cementum may or may not be present in normal relation to one another	Amelogenin, Keratins, BMP +ve, Vimentin, Osteonectin, Osteodentin +ve, and TGF-β +ve
Cystic calcifying odontogenic tumor [37, 38]	Ameloblastomatous epithelium with dental hard tissue resembling odontome along with limited dystrophic dentin	NFκβ, Ki-67 and MMP-9 +ve/-ve (weakly +ve), Podoplanin +ve
Dentinogenic ghost cell tumor [39]	Marked presence of GCs, occasional calcification, predominant dentinoid material, benign cellular stroma	PCNA and SBA strongly +ve, WGA, PC1 and UEA1 moderately +ve, DBA and ConA slightly +ve, β-catenin and Lef1 strongly +ve
Ghost cell odontogenic carcinoma [40]	Predominant GCs, rare calcifications, rudimentary dentinoid material, malignant odontogenic cells	Ki-67 >7.5%, MMP-9 +ve, Bcl-2 +ve, p53 +ve, BAX +ve and TRAP +ve
Pilomatricoma [41]	Sharply demarcated dermal nodules surrounded by the compressed fibrous tissue capsule, distinct circular cellular configuration within islands with peripheral nucleated basaloid cells and central GCs. Sheets of GCs turning into solid large cellular masses. Abundant calcifications and foreign body giant cell reactions	CD-138 and FAS weak to moderately +ve, basaloid cells +ve for AE1/AE3 and β-catenin
Craniopharyngiomas [41]	3 patterns: solid, cystic, mixed. Stellate reticulum like-epithelium in cords and lobules, bordered by basal cells with ameloblastic features. GC islands throughout epithelium.	CK-7, 8, 19 +ve, AE1/AE3 weakly +ve in GCs while strongly +ve in transitional cells, GLUT-1 +ve, β-catenin variably +ve

CONCLUSION

Ghost cell lesions are the uncommon entity and their presence for primitive head and neck pathologies is significant, suggesting aggressive nature or the prognostic implication. The imminent classification schemes of odontogenic lesions should emphasize on the ghost cell histopathology with emphasis on their clinical and pathological behavior. These lesions could be separated as prognostically distinct entities on the basis of their diversified nature as compared to conventional counterparts. Advanced diagnostic aids may add a new dimension to this unexplored domain in oral lesions. There is a definite scope of identifying a defining role of GCs in prognosis that may be conclusive based on further studies which can assess and evaluate the exact pathogenesis or origin in odontogenic and non-odontogenic lesions.

REFERENCES

1. Mankapure PK (2015), Ghost Cells and its Histogenesis: A Narrative Review. IJSS Case Reports & Reviews, 2: 35-9.
2. Mehendiratta M, Bishen KA, Boaz K et al. (2012), Ghost cells: A journey in the dark. Dent Res J (Isfahan), 9(Suppl 1):S1-S8.
3. Gold L (1963), The Keratinizing and calcifying odontogenic cyst. Oral Surg Oral Med Oral Pathol, 16:1414-24.
4. Thoma KH, Goldman HM (1960), Oral pathology. 5th ed. St. Louis: CV Mosby; pp. 1188-1190, 1218-31.
5. Ch'in KY (1938), Adamantinoma in Chinese. A pathological study of 41 cases. Chin Med J Suppl, 2:91-130.
6. Handousa AB (1951), Adamantinomas in relation to the nose. J Laryngol Otol, 65:715-23.
7. Husted E, Pindborg JJ (1953), Odontogenic tumours. Clinical and roentgenological aspects, treatment and pathology. Odontol Tidskr, 61:275-92.
8. Frissell CT, Shafer WG (1953), Ameloblastic odontoma. Report of a case. Oral Surg Oral Med Oral Pathol, 6:1129-33.
9. Jurgens PE (1962), An interesting odontoma: report of case. J Oral Surg, 20:516-20.
10. Rywkind AW, Shiltzow NS (1931), Beitrag zur Pathologie der Odontome [German] Vierteljahrsschr Zahnheilkd, 47:514-521.
11. Rywkind AW (1392), Beitrag zur Pathologie der Cholesteatome [German]. Virchows Archiv Pathol Anat Physiol klin Med, 283:13-28.
12. Sekine S, Takata T, Shibata T et al. (2004), Expression of enamel proteins and LEF1 in adamantinomatous craniopharyngioma: Evidence for its odontogenic epithelial differentiation. Histopathology, 45:573-79.
13. Tanaka A, Okamoto M, Yoshizawa D et al. (2007), Presence of ghost cells and the Wnt signaling pathway in odontomas. J Oral Pathol Med, 36:400-04.
14. Hassanein AM, Glanz SM, Kessler HP et al. (2003), β-Catenin is expressed aberrantly in tumors expressing shadow cells. Pilomatricoma, craniopharyngioma, and calcifying odontogenic cyst. Am J Clin Pathol, 120:732-36.
15. Sekine S, Sato S, Takata T et al. (2003), β-Catenin mutations are frequent in calcifying odontogenic cysts, but rare in ameloblastomas. Am J Pathol, 163:1707-12.
16. Highman B, Ogden GE (1944), Calcified epithelioma. Arch Pathol, 37:169-74.
17. Gorlin RJ, Pindborg JJ, Redman RS et al. (1964), The calcifying odontogenic cyst. A new entity and possible analogue of the cutaneous calcifying epithelioma of Malherbe.

Cancer, 17:723-29.
18. Chaves E, Pessoa J (1968), The calcifying odontogenic cyst. Report of two cases. Oral Surg Oral Med Oral Pathol, 25:849-55.
19. Abrams AM, Howell FV (1968), The calcifying odontogenic cyst. Report of four cases. Oral Surg Oral Med Oral Pathol, 25:594-606.
20. Levy BA (1973), Ghost cells and odontomas. Oral Surg Oral Med Oral Pathol, 36:851-55.
21. Sedano HO, Pindborg JJ (1975), Ghost cell epithelium in odontomas. J Oral Pathol, 4:27-30.
22. Kerebel B, Kerebel LM (1985), Ghost cells in complex odontoma: A light microscopic and SEM study. Oral Surg Oral Med Oral Pathol, 59:371-78.
23. Yamamoto Y, Hiranuma Y, Eba M et al. (1988), Calcifying odontogenic cyst immunohistochemical detection of keratin and involucrin in cyst wall. Virchows Arch A Pathol Anat Histopathol, 412:189-96.
24. Hong SP, Ellis GL, Hartman KS (1991), Calcifying odontogenic cyst. A review of ninety-two cases with reevaluation of their nature as cysts or neoplasms, the nature of ghost cells, and sub classification. Oral Surg Oral Med Oral Pathol, 72:56-64.
25. Gunhan O, Celasun B, Can C et al. (1993), The nature of ghost cells in calcifying odontogenic cyst: An immunohistochemical study. Ann Dent, 52:30-33.
26. Laba E, Dumitrescu G, Ardeleanu C, Gogalniceanu D, Laba CD (1997), Calcifying odontogenic cyst: report of two cases and review of literature Rom J Morphol Embryol, 43:205-12.
27. El-Sissy NA, Rashad NA (1999), CK13 in craniopharyngioma versus related odontogenic neoplasms and human enamel organ. East Mediterr Health J, 5:490-502.
28. Kim J, Lee EH, Yook JI et al. (2000), Odontogenic ghost cell carcinoma: A case report with reference to the relation between apoptosis and ghost cells. Oral Surg Oral Med Oral Pathol Oral Radiol Endod, 90:630-35.
29. Takata T, Zhao M, Nikai H, Uchida T, Wang T (2000), Ghost cells in calcifying odontogenic cyst expresses enamel-related proteins. Histochem J, 32:223-29.
30. Lan MY, Lan MC, Ho CY et al. (2003), Pilomatricoma of head and neck: A retrospective review of 179 cases. Arch Otolayrngol Head Neck Surg, 129:1327-30.
31. Kusama K, Katayama Y, Oba K et al. (2005), Expression of hard alpha-keratins in pilomatrixoma, craniopharyngioma, and calcifying odontogenic cyst. Am J Clin Pathol, 123:376-81.
32. Shear M, Speight P. In: Cysts of the oral and maxillofacial regions. 4th ed. Oxford, UK: Blackwell Publishing Ltd; 2007. Calcifying odontogenic cyst; pp. 101-07.
33. Gorlin RJ, Pindborg JJ, Clausen FP et al. (1962), The calcifying odontogenic cyst: A possible analogue of the cutaneous calcifying epithelioma of Malherbe. An analysis of fifteen cases. Oral Surg Oral Med Oral Pathol, 15:1235-43.
34. Barbosa AA, Jr, Guimarães NS, Sadigursky M et al. (2000), Pilomatrix carcinoma (malignant pilomatricoma): A case report and review of the literature. An Bras Dermatol, 75:581-85.
35. Nagaveni NB, Umashankara KV, Radhika NB et al. (2011), Eruption cyst: A literature review and four case reports. Ind J Denr Res, 22:148-51.
36. Cohen DM, Bhattacharyya I (2004), Ameloblastic fibroma, ameloblastic fibro-odontoma, and odontoma. Oral Maxillofac Surg Clin North Am, 16:375-84.
37. Lee SK, Kim YS (2014), Current concepts and occurrence of epithelial odontogenic tumors: II Calcifying epithelial odontogenic tumor versus ghost cell odontogenic tumors derived from calcifying odontogenic cyst. Korean J Pathol, 48:175-87.
38. Gong Y, Wang L, Wang H et al. (2009), The expression of NF-kappaB, Ki-67 and MMP-9 in CCOT, DGCT and GCOC. Oral Oncol, 45:515-20.
39. Bafna SS, Joy T, Tupkari JV et al. (2016), Dentinogenic ghost cell tumor. J Oral Maxillofac Pathol, 20:1-6.
40. Goldenberg D, Sciubba J, Tufano RP (2004), Odontogenic ghost cell carcinoma. Head Neck, 26:378-81.
41. Rumayor A, Carlos R, Kirsch HM et al. (2015), Ghost cells in pilomatrixoma, craniopharyngioma, and calcifying cystic odontogenic tumor: histological, immunohistochemical, and ultrastructural study. J Oral Pathol Med, 44:284-90.