

Full Length Research Paper

Neoplasms associated with odontogenic cysts

K. M. K. Masthan^{1*}, S. Rajkumari¹, M. Deepasree², N. Aravindh Babu¹ and S. Leena Sankari¹

¹Department of Oral Pathology and Microbiology, Sree Balaji Dental College and Hospital, Narayanapuram, Chennai, Tamilnadu, India.

²Department Of Oral Pathology and Microbiology, Rajah Muthiah Dental College and Hospital, Annamalai University, Chidambaram, Tamilnadu, India.

Accepted 14 January, 2019

The cysts that arise from odontogenic apparatus or those which have the ability to produce a lining similar to that of the tooth forming structures are referred to as odontogenic cyst. The cysts that are commonly considered to have neoplastic potential include dentigerous cysts, odontogenic keratocysts, calcifying odontogenic cysts, glandular odontogenic cysts and radicular cysts. The neoplastic component must be identified in the histopathology, since it is major factor in determining the diagnosis, treatment plan and prognosis.

Key words: Odontogenic cyst, carcinoma, dentigerous cyst, odontogenic keratocyst, calcifying odontogenic cyst, ameloblastoma, adenomatoid odontogenic tumor, odontoma.

INTRODUCTION

Neoplastic changes within simple odontogenic cysts appear to be a rare but definite entity (Muglali and Sumer, 2008). The neoplasms associated with epithelial lining of the odontogenic cyst include ameloblastoma, ameloblastic fibroma, calcifying epithelial odontogenic tumor, adenomatoid odontogenic tumor, odontoma, squamous cell carcinoma and mucoepidermoid carcinoma (Muglali and Sumer, 2008; Lin et al., 2004). Among the odontogenic cysts, neoplastic transformation is considered to be highest in keratocyst and dentigerous cyst.

CARCINOMAS ASSOCIATED WITH ODONTOGENIC CYST

The incidence of carcinomas arising in odontogenic cysts was reported to be approximately 1 to 2/1000 (Stoelinga and Bronkhorst, 1988). The pathogenesis is unknown, but long-standing inflammation and continuous intracystic pressure, keratinization of cystic epithelium were suggested as possible causative factors, however it is not mandatory in all situations. Malignant squamous epithelium

epithelium within an odontogenic cyst may represent (a) an invasion of the cyst from an adjacent primary carcinoma of the jaw, (b) a cystic change in a primary carcinoma, or (c) a malignant change within the cyst wall (Johnson et al., 1994). The histopathologic criterion employed to document malignant transformation of the cyst lining is the identification of a transition from the normal lining epithelium to dysplasia and to carcinoma (Bradley et al., 1988).

Dentigerous cyst and squamous cell carcinoma

The most common odontogenic cyst to show carcinomatous changes is the dentigerous cyst. Dentigerous cyst is defined as an epithelium-lined pathologic cavity that contains the crown of a tooth and fluid or semisolid material. This stringent definition is used rarely in practice; the surgeon often provides a clinical diagnosis of "dentigerous cyst" if a partially or fully impacted tooth shows a radiolucent band that is more than 3 mm thick directly adjacent to the entire crown or just one side of the crown, typically the distal aspect. The requirement for a pathologic cavity or luminal fluid is ignored; therefore, any thickening of pericoronal soft tissue may receive a clinicoradiographic diagnosis of "dentigerous cyst" even when a thickened dental follicle or pericoronitis causes the

*Corresponding author. E-mail: masthankmk@yahoo.com. Tel: +91-9841067822.

thickening (Kim and Ellis, 1993; Daley and Wysocki, 1995).

Clinically most of the carcinomas that arise in dentigerous cysts may present as an asymptomatic or painful pericoronal radiolucent lesion associated with an impacted mandibular third molar or canine (Yasuoka et al., 2000). About 25% of patients show swelling. Some lesions can cause osseous destruction around an adjacent erupted tooth or in adjacent edentulous bone (Johnson et al., 1994). Intraepithelial neoplasia that involves sulcular gingival epithelium, confluent with dental follicular epithelium can mimic carcinoma ex dentigerous cyst histologically. Histologically, the lesions demonstrate membranous connective tissue that is lined by stratified squamous epithelium that exhibits evidence of intraepithelial neoplasia or it is associated with an invasive well-differentiated or moderately-differentiated squamous cell carcinoma. The lining epithelium is derived from dental follicular epithelium or gingival sulcular epithelium (Slater, 2004).

Dentigerous cyst and mucoepidermoid carcinoma

The most common neoplasms that originate in the lining of cysts are benign odontogenic tumours. Non-odontogenic tumours that arise in conjunction with odontogenic cysts are usually malignant: epidermoid carcinoma and mucoepidermoid carcinoma. Gardner published an excellent review of epidermoid carcinoma that arose from cystic linings, but little is known about mucoepidermoid carcinoma (MEC) that arises within the jaws (Aggarwal and Saxena, 2011). Some central MECs were described in association with dentigerous cysts, radicular cysts, and ameloblastomas (Brookstone and Huvos, 1992). In addition, as in odontogenic cysts and tumors, the most common aspect of central MEC is an uni- or multi-locular radiolucency in the posterior mandible, frequently associated with impacted teeth. The possible relationship of central MECs with odontogenic lesions is also reinforced by the fact that central MECs outnumber other intraosseous salivary tumors such as pleomorphic adenoma and adenoid cystic carcinoma (Bouquot et al., 2000). Several sources of histogenic origin have been proposed for central MEC, including: (a) mucous metaplasia of odontogenic cyst epithelium; (b) entrapment of salivary tissues from the submandibular, sublingual, or minor salivary glands from the retromolar area during embryonic development; (c) maxillary sinus epithelium; (d) iatrogenic entrapment of minor salivary glands (e.g. chronic osteomyelitis and sinusitis); (e) remnants of the dental lamina. Although none of these possibilities is universally accepted (Bouquot et al., 2000; Waldron and Koh, 1990), the ability of the linings of benign odontogenic cysts to undergo mucous metaplasia is well documented. Aberrant salivary gland neoplasms

arise within the jaws as primary central bony lesions are rare, and makeup 2 to 3% of all mucoepidermoid carcinomas. Their relation to the unerupted molar raises the suspicion that they may have arisen from the lining of a dentigerous cyst.

Central mucoepidermoid carcinoma affects female patients twice as often as male patients. It has been reported in all ages ranging from 1 to 78 years with most occurring in the fourth and fifth decades of life (Aggarwal and Saxena, 2011). The criteria required for diagnosing a lesion as a central mucoepidermoid carcinoma, independent of whether it arises from an odontogenic cyst or tumor are: (a) the presence of intact cortical plates with no evidence of extension of an extraosseous soft tissue lesion into the jaws, (b) radio-graphic evidence of bone destruction, with poorly defined permeative margins, (c) histopathologic confirmation of a mucoepidermoid carcinoma, (d) positive mucin staining, (e) absence of primary lesions in neighboring salivary glands or other tissues mimicking the histological architecture of salivary gland tumors, and (f) exclusion of a metastatic lesion or an odontogenic tumor (Brookstone and Huvos, 1992). Radical resection offers the best chance of tumor eradication and prevention of local recurrence and late distant metastasis (Mark et al., 2008).

Carcinoma arising from residual cyst

Presence of radiolucency at the extraction site is considered to be a residual cyst which usually presents as cortical expansion or ulceration of surface mucosa with or without cervical lymphadenopathy. Histopathology reveals full thickness of the epithelium composed of large squamous cells with loss of the normal cell polarity and maturation, abnormal mitotic figures in the basal layer of the epithelium. The development of SCC from residual cysts is rare, however, it should always be considered in the differential diagnosis. Enucleation should be considered regardless of the risk of fracture. If marsupialisation is selected as a treatment choice, then a biopsy should be taken from different regions of the lesion (Muglali and Sumer, 2008; van der Wal et al., 1993). There are many possibilities of carcinoma arising from radicular cyst similar to that of a residual cyst.

Carcinoma ex odontogenic keratocyst

Makowski et al. (2001) identified 15 previously reported cases of squamous cell carcinoma that arose in an odontogenic keratocyst (OKC). In most cases, radiographic findings are those of a benign OKC and the unexpected carcinoma is encountered following incisional biopsy or enucleation. An aggressive carcinoma can emerge from

the affected jaw after several years, sometimes following repeated surgeries for recurrent OKCs. In reported cases, follow-up usually has been short; only one case developed cervical metastases and 3 of 11 patients died of the disease. Usually, the carcinomas have been treated by resection and postoperative radiation therapy (Keszler and Piloni, 2002) and infrequently with chemotherapy (Makowski et al., 2001). Due to the fact that cervical metastases seem to be uncommon, elective neck dissection may not be necessary. In the maxilla, OKC lining epithelium can fuse with buccal vestibular surface stratified squamous epithelium to form a chronic sinus tract that drains pus-like keratinaceous material; this "automarsupialized" cyst develops thickened nonkeratinized lining epithelium that is similar to that seen in a surgically decompressed OKC (August et al., 2003). A squamous cell carcinoma was reported to develop in association with an apparent "auto-marsupialized" orthokeratinized odontogenic cyst. Since the orthokeratinized odontogenic cyst is an entity that is distinct from OKC, such cases should not be categorized as carcinoma ex OKC. Primary intraosseous carcinoma (PIOC) that arises in a cyst that is lined by dysplastic thickened parakeratinized stratified squamous epithelium that lacks convincing features of classic OKC also cannot be classified assuredly as carcinoma ex OKC (Slater, 2004).

Glandular odontogenic cyst and Mucoepidermoid carcinoma

Glandular odontogenic cyst (GOC) is an uncommon lesion first described in 1987, whose origin is still debatable, although its histological features strongly suggest an odontogenic origin. It is sometimes very difficult to distinguish GOC from low-grade central MEC because of its histological similarity. In fact, it has been suggested that many cases formerly diagnosed as central MEC can be examples of GOC, and also some low-grade central MECs would have originated from GOCs in such a condition (Pires, 2004).

According to Magnusson et al. (1997) GOC may be regarded as the most benign end of the spectrum of central MEC. But, according to Waldron and Koh (1990), the distinguishing feature in GOC is the typical thin epithelial lining without any solid epithelial proliferation as seen in MEC and the presence of swirling spherical aggregates (epithelial plaque). The immunohistochemical examination performed by Semba et al. (1994) for expression of cytokeratins (Pires, 2004) and epithelial membrane antigen suggested that the lining epithelium of GOC was of odontogenic origin with metaplastic mucous-laden cells (Prabhu et al., 2010). Gardner et al. (1988) proposed the histopathologic diagnostic criteria for GOC and is as follows: (1) a cystic cavity lined by epithelium of

varying thickness with a flat interface between the epithelium and underlying connective tissue, (2) variable numbers of mucous cells in the epithelium, (3) eosinophilic cuboidal cells in the superficial layer, (4) localized plaque-like thickenings of the epithelium, (5) little inflammation, (6) occasional findings of hyperchromatic basal cells within the cyst lining. It is sometimes very difficult to differentiate a glandular odontogenic cyst from a predominantly cystic mucoepidermoid carcinoma, and may require careful analysis of several sections of tissue (Jean et al., 1997).

Metastatic carcinomas can be sometimes encountered in odontogenic cysts that requires a careful evaluation to distinguish the malignant transformation.

ODONTOGENIC TUMORS ASSOCIATED WITH THE ODONTOGENIC CYST

Adenomatoid odontogenic tumor

Adenomatoid odontogenic tumor (AOT) is a slow-growing, asymptomatic and uncommon lesion that arises from odontogenic epithelium with inductive effects on connective tissue (Bravo et al., 2005). In a series of publications (Philipsen and Reichart, 1996) it has been clarified that the adenomatoid tumor (AOT) constitutes an entity within the odontogenic tumors, clearly distinguishable from the classic intraosseous, infiltrative ameloblastoma but the clinical and radiographic presentation confuse with cystic odontogenic lesions. The benign non-invasive AOT appears in 3 clinic-topographic variants: (1) follicular, (2) extrafollicular, (3) peripheral. The first two variants are intrabony or central tumors and account for 97% of all AOTs of which 73% are of the follicular type (Philipsen et al., 1991). As it involves an unerupted tooth, it is often mistaken for a dentigerous cyst while the less common extra-follicular lesions can mimic peri-apical and globulo-maxillary cysts and are not associated with an unerupted tooth. They appear as well-defined, unilocular radiolucency is found between, above, or superimposed on the roots of erupted teeth. It has been theorized that the complex system of the dental laminae or its remnants is the likely origin of the AOT mimicking a periapical radiolucent lesion of the maxillary incisor area. Often, the site of an extrafollicular AOT in which the tumor produces a slowly enlarging swelling rarely accompanied by fluctuation. A distinct radiopaque border of the unilocular radiolucency is typical of the radiographic manifestation of an AOT. The periodontal ligament and lamina dura were found to be intact around teeth, an important finding that should make a periapical radiolucent lesion such as periapical cyst or granuloma less likely. Since, the extrafollicular AOT is situated outside the periodontal ligament, the nerve or blood supply through the apical foramen of a tooth is not affected and will give a positive vitality test result (Philipsen et al., 2002).

The lesion is slow growing and generally asymptomatic nature of the lesion most patients would tolerate the mass for years until it has produced a significant or obvious deformity and discomfort. Typically, the tumor would be 3 to 4 cm in maximum diameter at the time of clinical presentation. It often causes expansion of surrounding bone and displacement of adjacent teeth. There is a slight female predominance of 1: 1.2 to 2. Adequate of clinical and radiographic interpretation is essential for correct diagnosis, which otherwise may result in unnecessary endodontic treatment in case of extrafollicular variant while follicular variant does not differ much (Bravo et al., 2005).

Ameloblastoma

Unicyclic ameloblastomas (UAs) and dentigerous cysts (DCs) have an identical clinical and radiographic appearance. Some sub-types of UAs have a better prognosis than solid or multicystic ameloblastomas, and simple enucleation is the adequate treatment. UAs with small islands of ameloblastomatous epithelium may be misdiagnosed as a DC or keratocyst (Dunsche et al., 2003). Ameloblastoma may be the most important tumour in terms of its histology and all recent histological classifications have established a category for the variant of COC associated with ameloblastoma. The classification advocated by Hong et al.(1990) has two categories for COC associated with ameloblastoma: the ameloblastomatous cystic variant and the neoplastic variant associated with ameloblastoma (Iida et al., 2004). The former is characterized by a unicyclic structure in which the lining epithelium shows unifocal or multifocal intraluminal proliferative activity that resembles ameloblastoma and it contains isolated or clustered ghost cells and calcifications. The latter is called ameloblastoma arising from COC (ameloblastoma ex COC) and is characterized histopathologically as comprising of few or no ghost cells with calcifications in the transformed ameloblastomatous epithelial portion satisfying vicker's and gorlin criteria, while the cyst lining of the epithelium contains considerable number of ghost cells and calcifications (Nosrati and Seyedmajidi, 2009; Tajima et al., 1992).

Ameloblastic fibroma

The odontogenic tumors, such as ameloblastoma, adenomatoid odontogenic tumor (AOT), ameloblastic fibroma (AF), and ameloblastic fibro-odontoma may sometimes be associated with calcifying odontogenic cyst (COC), but their occurrence is reported to be extremely

rare. COC is known for its histologic diversity and variable clinical behaviour. The clinical significance of an association of COC with AF grasps an important place. Whether AF or COC arises first in cases of COC with AF is also still unknown. Altini and Farman believed that the development of the COC component is a secondary event within the pre-existing odontogenic tumor while Praetorius et al.(1981) defined the COC with dental hard tissues in close relation to the lining epithelium as the „odontome producing type“ and believed that the odontogenic tumor develops in the wall of the pre-existing COC. Takeda et al. (1990) investigated the histopathologic features of the satellite cysts and epithelial islands in the connective tissue wall of unilocular COC. Their results suggest that COC may arise de novo and is not a secondary phenomenon in pre-existing odontogenic tumors (Lin et al., 2004). However, the biologic mechanism causing such a unique combination is not readily apparent (Yoon et al., 2004).

Although enucleation and excision appeared to cure AF with COC, long-term follow-up data and additional cases are still needed to clarify the clinical significance of these lesions (Lin et al., 2004; Yoon et al., 2004).

Odontogenic keratocyst as a neoplasm - (keratocystic odontogenic tumor)

The term OKC was first used in 1956 by Philipsen to describe an odontogenic cyst with a keratinous epithelial lining. These cysts represent between 5 and 15% of all odontogenic cysts. Odontogenic keratocysts, like other odontogenic cysts, have been hypothesized to be developmental, arising from the dental lamina (Narasimhan et al., 2004).

The odontogenic keratocyst (OKC) is now designated by the World Health Organization (WHO) as a keratocystic odontogenic tumour (KCOT) and is defined as “a benign uni- or multicystic, intraosseous tumour of odontogenic origin, with a characteristic lining of parakeratinized stratified squamous epithelium and potential for aggressive, infiltrative behaviour.” WHO “recommends the term keratocystic odontogenic tumour as it better reflects its neoplastic nature” (Madras and Lapointe, 2008). Lesions which tend to behave aggressively and those with unusual recurrence, presence of cervical lymphadenopathy should hint the clinician to think in terms of neoplasm (Narasimhan et al., 2004).

In 1967, Toller suggested that the OKC must be regarded as a benign neoplasm rather than a conventional cyst, based on its clinical behaviour. In 1984, Ahlfors and others suggested that “if the OKC were recognized as a true, benign cystic epithelial neoplasia, the question of modified treatment schedules would be raised.” Factors that favour OKC as a neoplasm are:

1. Behaviour: As described earlier, the KCOT is locally destructive penetrating the cortical bone, extending into the surrounding soft tissue or into the maxillary sinuses. They are also prone to recurrence, with reported local recurrence rates ranging from 3 to 60% (Shear and Speight, 2007).

2. Histology: Histologically dysplastic and neoplastic transformation of the lining epithelium in OKC is an uncommon occurrence; however, studies had shown the basal layer of the KCOT budding into connective tissue and increased mitotic figures in the suprabasal layers (Barreto et al., 2000).

3. Genetics: PTCH ("patched"), a tumor suppressor gene involved in both NBCCS and sporadic KCOTs, occurs on chromosome 9q22.3-q31. PTCH is normally present in the cell membrane and forms a receptor complex with the oncogene SMO. This complex inhibits growth-signal transduction, when SHH binds to PTCH this inhibition is released and the proliferation-stimulation effects of SMO are permitted to predominate (Cohen, 1999).

Evidence has shown that the pathogenesis of NBCCS and sporadic KCOTs involves a "2-hit mechanism," with allelic loss at 9q22. The 2-hit mechanism refers to the process by which a tumour suppressor gene is inactivated. The first hit is a mutation in one allele, which, although dominantly inherited, has no phenotypic effect. The second hit refers to loss of the other allele and is known as "loss of heterozygosity" (LOH). In KCOTs, this leads to the dysregulation of the oncoproteins cyclin D1 and p53. Lench and others indicate that LOH in the 9q22.3-q31 region has been reported for many epithelial tumours, including basal cell carcinomas, squamous cell carcinomas and transitional cell carcinomas; they note that LOH is, by definition a feature of tumorigenic tissue (Madras and Lapointe, 2008, Muzio et al., 1999). Other studies that favour the aggressive character of OKC include increased expression of Ki-67, PCNA (Narasimhan et al., 2004).

Calcifying odontogenic cyst as a neoplasm

The calcifying odontogenic cyst (COC) was first reported as a separate pathologic entity by Gorlin et al in 1962. Because of its histological complexity and morphologic diversity, it is still debated whether COC is a cyst or a neoplasm. The WHO classified COC as a "benign neoplasm related to odontogenic apparatus" and defined it as "a cystic lesion in which the epithelial lining shows a well-defined basal layer of columnar cells, an overlying layer that is often many cells thick and that may resemble stellate reticulum, and masses of ghost epithelial cells that may be in the epithelial cyst lining or in the fibrous capsule" (Lin et al., 2004).

The components of other odontogenic tumours are

often observed in COC, and the most common one is odontoma. Ameloblastoma, AOT, odontoameloblastoma (OA), ameloblastic fibroma (AF), ameloblastic fibro-odontoma (AFO) and odontogenic myxofibroma (OM) have also been identified as components of COC. The possible pathogenic mechanisms would seem to be either a collision of 2 separate lesions or a transformation of one lesion to another (Yoon et al., 2004, Zeitoun et al., 1996). It is not fully understood whether the tumor or COCs that occurred secondarily, however, several investigators have suggested that proliferating odontogenic epithelial islands in COC might induce the adjacent mesenchymal tissue to develop features of other odontogenic tumors (Takeda et al., 1990).

ODONTOMA

Odontoma and dentigerous cyst

According to Shah et al. (2010), various factors are responsible for eruption delay of permanent teeth. The causes range from supernumerary teeth, neoplasms (e.g ameloblastic fibroma), hamartomatous lesions (e.g odontomas), cystic lesions (e.g dentigerous cyst). It is rare however for two pathological conditions i.e. a hamartoma and cystic lesion to occur in the same site simultaneously. According to 1992 WHO classification of odontogenic tumors, ameloblastic fibroma, odontoma and ameloblastic fibro-odontoma are considered as tumor of mixed tissue origin. In this regard, odontomas are hamartomas composed of various dental tissues enamel, dentin, cementum and sometimes pulp. They are slow growing benign tumors showing non-aggressive behaviour. They are classified as complex, when the calcified tissue present as an irregular mass composed mainly of mature tubular dentin or compound if there is superficial anatomic similarity to even rudimentary teeth. Complex odontomas are less common than compound in the ratio of 1:2. Complex odontomas tend to occur in the posterior region of jaw and compound odontomas are more common in the anterior maxilla. They may be discovered at any age; although they are commonly asymptomatic, clinical indicators of odontomas is retention of deciduous teeth, non eruption of permanent teeth sometimes pain, expansion of cortical bone, displacement of tooth, anaesthesia in the lower lip and swelling in the affected area may be present.

Clinically odontomas are either complex or compound and are classified as: (a) Intra-osseous: odontomas occur inside the bone and may erupt (erupted odontomas) into the oral cavity, (b) Extra-osseous: odontomas occurring in the soft tissue covering the tooth bearing portion of the jaws.

Odontomas presents as a well defined radio-opacity situated in bone, with a density that is greater than bone

and equal to or greater than that of tooth. It contains foci of variable density. A radiolucent halo, typically surrounded by thin sclerotic line, surrounds the radiopacity. The radiolucent zone is the connective tissue capsule of a normal tooth follicle. Hitchin suggested that odontomas are inherited through a mutant gene or interference, possibly post natal, with genetic control of tooth development. Surgical removal of odontomas is indicated in the absence of any contraindication. As a result of their odontogenic nature, including epithelial and mesenchymal tissue odontomas can develop cystic transformation into dentigerous cyst. This cyst results from the cystic degeneration of enamel organ after partial or total development of the crown, cystic transformation of the follicle associated with the unerupted tooth may also occur when its eruption is impeded by the odontoma. Enucleation of the cyst and excision of odontoma and packing the cavity open for the following reasons: a) Prevent nerve damage; (b) Decrease risk of pathological fracture; (c) Allow eruption of underlying permanent tooth.

Calcifying odontogenic cyst and odontoma

COC mostly commonly occur in association with odontoma. Buchner showed this association in 35% of his cases, Nagao et al.(1983) in 22% and Shamaskin et al.(1989) in 47% (Shah et al., 2010). Hirshberg et al. (1994) revealed 52 cases of COC associated with odontoma, and he classified it as a separate entity and suggested the term odontocalcifying odontogenic cyst.

Several possibilities are suggested regarding the pathogenesis of calcifying odontogenic cyst associated with odontoma (COCaO), (a) COC and the odontoma may represent coincidental juxtaposition (Shamaskin et al., 1989), (b) COC develops secondarily from odontogenic epithelium that participates in the formation of the odontoma (Toida et al., 1990), (c) odontoma develops secondarily from lining epithelium of the COC (Takeda et al., 1990). The cytokeratin expression in the COCaO has been studied by several authors (Fregnani et al., 2003) confirming its odontogenic origin. The neoplastic transformation of a pre-existing benign COC could happen, but is extremely uncommon (Alvarez et al., 2005).

Ghost cell odontogenic carcinoma

Ghost cell odontogenic carcinoma is a rare malignant tumor. It is believed that ghost cell odontogenic carcinoma may develop de novo or arise from a previously existed COC, calcifying cystic odontogenic tumor (CCOT) or from dentinogenic ghost cell tumor (DGCT) (Ledesma-Montes et al., 2008). They usually present as long-term persistent swelling of maxilla followed by the rapid growth

or multiple recurrences of COC (Lu et al., 1999) or they may develop de novo without history of COC (Nazaretian et al., 2007).

The diagnosis of ghost cell odontogenic carcinoma is based on the identification of a malignant epithelial tumor containing some features of CCOT or DGCT. The distinction from the benign entity was based on malignant cellular changes such as higher mitotic activity, higher number of cells expressing Ki-67 or proliferative cell nuclear antigen, over expression of p53 and extensive expression of matrix metalloproteinase-9 in stromal cells (Motosugi et al., 2009). Although a recent report indicated that most cases of the COC have a benign course, 3 of 122 cases of COC were malignant (that is, ghost cell odontogenic carcinoma); pathologists should be aware of this rare entity (Takeda et al., 1990).

Squamous odontogenic tumor

Squamous odontogenic tumor (SOT) is defined as a locally infiltrating neoplasm consisting of islands of well-differentiated squamous epithelium in a fibrous stroma. The SOT must be differentiated from an identical pathologic finding that occurs in odontogenic cysts, which Wright first reported as "squamous odontogenic tumor-like proliferations (SOTLP)." It is important to distinguish between these 2 pathologic conditions, in part because of differences in their biologic behavior. Of major importance is the fact that the histopathologic features of SOTLPs in odontogenic cysts bear a close resemblance to not only SOT but to acanthomatous ameloblastoma, desmoplastic ameloblastoma, and well-differentiated squamous cell carcinoma. Thus, misinterpretation of the microscopic features of the SOTLPs can result in significant errors in treatment. Opinions on the origin of the SOTLP epithelium in odontogenic cysts are varied. Shear and Speight (2007) theorized that the SOTLP epithelium in radicular cysts originates from the rests of Malassez. Unal et al.(1987) considered the SOT-like epithelial islands to be "hamartoid"; however, others have disputed this theory because of the SOTLP's proposed origin from a cystic surface. Philipsen et al. (1992) believe the SOTLPs are a result of a reactive, inflammatory hyperplasia of the epithelial cyst lining. Odell and Morgan (1990) favor a budding type of hyperplasia of the lining epithelium of radicular cysts as response to subsiding inflammation because it usually occurs in areas without inflammation. The SOTLP epithelium in radicular cysts represents a pseudoneoplastic reactive proliferation that mimics the benign, but sometimes locally aggressive SOT. The prevalence for SOTLP in radicular cysts is 3.4%, on the basis of a review of 1241 radicular cysts. The SOTLPs in radicular cysts have a marked predilection for maxillary incisor teeth. The findings of Parmar et al. (2011) support an

origin of the SOTLP to be from the epithelial lining of the cyst. The development of the SOTLPs in radicular cysts is most likely not dependent on the presence of inflammation. The SOTLPs in radicular cysts do not represent an early expression of neoplastic transformation. It depicts that the biologic behaviour of a radicular cyst with SOTLP is innocuous and shows no apparent potential for recurrence (Rinku et al., 2011).

Squamous odontogenic tumor-like proliferations can also be seen in association with other odontogenic cysts.

CONCLUSION

Differential diagnosis of odontogenic cyst and malignant tumor arising in the cyst may be difficult due to the nonspecific clinical and radiological presentation. The definitive diagnosis must be made by histological examination and appropriate histochemical analysis.

REFERENCES

- Agaram N, Bobby MC, Leon B, Deren L, Dalal A, Patrica S, Sydney F, Jennifer LH (2004). Neoplastic Status of Odontogenic Keratocysts, *Arch. Pathol. Lab. Med.*, 128: 313-317.
- Aggarwal P, Saxena S (2011) Aggressive growth and neoplastic potential of dentigerous cysts. With particular reference to central mucoepidermoid carcinoma. *Br. J. Oral Maxillofac. Surg.*, 11(16).
- Anjan S, Madhumati S, Shouvik C (2010). Complex Odontoma associated with Dentigerous cyst. *Int. J. Clin. Dent. Sci.*, 1: 89-92.
- August M, Faquin WC, Troulis MJ, Kaban LB (2003) Dedifferentiation of odontogenic keratocyst epithelium after cyst decompression. *J. Oral. Maxillofac. Surg.*, 61(6): 678– 83.
- Barreto DC, Gomez RS, Bale AE, Boson WL, De Marco L (2000). PTCH gene mutations in odontogenic keratocysts. *J. Dent. Res.*, 79(6): 1418–22.
- Bouquot JE, Gnepp DR, Dardick I, Hietanen JHP (2000). Intraosseous salivary tissue: jawbone examples of choristomas, hamartomas, embryonic rests, and inflammatory entrapment— another histogenetic source for intraosseous adenocarcinoma. *Oral. Surg. Oral. Med. Oral. Pathol. Oral. Radiol. Endod.*, 90(2): 205–12.
- Bradley N, Thomas DM, Antoniadis K, Anavi Y (1988). Squamous cell carcinoma arising in an odontogenic cyst. *Int. J. Oral. Maxillofac. Surg.*, 17: 260-263.
- Brookstone MS, Huvos AG (1992). Central salivary gland tumors of the maxilla and mandible: a clinicopathologic study of 11 cases with an analysis of the literature. *J. Oral. Maxillofac. Surg.*, 50(3): 229–36.
- Cheng-Chung Lin, Chung-Ho Chen, Li-Min Lin, Yuk-Kwan Chen, John M. Wright, Harvey P. Kessler, Yi-Shing Lisa Cheng, and Edward Ellis (2004). Calcifying odontogenic cyst with ameloblastic fibroma: Report of three cases. *Oral. Surg. Oral. Med. Oral. Pathol. Oral. Radiol. Endod.*, 98:451-60.
- Cohen MM (1999). Nevoid basal cell carcinoma syndrome: molecular biology and new hypotheses. *Int. J. Oral Maxillofac. Surg.*, 28(3): 216–23.
- Daley TD, Wysocki GP (1995). The small dentigerous cyst. A diagnostic dilemma. *Oral. Surg. Oral. Med. Oral. Pathol. Oral. Radiol. Endod.*, 79(1): 77 – 81.
- Dunsche A, Babendererde O, Lüttges J, Springer IN (2003). Dentigerous cyst versus unicystic ameloblastoma-differential diagnosis in routine histology. *J. Oral. Pathol. Med.*, 32(8): 486-91.
- Fabio RP, Sow-Yeh C, Danyel Elias da CP, Oslei Paes de A, Luiz PK (2004). Cytokeratin expression in central mucoepidermoid carcinoma and glandular odontogenic cyst. *Oral Oncol.*, 40: 545–55.
- Foley WL, Terry BC, Jacoway JR (1991). Malignant transformation of an odontogenic keratocyst: report of a case. *J. Oral. Maxillofac. Surg.*, 49(7): 768– 71.
- Fregnani E, Pires F, Quezada R, Shih leM, Vargas PA, de Almeida OP (2003). Calcifying odontogenic cyst: clinicopathological features and immunohistochemical profile of 10 cases. *J. Oral Pathol. Med.*, 32: 163-70.
- Hirshberg A, Kaplan I, Buchner A (1994). Calcifying odontogenic cyst associated with odontoma: A possible separate entity (odontocalcifying odontogenic cyst). *J. Oral Maxillofac. Surg.*, 52: 555-8.
- Iida S, Uedal T, Aikawa T, Kishino M, Okura M, Kogol M (2004). Ameloblastomatous calcifying odontogenic cyst in the mandible. *Dentomaxillofac. Radiol.*, 33: 409–412.
- Jean EB, Robert K, Carla P (1997). Glandular Odontogenic Cyst: A Case Report and Review of the Literature. *Col. Dent. Rev.*, 2:1.
- Johnson LM, Sapp JP, McIntire DN (1994). Squamous cell carcinoma arising in a dentigerous cyst. *J. Oral Maxillofac. Surg.*, 52: 987-990.
- Kamran N, Maryam S (2009). Ameloblastomatous Calcifying Odontogenic Cyst: A Case Report of a Rare Histologic Variant. *Arch Iranian Med.*, 12(4): 417- 420
- Keszler A, Piloni MJ (2002). Malignant transformation in odontogenic keratocysts- Case report. *Med. Oral*, 7(5): 331 –5.
- Kim J, Ellis GL (1993) Dental follicular tissue: misinterpretation as odontogenic tumors. *J. Oral Maxillofac. Surg.*, 51(7): 762–7.
- Ledesma-Montes C, Gorlin RJ, Shear M (2008). International collaborative study on ghost cell odontogenic tumours: calcifying cystic odontogenic tumour, dentinogenic ghost cell tumour and ghost cell odontogenic carcinoma, *J. Oral. Pathol. Med.*, 37:302-8.
- Lee J. Slater (2004). Odontogenic malignancies. *Oral Maxillofac. Surg. Clin. N. Amer.*, 16: 409–424.
- Lo Muzio L, Staibano S, Pannone G, Bucci P, Nocini PF, Bucci E (1999). Expression of cell cycle and apoptosis-related proteins in sporadic odontogenic keratocysts and odontogenic keratocysts associated with the nevoid basal cell carcinoma syndrome. *J. Dent. Res.*, 78(7): 1345–53.
- Lu Y, Mock D, Takata T, Jordan RC (1999). Odontogenic ghost cell carcinoma: report of four new cases and review of the literature. *J. Oral. Pathol. Med.*, 28:323-9.
- Madras J, Lapointe H (2008). Keratocystic Odontogenic Tumour: Reclassification of the Odontogenic Keratocyst from Cyst to Tumour. *JCDA*, 74(2):165
- Makowski GJ, McGuff S, Van Sickels JE (2001). Squamous cell carcinoma in a maxillary odontogenic keratocyst. *J. Oral Maxillofac. Surg.*, 59(1):76– 80.
- Mark RD, Bret MR, Cesare C, Thomas DD (2008). Pericoronal radiolucency in the posterior mandible. *Oral. Surg. Oral. Med. Oral. Pathol. Oral. Radiol. Endod.*, 105: 139-43.
- Miguel B, David W, Lili M, Robin C (2005). Adenomatoid odontogenic tumor mimicking a dentigerous cyst. *Int. J. Pediatr. Otorhinolaryngol.*, 69: 1685-1688.
- Muglali M, Sumer AP (2008). Squamous Cell Carcinoma Arising in a Residual Cyst: A Case Report, *J. Contemp Dent. Pract.*, (9)6: 115-121.
- Nazaretian SP, Schenberg ME, Simpson I, Slootweg PJ (2007). Ghost cell odontogenic carcinoma. *Int. J. Oral Maxillofac. Surg.*, 36: 455-8.
- Philipsen HP, Reichart PA (1996) The adenomatoid odontogenic tumour: ultrastructure of tumour cells and non-calcified amorphous masses. *J. Oral Pathol. Med.*, 25:491-6.
- Philipsen HP, Reichart PA, Zhang KH, Nikai H, Yu QX (1991). Adenomatoid odontogenic tumour: biological profile based on 499 cases. *J. Oral Pathol. Med.*, 20: 149-58.
- Philipsen HP, Thanapen S, Reichart PA (2002). Adenomatoid odontogenic tumor mimicking a periapical (radicular) cyst: A case report. *Oral Surg. Oral. Med. Oral. Pathol. Oral. Radiol. Endod.*, 94: 246-8.
- Prabhu S, Rekha K, Kumar GS (2011). Glandular odontogenic cyst mimicking central mucoepidermoid carcinoma. *J. Oral Maxillofac. Pathol.*, 14:12-5.
- Parmar RM, Brannon RB, Fowler CB (2011). Squamous Odontogenic Tumor-like Proliferations in Radicular Cysts: A Clinicopathologic Study of Forty-two Cases. *J. Endod.*, 37:623– 626.
- Shamaskin RG, Svirsky JA, Kangars GE (1989). Intraosseous and extraosseous calcifying odontogenic cyst, *J. Oral Maxillofac. Surg.*, 47:

- 562-5.
- Shear M, Speight P (2007). *Cysts of the oral and maxillofacial region*. Fourth edition.
- Silvia GA, Francisco MJ, Francisco JTG, Francisco JAV, Clara SF (2005). Calcifying odontogenic cyst associated with complex odontoma: Case report and review of the literature. *Med. Oral Pathol. Oral Cir. Bucal*, 10: 243-7.
- Stoelinga PJW, Bronkhorst FB (1988). The incidence, multiple presentation and recurrence of aggressive cysts of the jaws. *J. Cranio-Max-Fac Surg.*, 16: 184-95.
- Takeda Y, Suzuki A, Yamamoto H (1990). Histopathologic study of epithelial components in the connective tissue wall of unilocular type of calcifying odontogenic cyst. *J. Oral Pathol. Med.*, 19: 108-13.
- Toida M, Ishimaru JI, Tatematsu N (1990). Calcifying odontogenic cyst associated with compound odontoma. *J. Oral Maxillofac. Surg.*, 48: 77-81.
- Utaroh M, Ikuko O, Tetsuya Y, Takahiro A, Masashi S, Shin-ichi M, Masanori Y, Takaki S, Yoshihiko S, Michio S (2009). Ghost cell odontogenic carcinoma arising in calcifying odontogenic cyst. *Ann. Diagn. Pathol.*, 13:394-397.
- van der Wal KG, de Visscher JG, Eggink HF (1993). Squamous cell carcinoma arising in a residual cyst. A case report. *Int. J. Oral Maxillofac. Surg.*, 22:350-352.
- Waldron CA, Koh ML (1990). Central mucoepidermoid carcinoma of the jaws: report of four cases with analysis of the literature and discussion of the relationship to mucoepidermoid, sialodontogenic, and glandular odontogenic cysts. *J. Oral Maxillofac. Surg.*, 48(8): 871-7.
- Yasuoka T, Yonemoto K, Kato Y, Tatematsu N (2000). Squamous cell carcinoma arising in a dentigerous cyst. *J. Oral Maxillofac. Surg.*, 58(8): 900-5.
- Yoon JH, Kim HJ, Yook JI, Cha IH, Ellis GL, Kim J (2004). Hybrid odontogenic tumour of calcifying odontogenic cyst and ameloblastic fibroma. *Oral. Surg. Oral. Med. Oral. Pathol. Oral. Radiol. Endod.*, 98: 80-4.
- Yoshifumi T, Satoshi Y, Eiichi S, Yoshiro Y, Nobuo U (1992). Ameloblastoma arising in calcifying odontogenic cyst. *Oral Surg. Oral Med. Oral Pathol.*, 74: 776-79.
- Zeitoun IM, Dhanrajani PJ, Mosadomi HA (1996). Adenomatoid odontogenic tumour arising in a calcifying odontogenic cyst. *J. Oral Maxillofac. Surg.*, 54: 634-7.