TUMOUR PATTERNS- AN INTROSPECTIVE ANALYSIS

Abstract

Odontogenic tumours encompass a diverse group of uncommon tumours that are frequently aggressive in their biological behaviour. They comprise 2.4% of all the lesions biopsied in the dental office. Odontogenic tumours have for years been recognized for presenting clinical & histopathological challenges arising from epithelial, ectomesenchyme and/or mesenchymal elements of tooth forming tissues. Understanding of the most common and rare odontogenic tumours will be of great use in their study and clinical management. Histological patterns or sub-patterns are characteristic of particular tumours, hence serve as a proverbial beacon to arrive at a confirmatory histopathological diagnosis. The molecular mechanisms of Epithelial Mesenchymal Interaction (EMI) have long been studied as a basis for these versatile tumour patterns.

Morphogenesis and cell differentiation in the developing tooth are controlled by a series of reciprocal interactions between the epithelial and mesenchymal tissues. In these rare neoplasms, there is lack of information about ectomesenchymal interactions which is involved in the pathogenesis of these tumours.

Our paper aims to assess the validity of tumour pattern as a unique prognostic parameter for odontogenic tumours.

Keywords:- Odontogenic tumours, epithelial mesenchymal interactions, histopathologic patterns, classification

INTRODUCTION

Odontogenic tumours represent a spectrum of lesions ranging from benign and malignant neoplasms to dental hamartomas; formed generally in the same sequence as in normal tooth development and all arising from dental remnants[1] i.e. derived either from epithelial,
ectomesenchymal and/or mesenchymal elements of the tooth-forming apparatus.[2] In general, the more primitive the dental structures from which they are derived, the more aggressive they are thought to be and vice versa.[3]

Odontogenesis is an advancing process that is regulated by sequential and reciprocal interactions between the epithelial and mesenchymal tissues.[4,5] The exact molecular mechanisms operating in these interactions are currently unknown, but it is speculated that both structural components of the extracellular matrix (ECM) and diffusible growth factors are involved.[6] Epithelial mesenchymal interaction (EMI) has been postulated as a versatile mechanism which facilitates cellular repositioning and redeployment during embryonic development, wound healing, fibrosis, carcinogenesis, and tumor metastasis;[7,8] hence EMI is considered to be the key biological alterations that define the malignant character of cells.[4]

The odontogenic tumors are an unusual group of lesions of the jaws derived from embryologic tooth-forming tissues and presenting in a large number of diverse histopathologic types and clinical behavior.[9,10] The observation of their features is important both in the identification of the lesions and in their classification.[2] The appearance of the lesions and thus their classification also depends on the change in tumour tissue architecture takes place through epithelial-mesenchymal transition (EMT); this interaction, often referred to as inductive change, may result in cytodifferentiation that recapitulates the structures of the normal tooth-forming apparatus or enamel organ.[11,12]

Various classifications have been proposed for these tumors, most of which are pathologic curiosities; yet there is no well-accepted classification. Nonetheless their importance can not be underestimated.[13,14] The degree of differentiation in odontogenic neoplasms is significant in predicting biologic behaviour of these tumors.[15] Classification of jaw tumours is of interest because of the wide variety of pathological conditions from which they can arise like bone, soft tissue and dental tissue. A detailed and authentic classification is important to summarize all these timors.[16]
The earlier classifications were based on the nature of these tumors whether benign or malignant, and the latter ones on the histomorphogenesis of the lesions i.e. presumed tissue of origin, being epithelial, mesenchymal, or a mixed lesion. Studies of odontogenic tumors reveal that there is generally no clear divisions between most of these tumors, rather a transition from one form to another, as well as few of them showing overlapping patterns. Because of this, there have been numerous attempts at reclassification of these lesions and also introduce new variants of these lesions as they are reported.[3,11] Over the years there have been many attempts to produce a 'logical' classification of tumours and tumour-like lesions of the odontogenic tissues. Recent advances and cognition in the field of genesis, inception and nature of interaction in these tissues have provided a sounder scientific basis for classification, but uncertainties remain, partly because of the complexity and rarity of the tissues involved and partly because of the diverse and covert patterns exhibited by these lesions which makes it difficult to accumulate a large series for study and comparison.[17]

The primary purpose of the following classification is to list and define neoplasms, tumor-like lesions arising from the odontogenic apparatus based on their histological patterns.

**CLASSIFICATION** [18-32]

**GLANDULAR/ PSEUDOGLANDULAR** (Fig.1)
- Adenomatoid Odontogenic Tumor
- Calcifying Epithelial Odontogenic Tumor

**BIPHASIC / TRIPHASIC PATTERN** (Fig.2)
- Clear cell odontogenic carcinoma
- Adenomatoid Odontogenic Tumor
- Ameloblastic fibroma
- Ameloblastic fibrodentinoma
- Ameloblastic fibroodontoma
- Calcifying Epithelial Odontogenic Tumor
Complex odontoma

Compound odontoma

**CYSTIC / PSEUDOCYSTIC** (Fig.3)

- Adenomatoid Odontogenic Tumor
- Keratocystic Odontogenic Tumor
- Unicystic ameloblastoma
- Squamous Odontogenic Tumor

**BASALOID**

- Ameloblastic Carcinoma

**CORDS** (Fig.4)

- Ameloblastic fibroma
- Ameloblastoma
- Central odontogenic granular cell tumor
- Adenomatoid Odontogenic Tumor

**NESTS/ROSETTES/WHORLES** (Fig.5)

- Adenomatoid Odontogenic Tumor
- Ameloblastic fibroma
- Ameloblastoma
- Central Odontogenic Fibroma
- Squamous Odontogenic Tumor

**PALISADING** (Fig.6)

- Ameloblastoma
- Keratocystic odontogenic tumor

**SHEETS/ISLANDS** (Fig.7)

- Calcifying Epithelial Odontogenic Tumor
- Central odontogenic granular cell tumor
- Clear cell odontogenic carcinoma
- Primary intraosseous squamous cell carcinoma
- Squamous Odontogenic Tumor
- Cementoblastoma

SQUAMOUS CELLS (Fig.8)
- Ameloblastoma
- Squamous Odontogenic Tumor

SPINDLE CELLS (Fig.9)
- Adenomatoid Odontogenic Tumor
- Odontogenic fibroma
- Odontogenic myxoma

LEISGANG RINGS (Fig.10)
- Adenomatoid Odontogenic Tumor
- Calcifying Epithelial Odontogenic Tumor

WITH GIANT CELL COMPONENT :-
- Calcifying Epithelial Odontogenic Tumor

WITH OSTEOID COMPONENT :-
- Ameloblastoma

WITH AMYLOID COMPONENT :-
- Calcifying Epithelial Odontogenic Tumor

WITH CALCIFICATION :-
- Ameloblastoma
- Calcifying Epithelial Odontogenic Tumor
- Cementoblastoma
- Odontoma

WITH CLEAR/OSTEOID CELLS (Fig.11)
- Clear cell odontogenic tumor
- Ameloblastic carcinoma
WITH GRANULAR CELLS :-

- Granular cell ameloblastic fibroma
- Granular cell ameloblastoma

**DISCUSSION**

Odontogenic tumours can pose significant diagnostic dilemma for the pathologist owing to its low incidence, overlapping histology, subtle differentiating features and rarity of reports.[11]

In due course of time, odontogenic tumors have passed through several modifications.[33] Broca PP in 1868, first attempted to classify odontogenic tumors based on the stages of tooth development.[34,35] In 1887 Bland- Sutton modified the classified based on the the nature of the particular cells of the tooth germ from which the tumor arises.[34] British Dental Association adopted a classification in 1914 wherein all odontogenic tumors including cysts were referred to as odontomas. Finally in 1946, Thoma and Goldman divided the OTs into tumors of ectodermal, mesodermal and mixed origin;[34,35] which was accepted and adopted in the ‘American Academy of Oral Pathology’ published in 1952.[13] Further in 1958, Pindborg and Clausen proposed a classification based on the inductive effect of one dental tissue on the other.[13,34] Basically it distinguishes only the benign lesions from the malignant ones.[35] 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.[36] In 1961, Gorlin slightly modified the previous classification.[34] In 1966, WHO established a Collaborating Centre for the Histological Classification of Odontogenic Tumours and Allied Lesions (including jaw cysts) headed by Dr Jens Pindborg.[37] In 1971, WHO published the first guide for the classification of odontogenic tumors[33] the “Histological Classification of Odontogenic Tumours, Jaw Cysts and Allied Lesions”, edited by Professors Jens J.
Pindborg and Ivor R.H. Kramer.[36] Zollinger in 1972 reclassified Ameloblastoma as semi-malignant.[35] In 1982, Elzay proposed a modification in the malignant category of odontogenic tumors and late in 1984, Slootweg and Muller made modifications based on the features of malignancy.[15] In 1914, Gabell, James and Payne elaborated the classification by Bland and Sutton.[37] In 1992, Charles A. Waldron reclassified these tumors and added adenomatoid odontogenic tumor as an epithelial neoplasm.[38] In 1992, WHO revised the classification which was published in its second edition and was headed by Professors Kramer, Pindborg and Mervyn Shear.[36,39] In 2002, Philipsen and Reichart produced a revision of the 1992-edition and in 2003, the editors of the WHO Blue Book series: 'WHO Classification of Tumors' decided to produce a volume on the Head and Neck Tumors including a chapter on Odontogenic Tumors and Bone Related Lesions. In July of 2005 this volume was published by International Agency for Research on Cancer (IARC), Lyon.[37,40] An important modification included in this revision was the inclusion of keratocystic odontogenic tumor.[33] The updated classification partially retains the conceptual framework of tissue of origin, although several entities show features not found during normal odontogenesis and thus fall outside it.[41]

In 2005, Al-Nafussi Al proposed an elaborate classification of soft tissue tumors based on their histopathological patterns in the second edition of “Tumor diagnosis – practical approach and pattern analysis.” He conclude that this classification system provides a rapid tumor diagnosis when the only known factors are the histological patterns and the anatomical site. In addition to that it also provides a diagnostic clue for the identification of all the common tumors under that particular pattern.[18]

In 2013, Dr. Odel Edward pointed out the advantages of the WHO classification of odontogenic tumours; that it is easily understood and has broad consensus. The main drawback of this classification is that it is heavily weighted by the histological appearances of individual lesions. Radiological and clinical factors have not always been given the prominence they deserve.[42] In 2014, Alka M Dive, Ashish S
Bodhide, Minal S Mishra, Neha Upadhyaya classified the histological patterns that are encountered in head and neck tumors. They suggested that the tumor patterns seen on hematoxylin and eosin stained sections can be further confirmed by adopting advance techniques like special stains, immunohistochemistry and different molecular diagnostic aids.[19]

With the advancement of new technologies in diagnostic immunohistochemistry, molecular biology and genetics; critical observation of the clinical and histological features of the lesions; epidemiological follow-up of some of the lesions providing more insight into the trend of these rare lesions; emergence of new observations regarding the pathogenesis; necessitates the need to re-classify some of them according to their biological behaviour. It is well known that classifications have a short life and as evolution gains momentum 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 classifications.[36]

Tradition has dictated the classification of odontogenic tumors into the histogenetic groups of epithelial, mesenchymal, and mixed epithelial-mesenchymal types.[43] A classification based on the extent to which a tumor correlates with the basic cell type, dictates the choice of therapy needed and the determination of prognosis.[44] It provides insight into the utilization of diagnostic histopathology services and has a number of implications for the health system.[45] Refinement of this classification continues as more is learned of these unique and varied lesions.[43]

As odontogenic tumours arise due to uncontrolled odontogenesis, a precise knowledge of their histogenesis, extraordinary rarity, polymorphism in their nature, is important; thus the lack of agreement on a commonly accepted nomenclature and classification put nearly insurmountable difficulties in the way of every experiment to gather and analyse the different forms of these tumours.[46]

Thus, the need for a new classification can be attributed to factors like:-
Increase in the number of odontogenic tumor cases being reported.

More studies being done regarding the origin of these tumors.

Change in terminologies over the years.

Purposive role of epithelial-mesenchymal interaction in tumorigenesis.

Conversion of few odontogenic cysts into tumors.

Recognition of new variants of odontogenic tumors.

Lack of evidence regarding some odontogenic tumors.

Heterogeneity of the tumors.

Here we make an attempt to propose a comprehensive classification of odontogenic tumours based on their histological patterns by inculcating the preceding classification

**Fig. 1**

Glandular/Pseudoglandular Pattern

Adenomatoid odontogenic tumor. Gland-like spaces are surrounded by cuboidal to columnar cells (→). (HE × 160)[47]

**Fig. 2**

Biphasic/Triphasic Pattern
Clear cell odontogenic carcinoma. A biphasic tumour pattern with sheets of clear cells and irregular cords and strands of dark, basaloid cells, intersected by narrow bands of fibrous stroma.[48]

**Fig. 3**

Cystic/Pseudocystic Pattern

Unicystic ameloblastoma (luminal type), showing ameloblastomatous epithelial lining the "cyst" wall (H.E.; orig. magn. x 200)[49]

**Fig 4**

Cords Pattern
Plexiform ameloblastoma with anastomosing strands and cords of tumour cells (H.E.; orig.magn. x 200)[49]

**Fig. 5**

**Nests/Rosettes Pattern**

Photomicrograph showing the typical ductal and rosette pattern of tumor cells in an adenomatoid odontogenic tumor.[50] The tumor cells form balls of cells that are called rosettes.[51]

**Fig. 6**

**Palisading Pattern**
Follicular ameloblastoma. 1A. Follicles of ameloblastic epithelium displays squamous differentiation and microcystic formation (hematoxylin-eosin stain; original magnification x100). 1B. Higher magnification shows solid follicles with peripheral tall columnar basal cells displaying nuclear hyperchromatism, reverse polarization, palisading and a loose stellate-like reticulum in the center (hematoxylin-eosin stain; original magnification x200).[52]

**Fig. 7**

**Sheets Pattern**

Calcifying epithelial odontogenic tumour (Pindborg tumour) is composed of sheets of large eosinophilic cells showing pleomorphic nuclei and containing desmosomes.[11]

**Fig. 8**

**Squamoid Pattern**
Squamous odontogenic tumor exhibiting characteristic bland epithelial islands in a fibrous stroma.[53]

Fig. 9

Spindle cell Pattern

Adenomatoid odontogenic tumour shows noduli-forming spindle cells with connecting epithelial strands. In the nodules, lumina lined by columnar cells are present.[54]

Fig. 10

Leisgang rings Pattern
Calcifying epithelial odontogenic tumour. The neoplasm consists of islands or sheets of polyhedral epithelial cells close to eosinophilic material in a fibrous connective tissue stroma.[48]

**Fig. 11**

Clear/Ghost cells Pattern

Calcifying cystic odontogenic tumour, formerly known as keratinizing and calcifying odontogenic cyst, shows an epithelial lining that mimics ameloblastoma and contains ghost cells. In the fibrous stroma adjacent to the basal epithelial cells, homogeneous eosinophilic material resembling dentine is present.[54]

**CONCLUSION**
The knowledge of the prominent histopathological patterns of the odontogenic tumors serves as a useful diagnostic aid which can further corroborate the diagnosis and execution of a definite treatment plan. A histological classification elucidates the evolution and progression of the odontogenic tumors. Inspite of this the myriad of similar patterns in other related tumors makes it essential to rely on clinical and radiological data as vital adjuncts to the histopathological parameters in order to arrive at a definitive diagnosis.

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