Ghost Cells and its Histogenesis: A Narrative Review

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Many research workers have made an attempt to elucidate the nature of ghost cells by employing special histochemical methods, transmission electron microscopy, and scanning electron microscopy, and several hypotheses have been offered without any universal agreement. With the purpose of unraveling some of the facts regarding ghost cells with emphasis on their histogenesis, a comprehensive review of available literature on ghost cells and ghost cell containing pathologies was undertaken using PubMed database. A search revealed articles with different theories of histogenesis of ghost cells in various odontogenic and non-odontogenic pathologies. Most of the authors favored aberrant keratinization while abortive enamel matrix formation, degeneration, coagulative necrosis, metaplasia of odontogenic epithelium, abnormal terminal differentiation, or apoptosis were other theories of histogenesis. Recent articles suggested an accumulation of hard keratin in ghost cell cytoplasm and emphasized on role of Wnt-β-catenin pathway in tumorigenesis of ghost cell-containing tumors. Future molecular studies are required to clarify further genetic and predisposing factors along with types and role of keratins involved in ghost cell transformation.

Keywords: Craniopharyngioma, Keratins, Odontogenic tumors, Pilomatrixoma

INTRODUCTION

The term ghost is used for the soul of a dead person that can manifest as translucent or barely visible wispy shapes. From the pathologic perspective, the apparition of ghosts is metaphorically linked to ghost cells, red cell ghosts, and ghost teeth. Plasma membrane of red cells after osmolysis become permeable to hemoglobin, but the cytoskeleton maintains their shape (red cell ghosts). In regional odontodysplasia, thin dental hard tissues along with enlarged pulp chamber give ghost appearance to teeth radiographically. Similarly, the ghost cells in odontogenic lesions are enlarged epithelial cells that have lost their nuclei, leaving a faint outline of the original nuclei. Cells with similar morphological features are found in pilomatrixoma (PM) (where they are referred as shadow cells) and in craniopharyngioma. The WHO classification of odontogenic tumors (2005) considered ghost cells as transitory squamous cells at various stages of differentiation. However, nature and process of formation of ghost cells remains elusive till date.

PubMed database was used for the literature search. Key words for search were “ghost cells” or “shadow cells;” “ghost cell tumors;” and combination of “ghost cells” with “PM” or “calcifying epithelioma of Malherbe;” “calcifying odontogenic cyst (COC)” or “calcifying cystic odontogenic tumor (CCOT)” and “craniopharyngioma.” Only articles written in English were included and their number restricted to ghost cells, shadow cells, and ghost cell tumors. The online literature search was also supplemented by a manual search of English language oral pathology textbooks.

GHOST CELLS CONTAINING LESIONS

Several odontogenic and non-odontogenic lesions show the presence of ghost cells. In odontogenic lesions including calcifying CCOT, dentinogenic ghost cell tumor (DGCT), and ghost cell odontogenic carcinoma (GCOC), ghost cells are of diagnostic importance. Ghost cells are occasionally seen in odontoma, odontoameloblastoma, ameloblastoma, ameloblastic fibrodontoma, and clear cell odontogenic carcinoma. They are also reported in inner enamel epithelium of developing tooth and in eruption cysts. PM is a deep subepidermal tumor consisting of irregular islands of epithelial cells. The cells in the islands are arranged in a circular configuration, with nucleated basaloid cells on the periphery and enucleated shadow cells in the centre. Adamantinomatous craniopharyngioma (aCP) is said to have features of both CCOT and ameloblastoma, and ghost cells are pathognomonic features of them. Interestingly, ghost cell like transformation has been reported in non-odontogenic oral lesions such as irritational fibroma and oral submucous fibrosis by Sarode et al. Ghost cells were
reported in primary squamous cell carcinoma of lung with PM like features and also in tumors of colon and uterus.11

THEORIES OF HISTOGENESIS

Ghost cells whether odontogenic or non-odontogenic are always epithelial in origin. The illusional nature of ghost cells can be reflected in various confusing terminologies such as a form of true keratinization, prekeratin, stages in the process of ortho, para and aberrant keratin formation, abnormal/aberrant keratinization, highly keratinized epithelial cells, and cells which have lost their developmental and inductive effect.11

Local Hypoxia and Degeneration

Ischemia was considered in the mechanism, especially in odontomas where the disordered formation of hard tissue believed to cut off the blood supply of ameloblast like cells in their vicinity. The enlarged appearance of ghost cells was attributed to intracellular edema and dilated degenerated membranous organelles which appear to be in support of this theory.12 However, the occasional presence of ghost cells in the vicinity of blood vessels ruled out this hypothesis. Sarode et al. observed ghost cells in 4.43% and 3.63% cases of irritational fibroma and oral submucous fibrosis, respectively.10 They stated that fibrosis may cause a reduction in blood supply to the overlying epithelium. However, they observed patent vascular spaces in these lesions which also contradict the hypoxia hypothesis.

However, this evidence only ruled out local anoxia as a cause for degeneration. Degenerating foci is a prerequisite for dystrophic calcification, which may occur in some of the ghost cells, reinforcing the degenerating nature of ghost cells.13 Abrams and Howell speculated two unusual patterns of degeneration in CCOT leading to ghost cell formation.14 Yamamoto et al. founds intense staining of ghost cells with high molecular weight (HMW) keratins and concluded that ghost cell probably has different subclasses of keratins which have a strong tendency to degenerate.15

Form of Coagulative Necrosis

Features of ghost cells like loss of nuclei and clear preservation of basic cellular outlines are compatible with features of coagulative necrosis. Hong SP et al. in their study on COC suggested that same mechanism may operate during initiation of COC with coagulative necrosis occurring at the same time or later in portions of cyst lining with resultant ghost cell formation. It was considered that altered or absence of cytokeratin expression by ghost cells was probably due to this coagulative necrosis.16

Metaplastic Transformation

Sedano and Pindborg suggested that production of keratin is not a natural function of odontogenic epithelium, and these cells should be considered as products of metaplastic transformation.7 Ghost cells though have an odontogenic origin, usually show keratinization. Levy suggested ischemia as a reason for squamous metaplasia of odontogenic epithelium.12 Piattelli and Trisi in their study on odontomas, also stated in support of this theory that ghost cells originate through metaplasia of odontogenic epithelium with abnormal keratinization.17

Abnormal Terminal Differentiation or Apoptosis

Terminal differentiation of keratinocytes or cornification is believed to be a special variant of apoptosis. Kim et al.18 investigated the expression of the apoptotic and anti-apoptotic marker in COC and found that ghost cell was expressing Bax protein while nucleated cells adjacent to ghost cells expressing both Bax and Bcl-XL. TUNEL assay was positive in nucleated cells adjacent to ghost cells. They suggested that ghost cells are formed during terminal differentiation as an apoptotic process. However, the ghost cells were not exactly identical to the normal terminal differentiation of keratinocytes in that the positivity for cytokeratin and involucrin in the nucleated cells adjacent to the ghost cells started disappearing as the nuclei disappeared. So, they proposed that ghost cells might result from abnormal terminal differentiation toward keratinocytes or process of apoptosis of poorly differentiated odontogenic cells. Lan et al. observed some transitional cells between the basaloid cells and ghost cells representing apoptotic cells proceeding to ghost cells in PM.19

Abortive Formation of Enamel Matrix

Several investigators have found positive results for enamel matrix proteins in ghost cells of odontogenic lesions.7,12-26 Günhan et al. suggested that ghost cells originate from cells that are programmed for amelogenesis in CCOT through cytoskeletal reorganization. However, they fail to calcify into mature form because of the absence of odontoblasts and dentin.20 However, Mehendiratta M et al. mentioned about Zussman’s (1966) experiment which demonstrated through subcutaneous transplantation of enamel epithelium into homologous rats that ameloblasts can secrete enamel matrix without the presence of dentin matrix or odontoblasts.12 Enamel matrix proteins are expressed by ghost cells of CCOT and aCP which arise from oral ectoderm destined to contribute to enamel formation but not by PM which develops from skin ectoderm.18 Hassanein et al. thus suggested that the ghost cells would represent a manifestation of the “dead end” in the road to calcified enamel formation.25

Aberrant Keratinization and/or Accumulation of Hard Keratin

Ghost cells were stained positively with special stains for keratin.7,12,13,26 Crivelini et al. (2009) demonstrated that
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keratin distribution in CCOT was similar to that described in the squamous stratified epithelium with the basal layer expressing K14 and the upper cells K10/13. K10/13-positive cells were considered as squamous transitory elements toward ghost cells. They proposed that these transitory cells would accumulate another unknown intracytoplasmic substance during the differentiation process, and gradually repel the cytoskeletal system to the periphery, until becoming well developed K10/13-negative ghost cells. Regezi et al. also stated that ghost cells were not true keratin but represented an aberrant or unusual form of keratin.

Ghost cell keratinization differs from normal keratinization as:
- Ghost cells are larger than normal keratotic squames, often vacuolated, and the remnants of the nuclear membranes are more prominent.
- Ghost cells demonstrate coarse, thick tonofilament bundles arranged in various directions which differ from evenly distributed fine tonofilaments in keratinocytes.
- Ghost cells lack keratohyaline granules and thus proline and amino acids rich in sulfhydryl groups necessary for true keratinization.
- Ghost cells are negative for HMW cytokeratin and involucrin which are expressed by corneocytes.
- Ghost cells have a tendency to undergo dystrophic calcification.

Kusama et al. investigated immuno-reactivity of cells in CCOT, aCP, and PM for human hair proteins. They found positivity for only ghost cells in CCOT and aCP but in PM, for both shadow cells and transitional cells. Ghost cells were also immuno-reactive for phosphothreonine, which are detected in hard alpha keratins. So, he speculated that ghost cells accumulate hard keratin in their cytoplasm during the pathological transformation process. This finding has been validated by study of Tanaka et al. in which strong expression of hard keratins was detected in the ghost cells of odontomas. Lucchesse et al. with the use of confocal laser scanning microscopy demonstrated characteristic pattern of auto-fluorescence in ghost cells and attributed it to hard keratins.

Expression of β-catenin in all these lesions in nucleated cells adjacent to ghost cells or shadow cells but ghost cells failed to show positivity. Hard keratin genes possess Lef-1 binding sites and expression for Lef-1 was found positive in adjacent nucleated cells to ghost cells. Regezi et al. also stated that ghost cells were not true keratin but represented an aberrant or unusual form of keratin.

Nakano et al. demonstrated Notch signaling activation in the CCOT cells and believed in their role in daughter cell fate regulation. Notch family of proteins are involved in cell fate decisions via three distinct mechanisms; lateral inhibition, binary cell fate, and lateral induction. These various modes of signaling allow Notch to perform functions within the same tissue in a spatially and temporally regulated manner. Siar et al. investigated expression of Notch proteins in five cases of cystic CCOT and found that Notch 1 signal activation induced by Jagged 1 is necessary for specification of ghost cell fate. Ghost cells demonstrated co-expression for Notch 1 and Jagged 1 indicating that signaling might occur via lateral induction between Notch ligand and Notch receptor on adjacent ghost cells resulting in a positive feedback. On the other hand, the adjacent tumor epithelium only weakly expressed these molecules suggesting that probably Notch signal activation in ghost cells exerts a lateral inhibitory effect on the neighboring tumor epithelium blocking them from adapting the same cell fate. Their study also demonstrated positivity of mineralized ghost cells for Notch 1 and Jagged 1, which implicates that calcification process, might be associated with up-regulation of these molecules.

So, aberrant activation of Wnt-β-catenin pathway and notch signaling involved in tumorigenesis may be responsible for the formation of similar cells from ectodermal structures through, either aberrant keratinization of matrical cells (shadow cells) or abortive enamel formation and aberrant keratinization of odontogenic cells (ghost cells). Further studies are required in this field to specify the nature of alterations.

Mucin Induced Ghost Cell Transformation

Sarode et al. proposed this unique hypothesis for ghost cell transformation based on their observation in non-odontogenic oral lesions such as irritation fibroma and oral submucous fibrosis (Figure 1). They have differentiated ghost cell-like structures from individual cell keratinization, spongiotic artifact, and Totos bodies. Further studies are needed to elucidate the nature of changes associated with these non-odontogenic mucosal lesions and to correlate them with ghost cell histogenesis in odontogenic lesions.

Molecular Mechanism (Wnt-β-catenin-T-cell Factor [TCF]/Lymphoid-Enhancing Factor [Lef] Pathway and Notch Signaling)

Wnt-β-catenin-TCF/Lef pathway is said to be involved in tooth formation, hair formation, and formation of adenohypophysis, and mutation in one of these may be involved in tumorigenesis in the related tissues resulting in CCOT, PM, and craniopharyngioma, respectively. The commonality may be inferred further to be a result of all three tumors shared method of keratinization and ghost/shadow cell formation. Hassanein et al. demonstrated molecular mechanism of Wnt-β-catenin-T-cell Factor/Lymphoid-Enhancing Factor pathway and Notch Signaling.
CONCLUSION

Ghost cells are a typical characteristic of many odontogenic and non-odontogenic lesions. Craniopharyngioma, calcifying CCOT, and PM which are less proliferative and infiltrative lesions show more ghost cells while aggressive and proliferative lesions, such as ameloblastoma, DGCT, clear cell odontogenic carcinoma, GCOC, show less number of ghost cells. This finding implies that they do not affect the prognosis but rather reflect the behavior of that lesion.

Among various theories of histogenesis, recent studies suggest that tumor epithelium in the ghost cell tumors, i.e., CCOT, PM, and aCP; aborts their respective role in odontogenesis, hair formation, and formation of adenohypophysis, respectively, and accumulates hard keratin due to its inherent keratinization potential owing to their ectodermal origin. Degenerative change, coagulative necrosis, the metaplastic transformation of odontogenic epithelium, terminal differentiation, and apoptosis appears to supplement the pathologic progression of the odontogenic/non-odontogenic epithelium to ghost/shadow cells. The role of Wnt-β-catenin-Lef pathway and Notch signaling partially explains the link between tumorigenesis of these lesions and ghost/shadow cell formation and/or calcification. Future molecular studies are required to clarify further genetic and predisposing factors along with types and role of keratins involved in ghost cell transformation. All the theories of histogenesis and fate of ghost cells are summarized in Figure 2.

REFERENCES


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