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Pathogenesis of Adenomatoid Odontogenic Tumor – A Review

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Abstract: *Adenomatoid Odontogenic Tumorb (AOT) is a benign epithelial odontogenic tumour. Pathogenesis of AOT is explained with the help of many theories. Better understanding of the pathogenesis will help in developing new treatment approaches and better prognosis. An attempt is made to discuss the current concept of pathogenesis related to molecular and genetic changes.*

Keywords: *Odontogenic tumour, Pathogenesis, Adenomatoid odontgenic tumour*

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I. Introduction

The Adenomatoid Odontogenic Tumor [AOT] occurs only in the tooth bearing areas of jaws and shows histomorphologic resemblance to the tooth germ. AOT accounts for 3% to 7% of odontogenic tumours[1]. It has been reported from 3 to 38 years of age with 88% reported in second and third decade. It is more frequent in females, often located in the maxilla and is associated with unerupted permanent teeth[2]. AOT is considered as a hamartoma or developmental abnormality of remnant odontogenic epithelium[3]. It is a non invasive slow growing benign lesion. It arises from the remnants of dental lamina that persist in the jaws and teeth following Odontogenesis[4,5]

II. History

In 1948, Stafne first reported a series of Adenomatoid Odontogenic Tumor under the title "epithelial tumors associated with developmental cyst of maxilla"[6]. In 1950, Bernier and Tiecke published a case of AOT using the name 'Adeno ameloblastoma'[7]. In 1961, Gorlin et al introduced the term 'Ameloblastic adenomatoid tumour'[8]. In 1968, Abrams et al suggested the name Adenomatoid odontogenic tumour[9]. In 1969, Philipsen and Birn proposed the term Adenomatoid odontogenic tumour[10]. This term was adopted by WHO Histologic typing of Odontogenic tumours in 1971 and is retained till the new edition in 2017[11].

The epithelial rests are confined to the gabernaculum dentis which guides eruption of succedaneous teeth and permanent molars. When the tumor envelops the crown, it will disrupt the gabernaculum dentis. As the guiding influence of gabernaculum dentis is lost, the eruption of permanent tooth adjacent to odontogenic tumor will not occur. Hence a pericoronal lesion is associated with unerupted teeth. Electron microscopic and immunohistochemical studies have confirmed that AOT tumor cells are metabolically similar to ameloblasts during amelogenesis and are capable of generating enamel proteins and extracellular matrix molecules.[12,13,14]

The aim of the study is to update the pathogenesis of AOT. A PUBMED/MEDLINE search was done using the key words pathogenesis, Adenomatoid odontogenic tumour and relevant literature from reviewed from 1948 onwards.

III. Pathogenesis

According to kumamoto etal [15] Epithelial mesenchymal interactions play an important role in normal tooth development and in neoplasia. Hepatocyte growth factor [HGF] and Transforming growth factor β [TGF-β] play an important role in neoplastic cells and in the surrounding stromal cells. Activity of HGF and TGF-β were found to be marked in pseudoglandular cells in AOT and the epithelial differentiation characteristic of AOT is affected by these molecules.

Perdigao etal[16] suggested that Ameloblastin gene express a protein, AMBN which plays an important role in differentiation of ameloblast cells and epithelial mesenchymal signalling during odontogenesis. DNA extraction and mutation analysis of Adenomatoid odontogenic tumour [AOT] and normal mucosal cells were done using Polymerase chain reaction. The results demonstrated novel mutations in AOT, while normal mucosal cells showed the wild type of DNA sequence.

Crivelini etal[17] evaluated the Immunohistochemistry for cytokeratin, vimentin, laminin, Proliferating Cell Nuclear Antigen[PCNA], p53 in tumour. CK14 labelling indicated that the tumour showed differentiation grade for ameloblasts in secretory stage. Laminin found in the luminal surface of adenomatoid structures corresponds to the protective stage of amelogenesis. PCNA labelled specifically in the spindled areas and peripheral cords of AOT indicates the areas of tumour growth. The found that the results of their study suggest AOT to be a hamartomatous growth with origin from reduced enamel epithelium.

Fujitha etal[18] studied the immunohistochemical expression of nestin in adenamatoid odontiogenic tumour. Nestin is one of the intermediate filament constituiting the cytoskeleton. It is a marker of nestin stem cells or progenitor cells. It's expression is also related to tooth development and repair of dentine. They immunohistochemically studied the expression of nestin in Adenomatoid odontogenic tumour and found positivity for nestin in small nodular foci and rosette patterns.

Poomsawat etal[19] studied the expression of basement membrane components laminin 1and 5, collagen type IV and fibronectin in AOT. Lamini 1 was expressed in the cytoplasm of all cells. A linear labell]ing of laminin 1and5,collagen type IV and fibronecin. They suggested that laminin 1 may act as a chemoattractant of stromal and vascular cels and it modulates epithelial mesenchymal interactions leading to epithelial cell growth signals.

Moreira etal[20] used the Methylation specific polymerase chain reaction to evaluate the presence of methylation status of p16, p21, p27, p53 and RB1 gene in AOT. The methylated gene found in AOT were Cyclin dependent kinase inhibitor genes p16 and p21. p21 methylation is correlated with the transcriptional repression and could lead to defects in cell cycle regulation. AOT shows a distinct methylation profile in cell cycle associated genes. These findings shows that epigenetic alteration are common in this epithethelial tumours.

Freitas etal[21] showed the expression of matrix metalloproteinases in adenomatoid odontogenic tumour. MMPs play an important role in cell proliferation, angiogenesis and apoptosis. AOT showed strong expression of MMP-7 and MMP-26 in the epithelium as well as stroma, which suggests the role of MMP's in tissue remodelling.

Krishna etal[22] used a specific marker Murine Double Minute [MDM2] to identify proliferative activity and tumour aggressiveness. They found the expression of MDM2 expression found only in a minority of cases and the positivity was observed mainly in whorls and to a lesser extend in ducts and sheets.

Ide etal[23] AOT is a tooth associated lesion and the permanent successor has an eruptive pathway from the dental follicle to gingiva, the gabernaculum dentis. AOT may arise successfully from epithelial remnants in close proximity with crown of permanent tooth and gabernaculum dentis may be implicated in its development. Gabernacular cord is the fibrous band running in the bony channel that connects the perifollicular tissue of successional tooth with the overlying gingival. Grossly thickened gabernacular canal was continuous with fibrous capsule of AOT and dental follicle. Microscopically it resembled remnants of dental lamina.

Crivelini etal[24] Screening for expression of amelogenesis-related proteins represents a powerful molecular approach to characterize odontogenic tumors and investigate their pathogenesis. They examined the presence and distribution of odontogenic ameloblast-associated protein (ODAM), amelotin (AMTN), ameloblastin (AMBN), and amelogenin (AMEL) by immunohistochemistry in samples of adenomatoid odontogenic tumor (AOT) and found that amelotin stained the eosinophilic material of AOT's.

Poomsawat etal[25] Hepatocyte growth factor (HGF) and its receptor, c-met regulates cell proliferation, motility and morphology in a variety of cell types. HGF and c-met were generally immunolocalised in the cytoplasm of all epithelial cell tumour cells. This suggests that the HGF/c-met pathway is involved in the differentiation of odontogenic tumors. This pathway may promote tumor proliferation in odontogenic tumors due to its potent mitogenic effect.

Razavi etal[26] Ki-67 is a non-histone protein which is seen only in proliferating cells and this protein reveals mitotic activity in cells. Another protein used in the study was Bcl-2. This protein has an antiapoptotic effect on cell proliferation, so those cells express these markers behave in a tumoral manner. Adenomatoid odontogenic tumors were selected and immunohistochemical evaluation was done for Ki-67 and Bcl-2. The mean values of Labeling Index for Ki-67 and Bcl-2 found to be less in solid ameloblastomas which reflects the hamatomatous nature of Adenomatiod odontogenic tumor.

Karathanasi etal[27] studied the TGF-β/Smad signaling pathway which regulates different cellular functions, like development of tooth, and is also involved in numerous pathological processes such as tumorigenesis. AOT showed strong expression of Smad-1/-5/-8 and Smad 4. TGF-β/Smad signaling pathway is activated in AOT and these biomarkers can serve as a supplemental diagnostic aid.

Harnet etal[28] investigated for the first time the immunohistochemical and mutational status of β-catenin in adenomatoid odontogenic tumor. They evaluated the immunohistochemical expression of β-catenin and mutations of the β-catenin gene (CTNNB1). T found a strong cytoplasmic expression of β-catenin, but no

molecular anomaly was found within the exon 3 of CTNNB1. β-catenin is considered to play a role in cell differentiation processes.

Guimaraes etal [29] studied the expression of DNA methyl transferase in AOT. The DNA methyltransferases (DNMTs) catalyses the addition of methyl radical during the process of DNA Methylation which is considered to be an an important in regulation of gene expression. DNA methylation refers to the covalent addition of a methyl group to the 5-carbon position of a cytosine nucleotide. The high expression of DNMTs in AOT suggest that DNA methylation is an important process in the pathogenesis of these tumours.

Reichart etal[30] reviewed the immunoprofile of AOT including cytokeratin profiles, extracellular matrix proteins, Integrins, ameloblast-associated proteins resorption regulators (RANK, RANKL), p53, PCNA, MDM2 protein, cyclin D1, Ki-67, Bcl-2 metallothionein, metalloproteinases, D56 hepatocyte growth factor, c-met, DNA methyltransferase, podoplanin, TGF-*β*I, Smad-2/3, Smad-I-5/-8, Smad 4, beta- catenin, calretinin, and clonality. Review suggest that AOT shows the features of a hamartoma rather than a neoplasm.

Basilio etal[31] reviewed the epigenetic alterations reported in odontogenic tumours focusing mainly on DNA methylation which regulates the gene expression. Their review suggests that epigenetics is a emerging mechanism that should be considered in the etiopathogenesis of odontogenic tumours.

Tables [1]

Molecular Markers In AOT

MOLECULAR MARKER	EXPRESSION IN AOT	INDICATION
Transforming growth factor β	Increased	Promote Cellular differentiation
Hepatocyte growth factor	Increased	Promote tumor proliferation
Enamel proteins ameloblastin, amelogenin and amelotin	Increased	Cytodifferenciation
CK14, laminin, PCNA and p53	Increased	AOT is hamartomatous with histogenesis from the reduced enamel epithelium.
MMP-7 and MMP-26 [Matrix metalloproteinases]	Increased	MMP has a role in tissue remodelling
Ki-67 and Bcl-2	Increased	Mitotic activity, Antiapoptosis
β-catenin	Increased	Promote cell differentiation process
DNA methyl transferase	Increased	Methylation regulates gene expression

IV. Conclusion

Pathogenesis of Adenomatoid odontogenic tumour is multifactorial. Thorough understanding of the pathogenesis of Adenomatoid odnotogenic tumour will help in developing advanced techniques for the early diagnosis and better prognosis. The molecules involved in pathogenesis of AOT is summarized in TABLE [1] the molecules involved in pathogenesis can act as molecular markers.

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