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Odontogenic Tumour Patterns- An Introspective Analysis

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Authors' contributions

This work was carried out in collaboration between all authors. Author RKP designed the study. Author ES managed the literature searches and wrote the first draft of the manuscript. Authors SM and HCG modified the paper into the final draft. All authors read and approved the final manuscript.

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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, ectomesenchymal 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 and 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 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.

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1. INTRODUCTION

Odontogenic tumors 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 [2,3].

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 tumour metastasis [7,8]; hence EMI is considered to be the key biological alteration that defines the malignant character of cells. EMIs may also contribute to tumor initiation in the oral cavity [4].

The odontogenic tumours 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]. 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]. The observation of their features and hence the pattern is important both in the identification of the lesions and in their classification [2].The diagnosis is often made by pattern recognition of the lesion [3]. Hence the knowledge of various tumours having overlapping histologic pattern can help a pathologist to narrow down the spectrum of wide array of differential diagnoses. Paradoxically it also enables the pathologist to widen their dimensions of differentials in terms of lesions which are not clinically related but may have a similar or related histologic pattern.

The appearance of the lesions and thus their classification also depends on the change in tumour tissue architecture which takes place through epithelial-mesenchymal transition (EMT); this interaction, often referred to as inductive change, may result in cyto-differentiation that reviews and summarizes the structures of the normal tooth-forming apparatus or enamel organ [11,12].

Various classifications have been proposed for these tumours, most of which are pathologic curiosities; yet there is no well-accepted classification. Nonetheless their importance cannot be underestimated [13,14]. The degree of differentiation in odontogenic neoplasms is significant in predicting biologic behaviour of these tumours [15] which correlates with the prognosis of these tumours. 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 tumours [16].

The earlier classifications were based on thenature of these tumours 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 tumours reveal that there are generally no clear divisions between most of these tumours, rather a transition from one form to another, as well as few of them show overlapping patterns. Because of this, there have been numerous attempts at reclassification of these lesions and also due to introduction of 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 [18-35]

S. no.	Pattern	Tissues affected [18,19]	Histopathology
1.		**Glandular / Pseudoglandular pattern**	
	Adenomatoid odontogenic tumour	Site- tumour of two thirds-maxilla, females, anterior jaws, crown of impacted tooth Rx- enucleation Prognosis- no recurrences, excellent prognosis	The neoplastic cells form gland-like structures (false glands) due to acantholysis and degeneration of the cells or due to accumulation of basement membrane-like material within the cellular proliferation [20]. Eosinophilic, uncalcified, amorphous material can be found and is called "tumour droplets" [21].
	Calcifying epithelial odontogenic tumour	Site- mandible molar-ramus Gender- M=F Rx- enucleation to resection Prognosis- recurrence potential ~14%, poor prognosis	It is an epithelial odontogenic neoplasm composed of nests and islands of polygonal cells having centrally-placed nuclei and eosinophilic cytoplasm. Occasionally the cells form a pseudoglandular pattern. The nuclei appear vesicular and have an inconspicuous nucleoli [22].
2.		**Biphasic pattern**	
	Clear cell odontogenic carcinoma	Site- posterior mandible Gender- F>M Rx- surgical resection Prognosis- Recurrence ~50%, metastases to lungs and lymph nodes	A biphasic pattern is often exhibited. It is primarily composed of a fibrous stroma with islands of epithelial cells revealing clear to faintly eosinophilic cytoplasm, well-demarcated cell membranes and irregular dark-staining nuclei. Also cords of dark-staining basaloid cells with scant eosinophilic cytoplasm may be seen [23].
	Ameloblastic fibroma	Site- mandibular molar-ramus Gender- M=F Rx- surgical resection Prognosis- Recent studies suggest that more than 30% of ameloblastic fibrosarcomas arise from recurrent ameloblastic fibroma	Neoplastic cells originate both from epithelial and mesenchymal elements. The epithelium appears in strands and islands, often with a peripheral layer of cuboidal or columnar cells. The central area of epithelial islands resembles the stellate reticulum of the enamel organ. The connective tissue is very cellular, these cells are round or angular and mimic the dental papilla [24].
	Ameloblastic fibroodontoma	Site- posterior mandible Gender- M>F Rx- conservative surgical enucleation Prognosis- good prognosis, recurrence is rare	The epithelial and connective tissue components resemble ameloblastic fibroma occurring in conjunction with a mineralized component [24].
3.		**Cystic / Psuedocystic pattern**	
	Unicystic ameloblastoma	Site- posterior mandible Gender- F=M	Two histopathologic variants exist. The luminal variant is a cystic lesion

S. no.	Pattern	Tissues affected [18,19]	Histopathology
		Rx- curettage or enucleation Prognosis- better prognosis, recurrence rate <20%	lined by ameloblastomatous epithelium. In addition intraluminal extensions may occur. In the mural variant, the cyst wall is infiltrated by ameloblastomatous epithelium that exhibits either a follicular or plexiform pattern [23].
	Solid/Multicystic ameloblastoma	Site- mandible molar angle-ramus area Gender- M=F Rx- radical surgical intervention Prognosis- recurrences have been noted more than ten years after the initial treatment.	The plexiform pattern contains basal cells arranged in anastomosing strands with an inconspicuous stellate reticulum. The stroma is usually delicate, often with cyst-like degeneration [23]. Cyst formation is also common in follicular type [25].
	Keratocystic odontogenic tumour	Site- angle of the mandible Gender- F>M Rx- enucleation to resection Prognosis- recurrence 1%-8.7%	Exhibits a fibrous cyst wall with a uniform stratified squamous epithelium, six to eight cells in thickness. The luminal surface is parakeratotic with a corrugated appearance. The lumen contained keratinaceous and cellular debris [26].
	Squamous odontogenic tumour	Site- alveolar process, anterior>posterior Gender- M=F Rx- curettage or excision Prognosis- recurrence is rare	Individual tumour islands reveal a peripheral layer of low cuboidal or flat epithelial cells. Epithelial islands may undergo central microcystic degeneration [23].
	Calcifying cystic odontogenic tumour	Site- centrally in bone Gender- M>F Rx- surgical enucleation Prognosis- recurrence is rare	The cyst lining is composed of stratified squamous epithelium with a polarized basal layer [27].
4.		**Basaloid pattern**	
	Ameloblastic carcinoma	Site- posterior mandible Gender- M=F Rx- radical surgery with neck dissection Prognosis- local recurrences and metastasis to neck and lung	The neoplasm contains follicles and cords of cohesive, poorly differentiated malignant cells with a basaloid appearance. The cells display pleomorphism with hyperchromatic nuclei along with nucleoli and scant cytoplasm [28].
	Basal cell ameloblastoma	Site- mandible Gender- M>F Rx- radical treatment Prognosis- recurrences are reported	It is a rare type of lesion composed of nests of uniform basaloid cell, and they are histopathologically very similar to basal cell carcinoma of the skin [25].
5.		**Cords pattern**	
	Plexiform ameloblastoma	Site- posterior mandible Gender- M=F Rx- surgical intervention	Plexiform: (Means ‘network/tangle’ [Latin]) it is a variation of trabecular pattern that is characterized by the

S. no.	Pattern	Tissues affected [18,19]	Histopathology
		Prognosis- better prognosis than follicular type	presence of anastomosing cords and strands of proliferating tumor cells forming a network/mesh-like pattern [20].
	Ameloblastic fibroma	Prognosis- excellent prognosis, rarely recurs	The epithelial component of AF consists of branching and anastomosing epithelial strands that form knots of varying size. The epithelial cords lie in a myxoid cell-rich stroma with stellate-shaped fibroblasts with long slender cytoplasmic extensions resembling embryonic tooth pulp [23].
	Central odontogenic granular cell tumour	Site- posterior mandible Gender- F>M Rx- local enucleation Prognosis- recurrence is rare	Odontogenic epithelium may be found dispersed as islands or cords formed by two or more rows of cells. At the periphery low columnar cells are present immediately adjacent to which areas of hyalinized connective tissue can be appreciated [24].
	Adenomatoid odontogenic tumour	Prognosis- no recurrences, excellent prognosis	Solid areas, duct-like pattern, whorled arrangement of cells, and tubular appearance can also be seen. In addition to forming ducts, the cuboidal to columnar cells form convoluted cords in complicated patterns that often exhibit invaginations [23].
6.		**Nests / Rosettes / Whorled pattern**	
	Adenomatoid odontogenic tumour	Prognosis- no recurrences, excellent prognosis	Histopathology reveals cuboidal to columnar cells arranged in the form of nests and rosettes [29]. Rosette means resembling a flower, where the cells are radially arranged around the center. In this pattern, round cells show characteristic rosette formation [20].
	Follicular ameloblastoma	The follicular ameloblastomas were thought to have a higher recurrence rate than plexiform or unicystic	The most common and recognized lesion composed of small to large odontogenic epithelial nests (the folliculs) in various size and shape [25].
	Central odontogenic fibroma	Site- posterior mandible Gender- F>M Rx- enucleation with vigorous curettage Prognosis- recurrence rare	There is a whorled pattern of fibroblasts that elaborate varying amounts of collagen. The fibroblasts are mature. The connective tissue may appear myxoid (myxofibroma) and densely fibrous [24].
	Squamous odontogenic tumour	Prognosis- good, recurrence is rare	Histologic features includes oval, round and curvilinear nests of squamous epithelium throughout a mature collagenous stroma [27].
7.		**Palisading pattern**	
	Follicular ameloblastoma	Site- mandible	Tumor cells show parallel side by side alignment of nuclei [20].

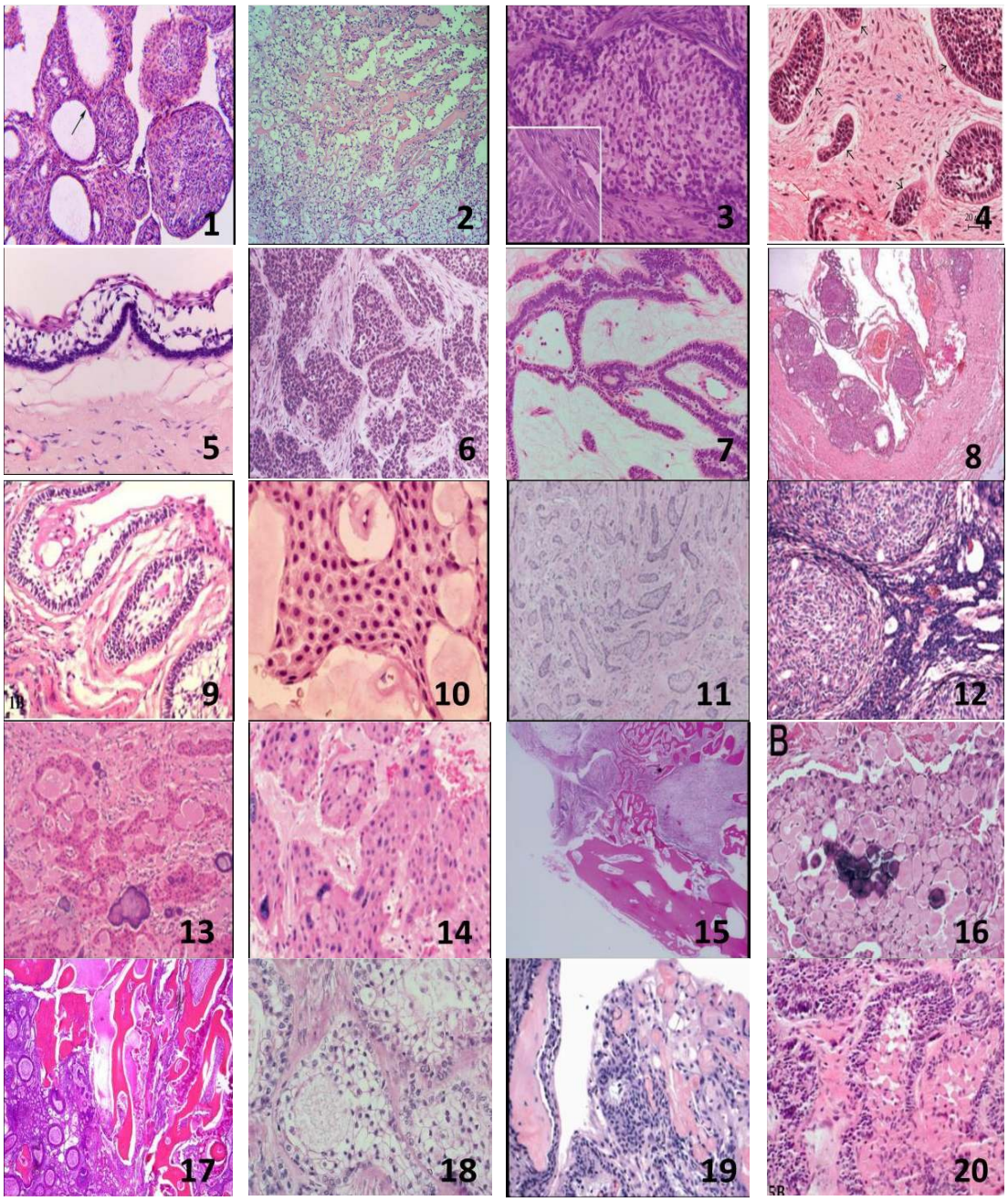
S. no.	Pattern	Tissues affected [18,19]	Histopathology
		Gender- M=F Rx- radical surgical intervention Prognosis- recurrences may occur	
	Keratocystic odontogenic tumour	Prognosis- good to moderate, recurrence 1%-8.7%	The epithelium is distinctive for a layer of columnar, pallisading, hyperchromatic basal cells. Rete ridges are generally absent and focally the epithelium may be detached from the underlying fibrous tissue [26].
8.		**Sheets / Islands pattern**	
	Calcifying epithelial odontogenic tumour	Prognosis- recurrence potential ~14%, poor prognosis	Sheets, nests and cords of eosinophilic epithelial cells prevail [27].
	Central odontogenic granular cell tumour	Prognosis- good, recurrence is rare	The epithelium is arranged in sheets of large, round cells with abundant eosinophilic, granular cytoplasm. The stroma contains areas of both loose and dense fibrous connective tissue with eccentric nuclei [24].
	Clear cell odontogenic tumour	Prognosis- Recurrence ~50%, metastases to lungs and lymph nodes	Islands and sheets of large cells with clear, vacuolated cytoplasm and a peripheral layer of cuboidal cells can be seen [30].
	Ameloblastic carcinoma	Prognosis- local recurrences and metastasis to neck and lung	Shows odontogenic epithelium arranged in strands, cords and follicles. In some areas, sheets of tumor cells show peripheral columnar cells and loosely arranged central cells resembling stellate reticulum like cells [31].
	Primary intraosseous carcinoma	Site- posterior mandible Gender- M>F Rx- radical surgery Prognosis- 5-year survival rate is 30 to 40%	Histologically, these are squamous cell carcinomas that may range from well to poorly differentiated lesions. Small to large islands of squamous cells can be seen [30].
	Cementoblastoma	Site- root of posterior teeth; mandible>maxilla Gender- M=F Rx- enucleation Prognosis- no recurrence	Histologically, this tumour presents sheets of cementum like tissue, which may contain a large number of reversal lines with active cementoblasts. The irregularly mineralized trabeculae of cementum are fused to the root of the tooth. A band of fibrous connective tissue at the periphery resembling capsule may be present [32].
	Ameloblastic fibroma	Prognosis- variable, ~30% of ameloblastic fibrosarcomas arise from recurrent	Shows strands and islands of odontogenic epithelium showing peripheral palisading, embedded in a

S. no.	Pattern	Tissues affected [18,19]	Histopathology
		ameloblastic fibroma	cell-rich ectomesenchyme resembling the dental papilla. These have a peripheral rim of columnar cells similar to the inner enamel epithelium that embraces a loosely arranged spindle-shaped epithelium identical to stellate reticulum [23].
9.		**Squamous cells pattern**	
	Squamous odontogenic tumour	Prognosis- good, recurrence is rare	Tumor cells have epithelial/epithelioid morphology with abundant hyalinized cytoplasm. Marked cytoplasmic eosinophilia may be encountered in certain tumors, which gives a squamous look to the tumor; However, they might not be necessarily squamous in origin [20].
	Acanthomatous ameloblastoma	Site- mandible- ramus Gender- M=F Rx- surgical excision Prognosis- recurrence is rare	Squamous metaplasia such as that seen in acanthomatous ameloblastoma may be attributed to chronic irritation [33].
10.		**Spindle cells pattern**	
	Calcifying epithelial odontogenic tumour	Prognosis- recurrence potential ~14%, poor prognosis	Microscopic features include a thick fibrous capsule with an inner epithelial neoplastic component composed of organoid clusters of spindle cells. Columnar cells are arranged in rosettes or ductal patterns dispersed throughout the organoid clusters [27].
	Central odontogenic fibroma	Prognosis- good, recurrence is rare	The epithelium-rich type of COF is composed of cellular, fibroblastic connective tissue interwoven with less cellular and often vascular areas [23]. There is a whorled pattern of spindle shaped fibroblasts that elaborate varying amounts of collagen. The fibroblasts are mature [24].
	Odontogenic myxoma	Site- any area of jaws Gender- F>M Rx- curettage to radical resection Prognosis- good prognosis, rare recurrence upto 10%-33%	The stroma is delicate with sparse cellularity consisting of spindle, round, or stellate cells without pleomorphism. The cells secrete mucopolysaccharides resulting in an abundant extracellular matrix [24].
11.		**Leisegang rings pattern**	
	Calcifying epithelial odontogenic tumour	Prognosis- recurrence potential ~14%, poor prognosis	Small psammoma-like concentric calcifications called Liesegang rings are seen within the epithelial islands [27]. These eosinophilic, homogeneous hyaline material aid in diagnosis [23].

S. no.	Pattern	Tissues affected [18,19]	Histopathology
	Adenomatoid odontogenic tumour	Prognosis- no recurrences, excellent prognosis	Some amount of calcification, eosinophilic material, and leisegang ring formation can also be observed. Leisegang pattern is seen as calcification in the form of globular or spheroidal masses [29].
12.		**With giant cells**	
	Calcifying epithelial odontogenic tumour	Prognosis- recurrence potential ~14%, poor prognosis	Multinucleated cells are occasionally present [34]. Giant and pleomorphic nuclei in the absence of mitoses are frequently found and do not indicate malignancy [23].
13.		**With osteoid**	
	Central odontogenic fibroma	Prognosis- good, recurrence is rare	Islands or strands of inactive-looking odontogenic epithelium are an integral component; they may be sparse but are often conspicuous. This type shows foci of calcified material considered to be metaplastically produced dysplastic cementum/osteoid/dentin [23]
14.		**With amyloid**	
	Calcifying epithelial odontogenic tumour	CEOT with amyloid are known to be less aggressive and are amenable to more conservative surgical treatment	Interspersed amidst the tumor cells are amorphous, acellular, eosinophilic, amyloid-like material, which show metachromasia with crystal violet and green birefringence on Congo red staining [22].
15.		**With calcification**	
	Ameloblastic fibroodontoma	Prognosis- excellent	The calcified areas may be in the form of dentinoid, cementum or in the form of well defined teeth [24].
	Calcifying epithelial odontogenic tumour	Presence of calcification indicates more tumour differentiation and hence favours less chance of recurrence.	Large and numerous calcifying spherules are present within eosinophilic cytoplasm of large cells along with smaller cells with hyperchromatic nuclei [35]. Also present are various stages of psammomatous microcalcification, which coalesce to form large calcific masses [34].
	Cementoblastoma	Prognosis- recurrence may occur, though rare	Plump cementoblasts surround the calcified tissue. The cementoblasts stain densely basophilic. The calcified mass is attached directly to the root obliterating the periodontal ligament and resorbing or even replacing the root [24].
	Central odontogenic fibroma	Prognosi- good, recurrence is rare	Foci of calcified material in the form of dental hard tissue is likely to be found, especially in specimens from older patients [24].

S. no.	Pattern	Tissues affected [18,19]	Histopathology
16.		**With clear cells**	
	Clear cell odontogenic tumour	Exhibits an aggressive growth pattern and frequently recurs	It displays islands and sheets of large cells with clear, vacuolated cytoplasm and a peripheral layer of cuboidal cells [30].
	Clear cell ameloblastoma	Site- mandible Gender- F>M Rx- surgical resection Prognosis- recurrences with or without lymph node metastasis	In addition to the characteristic features of conventional ameloblastoma, many cells with clear cytoplasm and centrally placed nuclei can be observed [31].
	Clear cell variant of calcifying epithelial odontogenic tumour	more aggressive and has a higher rate of recurrence than conventional pindborg's tumour	It includes cells having clear or pale staining cytoplasm referred to as clear cell. Presence of glycogen or mucin and virally infected cells also show ballooning degeneration, giving cells clear appearance or processing artifacts also gives typical clear appearance [20].
17.		**With ghost cells**	
	Ghost cell odontogenic tumour	The prognosis is unpredictable due to a wide spectrum of growth patterns. The overall five-year survival rate is 73%. Recurrences are common	The malignant component consists of rounded epithelial islands in a fibrous stroma. The epithelial cells are either small, rounded with dark nuclei or larger with vesicular nuclei. Many mitoses are seen. Ghost cells are found in varying numbers either isolated or in clusters [23].
	Calcifying cystic odontogenic tumour	Prognosis- good, recurrence is rare	The lumen contains eosinophilic keratinized cells devoid of nuclei (ghost cells) [27].
	Odontoma	Site: maxilla>mandible Gender: M>F Rx: Enucleation Prognosis: Odontomes have limited growth potential and recurrences do not occur.	The lesion consists mainly of wavy and plicated walls of tubular or dysplastic dentin covered by enamel. Between these walls are irregular curvilinear clefts that contain enamel matrix producing epithelium and connective tissue. Scattered ghost cells may be present [23].
18.		**With granular cells**	
	Granular cell ameloblastoma	Site- angle of the mandible Gender- M=F Rx- radical surgery Prognosis- recurrence rate ~33%	The epithelial cells have abundant cytoplasm filled with eosinophilic granules that resemble lysosome ultrastructurally and histochemically. This variant has been seen in young patient and in clinically aggressive tumours [25].
	Granular cell ameloblastic fibroma	Site- posterior mandible Gender- F>M Rx- curettage Prognosis- recurrence is rare	The epithelial component resembles ameloblastoma. The stromal component however differs in that it is an immature cell-rich myxoid tissue with an embryonic appearance. Some of the ameloblastic fibroma may contain granular cells [23].

S. no.	Pattern	Tissues affected [18,19]	Histopathology
	Central odontogenic granular cell tumour	Prognosis- good, recurrence is rare	Immunohistochemical staining of the granular cells show that there is no keratin, and the stroma stains strongly positively for CD 68, CK 14 and weakly for CK 13. This indicates that the granular cells are not of epithelial origin. They also stain negatively for S-100 protein [24].



Figs. 1-20. Odontogenic tumours- histologic patterns

Glandular/Pseudoglandular pattern

It exhibits cells arranged in a gland or gland like structures.

Fig. 1

Adenomatoid odontogenic tumour- Gland-like spaces are surrounded by cuboidal to columnar cells (→). Eosinophilic, uncalcified, amorphous material can be found and is called "tumour droplets"(HE × 160) [21].

Fig. 2

Calcifying epithelial odontogenic tumour- large portion of the tumour was arranged in a pseudoglandular pattern consisting of nests of pale, uniform, clear cells with dark-stained nuclei (x340) [36].

Biphasic/Triphasic pattern

Fig. 3

Biphasic pattern show two different components, either epithelial or glandular [20].

Clear cell odontogenic tumour- Under higher magnification, it exhibits biphasic population of cells characterized by polygonal, clear cells and irregular cords and strands of hyperchromatic, basaloid cells with eosinophilic cytoplasm; intersected by narrow bands of fibrous stroma. (H&E x100; Inset x400) [23,37].

Fig. 4

Ameloblastic fibroodontoma- Strands (red arrow) and islands (black arrows) of odontogenic epithelium showing peripheral palisading and loosely arranged central cells, identical to stellate reticulum embedded in myxoid cell-rich stroma resembling the dental papilla (*) [38].

Cystic/Pseudocystic pattern

Fig. 5

Unicystic ameloblastoma (luminal type), showing ameloblastomatous epithelial lining the "cyst" wall. A biopsy of a primary unicystic ameloblastoma may not always show the typical features of ameloblastoma, which may result in an underdiagnosis and, as a result, possibly in incorrect management. (H&E x 200) [39].

Basaloid pattern

Fig. 6

An ameloblastic carcinoma with hypercellularity and hyperchromatism. The neoplasm contains follicles and cords of cohesive, poorly differentiated malignant cells with a basaloid appearance [40].

Cords pattern

Fig. 7

Plexiform ameloblastoma with anastomosing strands and cords of tumour cells. It contains basal cells arranged in interconnecting strands with an inconspicuous stellate reticulum. The stroma is usually delicate, often with cystlike degeneration (H&E x200) [39].

Nests/Rosettes pattern

Fig. 8

Adenomatoid odontogenic tumor- Microscopic examination reveal extremely vascular encapsulated lesion showing multivariate patterns of cellular arrangements ranging from sheets of polygonal cells arranged in ductal pattern, rossetes to solid sheets of cells. In the centre of these ducts, eosinophilic amyloid-like material can also be seen [41].The tumour fills the central cavity, there is little stroma. The tumor cells form balls of cells that are called rosettes [42].

Palisading pattern

Fig. 9

Follicular ameloblastoma- 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 centre (H&E x200) [43].

Sheets pattern

Fig. 10

Calcifying epithelial odontogenic tumour (Pindborg tumour)- is composed of sheets of large eosinophilic cells showing pleomorphic nuclei and containing desmosomes. The presence of pleomorphism may lead to an

erroneous diagnosis of malignancy and care should be taken to examine the lesion carefully for other features. The presence of amyloid is characteristic [11].

Squamoid pattern

Fig. 11

Microscopically, squamous odontogenic tumour appears as islands of bland squamous epithelium (no cellular atypia or mitotic figures) without an inflammatory infiltrate. Peripheral palisades are not seen. There is superficial resemblance to ameloblastoma (acanthomatous type) and well-differentiated squamous cell carcinoma [40].

Spindle cell pattern

Fig. 12

Adenomatoid odontogenic tumour- consists of spindle-shaped cells forming nodules that may contain droplets of eosinophilic material and columnar cells lining spaces that are either empty or contain eosinophilic material. In some AOTs, areas of eosinophilic cells with well-defined cell boundaries and prominent intercellular bridges similar to those observed in CEOT are seen. They do not influence the biological behaviour of this tumour and are considered to be part of its histological spectrum [44].

Leisegang rings pattern

Fig. 13

Calcifying epithelial odontogenic tumour- The neoplasm consists of islands or sheets of polyhedral epithelial cells with sharply defined cell borders and well-developed intercellular bridges in a fibrous connective tissue stroma. Their nuclei are frequently pleomorphic, with giant nuclei being common.It is a locally invasive tumour [23].

With giant cell component

Fig. 14

Calcifying epithelial odontogenic tumour- Giant and pleomorphic nuclei in the absence of mitoses are frequently found and do not indicate malignancy. Note intracellular homogenously dispersed eosinophilic material representing amyloid [23].

With osteoid component

Fig. 15

Central odontogenic fibroma with osteoid formation- Reactive woven bone formation and bone resorption were found in the proximal margins (HE staining, magnification x10) [45].

With amyloid component

Fig. 16

Calcifying epithelial odontogenic tumour- amyloid droplets with dystrophic calcification in epithelial field [40].

With calcification

Fig. 17

Ameloblastic fibro-odontoma showing ameloblastomatous epithelium, Delicate stroma resembling ectomesenchyme along with large calcified areas resembling dentinoid and enamel matrix [46].

With clear cells

Odontogenic tumours composed predominantly or exclusively by clear cells are very rare.

Fig. 18

Clear-cell odontogenic tumour- Microscopically, nests and cords of clear cells are seen. Some peripheral palisading may be present. This rare lesion has an aggressive biologic behaviour [40].

With ghost cells

Fig. 19

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 dentin is present [44].

With granular cells

Fig. 20

Granular cell ameloblastoma- In this field, numerous granular cells are seen in the centre of

the follicles. In addition, the granular cells replace some of the basal peripheral cells (H & E x 200) [43].

2. 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]. They comprise 2.4% of all the lesions biopsied in the dental office [18].

In due course of time, odontogenic tumors have passed through several modifications [47]. Broca PP in 1868, first attempted to classify odontogenic tumours based on the stages of tooth development [48,49]. In 1887 Bland- Sutton modified the classification based on the nature of particular cells of the tooth germ from which the tumour arises [48]. British Dental Association adopted a classification in 1914 wherein all odontogenic tumours including cysts were referred to as odontomas. In 1914, Gabell, James and Payne elaborated the classification by Bland and Sutton [50]. Finally in 1946, Thoma and Goldman [18] divided the odontogenic tumours into ectodermal, mesodermal and mixed origin [48,49]; which wasaccepted and adopted in the 'American Academy of Oral Pathology' and 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 [13,48]. Basically it distinguishes only the benign lesions from the malignant ones [49]. 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 [25]. In 1961, Gorlin slightly modified the previous classification [48]. 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 [50]. In 1971, WHO published the first guide for the classification of odontogenic tumours [47] the "Histological Classification of Odontogenic Tumours, Jaw Cysts and Allied Lesions", edited by Professors, Jens J. Pindborg and Ivor R.H. Kramer [25]. Zollinger in 1972 reclassified ameloblastoma as semi-malignant [49]. In 1982, Elzay propsed a modification in the malignant category of odontogenic tumours and late in 1984, Slootweg and Muller made modifications based on the features of malignancy [15]. In 1992, Charles A. Waldron reclassified these tumours and added adenomatoid odontogenic tumour as an epithelial neoplasm [51]. In 1992, WHO revised the classification which was published in its second edition and was headed by Professors Kramer, Pindborg and Mervyn Shear [50,52]. 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 Tumours' decided to produce a volume on the Head and Neck Tumours including a chapter on Odontogenic Tumours and Bone Related Lesions. In July of 2005 this volume was published by International Agency for Research on Cancer (IARC), Lyon [25,53]. This revision has included keratocystic odontogenic tumour which was reclassified by the WHO as a cystic lesion becoming a benign tumour [47]. 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 [54].

In 2005, Al-Nafussi proposed an elaborate classification of body tumours based on their histopathological patterns in the second edition of "Tumour diagnosis – practical approach and pattern analysis." He concluded that this classification system provides a rapid tumour 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 tumours under that particular pattern [34].

The pathological events leading to the neoplastic transformation of cells may occur in odontogenic tumours as well [55]. Genetic alterations can induce the odontogenic epithelium to proliferate. These perturbations include cell cycle regulators (Cyclin D1, p16 INK4a, p21 WAF/Cip1, p27 Kip1), chromosomal and point mutations in oncogenes (Ras, Myc, Fos), or inactivation of the inhibitory function of tumour suppressor genes (p53, adenomatous polyposis coli (APC) [56]. Odontogenic tumours like ameloblastoma, ameloblastic fibromas and odontogenic myxomas, selectively express p21Ras in the epithelial cells. Whereas primary intraosseous carcinomas, malignant ameloblastoma, and ameloblastic fibrosarcoma exhibit overexpression of p53 gene. Increased reactivity of p14ARF, MDM2 and p53 have also been noted in benign as well as malignant tumours of odontogenic epithelium [57].

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 [58]. In 2014, Dive et al classified the histological patterns that are encountered in head and neck tumours. They suggested that the tumour 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 [20].

Classification of odontogenic tumours based on their patterns provide a clue regarding the histogenesis and nature of the tumour which may guide in treatment planning.

Epidemiological follow-up of these lesions provide an insight into the trend of these rare lesions as well as provide new observations regarding the pathogenesis. This necessitates the need to re-classify odontogenic tumours based on 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 tumours may be properly defined in future classifications [50].

Tradition has dictated the classification of odontogenic tumours into the histogenetic groups of epithelial, mesenchymal, and mixed epithelial-mesenchymal types [59]. A classification based on the extent to which a tumour correlates with the basic cell type, dictates the choice of therapy needed and the determination of prognosis [60]. It provides an insight into the utilization of diagnostic histopathologic services and has a number of implications for the health system [61]. Refinement of this classification continues as more is learned of these unique and varied lesions [44].

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 [62].

Thus, the need for a new classification can be attributed to factors like- Increase in the number of odontogenic tumour cases being reported; more studies being done regarding the origin of these tumours; change in terminologies over the years; purposive role of epithelial-mesenchymal interaction in tumorigenesis; conversion of few odontogenic cysts into tumours; recognition of new variants of odontogenic tumours; lack of evidence regarding some odontogenic tumours; heterogenicity of the tumours.

Here we make an attempt to propose a comprehensive classification of odontogenic tumours based on their histological patterns by inculcating the preceding classification which can aid in arriving at a diagnosis in similar lesions.

3. CONCLUSION

The knowledge of the prominent histopathological patterns of the odontogenic tumours serves as a useful diagnostic aid which can further corroborate the diagnosis and a definite treatment plan. A histological classification elucidates the evolution and progression of the odontogenic tumours. Thus we conclude that along with clinical and radiological data as vital adjuncts; the histopathological parameters of odontogenic tumours can help a pathologist to arrive at a definitive diagnosis.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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