ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

Association of Cholesterol Crystals in Odontogenic Cysts: A Histological Review.

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ABSTRACT

Cholesterol crystals are normally seen in odontogenic cysts. The origin of cholesterol crystals is still not clear. Some found they originate from disintegrating erythrocytes and degenerating epithelial cells. Odontogenic cysts often contain macrophages and cholesterol have been found within foamy macrophages. Macrophages also appear to be an origin of cholesterol crystals. Cholesterol crystals are more commonly seen in inflammatory cyst compared to non-inflammatory cysts. This review analyzes the origin of cholesterol crystals in cysts and histopathological features of odontogenic cysts.

Keywords: Cholesterol crystals, Erythrocytes, Radicular cyst, Macrophage.

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ISSN: 0975-8585

INTRODUCTION

The term cyst is derived from the Greek word '*Kystis*' meaning sac or bladder [1]. Cyst is defined as "a pathological cavity having gaseous, fluid and semi fluid contents and which is not created by the accumulation of pus". Most cysts, but not all, are lined by epithelium [2]**.** Odontogenic cysts are the most common form of cystic lesions that affect the maxillofacial region [3].

Developmental cysts are usually asymptomatic, but they can develop into an extremely large lesion resulting in bone expansion and erosion**.** Dentigerous cyst develop from reduced enamel epithelium and odontogenic keratocyst develop from the remnants of dental lamina [4]**.** Radicular cysts are the most commonly seen inflammatory cyst of the jaw. It is thought to originate from cell rests of Malassez's, secondary to pulpal necrosis [5]**.**

In this review we have discussed about the mechanism of cholesterol crystal formation in various odontogenic cysts, mainly odontogenic keratocyst, dentigerous cyst and radicular cyst. It was found that degenerating erythrocytes are the origin of cholesterol clefts in odontogenic cysts. In this review we will discuss the association between haemosiderin and cholesterol clefts, in addition the presence of foamy macrophages was studied, an aspect of odontotgenic cysts.

Classification

Cysts are generally classified into odontogenic and nonodontogenic cysts. Odontogenic cysts are again classified into developmental cyst and inflammatory cyst [3].

Developmental cysts include,

- Odontogenic keratocyst
- Dentigerous cyst
- Eruption cyst
- Gingival cyst of newborn
- Gingival cyst of adults
- Glandular odontogenic cyst and
- Calcifying odntogenic cyst.

Inflammatory cyst include,

- Radicular cyst
- Residual cyst and
- Paradental cyst
- Inflammatory collateral cyst.

Histological features of radicular cyst, odontogenic keratocyst and dentigerous cyst.

Radicular cyst

Macroscopically, intact radicular cysts presented for histopathological evaluation may be spherical or ovoid, but often collapsed during surgical removal. Those lesions are often fragmented or irregular. Microscopically, radicular cyst is lined by partially or completely by non-keratinized stratified squamous epithelium. If it is keratinized orthokeratinization is more common than parakeratinization. The nature of epithelial lining depends on the stage of developmental of the cyst, and also the severity of inflammation. The epithelium of radicular cyst contains 6-20 cell layer thickness. The epithelium may show arcading pattern penetrating into the underlying capsule. The epithelium may also show spongiosis and in some cases neutrophils may be seen [3,6]. The epithelium of radicular cysts may also show metaplastic changes in the form of mucous or ciliated cells. Mucous cells usually present in the superficial layers of the epithelium, either as scattered cells or as a continuous layer [7-9]. In addition epithelium may contain linear, straight, curved or hairpin shaped hyaline bodies. Occasionally these hyaline bodies are concentrically laminated circular or polycyclic in form [3,10,11]. The presence of cholesterol clefts in odontogenic cysts is recognized as a characteristic feature [7] and this is no longer accepted. In routine hematoxylin and eosin staining, cholesterol crystals are dissolved during dehydration and subsequent processing of tissues, leaving needle-shaped clefts known as "cholesterol clefts" within the cyst walls and cavities [12].

Odontogenic keratocyst

Macroscopically the linings of cyst are rarely received intact from the laboratory. They are usually thin walled, collapsed and folded. The cyst cavities of odontogenic keratocysts contain pale white granular material. Microscopically, the cyst cavity contents of odontogenic keratocysts are usually composed of keratinous cells. The cyst linings are typically comprised of a parakeratinized stratified squamous epithelium. In some cysts the linings are orthokeratinized [3, 13]. The epithelium of these lesions is usually 6-8 cell layers thick, with a palisading basal layer which are hyperchromatic. While the parakeratinized surface is usually corrugated or folded. The junction between the epithelium and connective tissue stroma is usually flat and devoid of rete ridges, and the epithelium often seperates from the connective tissue. Rarely, the cyst walls of odontogenic keratocysts contain cholesterol clefts and haemosiderin deposits.

Dentigerous cyst

Macroscopically the cyst is seen attached to the cemento-enamel junction of the associated teeth. Microscopically the epithelial linings of dentigerous cysts resemble the reduced enamel epithelium, and consist of flat or cuboidal cells of 3-5 cell layer thickness. The epithelium may also contain mucous producing or ciliated cells representing metaplastic change. Occasionally dentigerous cyst contains Rushton's hyaline bodies similar to those reported in radicular cyst [11]. The stroma is usually uninflammed, although inflammation is seen when cyst becomes infected [14]. Inflamed dentigerous cyst walls occasionally contain cholesterol clefts and haemosiderin pigments [3].

ISSN: 0975-8585

DISCUSSION

Cholesterol crystals – Origin?

The origin of cholesterol crystals in odontogenic cysts is still unclear. R.M. Browne from his study found that cholesterol clefts were more prevalent in cases where there was haemosiderin pigment. He stated that the main cause for cholesterol crystals was disintegrating erythrocytes [7]**.** Some authors suggest that cholesterol clefts accumulate in the tissues as a result of degeneration and disintegration of epithelial cells [15]**.**

Cholesterol clefts associated with giant cells are usually seen within the lumen and in the connective tissue wall of a radicular cyst. The length of a cholesterol cleft can vary from 0.2-1.3 mm [16]. The possible mechanisms suggested for cholesterol crystals formation are,

- Breakdown of RBCs
- Deposition of hemosiderin.
- Foam cells resulting from local metabolic activity.
- Ingestion of RBCs by macrophages leading to intracellular formation of cholesterol esters.
- Poor lymphatic drainage leading to accumulation of cholesterol.

In one series, cholesterol crystals were seen in 57 of 200 dental cysts (28.5%) [3]. while in a separate study such clefts were seen in 216 of 537 odontogenic cysts (40.2%) [16]**.** The incidence of cholesterol crystals is reported as highest(43.5%) in inflammatory cyst, particularly in radicular cyst, while the lowest incidence (17.1%) is reported for cysts of non-inflammatory origin such as odontogenic keratocyst [7]**.** This suggests that the inflammatory process palys an important role in the pathogenesis of cholesterol clefts.

RM Browne analysed 535 odontogenic cysts, including 402 radicular cyst [7]**.** In his study, cholesterol clefts were more prevalent in cases where there was haemosiderin pigment. He stated that the main source of cholesterol crystals was disintegrating erythrocytes. Approximately 55% of the erythrocyte membrane lipid is phospholipid , 42% is cholesterol and 3% glycolipid is seen. Cholesterol in the erythrocyte membrane is present in its free and non-esterified form [17]**.** Internal membranes are not present in erythrocytes, and the plasma membrane is the only source of erythrocyte cholesterol, the amount of cholesterol present in the lipid layer of erythrocyte membrane is little, so that it is difficult to see how the large volume of cholesterol crystals seen in odontogenic cysts could be derived from erythrocyte membrane alone.

Macrophages phagocyte large number of degenerated cells has a foamy appearance from accumulated lipid in their cytoplasm [18]. Foamy macrophages are noted to be present in odontogenic cysts and Cholesterol crystals have been suggested forming both within foamy macrophages, as well as in the extracellular matrix in atherosclerosis. This suggests that foamy macrophages appear to be the origin of cholesterol crystals.

Notably cholesterol crystals are also reported in chronic periapical periodontitis [19], consistent with an inflammatory basis. While the earlier study it was recognized that erythrocytes were possibly a source of cholesterol [7].

Cholesterol crystals in odontogenic cysts

Odontogenic cysts contain Cholesterol crystals. These crystals are seen in dentigerous cyst, odontogenic keratocyst and radicular cyst. The presence of cholesterol crystals in radicular cyst fluid has in the past been recognized as a characteristic feature [7], although this is no longer accepted as a pathognomonic feature. When such cyst fluid is examined macroscopically with transmitted light, cholesterol crystals shows a shimmering appearance to the gold or straw colored fluid [33]. If an unstained smear of cystic fluid is examined using a light microscope, cholesterol crystals are seen to have a typical rhomboid shape. In paraffin sections processed for routine hematoxylin and eosin staining, these crystals are dissolved by fat solvents used in dehydration and infiltration, leaving needle-shaped clefts known as "cholesterol clefts" within the cyst walls and cavities [12]. Notably, once cholesterol crystals have been deposited in the cyst wall, they behave as foreign bodies and express a foreign body giant cell reaction. Cholesterol clefts in histological sections are seen surrounded by multinucleated foreign body type giant cells [3]. It is important to note that cholesterol crystals are frequently seen in atherosclerotic plaques [20] and this may have implications for the origin of such crystals in odontogenic lesions. Similarly, it is interesting that cholesterol crystals are occasionally seen in non-odontogenic lesions, including lesions of breast [21].

CONCLUSION

Odontogenic cysts often contain cholesterol crystals. In this review we have discussed the various causes and the presence of cholesterol clefts in odontogenic cysts. Various studies demonstrate correlation between haemosiderin and cholesterol clefts in odontogenic cysts suggesting that cholesterol may accumulate in these lesions from degenerating erythrocytes. The presence of cholesterol clefts in odontogenic cysts is recognized as a characteristic feature and this is no longer accepted. In this review we found that cholesterol crystals are seen in chronic periapical periodontitis, which could be due to the inflammatory reaction. We also found Foamy macrophages are noted to be present in odontogenic cysts and Cholesterol crystals have been suggested forming both within foamy macrophages, as well as in the extracellular matrix in atherosclerosis. This suggests that foamy macrophages also appear to be the origin of cholesterol crystals.

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