Ghost cells, aberrant keratin, degeneration, calcification

**Table 1: Hypothesis in ghost cells origin**

<table>
<thead>
<tr>
<th>INVESTIGATOR(S)</th>
<th>YEAR</th>
<th>HYPOTHESES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Highman and Ogden</td>
<td>1936</td>
<td>Described GCs as dyskeratotic cells with viable cellular outline in pilomatricoma [16]</td>
</tr>
<tr>
<td>Gorlin et al.</td>
<td>1962</td>
<td>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]</td>
</tr>
<tr>
<td>Chaves</td>
<td>1968</td>
<td>GC formation considered as marked degeneration with aberrant keratinization [18]</td>
</tr>
<tr>
<td>Howells and Abrams</td>
<td>1968</td>
<td>Speculated unusual degenerative patterns related to GC formation. Transformation of large squamous mural cells to eosinophilic cells with intact nuclear outline. Stellite and basal cells enlargement with peripheral nuclear displacement suggested keratin. This caused breach in basement membrane with connective tissue herniation, and GC formation [19]</td>
</tr>
<tr>
<td>Levy et al.</td>
<td>1973</td>
<td>Hypoxic metaplasia of odontogenic epithelium led to dissolution of surrounding hard tissue calcification causing apoptosis and keratinization in odontomas [20]</td>
</tr>
<tr>
<td>Sedano, Pindborg and Kerebel et al.</td>
<td>1975 and 1985</td>
<td>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]</td>
</tr>
<tr>
<td>Yamamoto et al.</td>
<td>1988</td>
<td>Epithelial cells undergoing abnormal terminal differentiation synthesize altered homogenous acellular products and degenerated GCs. Confirmed by involucrin and high molecular weight keratin staining [23]</td>
</tr>
</tbody>
</table>

**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, Rykkind 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.
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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

<table>
<thead>
<tr>
<th>Lesion</th>
<th>Histopathology</th>
<th>Stains/ IHC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eruption cyst [35]</td>
<td>Reduced enamel epithelium</td>
<td>CK-10, 14 +ve/-ve, Tenascin and EGFR +ve/-ve</td>
</tr>
<tr>
<td>Type-I Calciﬁng odontogenic cyst [24]</td>
<td>Columnar cells with overlying stellate reticulum-like cells with or without dentinoid material and dysplastic calcifications</td>
<td>Amelogenin +ve, Enamelin, Sheathlin and Enamelysin +ve/-ve</td>
</tr>
<tr>
<td>Ameloblastic ﬁbroodontoma [36]</td>
<td>Ameloblastic ﬁbroblast along with typical Composite odontome</td>
<td>CK-8, 13, 14, 16, 18, 19 +ve, PCNA +ve and BrdU +ve</td>
</tr>
<tr>
<td>Odontoadameloblastoma [36]</td>
<td>Sheets of typical ameloblastoma with columnar, squamous and undifferentiated epithelial cells along with enamel, dentin, osteodentin, dentinoid, osteoid, cementum and bone</td>
<td>CK-8, CK-13, CK-14, CK-16, CK-18, CK-19 +ve, PCNA +ve and BrdU +ve</td>
</tr>
<tr>
<td>Odontoma [21, 36]</td>
<td>Enamel, dentin, pulp, cementum may or may not be present in normal relation to one another</td>
<td>Amelogenin, Keratins, BMP +ve, Vimentin, Glut-1, β-catenin, Osteodentin +ve, and TGF-β +ve</td>
</tr>
<tr>
<td>Cystic calcifying odontogenic tumor [37, 38]</td>
<td></td>
<td>NFe and Ki-67 and MMP-9 +ve/-ve (weakly +ve), Podoplanin +ve</td>
</tr>
<tr>
<td>Ameloblastomatous epithelium with dental hard tissue resembling odontome along with limited dysplastic dentin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dentinogenic ghost cell tumor [39]</td>
<td>Marked presence of GCs, occasional calcification, predominant dentinoid material, benign cellular stroma</td>
<td>PCNA and SBA strongly +ve, WGA, PC1 and UE1A moderately +ve, DBA and ConA slightly +ve, β-catenin and Lef1 strongly +ve</td>
</tr>
<tr>
<td>Ghost cell odontogenic carcinoma [40]</td>
<td>Predominant GCs, rare calcifications, rudimentary dentinoid material, malignant odontogenic cells</td>
<td>Ki-67 &gt;7.5%, MMP-9 +ve, Bel-2 +ve, p53 +ve, BAX +ve and TRAP +ve</td>
</tr>
<tr>
<td>Pilomatricoma [41]</td>
<td>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. Absent calcifications and foreign body giant cell reactions</td>
<td>CD-138 and FAS weak to moderately +ve, basaloid cells +ve for AE1/AE3 and β-catenin</td>
</tr>
<tr>
<td>Craniofacial squamous cell carcinoma [41]</td>
<td>3 patterns: solid, cystic, mixed. Stellate reticulum-like epithelium in cords and lobules, bordered by basal cells with ameloblastic features. GC islands throughout epithelium.</td>
<td>CK-7, 8, 19 +ve, AE1/AE3 weakly +ve in GCs while strongly +ve in transitional cells, GLUT-1 +ve, β-catenin variably +ve</td>
</tr>
</tbody>
</table>

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

Cancer, 17:723-29.


