Publication Types: Editorial

New findings and controversies in odontogenic tumors

Adalberto Mosqueda Taylor

Head of the Clinical Research Area, Health Care Department, Universidad Autónoma Metropolitana Xochimilco. México, D.F.

Correspondence:
Prof. Adalberto Mosqueda Taylor
Departamento de Atención a la Salud
Universidad Autónoma Metropolitana Xochimilco
Calzada del Hueso 1100
Col. Villa Quietud
México, D.F. 04960
México
E-mail: mosqueda@correo.xoc.uam.mx

Received: 09/01/2008
Accepted: 10/07/2008

Indexed in:
-Index Medicus / MEDLINE / PubMed
-EMBASE, Excerpta Medica
-SCOPUS
-Indice Médico Español
-IBECS

Mosqueda-Taylor A. New findings and controversies in odontogenic tumors. Med Oral Patol Oral Cir Bucal. 2008 Sep1;13(9):E555-8.

http://www.medicinaoral.com/medoralfree01/v13i9/medoralv13i9p555.pdf

Abstract
Odontogenic tumors comprise a heterogeneous group of lesions that ranges from hamartomas to benign and malignant neoplasms of variable aggressiveness. This article shows how the lack of uniform criteria employed for their proper identification, as well as the histomorphologic similitude found among some of them which behaves in different way, and the scantiness of proper methods to determine their precise origin makes necessary to recognize that at present, in spite of having more or less strict diagnostic criteria which have been internationally accepted, there is a need to continue developing research in the epidemiological, clinico-pathological, morpho-physiological and therapeutical fields in this area of the maxillofacial pathology.

Key words: *Odontogenic tumors, jaws, ameloblastoma, myxoma.*

Introduction
Odontogenic tumors (OT) are lesions that derive from the tooth-producing tissues or their remnants that remain entrapped either within the jawbones or into the adjacent soft tissues. From a biological point of view, some of these lesions represent hamartomas with varying degrees of differentiation, while the rest are benign or malignant neoplasms with variable aggressiveness and potential to develop metastasis.

Since the first attempt to classify these lesions published by Broca in 1868 (1), numerous works have been done in this respect, but it was not until the 1960´s decade, when a group of experts from different countries, sponsored by the World Health Organization produced a consensus-based classification aimed to define the clinico-pathological criteria necessary to diagnose these entities. This effort lead in 1971 to the publication of the first edition of the "Histological Classification of Odontogenic Tumours, Jaw Cysts and Allied Lesions", which had Professors Jens J. Pindborg and Ivor R.H. Kramer as editors (2). Due to the very low incidence of many of the lesions included in that work, as well as to the need of re-classification of some of them because of advances in knowledge of the oral and maxillofacial embriology and the identification of new entities during the following years, it was necessary to update that classification, and the second edition appeared in 1992, headed by Professors Kramer, Pindborg and Mervyn Shear (3). Since then, the development of new technologies in diagnostic immunohistochemistry, molecular biology and genetics, as well as the clinical and epidemiological follow-up of some of the lesions included in the previous editions, disclosed the need of re-classify some of them according to their probable histogenesis (e.g. adenomatoid odontogenic tumor is now classified as an epithelial tumor without odontogenic ectomesenchyme), or according to their biological behavior (the former clear cell odontogenic tumor is now identified as a type of carcinoma, and the odontogenic keratocyst is considered as a benign locally aggressive neoplasm that

has been re-named as keratocystic odontogenic tumor). These and other important changes have been included in the most recent WHO classification of head and neck tumors published in 2005, which is a guide for diagnosis of these lesions nowadays and was produced with the collaboration of numerous colleages from countries of the five continents, headed by Prof. Peter Reichart from the University of Berlin (4). It is well known that classifications had a short life, depending on the persistence of the basic concepts that support the existence of a given entity, and therefore one can expect that in the future some of the less common lesions known nowadays or those as yet unclassified odontogenic tumors may be properly defined in future editions of this classification.

At present, it is known that the potential sources to develop an odontogenic tumor are varied, and these include:
1. The pre-functional dental lamina (odontogenic epithelium with ability to produce a tooth), which is more abundant for obvious reasons distally to the lower third molars.
2. The post functional dental lamina, a concept that covers those epithelial remnants such as Serre´s epithelial rests, located within the fibrous gingival tissue; the epithelial cell rests of Malassez in the periodontal ligament and the reduced enamel organ epithelium, which covers the enamel surface until tooth eruption.
3. The basal cell layer of the gingival epithelium, which originally gave rise to the dental lamina.
4. The dental papilla, origin of the dental pulp, which has the potential to be induced to produce odontoblasts and synthesize dentin and/or dentinoid material.
5. The dental follicle.
6. The periodontal ligament, which has the potential to induce the production of fibrous and cemento-osseous mineralized material.

The lack of specific markers to confirm the odontogenic origin of all the lesions included in the current W.H.O. classification makes diagnosis to be based mainly in anatomic considerations, dentigerous relationship or in the histomorphological similarities among some tumors with the above mentioned odontogenic structures. However, as most OT contain variable amounts of epithelium, and the fact that such tissue may express several of the more than 20 cytokeratin markers (intermediate filaments of the epithelial cells) known to date, there are some studies that have demonstrated that cytokeratins 14 and 19 are the more frequently expressed by OT, and that these are also expressed in the different epithelial structures of the developing tooth (5,6), leading to promote their use as a diagnostic tool to support the odontogenic nature of these entities. Additionally, the expression of amelogenin, a representative protein of the enamel matrix, which is produced by secretory ameloblasts and that seem to actively participate in the process of production and mineralization of enamel, has been consistently demonstrated within the enamel matrix and the cytoplasm of the cells of the reduced enamel epithelium, stratum intermedium and stellate reticulum of the enamel organ, as well as in some epithelial OT, particularly at the basal endings of the cuboidal or columnar cells of ameloblastomas and in cells of calcifying epithelial odontogenic tumor, malignant ameloblastoma and ameloblastic carcinoma (6). Therefore, the use of these markers is a valuable tool to discard other types of epithelial lesions that may develop within the oral and maxillofacial regions. More recently, calretinin, a 29-kDa calcium-binding protein has been shown to be expressed in both unicystic and solid ameloblastomas but not in other types of odontogenic cysts, and this finding led some authors to propose it may be considered a specific immunohistochemical marker for neoplasitic ameloblastic epithelium (7) and an important diagnostic aid in the differential diagnosis of cystic odontogenic lesions, particularly the keratocystic odontogenic tumor (8). In the same way, the expression of cytodifferentiation of neoplastic epithelium via epithelial-mesenchymal interactions and mineralization markers, such as bone morphogenetic protein (BMP) is of great value to study those lesions that are characterized by the production of hard dental tissues (9,10).

OT are very infrequent lesions as compared to other pathologic processes of the oral and maxillofacial regions, as some studies have shown that these represent between 0.8% and 3.7% of all specimens sent to oral pathology laboratories (11-13). More than 95% of all OT reported in large series are benign and around 75% are represented by odontomas, ameloblastomas and myxomas (which could be considered as "relatively frequent OT"). Due to the inclusion of the odontogenic keratocyst as a tumor, these figures will be modified significatively, as this lesion is more frequently diagnosed than the other three entities. Some studies have shown epidemiological data that demonstrate that there is a second group of OT, which, although rare in terms of general pathology, are of "intermediate frequency" with respect to other OT, which have to be considered in the differential diagnosis of tumors of the oral and maxillofacial regions and therefore have to be included within the contents of pathology of the graduate and post-graduate courses of oral and general pathology. This group of lesions includes adenomatoid odontogenic tumor (AOT), calcifying cystic odontogenic tumor (previously known as calcifying odontogenic cyst or Gorlin´s cyst), ameloblastic fibroma, ameloblastic fibro-odontoma, peripheral odontogenic fibroma and cementoblastoma, which have relative frequencies usually above 1% and less than 10% of all OT. Finally, there is a less common group of lesions, considerd as "very low frequency" tumors, as each of them represent less than

1% of all OT in most of the published series worldwide. These include the calcifying epithelial odontogenic tumor (Pindborg´s tumor), squamous odontogenic tumor, ameloblastic fibro-dentinoma, odontoameloblastoma, ghost cell dentinogenic tumor, central odontogenic fibroma and all variants of the malignant OT (14).

Epidemiological studies are important because they allow to know more precisely the occurrence of these lesions in the diverse populations, which in turn help to identify the groups at risk and posible factors associated to their development. In this respect, and as an example of this situation, there are studies that demonstrate that in Africa solid/multicystic ameloblastomas are more frequent than unicystic subtypes, while in Latin American population the unicystic subtypes (which pose a better prognosis) are more frequent than solid neoplasms (15). The main problem to allow comparison among the different studies is that there are no uniform criteria employed in most of the previously published works, since although some authors used criteria based on the W.H.O. classifications, other used different definitions or older concepts that includes more than one lesion under a single designation (for example, all subtypes of ameloblastoma were very often considered as a single diagnostic category, making no distinction among the four subtypes known to date).

In the same way, there are works that show wide variations with respect to the relative frequency of the diverse OT, as there are some series that do not include odontomas in their results, possibly because these are asymptomatic lesions that are usually removed in the dental office and they frequently are not sent to the laboratory for histopathological analysis or, even worst, very often these lesions are only diagnosed on clinico-radiological grounds, which produces an under-estimation of their true frequency in many of the published series (16). Odontomas are hamartomatous lesions that usually do not produce clinical symptomatology but sometimes may be associated to other OT, such as calcifying cystic odontogenic tumor or may develop dentigerous cysts ("cystic odontoma") and therefore the lack of histopathological analysis of every sample may underestimate the true frequency of these and other possibly related lesions; in addition, it is important to remember that there are certain syndromes, such as Gardner syndrome and some other in which odontomas, particularly when multiple, may be one of the earlier manifestations of the genetic disorders and their identification allow an early diagnosis and may improve its prognosis favoring an early and proper management of the more severe manifestations of such syndromes (17,18).

Regarding the mesenchymal and ectomesenchymal odontogenic tumors, it is not clearly demonstrated the exact source of some of them. For example, although the classical image of the odontogenic myxoma seem to be at first sight similar to the dental papilla or the dental follicle, there are marked differences between them, as for example, the amount and types of proteoglycan they contain. In this respect, some authors have found that hyaluronic acid concentration in odontogenic myxomas is four times higher than those of other glycosaminoglycans, such as chondroitin sulphate, which is inverse to what has been found in mesenchymal tissues from dental pulp, gingiva and periodontal ligament (19-21). Other have suggested that the characteristic microscopic aspect of this neoplasm could be the result of a myxoid change in a pre-existent mesenchymatous lesion or that it may represent a degenerative form of odontogenic fibroma (22). In addition, a recent study which analyzed the clinico-pathological and immunohistochemical features of 62 cases of odontogenic myxomas found that in this lesion a varied mesenchymal cellular population do exist, in which the specific role the myofibroblasts, mast cells and their products play is still not defined. In the same way, only a small percentage of these cases exhibited epithelial islands and interestingly, most of them did not express immunophenotypic features suggestive of odontogenic origin (positivity to CK 14 and CK 19), and therefore the presumed odontogenic nature of this neoplasm remain to be determined. The authors concluded that odontogenic myxoma is a mesenchymal neoplasm in which there are several factors that may contribute to its pathogenesis and expansion (23).

Finally, other problems that remain to be resolved are derived from the very low frequency of some OT, such as odontoameloblastoma, the recognition of some odontogenic lesions not yet included in the current W.H.O. classification (for example, adenomatoid odontogenic hamartoma) and the position on the biological spectrum of those hybrid odontogenic tumors (for example, cases of ameloblastic fibromas or fibro-odontomas with calcifying cystic odontogenic tumor, central odontogenic fibromas with giant cell lesions and some other combinations), as there is not enough experience to determine the proper therapeutic behavior in such cases; therefore, it is encouraged the report of these kind of cases as well as to carry out studies directed towards the identification of their pathogenesis and their possible relationship with well established entities and to know more about their biological behavior on the long term.

References

1. Broca P. Recherches sur un nuveau grupe des tumeurs désignées sous le nom d'odontomes. Gaz Hebd Sci Med. 1868;5:70.
2. Pindborg JJ, Kramer IRH. Histological Typing of Odontogenic Tumours, Jaw Cysts and Allied Lesions. 1th ed. Geneva: World Health Organization; 1971.
3. Kramer IRH, Pindborg JJ, Shear M. Histological Typing of Odontogenic Tumours. 2th ed. Berlin: Springer-Verlag; 1992.
4. Barnes L, Eveson JW, Reichart P, Sidransky D. (Eds.). World Health Organization Classification of Tumours. Pathology and Genetics of

Head and Neck Tumours. Lyon: IARC Press; 2005. p. 283-328.
5. Crivelini MM, De Araújo VC, De Sousa SO, De Araújo NS. Cytokeratins in epithelia of odontogenic neoplasms. Oral Dis. 2003 Jan;9(1):1-6.
6. Kumamoto H, Yoshida M, Ooya K. Immunohistochemical detection of amelogenin and cytokeratin 19 in epithelial odontogenic tumors. Oral Dis. 2001 May;7(3):171-6.
7. Coleman H, Altini M, Ali H, Doglioni C, Favia G, Maiorano E. Use of calretinin in the differential diagnosis of unicystic ameloblastomas. Histopathology. 2001 Apr;38(4):312-7.
8. DeVilliers P, Liu H, Suggs C, Simmons D, Daly B, Zhang S, et al. Calretinin expression in the differential diagnosis of human ameloblastoma and keratocystic odontogenic tumor. Am J Surg Pathol. 2008 Feb;32(2):256-60.
9. Kumamoto H, Ooya K. Expression of bone morphogenetic proteins and their associated molecules in ameloblastomas and adenomatoid odontogenic tumors. Oral Dis. 2006 Mar;12(2):163-70.
10. Gao YH, Yang LJ, Yamaguchi A. Immunohistochemical demonstration of bone morphogenetic protein in odontogenic tumors. J Oral Pathol Med. 1997 Jul;26(6):273-7.
11. Mosqueda-Taylor A, Ledesma-Montes C, Caballero-Sandoval S, Portilla-Robertson J, Ruíz-Godoy Rivera LM, Meneses-García A. Odontogenic tumors in Mexico: a collaborative retrospective study of 349 cases. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 1997 Dec;84(6):672-5.
12. Ochsenius G, Ortega A, Godoy L, Peñafiel C, Escobar E. Odontogenic tumors in Chile: a study of 362 cases. J Oral Pathol Med. 2002 Aug;31(7):415-20.
13. Buchner A, Merrell PW, Carpenter WM. Relative frequency of central odontogenic tumors: a study of 1,088 cases from Northern California and comparison to studies from other parts of the world. J Oral Maxillofac Surg. 2006 Sep;64(9):1343-52.
14. Mosqueda Taylor A, Meneses García A, Ruíz Godoy Rivera LM, Suárez Roa Mde L, Luna Ortiz K. Malignant odontogenic tumors. A retrospective and collaborative study of seven cases. Med Oral. 2003 Mar-Apr;8(2):110-21.
15. Ledesma-Montes C, Mosqueda-Taylor A, Carlos-Bregni R, De León ER, Palma-Guzmán JM, Páez-Valencia C, et al. Ameloblastomas: a regional Latin-American multicentric study. Oral Dis. 2007 May;13(3):303-7.
16. Fregnani ER, Fillipi RZ, Oliveira CR, Vargas PA, Almeida OP. Odontomas and ameloblastomas: variable prevalences around the world. Oral Oncol. 2002 Dec;38(8):807-8.
17. Schmidseder R, Hausamen JE. Multiple odontogenic tumors and other anomalies. An autosomal dominantly inherited syndrome. Oral Surg Oral Med Oral Pathol. 1975 Feb;39(2):249-58.
18. Wijn MA, Keller JJ, Giardiello FM, Brand HS. Oral and maxillofacial manifestations of familial adenomatous polyposis. Oral Dis. 2007 Jul;13(4):360-5.
19. Slootweg PJ, Van den Bos T, Straks W. Glycosaminoglycans in myxoma of the jaw: a biochemical study. J Oral Pathol. 1985 Apr;14(4):299-306.
20. Sakamoto N, Okamoto H, Okuda K. Qualitative and quantitative analysis of bovine, rabbit and human dental pulp glycosaminoglycans. J Dent Res. 1979 Feb;58(2):646-55.
21. Embery G. Glycosaminoglycans of human dental pulp. J Biol Buccale. 1976 Sep;4(3):229-36.
22. Adekeye EO, Avery BS, Edwards MB, Williams HK. Advanced central myxoma of the jaws in Nigeria. Clinical features, treatment and pathogenesis. Int J Oral Surg. 1984 Jun;13(3):177-86.
23. Martínez-Mata G, Mosqueda-Taylor A, Carlos-Bregni R, De Almeida OP, Contreras-Vidaurre E, Vargas PA, et al. Odontogenic myxoma: clinico-pathological, immunohistochemical and ultrastructural findings of a multicentric series. Oral Oncol. 2008 Jun;44(6):601-7.