The Keratocystic Odontogenic Tumor

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Summary and conclusions

Cyclooxygenase-2 (COX-2) levels are increased in various tumors, particularly those involving the esophagus, stomach, breast, pancreas, lung, colon, skin, urinary bladder, prostate and head and neck. The tumorigenic mechanisms of COX-2 overexpression still remain poorly understood and may include mechanisms that act at different stages of the disease. The literature shows increasing evidence that overexpression of COX-2 plays an important role in tumor growth and spread of tumors by interfering with different biological processes such as cell proliferation, cell adhesion, immune surveillance, apoptosis, and angiogenesis[1,2,3,4,5,6] . The expression of COX-2 might shed some light over the physiopathology and clinical behaviour of tumors of the head and neck, including benign odontogenic neoplasms of the jaws with an aggressive behaviour, such as keratocystic odontogenic tumors (KCOTs).

In the classification of Head and Neck Tumors published in 2005 by the World Health Organization (WHO), the previously designated “parakeratinized odontogenic keratocyst” has been reclassified as a benign intraosseous neoplasm, naming it “KeratoCystic Odontogenic Tumor” (KCOT), due, among other things, to its sometimes aggressive behaviour leading to high recurrence rates. Cystic lesions lined by orthokeratinizing epithelium were excluded by the WHO from the diagnosis of KCOT. This variant is now known as an orthokeratinized odontogenic cyst[7].

The recurrence rate after conservative surgical treatment, without adjunctive treatment, of the KCOT has been studied in a total number of 68 patients from the Department of Oral and Maxillofacial Surgery/Pathology of the Vrije Universiteit medical center (VUmc)/ ACTA, previously untreated and fulfilling the histopathological criteria provided by the 2005 WHO classification. The study period lasted from 1975 to 2009. Treatment consisted of either enucleation or marsupialization; the mean follow-up period was 65 months. No involved or adjacent teeth were removed, except for wisdom teeth and badly decayed teeth. After enucleation, the recurrence rate was 20.7% in a mean follow-up period of 46 months, while 40% of the marsupialized KCOTs recurred in a mean follow-up period of 58 months. In none of the patients permanent loss of nerve function has been observed.

Due to the recurrence rate observed in the present study, and in view of the potential benefit of adjunctive treatment in KCOT, particularly with regard to the use of Carnoy's solution, we performed a review of the various treatment modalities, ranging from simple enucleation to radical surgery. As it was also confirmed in a recent Cochrane study[8], no scientific evidence was found for the adjunctive use of Carnoy's solution with regard to the risk of recurrence. Furthermore, no prognostic factors based on clinicopathologic and immunohistochemical findings for determining the potential for recurrence of KCOT are available yet.

A review of the histopathological features and biological behaviour of this recognized aggressive pathological entity of the jaws and a contemporary outline of the molecular (growth factors, p53, PCNA and Ki-67, bcl-2) and genetic (PTCH, SHH) alterations associated with this odontogenic neoplasm has provided a thorough understanding of the physiopathological mechanisms involved in the development of this neoplasm of the jaws. There are, indeed, significant differences on the molecular level between KCOT and other odontogenic cystic lesions, suggestive of a different biological behaviour[7,9].

The current knowledge of the overall role known to be played by COX-2 in tumorigenesis suggest that COX-2 may be an important marker involved in the biological behaviour of the KCOT. Therefore, we performed a study to assess the expression of COX-2 in 116 specimens of KCOTs retrieved from the files of the Department of Oral and Maxillofacial Surgery/Pathology of the Vumc/ACTA. Mild to strong expression of COX-2 was observed in 83 (71,6%) cases, 34 (29,3%) of which were mildly positive and 49 (42,2%) were strongly positive. COX-2 stain was detected mainly in the epithelial lining. The expression of COX-2 in KCOTs and the current knowledge of the role played by COX-2 in tumorigenesis further strengthen the concept that the KCOT should be regarded as a neoplasm.

Although COX-2 has rarely been used to assess the biological activity of the KCOT, our comparative results involving p53, Ki-67 and COX-2 found no statistically relevant difference between the molecular expression of these markers.

We have also carried out a study in 10 dentigerous cysts to assess the expression of COX-2 and found a positive expression of COX-2 in 6 out of the 10 dentigerous cysts. These results - not published - substantiate the hypothesis that SHH may in fact be an instigating factor behind developmental cysts, with concomitant aberrant expression of molecular markers being the

natural consequence not of genetic changes but rather of an amplified physiological process, thus leading to expression of COX-2 in developmental cysts, such as dentigerous cysts.

In fact, Zhang et al have recently reported immunoreactivity for SHH, PTCH, SMO, and GLI1 in the epithelial cytoplasm of dentigerous and glandular odontogenic cysts[10]. Pavelić et al, have also reported evidence of PTCH expression in dentigerous cyst lining, with loss of heterozygosity (LOH) for the D9S287 marker and/or D9S180 marker in about 50% of dentigerous cysts, substantiating a more direct argument for PTCH involvement in cystic growth[11]. On the other hand, Barreto et al found no correlation between the immunoreactivity of PTCH in the superficial epithelial layers of odontogenic cysts and an actual mutation of the PTCH as assessed by direct sequencing[12]. Moreover, both p53 and Ki-67 have also been previously reported to be overexpressed in developmental cysts such as dentigerous cysts[9]. Therefore, despite the important role played in the molecular network responsible for odontogenic tumorigenesis, SHH also plays a relevant role in odontogenesis, which may support Pavelić's hypothesis that the malfunctioning pathway might be the cause of either DC or KCOT growth[11]. However, these results could explain why the cases reporting carcinomatous changes in the epithelium of odontogenic cysts/tumors involve mainly KCOTs and dentigerous cyst[13-21].

The multitude of markers known to be overexpressed in KCOTs is suggestive of what could be called a "network addiction" pattern, rather than a pathological mechanism dependant on a specific activated/suppressed gene, thus explaining its aggressive behaviour. The key element for future management of the KCOT will probably be based on thorough knowledge of the biological basis of this tumor, thereby enabling a more tailored treatment approach. In fact, there are rather toxic drugs against p53, SMO or EGFR being used in the treatment of tumors. By providing a new molecular target, one may use drugs aimed at COX-2 as an adjunctive therapy, thus circumventing more aggressive surgical treatments and decreasing the risk of recurrences.

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