Malformations vs. Neoplasia in the Oral Cavity: Special Emphasis on Mixed Odontogenic Tumors

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Abstract

Background: The terminology surrounding developmental lesions in the oral cavity is widely applied, often leading to confusion in differentiating between developmental malformations and neoplasia. Odontogenic tumor classification includes both true neoplasms and malformations which make it very complex and dynamic.

Method and conclusion: In this brief report, we will first discuss the concepts of malformations and neoplasia and then focusing on their relevance to odontogenic tumors, which impacts their classification and treatment, particularly mixed odontogenic lesions.

Keywords: ameloblastic fibroodontoma; hamartoma; neoplasia; odontogenic tumours; odontoma.

1 Introduction

The classification of developmental lesions in the oral cavity is commonly employed, yet it frequently causes confusion when distinguishing between malformations and neoplastic conditions. Odontogenic tumors are also a heterogeneous group of lesions of diverse clinical behavior and histopathologic types, ranging from hamartomatous lesions to true neoplasia. As in normal odontogenesis, these lesions are capable of inductive interactions between odontogenic ectomesenchyme and epithelium, and the classification of odontogenic tumors is essentially based on this interaction that makes it very complex.

This report aims to further define and clarify the terminology used in diagnosing these complex conditions, thus improving both academic understanding and clinical practice. Additionally, the discussion focuses on their implications for odontogenic tumors, influencing both their classification and therapeutic approaches, especially with mixed lesions. It also critically evaluates the implications of recent molecular findings on traditional classifications, advocating a more integrated diagnostic approach.

2 Neoplasia and Malformations

2.1 Neoplasia

Neoplasia refers to ‘new growth.’ Neoplastic cells exhibit disordered, non-physiological growth that continues even after the initial stimulus for this alteration has subsided. Although neoplasms depend on the host for their nutrition and blood supply, they have a certain degree of autonomy and continue to grow independently from their local environment and are not subject to most normal growth control mechanisms in tissues [1]. It is important to note that the currently used definition of neoplasia largely relates to clinical behavior and has preceded the detailed molecular understanding of these lesions by several decades. The limitations of such a clinically based definition in the molecular age are now evident. Thus, integration of molecular data into these clinical concepts will help to refine this definition and ensure its future conceptual usefulness.

2.2 Malformations

Malformations are primary errors of morphogenesis, defined as an abnormal developmental process. Some malformations may remain asymptomatic or appear later with complications such as infection. Among the various types of malformations, terms such as hamartoma, choristoma, and teratoma still cause confusion among students and professionals [2].

Fundamentally, the term 'hamartoma' indicates a well-circumscribed mass found at any site in the body, typically asymptomatic and without malignant potential, composed of the same cellular and non-cellular elements as the surrounding organ but with an abnormal tissue architecture. Similarly, choristomas are also histologically normal masses of tissue, but in an abnormal location. A teratoma is defined as a mass lesion which comprising tissue derivatives from all three primordial germ layers.

As the definitions are important when considering the pathogenesis and taxonomic nomenclature of these lesions [3], it is beneficial to explain these terms by delving deeper into their origins. The term "hamartoma" was introduced at the beginning of the twentieth century and refers to a tumor-like but non-neoplastic developmental anomaly. Batsakis expanded the definition of hamartoma as a tissue mass that incorporates the following characteristics: (1) being present during or shortly after birth, (2) consisting of relatively normal tissue inherent to the specific site, and (3) being limited to lesions that clearly exhibit developmental abnormalities or excessive growth at birth [2]. Therefore, in contrast to a neoplasm, a hamartoma is characterized as an abnormal mixture mass of specialized cells or tissues native to the constituent organ, with excessive but non-autonomous focal overgrowth.

Traditionally hamartomas are considered developmental malformations; however, many hamartomas have clonal chromosomal alterations acquired through somatic mutations [1]. Therefore, clonal mutations are not sufficient to define a lesion as neoplastic or a hamartoma. We believe the presence of a mutation alone is typically insufficient to classify a lesion as neoplastic. Neoplasia is a complex process involving multiple genetic alterations and dysregulated cellular growth. While mutations can be important molecular markers in the diagnosis and classification of neoplastic lesions, additional factors such as biological behavior, histologic features, epigenetic changes, and clinical presentation need to be considered to make a definitive determination. The presence of a mutation may indicate a higher likelihood of neoplastic transformation, but a comprehensive assessment of the above-mentioned factors is necessary for a conclusive diagnosis.

A choristoma also has etymology from ancient Greek and is a compound word from the root "choristos" meaning "separated" [3]. In contrast to hamartomas, Batsakis defined choristoma as a displaced anlage, representing a tissue mass that is histologically normal for a particular organ or tissue but foreign to its current location or surrounding tissue [2]. Another confusing term, teratoma, is derived from the Greek root of the term "teraton" meaning "monster". These lesions are more complex, as they are developmental tumors composed of tissues derived from all three germ layers: ectoderm, mesoderm, and endoderm and distinguishing itself from a choristoma by its multiplicity of tissue types [3].

At times, the most appropriate terms and definitions to use in relation to a particular lesion is unclear and may even be controversial. In the context of lesions arising from the odontogenic tissues, it is essential to clarify the concepts that influence the pathogenesis of developmental odontogenic lesions, thus aiding our understanding of their clinical behavior. Therefore, this

critical commentary aims to identify the terms that should be used in a way that is indicative of its benign, non-aggressive nature and limited possibilities for growth.

3 Mixed Odontogenic Tumors: Hamartoma or Neoplasia?

Despite efforts to differentiate between developmental malformations and neoplasia, a clear distinction between the two remains difficult in some cases. This uncertainty makes the classification of lesions in the mixed odontogenic tumor group in particular more complex. In the 2005 WHO odontogenic tumor classification, ameloblastic fibroma (AF), ameloblastic fibrodentinoma (AFD), and ameloblastic fibro-odontoma (AFO) were classified as distinct entities based on the presence or absence of dental hard tissue. AFD and AFO were accepted as separate from AF due to the formation of dental hard tissues. In the 2017 WHO classification, AFD and AFO were removed as independent entities. Evidence was presented, suggesting that once dental hard tissues form, these lesions most likely develop into odontomas. The consensus was that AFD and AFO represent maturing lesions on the pathway to becoming odontomas, rather than distinct neoplastic entities. Similarly, in the most recent, WHO classification (2022); AFD and AFO are considered intermediate lesions between AF and odontomas, being classified as developing odontomas [4], which means, by definition, that they are hamartomas, not neoplasms. Although the authors recognize that, on occasion, AFO/AFD develop which are large, show a locally aggressive biological behavior, and may ultimately recur, it is stated that such lesions represent a minority of the overall group of lesions previously diagnosed as AFD or AFO. Thus, they have been classified as developing odontomas to avoid overtreatment of patients. However, some large, aggressive, and recurrent cases of AFD and AFO may still represent true neoplasms. It is important to remember that the absence of an entity in the classification does not mean that it does not exist, so in these controversial lesions, each case should be evaluated individually, regardless of the classification.

The complexity of these “mixed” odontogenic lesions does result in difficulties in their classification. Indeed, on a progressive evolutionary view across the whole group of lesions, ameloblastic fibroma would be considered the least differentiated tumor, followed by ameloblastic fibro-odontoma, and finally, complex odontoma [5]. However, according to this theory, these lesions should appear in successive age groups, according to the lesion's evolution period.

An important aspect of hamartomatous lesions is that they appear histologically similar to the same period of the organ or structure development to which they are related [6]. Thus, lesions related to the odontogenic apparatus can only be classified as hamartomas if they develop during the period of embryogenesis or the time when odontogenesis is completed, which occurs around 22 years of age [6]. As AFD and AFO may also occur above this age, such lesions may not fit the definition of a hamartoma.

Although the histologic appearances of AFD and AFO are indistinguishable from those of developing odontomas, there is enough data to support the concept that some examples of these are truly neoplastic in nature. One study has shown that radiographic appearance, patient age, and lesion size may help distinguish these lesions [7]. Retrospective studies have analyzed the clinical data of mixed odontogenic tumors and do not support their progressive maturation theory to odontoma [8, 9]. Furthermore, unlike odontomas, malignant transformation does occur in these other mixed odontogenic tumors.

Using targeted next-generation sequencing and allele-specific quantitative PCR of laser capture samples of odontogenic tumors, Coura et al. [10] found additional evidence for the neoplastic nature of AFD, and AFO which is the presence of the BRAF p.V600E mutation like AF but absent in odontomas, present a different overall molecular profile.

In conclusion, clinical and radiological features are increasingly recognized as valuable tools in diagnosing different pathological conditions. Considering all the literature regarding mixed odontogenic tumors, pathologists could incorporate these aspects in their reports. As proposed by Gardner [6], a small lesion situated over the occlusal surface of an unerupted molar in a child would be better classified as a developing odontoma, no matter whether the histopathological features are compatible with AF, AFD, or AFO. Soluk-Tekkesin and Vered [7] also suggested that at least a part of the AFOs, especially those in patients younger than 13.5 years with lesions of 2.1 cm and larger in diameter, as representing true tumours rather than developing odontomas. These clinical and radiological features can guide more accurate pathology reports and, in cases involving incisional biopsy, prevent overtreatment by distinguishing between benign neoplasia and potentially developing odontomas.

It is also crucial to highlight that relying solely on an incisional biopsy can be misleading, particularly in odontogenic tumors where pathognomic features are almost impossible to detect. Pathologists should, therefore, exercise caution and avoid making definitive diagnoses based on small biopsy specimens, even when radiological images are available. In cases of uncertainty, requesting additional and more comprehensive biopsies is highly advisable. Moreover, the integration of molecular data in the future can provide additional insights and contribute to a more conclusive diagnosis.

Author Contributions

M.S.T., K.D.H and R.S.G: conceptualization, design, investigation and writing – original draft.; R.B.-M., K.M, W.v.H., L.R., E.A.B., H.M.H., A.O.A., W.M.T., and J.L.: investigation, review and editing. All authors read and approved the final paper.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The authors have nothing to report.

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