New Diagnostic Biomarkers and Molecular Markers in Odontogenic Tumors

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ABSTRACT

Odontogenic tumors consist of a group of complex heterogeneous lesions that may range from hamartomas to malignant tumors that elicit different behavior and histopathological features. The etiology of odontogenic tumors is not exactly determined and pathologists face innumerable challenges in framing the exact diagnosis of odontogenic tumors because of their rare incidence and difficulty in evaluating the obtained experiences. In this study, the immunohistochemical and molecular markers in the diagnosis of odontogenic tumors have been described. Immunohistochemical features of odontogenic tumors besides the clinical features and radiological finding scans help in determining the correct diagnosis. Although the remarkers are neither specific nor sensitive enough, analysis of gene expression provides definitive confirmation of diagnosis. In addition,"-omics" technology detected specific molecular alternation associated with etiology such as genomics, epigenomics, transcriptomics, proteomics, and metabolomics. The post-transcriptional events such as DNA methylation and chromatin remodeling by histone modification bring about changes in the epigenome. Furthermore, non-coding RNAs like micro-RNAs, long noncoding RNA (lncRNA), and small non-coding RNA (snoRNA) play a regulatory role and modify odontogenesis. Molecular marker proposes their potential role in the etiopathogenesis of odontogenic tumors and comprises essential adjuncts in diagnostic, prognostic, and therapeutic approaches in addition to patient management.

INTRODUCTION –

Odontogenic tumors belong to a group of complex heterogeneous lesions that originate from ectomesenchyme and/or epithelial odontogenic tissues and may manifest following normal tooth development. They show diverse morphology ranging from hamartomas to malignant tumors and elicit different behavior, histology, and even different geographical distribution.[1] The odontogenic tumors manifest variant clinical features that include disfigurement of the face, jaw expansion, and extension, root and bone resorptions, teeth mobility, and alternation in bone density.[2] WHO categorized the new edition based on the origin of tissue and histological characteristics in 2017 that are mentioned in Table 1 [3,4] It was reported that among all oral tumors, odontogenic tumors are less than 1%, and also 99.2% of them are benign type. [5] Markers are molecules, genes, or molecular features in the pathogenesis of disease that play a critical role in the diagnosis and management of patients, especially in tumorigenic cases.[6]Although histological features of odontogenic tumors such as morphology along radiology provide clinical diagnosis, cystic lesions, tiny biopsies, and determination of malignancy changes are some problems.[7]]. Also, over/under-expression of some genes are reported as molecular markers in odontogenic tumors.[8] Therefore, the specific markers help in establishing the correct diagnosis of special types of odontogenic tumors and increase our knowledge about etiopathogenesis and molecular genetic features of the lesions.

DIAGNOSTIC MARKERS IN ODONTOGENIC TUMORS –

IMMUNOHISTOCHEMICAL MARKERS –

Immunohistochemistry (IHC) is an immunostaining technique that detects antigens(proteins)by binding antibodies into the cells or tissues. The main benefit of IHC is the detection of the specific target following antibody-antigen interaction and application in the diagnosis of cancerous tumors secondary to cell proliferation or death. In addition, the IHC markers help in the localization and distribution of expressed proteins that are present in various parts of the tissue. For instance, significant expression of podoplanin was reported in invasive odontogenic tumors by immunohistochemistry technique that expressed the importance of this diagnostic marker in predicting neoplastic behavior. [9]Also, overexpression of MDM2 and p53 was demonstrated in solid multicystic ameloblastoma (SMA) and keratocystic odontogenic tumor(KOT) as IHC markers. [10] In addition, histological features of the lesion can be helpful in the differential

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diagnosis of rare extension cases such as calcifying epithelial odontogenic tumor (CEOT) or Pindborg tumor that expand to the antrum.[11] The high expression of Cripto-1or teratoma-derived growth factor 1 (TDGF-1) in almost aggressive odontogenic lesions proposed the involvement of these molecules in etiopathogenesis. [12]

The correct diagnosis helps us for better patient management in therapy. Some side effects of radiotherapy for head and neck cancers include xerostomia, dental caries, and oral ulcers that affect oral intake and difficulty in speech. Moreover, radiotherapy increases osteosarcoma and oral infection like *oral candidiasis* because stomach reflex manifests following nausea and vomiting.[13] So, biomarker diagnosis plays an important role in patient management. Some of the diagnostic proteins are mentioned in table 2.[14,15]

POTENTIAL MOLECULAR MARKERS IN DIAGNOSIS OF ODONTOGENIC TUMORS

The next-generation sequencing demonstrated specific mutation enhanced the biological process in tumorigenesis of odontogenic tumors. They involve cell proliferation and differentiation, control of cell cycle, regulation of tooth development or be growth factor and receptors, telomerase, apoptotic factors, and extracellular matrix remodeling. [16] On the other hand, post-transcriptional events such as methylation influences gene activity without any changes in DNA sequence. In this manner, DNA methylation and chromatin remodeling by histone modification inhibits the recruitment of splicing or transcription factors. So imprinting or suppressor gene expression result in tumor development.[17] The biology of the tumor and its progression depends on the genome and the epigenome. In addition, some non-coding RNAs like micro-RNAs—smallnoncodingRNAwith21–25nt—have regulatory role and impact odontogenesis. For example, miR-16–1andmiR-15a play tumor suppressor role by repression of *BCL-2*geneand induce apoptosis. It was shown that the expression of *BCL-2* is increased in KOT, but the expression of mir-16–1andmir-15aarereduced.[18]

Profile of micro-RNA expression emerged 40 micro-RNAs with different expression in ameloblastoma compare to the control group. [19] Long-noncoding RNA(lncRNA)is another regulatory molecule—more than 200nt in length—that participate sin chromatin modulation and affects transcription and translation.[20]Result of RNA microarray analysis demonstrated LINC-340 up regulated in a meloblastoma and associated with the size of the tumor. [21]Further more, another class of small non-coding RNA (snoRNA) that modified ribosomal RNA positively

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correlated to size of tumor such as SNORA11 in ameloblastoma.[21]This significant different expression of the molecular marker proposes potential role of them in etiopathogenesis of odontogenic tumors and suitable candidate in diagnostic and therapeutic approaches.

In recent years"-omics" studies discover potential candidate biomolecules in pathogenesis of odontogenic lesions.[19]"-omics" technology provides comprehensive biological information that analyses specific types of molecules. For example, genomics, epigenomics, transcriptomics, proteomics and metabolomics are different levels of this technology that evaluates alterations in DNA, non-DNA sequence, RNA, proteins and metabolites, respectively (Figure 1) [21] This technology enables to detect molecular mechanism, etiology, for better management of affected odontogenic patients. In this regard, some studies exhibit the result of"-omics" in odontogenic cases that can apply in diagnostic approaches.[19]]. In Toronto-genic tumors, proteomics emerged significant alternation of protein levels in some classified types. For instance, it was reported the increasing level of AIDA protein in odontogenic kerato cyst. [22] immunostaining of ameloblastoma cases demonstrated p53and MDM2 was high in odontogenic kerato cyst (OKC)followed by solid multicystic ameloblastoma (SMA).[10] Also, immune expression of PTEN in ameloblastoma cases showed a significant reduction in immunoactivity.[23]

DISCUSSION

The pathologists face many challenges in framing a correct diagnosis of odontogenic tumors because they are rare and obtained experiences are difficult to be collected and evaluated. The diagnosis is determined based primarily on the morphology, clinical manifestation, and radiological features, but the outcome of many studies demonstrated that the immune-histochemical marker can help in diagnosing some odonto genic tumors. Although these markers are neither specific nor sensitive enough, but analysis of gene expression can help in definitive confirmation and establishment of diagnosis based on the molecular pathway involved in the lesions as overexpression or aberrant expression. In addition, "-omics" technology detected specific molecular alternation associated with etiopathogenesis of the disease. Whole-genome sequencing and transcriptomics ghost cell odontogenic carcinoma manifested involving of NOT CH and SHH pathways including increased copy number of *SHH*, *GLI1*, *JAG1*, *DTX3*, and *HEY1* that result in overexpression of them. Furthermore, the fusion of *TCF4* and *PTPRG* genes defects tumor suppressor activity of tyrosine phosphatase receptor type G-protein.[24]

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Understand of odontogenic pathogenesis of odontogenic tumors assistances with a diagnosis of malignant transformation, development and progression of lesions. It seems if that tissue samples after collection embedded in paraffin or formalin-fixed can be saved as a biobank for future evaluation. Recent technologies provide easy access to genome, transcript to meorproteome of saved samples with sufficient integrity and quality. [25] Organoid provide optional treatment for patient′s tumor attention to site, stage and personal factors and variation in their genetic profile as personalized medicine. For example, different drug dosage or combination therapy can be applied in anorganoid and the outcome determined the best choice for therapy. [26] Further, organoidled to collect biobank from different tumor cell lines and study genome features following cell propagation and development, so alternation in genetic profile such as mutations can be studied between tumouroid line and a derived tumor.[27]

The first study with long-term 3D primary culture was performed for odontogenic myxoma and the cemen to-ossifying fibroma with cell expansion more than one month.[28] More investigation is continued for human head and neck tumors with organoids. For example, 3D organoid provides target therapeutic screening based on a non-surgical method. [29] Detection of genetic factors that are involved in the molecular pathogenesis of odontogenic tumors helps us in target therapy, special gene therapy when surgical treatments are contraindicated.[30] This can serve as an alternative for other odontogenic lesions as non-surgical therapeutic approaches. (figure 2).

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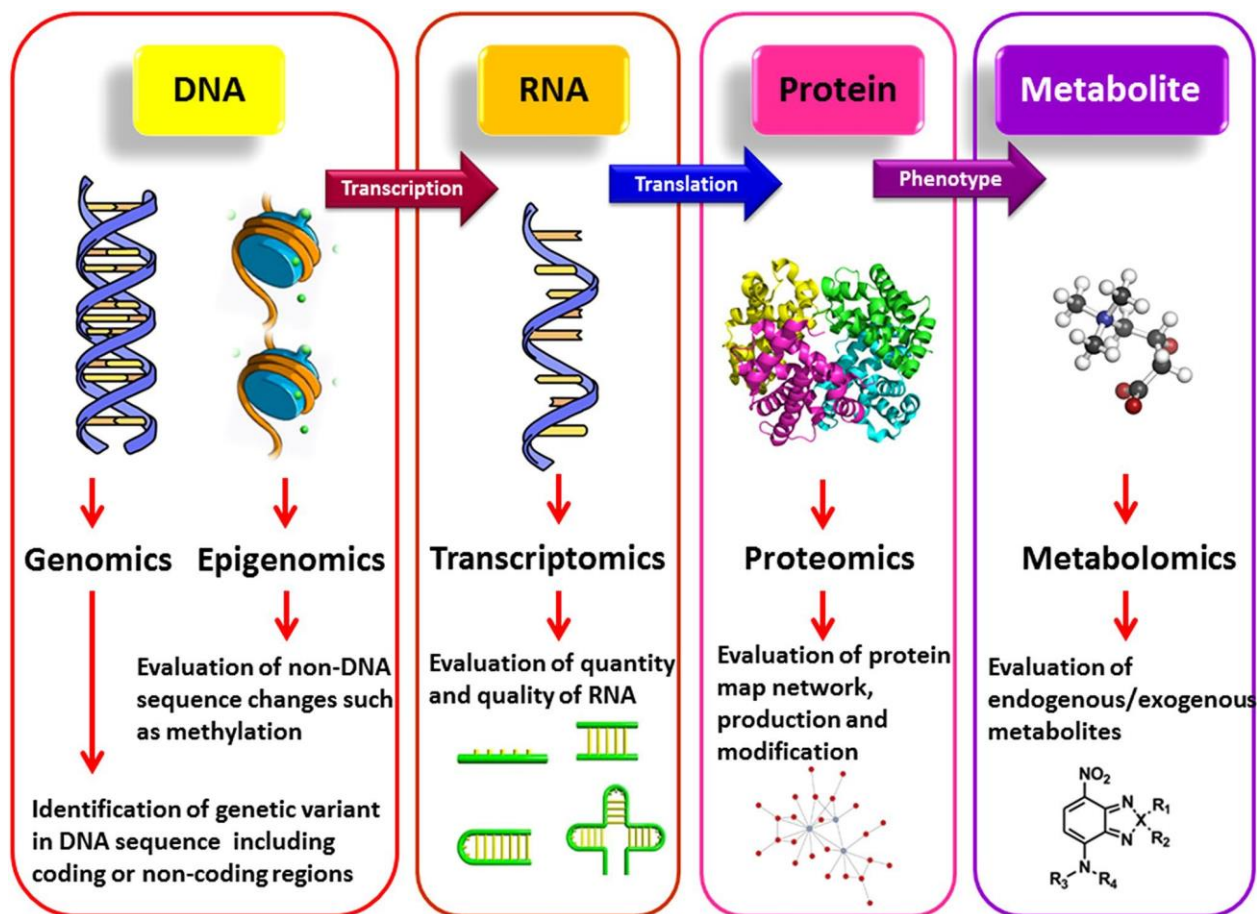
Fig. 1 Different main levels of "-omics" technology for evaluation of comprehensive molecules in the cell including genetic variants in DNA sequence (Genomics), non-DNA sequence alternation such as histone modification and methylation (Epigenomics), analysis of expression and structural changes in RNA and variants like splicesites(Transcriptomics), evaluation of an expression, modification and net protein interactions (Proteomics) and description of functional metabolites in cell (Metabolomics). The mix of different types of "-omics" technology can help us indiagnose, prognoses and therapeutic approaches of tumors.

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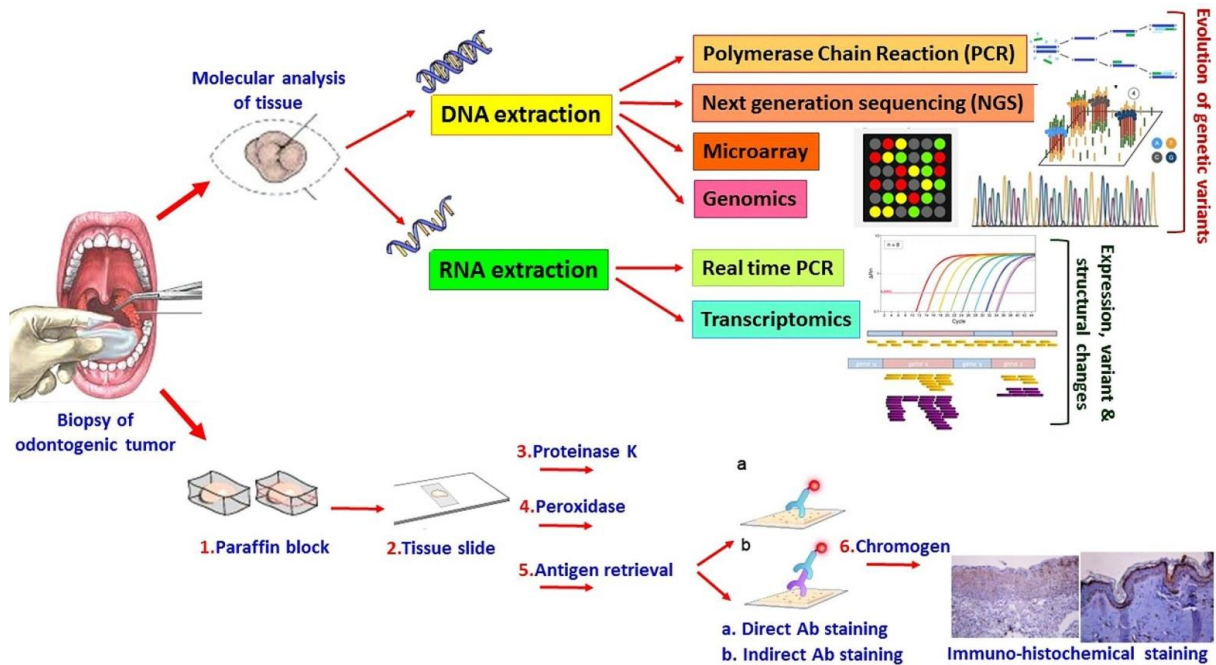
Fig.2 Summary of molecular genetics approaches and immune- histochemical method in diagnosis of odontogenic tumors

CONCLUSION

The restricted origin of odonto genic tumors (epithelial, mesenchymal, or mixed) might appear with similar morphology and histochemical features in differential diagnosis. So, mistaken diagnosis provides improper treatment because some odontogenic tumors need invasive therapy but others do not. The molecular advanced technology like next-generation sequencing or "omics" can identify all aspects of tumor changes and help us to consider more candidates in diagnosis, prognosis and therapeutic approaches. Target therapy in oral pathology needs more investigation, and it seems ethiopathological information of familial odontogenic tumors in different geographical regions can help us to modify our attitude to the pathogenesis of these lesions.

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Table 1 The last WHO classification of odontogenic tumors (2017) with diagnose and prognoses features

Odontogenic tumor	Clinical feature	Histopathologic feature	Differential diagnosis	Prognosis and treatment
Odontogenic carcinoma				
Ameloblastic carcinoma	Irregular marginated radiolucency. cortical expansion, perforation and infiltration into adjacent structures	Histological characters of malignancy in ameloblastoma	- Any odontogenic tumor with ameloblastic differentiation	- In 1/3 of patient metastasis to pulmonary - Most survival age is ~5 years - primary treatment: radical surgical excision - aggressive multimodality from the outset
Primary intraosseous carcinoma (PIOC), NOS	Slow growing of, pain, ulceration, loosening of teeth, non-healing extraction socket, and pathological fracture and nerve signs	small nest of neoplastic squamous without prominent keratinization	Squamous odontogenic tumors,intra osseous mucoepidermoid carcinoma, primary jaw SCC	- best predicted by histological grade - primary treatment: radical resection with neck dissection or for metastasis or reconstruction - multimodality treatment
Sclerosing odontogenic carcinoma (SOC)	Swelling, sometimes with nerve sign, sinus involvement	Single-file thin cords, nests and strands of epithelium in a densely sclerotic stroma	- Calcifying epithelial odontogenic tumor - Desmoplastic ameloblastoma	- Main treatment: resection
Clear cell odontogenic carcinoma	Almost are asymptomatic	Lobular sheets or islands composed of clear to faintly eosinophilic cytoplasm	Pindborg tumor (clear cell type), intra osseous mucoepidermoid carcinoma	- Variant behavior from indolent tumors to cases that frequently recur - Complete surgical resection
Ghost cell odontogenic carcinoma (GCOC)	Slow growing, swelling of the jaw, pain, ulceration, loosing of teeth, nerve signs, root resorption and sometimes soft tissue invasion	cytological evidences of malignancy associated with ghost cells, dentinoid formation		from slow growing, locally invasive carcinomas to highly aggressive and rapidly growing tumors with local recurrence and metastasis
Odontogenic carcinosarcoma				
Odontogenic sarcomas				
Benign epithelial odontogenic tumors				
Ameloblastoma:	Slow and painless loosening of teeth, paraesthesia, pain, soft tissue invasion, facial deformity, limited mouth opening	Ameloblastic differentiation,reverse polarity and central loosely arranged, stellate cells	- Any odontogenic lesion with ameloblastic differentiation	- Current treatment: surgical excision - New therapeutic approach based on *BRAF* targeting complement surgery
Ameloblastoma, unicystic type (UAM)	- Asymptomatic painless jaw expansion - Unilocular radiolucency	- Luminal, intraluminal types	odontogenic cysts - benign odontogenic tumors	- Initial treatment: enucleation - Further treatment is determined by pattern and extend of the ameloblastomatous proliferation
Ameloblastoma, extraosseous/ peripheral type	- Painless, sessile, exophytic lesion	ameloblastic differentiation,reverse polarity and central loosely arranged, stellate cells	- Peripheral odontogenic lesions - Reactive lesins	- Conservative removal with free margins is expected to be curative - Recurrence is rare, but long tem follow up is warranted
Metastasizing ameloblastoma	- More determined by clinical behavior - Diagnosis made only in retrospect			- - -

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Table 1 (continued)

Odontogenic tumor	Clinical feature	Histopathologic feature	Differential diagnosis	Prognosis and treatment
Squamous odontogenic tumor (SOT)	- Asymptomatic - Tumor grow slowly with bone expansion - Unilocular radiolucency	Differentiated squamous epithelium of varying shape and size cell keratinization	- Acanthomatous Ameloblastoma -desmoplastic variants -squamous cell carcinoma	- Remove by surgery - Recurrence is rare
Classify epithelial odontogenic tumor (CEOT)	grows slowly with bone expansion - Unilocular or multiocular mixed radiolucency	islands, cords and sheets of neoplastic polyhedral epithelial cells with relative pleomorphism, liesegang rings, without prominent mitotic activity	- Primary intraosseous squamous cell carcinoma -Central mucoepidermoid carcinoma, metastatic renal cell carcinoma, clear cell odontogenic carcinoma	- most cases treated with local surgical removal - recurrence rate is about 15%
Adenomatiod odontogenic tumor (AOT)	- Limit growth but many hamartomas - symptomatic with/without bony expansion - small loci of radiopacity	- encapsulated spindled epithelial cells, Rossette or duct like spaces, - Eosinophilic material within tumor like secretion product	- Odontoma - Ameloblastoma Classifying epithelial odontogenic tumor	- They are encapsulated and envariably enucleated - Recurrence rates are exceeding low
Benign mixed epithelial and mesenchymal odontogenic tumors				
Ameloblastic fibroma (AF)	- Slow growing, painless - Unilocular radiolucency, multicular related to larger lesions	- Mesenchymal component: myxoid, cell-rich and resembled the dental papilla of the tooth bud - Epithelial component: pattern of narrow, elongated strands of two tight and parallel-running with budding, layers of cuboidal to columnar cell or assembled follicular stage of enamel	- Early stage odontoma -Early stage Ameloblastic fibroodon-toma - Ameloblastoma	- Small, asymptomatic tumors (especially in young children) are removed conservatively; however, ulteraconservative treatment might result in recurrence - Extensive, destructive tumors treated radically
Primordial odontogenic tumor	- An unerupted tooth (most commonly the lower third molar) with apparent pericoronal relationship on radiographical image. - Most asymptomatic	loose fibrous tissue with variant fusiform and stellate fibroblast and peripheral columnar/cuboidal epithelium	- Odontogenic myxoma - Ameloblastic fibroma - Centeral odontogenic fibroma	- local excision - no recurrence until 20 years

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Table 1 (continued)

Odontogenic tumor	Clinical feature	Histopathologic feature	Differential diagnosis	Prognosis and treatment
Odontoma: Odontoma, compound type Odontoma, complex type	- Related to unerupted tooth and detectable in radiographs - Asymptomatic but may inflamed during trauma or eruption - Well-demarcated radiopacity surrounded by a thin soft tissue capsule and an adjacent corticated layer of bone - Radiological features: Compound type: diagnostic, many tooth-like structures. complex type: disorganized mass of classified tissues might in distinguish from other classified bone lesions	- Compound type: multiple rudimentary teeth demonstrating dentin, cementum, enamel matrix, pulp and adjacent fibrous with dental follicle - Complex type: tubular dentin enclosed zones of enamel matrix, decreased enamel epithelium with infrequent scattered ghost cell - A narrow layer of cementum in peripheral of mass	- Ameloblastic fibroma -Odontoameloblastoma	- Remove by conservative surgery if be low growth - Prognosis is excellent
Dentinogenic ghost cell tumor (DGCT)	- cortical bone expansion - unilocular or multilocular radiolucency radiolucent,mixed or radiopaque, well defined border	- Odontogenic epithelium with areas closely resembling ameloblastoma - Presence of ghost cells: Abberant keratinization with calcification	Ameloblastoma with ghost cell	- recommended treatment: segmental surgery - Conservative surgery (enucleation, curettage/simple excision), rate of recurrence: 73% until 20 years - radical surgery: marginal/segmental resection, rate of recurrence: 33% more than 1 years
Benign mesenchymal odontogenic tumors				
Odontogenic fibroma	asymptomatic, but large with pain, bony expansion, - Radiological features uniocular or multiocular - corticated margin	cellular or collagenous connective tissue with varying amounts of inactive-looking odontogenic epithelial islandshard tissue formation may observed	desmoplastic fibroma, Odontogenic myxoma, desmoplastic ameloblastoma, ameloblastic fibroma,— peripheral odontogenic fibroma: peripheral	- Treat of central odontogenic fibroma: enucleation, curettage,and need removal of adjacent involved teeth - Treat of peripheral odontogenic fibroma: surgical excision, extend down to periosteum Recurrence rate is 50%
Odontogenic myxoma/myxofibroma	- Slow, painless expansion - Early lesion are unilocular radiolucency but following enlargement become multilocular - Well-defined margin on radiographs - Soap-bubble or cubweb shape	- Resemble to dental papilla and follicle of the developing tooth - Proliferation of spindle-shaped to stellate fibroblast in back ground	- Primordial odontogenic myxoma - Central myxoid neurofibroma - Chondromyxoid fibroma - Myxoid chondrosarcoma	Small lesion: curtage, large lesion: en bloc or segmental resection Recurrence in ¼ of ceses with conservative therapy following incomplete excision

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Table 2 Summery of immune-histochemical odontogenic tumor markers

Marker	Function	Diagnostic marker
Cytokeratin (CK)	An intermediate filament (structural cytoskel-eton protein)	-
		- Ameloblastoma express CK 5, 14, 19, 56
		- Clear cell odontogenic carcinoma express CK5, 6, 14, 19 and pancytokeratin AE1/AE3
- Odontogenic tumors with epithelial originexpress CK14 and CK19		- Primordial odontogenic tumor strongly posi- tive for CK5, 14 and pancytokeratin AE1/AE3
- AOTs express CK 5, 14, 19		- DGCT epithelial cells express CK5, 7, 14, 19
		- CEOT express CK5, 6
		- Odontogenic fibroma positive for AE1/3,K8/18, K14, and K19
Amelogenin	Enamel matrix protein that organize enamelrods and mineralize enamel	- Express in odontogenic tumors with epithelialorigin such as ameloblastoma, AOT, CEOT, AF, malignant ameloblastoma and ameloblas-tic carcinoma
Ameloblastin (AMBN)	A cell adhesion molecule that inhibit amelo-blasts proliferation	Ameloblastoma, AOT, SOT, CEOT
Calretinin (calbindin-2)	A calcium-binding protein that modulate intracellular Ca^{++} ion	- Express in solid and unicystic ameloblastomas
Bone morphogenetic proteins (BMPs) differentiation,	Play role in cell proliferation, chemotaxis, extracellular matrix production, apoptosis and mesenchymal cell differentia-tion formation of calcified dental tissues and odon-togenic tumor development	- Express in epithelial odontogenic tumors suchas ameloblastomas and adenomatoid odonto- genic tumor
Tenascin	A glycoprotein play role in cell–cell and cell-extracellular matrix interactions	- Form calcifying mass in CEOT, ameloblasticfibro-odontoma (AFO) and odontoma
Nestin	A intermediate filament (structural cytoskel-eton protein)	- Odontogenic ectomesenchyme in mixed tumours such as AF, AFO, ameloblastic fibro-dentinoma (AFD) and ameloblastic fibrosar- coma (AFS)
High-mobility group A protein 2 (HMGA2)	Non-histone chromatin factor	- Over express in odontogenic mesenchymal tumors such as OM, odontogenic myxofi-broma
Basement membrane proteins	Distinction of extracellular matrix (ECM) and epithelium, adjacent connective tissuestroma	- Express in odontogenic tumors epitheliumsuch as laminin
Cytoskeleton remodeling protein (moesin andRhoA)	Connect the plasma membrane and cytoskel- eton with maintaining and remodeling them	- Strongly express in odontogenic epithelialcells and involvement in development of benign odontogenic l

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