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EDITORIAL

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Odontogenic cysts and tumours: past, present and future

Odontogenic cysts and tumours comprise about 40% of all lesions encountered in the oral and maxillofacial regions and more than 80% of lesions of the jawbones. Although the majority are simple odontogenic cysts a significant subset pose diagnostic and therapeutic challenges due to their variable histological features and unpredictable clinical behaviour. Despite hundreds of years of research and investigation, the classification and pathogenesis of these lesions is still poorly understood and widely debated. Recent advances in molecular analysis have begun to improve our understanding of odontogenic lesions and have led to advances in diagnostics and in the field of targeted therapies.

Lesions in the jawbones have been recognised and described in the medical and dental literature for well over 250 years. X-rays were not invented until the 1890s, so early lesions were identified as swellings with characteristic clinical features or unusual findings after surgery. The first description of a "dental cyst" has been ascribed to John Hunter in his book *"The natural history of the human teeth"* written in 1771[1]. More detailed descriptions of dental lesions followed and by the mid-1800s a number of odontogenic tumours and cysts had been described using terms that we may recognise today. Ameloblastoma was first described by Cusack in 1827[2], but was then called *adamantinoma* before being designated as *ameloblastoma* in the 1930s. The odontogenic keratocyst was probably first described in 1813 by Barnes (reviewed by Ide et al.[3]) but at the time the terminology used related to the contents of the cyst or to comparisons of other known lesions. Barnes first called it "lardaceous cyst" after the contents, but later it was named the "buttery cyst"[3]. Other terms included "cholesteatoma cyst" or names such as dermoid or epidermoid as comparisons to more commonly encountered skin lesion. Many authors used the term "dentigerous cyst" for all cyst types in the jaws, simply because of their close association to the teeth. By the mid-1800s however Oral Pathology as a specialty had begun to develop and the dental literature began to contain many reports and more accurate descriptions of odontogenic lesions[4]. A number of workers began to develop classifications of odontogenic cysts and tumours, but detailed classifications based on consensus and consultation did not emerge for many years, most notably those of Robinson in 1945[5] and Thoma in 1949[6]. These early classifications led directly to the classifications and terminology that we use today.

However, even after 250 years there is still no single satisfactory classification of odontogenic cysts and tumours. This is because terminology varies across the world, and authors use classification systems to serve different purposes. Surgeons prefer simple classifications that place lesions into prognostic groups that inform management decisions, while pathologists tend to subdivide lesions into multiple variants based on histological or clinical features. The Oral Pathology literature contains many detailed descriptions of variants of most types of cysts and tumours. Although this may lead to confusion over terminology and categorisation, detailed analyses of variants are useful for research, and occasionally a well-recognised variant may eventually emerge as a new entity. A good example of this is the first reports of an orthokeratinised variant of the odontogenic keratocyst[7] that over time has been shown to be a distinctive entity with specific clinicopathological features — the orthokeratinised odontogenic cyst. Other variants however, such as the bay or pocket variant of the radicular cyst, are of academic interest but do not affect clinical management. The best classifications should be simple, should use a universally agreed terminology and should be relevant for clinicians who treat the lesions. Pathologists should also agree the criteria for diagnosis so that lesions are correctly reported and communication between clinical specialties is accurate.

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Appropriate international standards for classifications were first developed by the World Health Organization (WHO) in 1952 (reviewed by Sobin[8]). Classifications were developed by groups of international experts who reviewed multiple cases and agreed a uniform terminology and described practical and clinically relevant criteria for diagnosis. The first WHO classification of odontogenic cysts and tumours[9] was developed by a large group of experts that included a number of pathologists who have become household names within our profession — they were led by Jens Pindborg and Ivor Kramer, and included Barbosa, Dahlin, Gorlin, Lucas, Shear and Shafer. This first edition was a comprehensive classification of all cysts and tumours of the odontogenic tissues with clear and concise descriptions of the clinical, radiological and histological features, as well as descriptions of known histological variants. The 2nd edition[10] was published 20 years later, and also included cysts of the jaws, but inexplicably, the 3rd edition[11] omitted cysts and restricted the classification to tumours and selected "tumour-like" lesions. Subsequently however the 4th and 5th editions[12,13] include odontogenic cysts and have restored the status of the book as a complete classification of lesions of the odontogenic tissues.

It is important to note that the WHO classifications have changed little over the half century since the first edition, and still maintain the original principles of simplicity, relevance and a uniform and well recognised terminology. The most significant change in the most recent editions is the inclusion of molecular data and its potential role in our understanding of pathogenesis, diagnostics and therapeutics.

Over the previous two or three decades, there have been many important advances in our molecular understanding of the odontogenic lesions[14–17]. A consistent finding is that many odontogenic cysts and tumours show genetic changes in the signalling pathways that regulate normal tooth development. Most commonly these aberrations involve the MAPK, Sonic Hedgehog (SHH) and WNT/β-catenin signalling pathways and the most commonly affected genes are *BRAF*, *PTCH* and *CTNNB1* respectively. In all cases the changes activate the signalling pathways leading to persistent and aberrant cell proliferation, growth and differentiation. Many other, although less common, genetic changes have been found including mutations or activation of *FGFR2*, *KRAS*, *NRAS* and *HRAS* in the MAPK pathway, *PTCH2*, *SMO*, *GLI1* and *GLI2* in the SHH pathway. Changes have also been found in a wide range of lesions including adenomatoid odontogenic tumour, calcifying epithelial odontogenic tumour, glandular odontogenic cyst, clear cell odontogenic carcinoma and even in dentigerous and radicular cysts[15,16]. Although these molecular findings have informed our understanding of the pathogenesis of these lesions they are not yet sufficiently well studied or specific to be used in the overall classification of odontogenic cysts and tumours. They have however driven the debate regarding the possible neoplastic origin of a number of lesions that have always been regarded as developmental cysts. This includes the calcifying odontogenic cyst (*CTNNB1* mutations) and most notably the odontogenic keratocyst (*PTCH* mutations). A major problem however is that there is no clear molecular definition of neoplasia and the finding of a single mutation or gene change cannot be regarded as a defining criteria for neoplasia. In the case of the keratocyst however there is some good evidence that at least a subset of lesions maybe neoplastic. A number of studies have shown that keratocysts may occasionally show mutations in both copies of the *PTCH* gene[18–20]. More recently it has been shown that biallelic loss of *PTCH1* may be found in 80% of sporadic keratocysts[21]. This meets the "two-hit hypothesis" of Knudson[22] that suggests that loss of both alleles of a gene is a key driver of neoplasia, and provides some good evidence that at least some keratocysts may be neoplastic. Keratocysts in patients with the naevoid basal cell carcinoma syndrome are probably more likely to be truly neoplastic because these patients have a *PTCH* gene germline mutation, and are much more likely to have a second mutation. It remains to be determined however if there are clinicopathological or behavioural differences between cysts with and without biallelic changes.

There are also examples where molecular studies have been valuable with regards to classification or diagnostics. Adenoid ameloblastoma has always been thought of as a variant or subtype of ameloblastoma[17], but histological diagnosis is difficult because it has few clear diagnostic criteria and shares features with ameloblastoma, adenomatoid odontogenic tumour and dentinogenic ghost cell tumour. Recent molecular studies have shown that it does not share *BRAF* mutations with ameloblastoma nor *KRAS* mutations with adenomatoid odontogenic tumour. It does however share features with ghost cell lesions including the presence of ghost cells, nuclear β-catenin expression and activation of the WNT/β-catenin signalling pathway via *CTNNB1* mutations. For these reason it has been recognised as a new entity in the latest WHO classification[13,17]. Because it is not related to ameloblastoma, and the evidence

suggests that it may be a member of the family of ghost cell lesions a good case can be made for a change of name.

An example of the diagnostic utility of molecular analysis is clear cell odontogenic carcinoma. This lesion shows an *EWSR1* gene rearrangement in 80% to 100% of cases. Although this rearrangement is seen in a number of non-odontogenic clear cell carcinomas, including some of salivary origin, it is not found in clear cell variants of other odontogenic tumours or in clear cell variant of intraosseous mucoepidermoid carcinoma. Mucoepidermoid carcinoma however often shows a *MAML2* translocation. These findings can be very useful in the differential diagnosis when faced with an intraosseous clear cell lesion.

Another ongoing debate relates to ameloblastic fibroma (AF), ameloblastic fibro-odontoma (AFO) and ameloblastic fibrodentinoma (AFD). In the 4th edition of the WHO classification[12], AFO and AFD were removed as entities because they were regarded as developing odontoma. Molecular studies however have shown that about 50% of AF harbour *BRAF* mutations common with ameloblastoma. Furthermore, a subset of AFO and AFD show the same mutation. Odontomas do not show changes in *BRAF*. This suggests that at least some AFO and AFD are true neoplasms related to AF, and these lesions are now included as variants of AF in the latest WHO classification[13]. On the other hand, AF, AFO and AFD with wild-type *BRAF* are probably developing odontoma, but at present there are no histological features that can be used to differentiate between neoplastic and non-neoplastic lesions. The debate will continue, but it may never be possible to differentiate between these lesions until molecular testing becomes commonplace or new markers are developed.

A further, and more exciting application of these molecular findings is the opportunities for targeted personalised medicine. Already, there have been a number of small trials using signalling pathway blockers to treat odontogenic lesions. Most studies have been on ameloblastomas and have concentrated on the MAPK pathway using inhibitors targeting lesions with *BRAF* mutations[23,24]. Almost all lesions have shown a treatment response with occasional complete remission. Similar targeted therapies are being proposed for odontogenic keratocyst, using inhibitors of the SHH pathway[25]. It seems certain that in the future targeted therapy will be increasingly used for the treatment of odontogenic lesions, and will be particularly useful for the management of large inoperable ameloblastomas or ameloblastic carcinomas, or for lesions that are unusually aggressive or metastatic.

CONFLICT OF INTEREST STATEMENT

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REFERENCES

1. Hunter J. The natural history of the human teeth. Explaining their structure, use, formation, growth, and diseases. London: J. Johnson, 1771.
2. Cusack JW. Report of the amputations of the lower jaw. Dublin: Hodges and M'Arthur; 1827.
3. Ide F, Ito Y, Muramatsu T, Miyazaki Y, Nishimura M, Kikuchi K, et al. The advent of studies on jaw cysts with keratinization: a review of overlooked papers on odontogenic keratocyst and orthokeratinized odontogenic cyst. Head Neck Pathol. 2020;14(3):785-91. https://doi.org/10.1007/s12105-019-01115-0
4. Bouquot JE, Lense EC. The beginning of oral pathology. Part I: first dental journal reports of odontogenic tumors and cysts, 1839-1860. Oral Surg Oral Med Oral Pathol. 1994;78(3):343-50. https://doi.org/10.1016/0030-4220(94)90066-3
5. Robinson HBG. Classification of cysts of the jaws. Am J Orthod Oral Surg. 1945;31(6):A370-A372, IN1, A373-A375. https://doi.org/10.1016/0096-6347(45)90114-1
6. Thoma KH. Oral and dental diagnosis. Philadelphia: WB Saunders; 1949.
7. Wright JM. The odontogenic keratocyst: orthokeratinized variant. Oral Surg Oral Med Oral Pathol. 1981;51(6):609-18. https://doi.org/10.1016/s0030-4220(81)80011-4
8. Sobin LH. The World Health Organization's programme for the histopathological definition and classification of tumours. Methods Inf Med. 1971;10(2):120-2. PMID: 5566165.
9. Pindborg JJ, Kramer IRH. Histological typing of odontogenic tumours, jaw cysts, and allied lesions. Geneva: World Health Organization; 1971.
10. Kramer IRH, Pindborg JJ, Shear M. Histological typing of odontogenic tumours. Berlin: Springer Verlag; 1992.
11. Barnes L, Eveson JW, Reichart P, Sidransky D. World Health Organization Classification of Tumours. Pathology and genetics of head and neck tumours. Lyon: IARC Press; 2005.
12. El-Naggar AK, Chan JKC, Grandis JR, Takata T, Slootweg PJ. WHO classification of head and neck tumours. Lyon: IARC; 2017.
13. World Health Organization. WHO Classification of Tumours Editorial Board. Head and neck tumours. Lyon: IARC; 2024.
14. Diniz MG, Gomes CC, Sousa SF, Xavier GM, Gomez RS. Oncogenic signalling pathways in benign odontogenic cysts and tumours. Oral Oncol. 2017;72:165-73. https://doi.org/10.1016/j.oraloncology.2017.07.021
15. Duarte-Andrade FF, Vitório JG, Pereira TSF, Gomes CC, Gomez RS. A review of the molecular profile of benign and malignant odontogenic lesions. Oral Surg Oral Med Oral Pathol Oral Radiol. 2020;129(4):357-68. https://doi.org/10.1016/j.oooo.2019.12.017

16. Gomes IP, Bastos VC, Guimarães LM, Gomes CC. The molecular basis of odontogenic cysts and tumours. J Oral Pathol Med. 2023;52(4):351-6. https://doi.org/10.1111/jop.13401
17. Odell EW, Gomes CC, Thavaraj S. The evolving molecular characterisation, histological criteria and nomenclature of adenoid ameloblastoma as a World Health Organisation tumour type. Histopathology. 2024;85(6):846-52. https://doi.org/10.1111/his.15270
18. Levanat S, Gorlin RJ, Fallet S, Johnson DR, Fantasia JE, Bale AE. A two-hit model for developmental defects in Gorlin syndrome. Nat Genet. 1996;12(1):85-7. https://doi.org/10.1038/ng0196-85
19. Sun LS, Li XF, Li TJ. PTCH1 and SMO gene alterations in keratocystic odontogenic tumors. J Dent Res. 2008;87(6):575-9. https://doi.org/10.1177/154405910808700616
20. Pan S, Dong Q, Sun LS, Li TJ. Mechanisms of inactivation of PTCH1 gene in nevoid basal cell carcinoma syndrome: modification of the two-hit hypothesis. Clin Cancer Res. 2010;16(2):442-50. https://doi.org/10.1158/1078-0432.CCR-09-2574
21. Stojanov IJ, Schaefer IM, Menon RS, Wasman J, Gokozan HN, Garcia EP, et al. Biallelic PTCH1 inactivation is a dominant genomic change in sporadic keratocystic odontogenic tumors. Am J Surg Pathol. 2020;44(4):553-60. https://doi.org/10.1097/PAS.0000000000001407
22. Knudson AG. Hereditary cancer: two hits revisited. J Cancer Res Clin Oncol. 1996;122(3):135-40. https://doi.org/10.1007/BF01366952
23. Graillon N, Akintoye SO, Iocca O, Kaleem A, Hajjar S, Imanguli M, et al. Current concepts in targeted therapies for benign tumors of the jaw – a review of the literature. J Craniomaxillofac Surg. 2023;51(10):591-6. https://doi.org/10.1016/j.jcms.2023.10.003
24. Bologna-Molina R, Schuch L, Magliocca K, van Heerden W, Robinson L, Bilodeau EA, et al. Targeted therapies in ameloblastomas and amelobastic carcinoma – a systematic review. Oral Dis. 2024;30(6):3571-81. https://doi.org/10.1111/odi.14962
25. Wang S, Hong Y, Qu J, Zhang J, Zhang Y, Zhai J, et al. PTCH/SMO gene mutations in odontogenic keratocysts and drug interventions. J Oral Pathol Med. 2023;52(9):867-76. https://doi.org/10.1111/jop.13473