Odontogenic keratocysts/keratocystic odontogenic tumours: biological characteristics, clinical manifestation and treatment

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Background. Odontogenic keratocysts (OKCs) now reclassified as Keratocystic odontogenic tumours (KCOTs) are a clinical entity with a characteristic microscopic picture, kinetic growth and biological behaviour. They arise from the proliferation of the epithelial dental lamina in both maxilla and mandible and occur in patients of all ages. 70-80% of keratocysts are found in the mandible commonly in the angle between the jaw and mandibular branch and maxillary region of the third molar. The cysts are long latent, often symptomless and may attain remarkable dimensions without significant deformation of the jaw bones. They are often found during routine dental X-ray examination. Compared to other types of jaw cyst, odontogenic cysts have a striking tendency to rapid growth and re-occurrence.

Aims. This review focuses on the biological characteristics, clinical behaviour and treatment of KCOTs.

Methods. The databases searched were the PubMed interface of MEDLINE and LILACS.

Results and conclusions. Odontogenic keratinocysts are not currently a diagnostic problem. Orthopantomograms which are today ordinary tools of dental investigation enable diagnosis of clinically asymptomatic cystic lesions. The problem remains the optimal therapeutic approach to reduce the still high likelihood of postoperative recurrence. There is no complete consensus on the ideal operating procedure but cystectomy with delayed extirpation is favoured. An open question also remains the timeliness of screening for postoperative recurrences. Given that the first clinical manifestation of Nevoid Basal Cell Carcinoma Syndrome (NBCCS) may be lesions of this type, routine histopathological classification supplemented by analysis of immunophenotype should be done. Patients with proven sporadic and especially syndromic OKC should be long term screened. In patients with NBCC preventive X ray examination is recommended only once a year.

Key words: odontogenic keratocysts, keratocystic odontogenic tumours, biological characteristics, diagnosis, treatment, nevoid basal cell carcinoma syndrome

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INTRODUCTION

Cysts of the jaw are a common clinicopathological finding. From the viewpoint of assumed origins, they can be divided into odontogenic (lining of the cystic sac arising from epithelial remnants of embryonic tooth base) and non-odontogenic (the cyst lining is of another origin). The basis of this classification was studies on the distribution of cytokeratins in the epithelium of the cyst lining.

Keratocystic odontogenic tumours (KCOTs) are an independent clinical entity with a typical microscopic picture, clinical growth and biological behaviour. They arise from proliferation of the epithelial dental lamina of the upper and lower jaw. In most cases they are benign lesions with aggressive behaviour and a significant tendency to recurrence following surgical removal. They occur in patients of all ages though diagnosis is most common in the second and third decades of life. 70-80% keratocysts are found in the lower jaw most commonly in the angle between jaw and mandibular branch and in the maxilla in the area of the third molar. They differ from radicular and follicular cysts identifiable by the typical alveolar bulge caused by expansive growth in that the developing odontogenic keratocysts are long covert, often without clinical symptoms and discovered during incidental X-ray examination.

Growth is chiefly in the anteroposterior dimension and the lesions may attain remarkable size without significantly deforming the jaw skeleton. Multiple lesions of this kind are rarer but not unexceptional. The particular tendency to rapid growth is due to higher activity of the epithelial cells of the cyst lining stimulating osteolytic activity of prostaglandin substances in the cell population of the cyst lining and higher accumulation of hyperkeratotic scales in the lumen of the cyst with resulting greater difference in hydrostatic pressure.
HIStOPATHOLOGY

The histopathological picture of OKCs/KCOTs is a characteristic thin epithelial layer, composed of from 8 to 10 cell layers. The basal layer shows palisade organised cells with a uniform nucleus. In the direction of the cyst lumen there is parakeratosis with a focal zone created of orthokeratin. Sometimes there is invasion of the basal cell layer into the region of surrounding connective tissue and the formation of satellite micro-cysts. The fibrous walls of the cells may be relative thin and usually without inflammatory cell infiltrates. In addition to the parakeratotic type of OKC also described is an orthokeratinised type with a prominent granular layer lying immediately under the thin surface layer. Recently, several new variants of OKC have been described, for example the solid variant, and the peripheral OKC (ref.2). The frequent occurrence of microscopic satellite cysts connected to fragile relatively thin vacuoles is considered the main cause of the high tendency to postsurgical recurrence (10-60%). The tendency to recurrence is particularly high in patients with multiple lesions.

In the past, published studies aimed to make accurate typization of these lesions with the help of histochemistry, immunohistochemistry and molecular biology techniques. Relatively frequent was focus on the significance of suppressor gene p53 expression3. The results showed that immunohistochemically detected overexpression of p53 was caused more by overproduction or increased stabilization of the protein than gene amplification. The finding of overexpressed p53 and cyclin D1 in OKC in NBCCS is probably the expression of mutated phenotype. This led to the hypothesis if the aggressive clinical behaviour of these lesions could not be connected to dysregulation of the expression of cyclin D1 and/or p53 which are involved in cell cycle regulation.

KCOTs are unique due to their histological features, clinical characteristics and biological behaviour among odontogenic cysts15-16. There are several signs that point to the tumour character of these lesions. There is also a risk for the malignant transformation of OKCs with clinical manifestations of spinocellular carcinoma17,18. Several authors have described the abnormal expression of tumour suppressor genes and oncogenes in the epithelium of the cysts but these studies only sporadically dealt with apoptosis and the mechanisms regulating proliferation13-15. In general, he suggested that several cytokeratins but above all cytokeratin 10, could be a valuable marker for differentiating odontogenic cysts. Several recent studies have confirmed the significance of p53, MDM2 and some other markers for histopathological diagnosis19,20. The aim of some studies was examination of the components of the basal membrane18 and immunocompetent CD1a positive cells in the cystic epithelium19. It was found that proteins in the basal membrane – fibronectin and collagen I and III, are expressed in OKC/KCOTs in non-fibrillary form and that lamina and collagen IV were stained discontinuously. These results show an assumed defect in the connective tissue forming the envelope of the OKC, and in a greater number of antigens present as Langerhans cells in well-differentiated OKCs. However, with the exception of cytokeratin 10, none of these studies has addressed the use of these findings for histopathologic diagnosis.

Much greater hope has been generated by several studies on the expression of proteins involved in cell cycle regulation and apoptosis. Some authors analysed the expression of proliferating antigens such as PCNA and Ki-67 (ref.17,20-24). Lo Muzio et al.21 studied expression of PCNA in syndromic and sporadic OKCs. They found no significant difference between the two types for either PCNA or Bcl-2. On the other hand, they found increased expression of p53 and cyclin D1 in syndromic OKCs. Kolar et al.25 confirmed these findings for PCNA. These authors discovered that there was no significant difference in p53 expression but bcl-2 expression was significantly higher in syndromic OKCs. These different conclusions may be due to the greater sensitivity of the detection system used (Envision Dako Cytomation) or more specific antibody against Bcl-2 (clone 100 Biogenex). The same authors described as a new finding, significantly higher expression of endogenic inhibitor cyclin dependent kinase p27Kipl and oncogene c-erbB-2 in basal cell syndromic OKC and lower expression of the proliferative antigen Ki-67. The role of the aberrant expression of p27Kipl protein in cancerogenesis of the breast has been well-documented. The results of Kolar et al.26 correspond more closely with those of Tosios et al.17 who described higher expression of Bcl-2 and lower expression of Ki-67 and p53 in glandular odontogenic cysts compared to follicular cysts. Kim et al.27 showed higher proliferative potential on the basis of the expression of Ki-27 and higher grade of apoptosis in OKCs/KCOTs than in follicular cysts. A direct relation between proliferative activity and inflammation in OKC was reported by De Paula et al.23 and Nickolaychuk et al.28. Wagner et al.29 focused on p53 expression in OKC. Their promising results however were never later confirmed. Carvalhais et al.24 described only higher positivity for protein MDM2 (a p53 protein with regulatory effects) while Lo Muzio et al.21 showed only p53 expression involved in syndromic OKC. It is possible that syndromic OKC has a different phenotype to sporadic OKC which is characterised by higher expression of Bcl-2, p27Kipl and C-erbB-2 (in non-specific odontogenic cysts also p53), lower proliferation in basal cell layers and much higher

BIOLoGICAL MARKERS OF OKCs/KCOTs

A range of studies is currently focused on identifying markers that could predict the biological behaviour of these lesions and clarify the mechanisms leading to frequent postoperative recurrence. The monoclonal and polyclonal antibodies now available to accurately define the peptide character of antigens make this technically possible.

The significance of immunohistochemical analysis of epithelial cell markers was handled extensively by Sheer13-15. The aim of some studies was examination of the components of the basal membrane18 and immunocompetent CD1a positive cells in the cystic epithelium19. It was found that proteins in the basal membrane – fibronectin and collagen I and III, are expressed in OKC/KCOTs in non-fibrillary form and that lamina and collagen IV were stained discontinuously. These results show an assumed defect in the connective tissue forming the envelope of the OKC, and in a greater number of antigens present as Langerhans cells in well-differentiated OKCs. However, with the exception of cytokeratin 10, none of these studies has addressed the use of these findings for histopathologic diagnosis.
proliferation in suprabasal layers. Sporadic OKC shows only some of these characteristics, which may be used to advantage for more precise differential diagnosis between the two types.35

**CLINICAL MANIFESTATION AND TREATMENT OF OKSs/KCOTs**

As mentioned, OKCs/KCOTs are characterised by high tendency to postoperative recurrence (30-60%) (ref.35). The origins of this may be incomplete removal of the vacuole, or satellite microscopic cysts in the connective tissue wall of the OKC.

In connection with clinical manifestations of Nevoid Basal Cell Carcinoma Syndrome (NBCCS), some authors distinguish between keratocysts arising sporadically and so-called syndromic keratocysts25,28-30. For “syndromic keratocysts” bound to NBCCS characteristic is a large number of microscopic satellite cysts with a high tendency to recurrence and the presence of solid islets of epithelial proliferation in the wall, with high mitotic activity of the lining. OKCs as one of the chief diagnostic criteria for NBCCS are very often the first signs of its clinical manifestation30. The follow-up of these patients is essential not only with a view to the risk of malignant changes after post surgical recurrences but also increased incidence of basal cell carcinoma which appears between puberty and 35 years of age usually on the face, back and chest. The tumour changes which may occur in 3-4% of patients with NBCCS, are, as for basal cell carcinoma, astrocytoma, ovarian cancer and medulloblastoma, deletion of chromosome 9q22.1-31 connected to loss of heterozygosity of the gene on the homologous chromosome which means that the gene probably functions as a tumour suppressor. From immunohistochemical analyses published in recent years it increasingly appears that syndromic OKC is more a benign cystic tumor than developmental abnormality.13,15,30,11

Lindeboom et al.34 reported on the multiple occurrences of OKCs in connection with the oral, facial and digital syndrome (OFDS) which was described first in 1954. This syndrome includes the typical combination of cleft lip and palate with malformations and anomalies of tongue and finger shape (syndactyly, polydactyly, brachydactyly, and clinodactyly). Pazdera et al.35 and Wang et al.36 described multiple syndromic OKC of the jaw bone in two relatives of the same sex with genetic attributes of NBCCS.

Blanas et al.7 described treatment issues. Given the average high % of post surgical recurrence and complications of healing, the usual operational methods are modified in some way.3,37,41. For bone cavity after removal of cystic lining, the strongly corrosive fixation Carnoys solution (a mixture of alcohol, acetic acid and chloroform) which destroys the microscopic satellite cysts in the walls of the bone defect, is applied. An interesting comparison of modified operational method is the work of Chinese authors41 who described their experience with the treatment of a large sample of 489 OKCs over a period of 37 years. After simple extirpation of the cyst, the postoperative recurrence was 18%, after modified extirpation using Carnoys solution, 6%. In 52 patients treated with marsupialisation and subsequent extirpation, no recurrence was experienced and the same in 52 patients treated with extirpation accompanied by partial resection of the lower jaw. Given the biological characteristics of some types of keratinised cysts the risk of postoperative recurrences becoming malignant cannot be underestimated. Primary intraosseous carcinomas occur especially in the lower jaw and are not as rare as they might seem. Theoretically they can arise from the remnant of the odontogenic embryonic epithelium, or malignant transformation of the lining of the odontogenic cyst or tumour.40,42,43 We ourselves recently encountered a recurrence of a malignant nature in one OKC/KCOT patient. The tumor grew aggressively, metastasizing into regional lymph nodes. There is also the possibility transformation of the OKC into the cystic form of ameloblastoma.43

Smooth healing of the defects after extirpation of large jaw cysts is frequently complicated by infection and the disintegration of clot with subsequent dehiscence of the surgical wound.

The increased frequency of post operative complications is compounded by the fact that for these large cysts we cannot usually suture the wound above the hard bone ground. Long-term treatment of lesions of secondary healing is unpleasant for the patient and time-consuming for the physician. Under these circumstances, it is natural to seek the best and most usable augmentation materials44,45. Requirements for the augmentation material properties were summarized by Sailer1. The ideal material should stimulate ossification of the defect, be biocompatible, X-ray contrastable, easily accessible and readily applicable. The augment on the other hand, should not cause local inflammatory reactions from the surrounding fibrous connective tissue, trigger an immune response, initiating malignant transformation, create toxic by-products, have electrolytic or galvanic effects or be a source of infection.

For augmenting the bone defect of the jaw bone, a whole range of possibilities exists. With biological material preferred is material that autologous or homologous to bone, lyophilized cartilage chips or biologically inert materials on the basis of hydroxyapatite, tricalcium phosphate or glass ionomer1.

From a rational point of view, it seems advantageous to fill the defect with autogenic bone graft. The best sampling points for compensation for defects of the facial skeleton are considered the skull area, ribs and iliac crest, in the lower jaw the chin area or mandibular angle. Autogenic graft for augmentation is performed in a single surgical operation. Before application to the defect, the bone graft must be processed using a bone mill to grind or crush the bone. This is expensive and prolonged. A pre-requisite is to undertake graft sampling in surgery under general anaesthesia as taking place after the surgery is painful. Another possibility is to use for augmentation of the bone defect, homologous lyophilised ground or crushed compact or spongy bone, or cartilage chips. Material obtained and processed under strict sanitary
safeguards, and radiation sterilized can be ordered in the required amount from the tissue bank and long-term storage at room temperature is possible. Crushed bone which is rehydrated before use in antibiotic solution provides flexibility of use and reduces the chance of inflammatory complications of healing. Among the spectrum of antimicrobials, metronidazole and tetracyclins suitably complement each other.

Tetracycline acts as an important inhibitor of collagenase. This avoids single, rapid resorption of homologous material but rather its gradual replacement by autologous newly formed bone. Tetracycline inhibits the oxidative activity of latent procollagenase and has anti-inflammatory properties, which underscores its role in the reparative phase of healing the defect.

Experience with augmenting postoperative bone defects of jaw bone was published by Pazdera et al. and Zboril et al. For augmentation of bone defects in 75 patients operated for large odontogenic cysts lyophilised, ground homologous spongy bone, sterilised in radiation and delivered to a tissue bank, was used. Before use, it was rehydrated in solution using tetracyclins and metronidazole, just before applying the material mixed with the venous blood of the patient. Compared with a control group of 50 patients treated with ordinary methods (without postoperative augmentation of residual bone cavity), it showed fewer complications of healing, lower tendency to postoperative recurrence and accelerated ossification of bone defect.

In practice used today is a whole range of biologically inert materials on the basis of tricalcium phosphate, synthetic or biological hydroxypatite or glass ionomere. These materials have an osseointductive potential. However the above mentioned criteria are only partially met. Their use is limited by the anatomy at the application site: it cannot generally be used in the alveolar ridge.

In the case when the cyst is diagnosed at the stage when due to size it markedly weakens the skeleton in the lower jaw, marsupialisation with drainage to oral cavity (fenestration) and delayed extirpation is recommended. The vacuole is totally removed after a waiting period of 4 - 6 months, when the size of the cyst is usually reduced and surrounding skeleton is in contrast amplified. Some surgeons try this method before cystectomy. If there is decompression of the internal cyst vacuole, marsupialisation may be the cause of changed immunohistochemical and biological properties of the lesion in the direction of lower aggressive growth and less tendency to postoperative recurrence.

From a clinical perspective, the complications of healing a big postoperative cystic defect (prolonged and often incomplete ossification and in keratinized lesions relatively high percentage of postoperative recurrence with determined risk of malignant changes) remain a problem. In this connection, postoperative check-up and long-term, continuous evaluation of treatment results are important. The quality of classic X-ray is influenced by a range of factors (type of projection, length of exposure, quality of film). For this reason the results of routine dental X-ray need not have always be optimal. Use of modern modification of classic X-ray (digitalisation) and/or spiral CT (that is in patients with demonstrably higher risk of postoperative recurrence) is essential. For the on-going process of ossification it is possible to use multiplane CT reconstruction which makes possible construction of cross sections in the lower jaw, perpendicular to its long axis. For economic reasons detailed investigation for each patient is not possible.

Ondontogenic keratocystic tumours are not currently a diagnostic problem. Orthopantomograms which are today ordinary tools of dental investigation, make possible the diagnosis of clinically asymptomatic cystic lesions. The problem remains the optimal therapeutic approach to reduce to a minimum the still high likelihood of postoperative recurrence. There is no complete consensus on the ideal operating procedure even today but marsupialisation with delayed extirpation seems to be favoured. An open question also remains the timeliness of screening for postoperative recurrences. In this regard, in patients with NBCC it is recommended that follow-up X ray is performed only once a year.

CONCLUSIONS

Clinical and histopathological work should involve paying attention to the increase in odontogenic cysts. Given that the first clinical manifestation of NBCCS may be really lesions of this type, routine histopathological classification supplemented by analysis of immunophenotype should be done. Patients with proven sporadic and especially syndromic OKC/KCOTs should be long term screened.

CONFLICT OF INTEREST STATEMENT

Author’s conflict of interest disclosure: The authors stated that there are no conflicts of interest regarding the publication of this article.

REFERENCES