Review Article

PATHOGENESIS OF ODONTOGENIC TUMORS OF EPITHELIAL ORIGIN- A REVIEW

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Abstract:
Odontogenic tumours are lesions derived from the epithelial and/ or mesenchymal elements of the tooth forming apparatus and are therefore found exclusively within the jaw bones. Histologically, they may resemble soft tissues of the enamel organ or dental pulp, or they may contain hard tissue elements of enamel, dentine, and/ or cementum. Lesions in this group range from hamartomatous proliferations to malignant neoplasms with metastatic capabilities. An understanding of the biologic behaviour of the various odontogenic tumours is fundamentally important to the overall treatment of patients. This review discusses the pathogenesis of odontogenic tumours of epithelial origin: Ameloblastoma, Squamous odontogenic tumour, Calcifying epithelial odontogenic tumour and Adenomatoid odontogenic tumour.
Key words: Ameloblastoma, Squamous odontogenic tumour, Calcifying epithelial odontogenic tumour and Adenomatoid odontogenic tumour.

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INTRODUCTION

Odontogenic tumours are lesions derived from the epithelial and/ or mesenchymal elements of the tooth forming apparatus and are therefore found exclusively within the jaw bones. These development associated tumours (i) often occur in children or young adults and exhibit considerable histologic variation, (ii) are usually intraosseous tumours that contain various amounts of epithelial components and interact with their specific microenvironment, and (iii) are generally benign tumours, but several odontogenic tumours show locally invasive behaviour with a high risk of recurrence.

Histologically, they may resemble soft tissues of the enamel organ or dental pulp, or they may contain hard tissue elements of enamel, dentine, and/ or cementum. Lesions in this group range from hamartomatous proliferations to malignant neoplasms with metastatic capabilities. An understanding of the biologic behaviour of the various odontogenic tumours is fundamentally important to the overall treatment of patients.

Several histologic classification schemes have been devised for this complex group of lesions. Common to all is the division of tumours into those composed of odontogenic epithelial elements, those composed of odontogenic mesenchyme, and those that are proliferations of both epithelium and mesenchyme.

This review discusses the pathogenesis of odontogenic tumours of epithelial origin: Ameloblastoma, Squamous odontogenic tumour, Calcifying epithelial odontogenic

tumour and Adenomatoid odontogenic tumour.

AMELOBLASTOMA

Ameloblastomas are benign odontogenic tumours, of epithelial origin. Their histological appearance resembles that of developing tooth. The tumour islands are lined by cuboidal or columnar epithelium, resembling pre ameloblast and centrally loosely connected cells, which resembles stellate reticulum cells.[1]

The pathogenesis of ameloblastoma has remained an intriguing area for scientific investigations. Leider et al suggested that ameloblastomas may recapitulate some of the cell types and developmental events, observed in the developing enamel organ, but the tumour cells fail to synthesize enamel matrix protein.[2] The suggested tissues for origin of this tumour are- Enamel organ, Remnants of dental lamina, Rests of Malassez, Epithelial lining of odontogenic cysts and Oral epithelium.

Confirmation of the origin of ameloblastomas from odontogenic epithelium has been provided by many studies. Theselff and Ekbolm showed that distribution of keratin and laminin are comparable in enamel organ of developing tooth with that of epithelium in ameloblastomas. The difference lies in the fact that, the basement membrane connected with pre ameloblast like cells in tumour islands does not break down, as it does during normal odontogenesis when ameloblast differentiate. Because of this, tumour epithelium never undergo differentiation to the point of enamel formation.[1] Although differentiation to ameloblasts does not occur, the basal cells mimic inner enamel epithelium cells of the bud to bell stage.[3] Theselff[1] in his study concluded that, odontogenic cells are progenitor cells from which ameloblastomas arise. This view was further supported by studies of Kollar, who underlined the importance of interactions between epithelial cells and underlying mesenchyme, necessary for epithelial differentiation. The presence of amelogenin in ameloblastomas has further confirmed their odontogenic origin. The more probable origin for ameloblastomas is from odontogenic rests of dental lamina. These are most common in the vicinity of the roots of teeth, but they may be present in the overlying mucosa. They could therefore be a source of both, intraosseous and extraosseous ameloblastomas. The frequent occurrence of the tumour at the angle of the mandible is explained by the fact that posterior end of dental lamina proliferates continuously and that aberrant tooth germs are most often found in this region.

The observation that ameloblastoma may show a connection with the oral mucosa has led to the theory that ameloblastomas arise from basal offshoots of basal layer of oral mucous membrane. This theory is not acceptable because, growth of an ameloblastoma from within the jaw can extend until the alveolar mucosa is reached and then the two different epithelia's fuse together. Ameloblastomas certainly do not arise from oral mucosa unrelated to tooth bearing areas, which further refutes the above hypothesis.

Currently the theory of defective cell interaction is believed to play a role in the pathogenesis of ameloblastomas.[1] With the above evidences it can be hypothesized that ameloblastomas represent derangement in the reciprocal exchange of instructive signalling, which normally operates in developing tooth organ. Epidermal growth factor is one such signalling molecule contributing to odontogenic tumorigenesis.[4]

It was also believed that some ameloblastomas can originate from epithelial linings of non neoplastic odontogenic cysts. Since both lesions originate from odontogenic epithelium, the possibility of neoplastic change in this epithelium cannot be denied. However this seems less likely because many of the reported cases of ameloblastomas arising in odontogenic cysts were indeed unicystic ameloblastomas.[5]

In 1977, Robinson and Martinez described a distinct variety of ameloblastoma known as unicystic ameloblastoma. The gross and microscopic features indicted that this variant was associated with a large cystic cavity with either luminal or mural proliferation.[2] Leider et al, proposed three plausible pathogenic mechanisms for it, which are:-

1. The reduced enamel epithelium associated with a developing tooth undergoes ameloblastic transformation with subsequent cystic development.
2. The ameloblastomas may arise in dentigerous or other type of dental cyst in which the neoplastic ameloblastic lining is preceded temporarily by a non neoplastic stratified squamous epithelial lining.
3. A solid tumour undergoes cystic degeneration of ameloblastic islands with subsequent fusion of multiple microcysts to develop a multicystic lesion.

Another variant of ameloblastoma is a granular cell ameloblastoma. Histochemical and ultrastructural studies of this variant have suggested that the cytoplasmic granularity is due to high content of lysosomes. During normal amelogenesis, ameloblasts show an increase in autophagic lysosomes between the secretive and absorptive stages and during transformation from reduced enamel epithelium to squamous epithelium. Thus the odontogenic epithelium seems to undergo granular changes in this condition.[5]

It is currently thought that the granular change probably occurs as a consequence of an altered function of tumour cells, a hypothesis supported by the finding that this tumour is age related.

It is generally accepted that an ameloblastoma has the potential to arise from the epithelial rests of Malassez, reduced enamel epithelium that envelops the impacted teeth, or the gingival epithelium.[6] Many desmoplastic ameloblastomas on coronal CT images appear to be continuous with periodontal space. These images might suggest that desmoplastic ameloblastoma arises from the periodontal ligament, but just radiographic evidence is not enough. However support may be garnered from the presence of oxytalan fibers in the stromal tissue of this tumour. These oxytalan fibers are characteristically seen in periodontium.[7]

On the basis of these radiographic and histologic findings, it is believed that the tumour might have initially developed in periodontal tissues, with subsequent growth onto the surface of original cortex and eventual elevation of the periosteum. Finally newly formed periosteal bone could have been laid down on the surface of the tumour, resulting in the radiographic appearance of the lesion as smoothly outlined and with thinning of cortices.

This tumour can be differentiated from peripheral ameloblastoma because the latter actually originates from the gingival surface epithelium, therefore, compressing the periosteum, not elevating it.[8]

Myoken et al demonstrated the expression of growth factors and their receptors in ameloblastomas and suggested them as a contributing factor for tumour progression. The idea that growth factors may have a role in tumour growth as well as in development is a striking hypothesis. Recently it has been reported that FGF and their receptors are highly expressed in ameloblast layer of tooth germ in mouse embryos. It was demonstrated that in ameloblastomas, FGF-1 was present in ameloblast like cells and stellate reticulum – like cells, but absent in basement membrane. FGF-1 acts as a potent autocrine factor on the ameloblastic cells enhancing their growth. FGF-2 was present in more amounts in basement membrane. FGF-2 may be secreted by an unknown mechanism from epithelial component of ameloblastomas and may bind to basement membrane. It has been reported that FGF-2 increases production of collagenases and

plasminogen activator, which are thought to be critical events in tissue remodelling. Thus FGF-2 expression in ameloblastoma may lead not only to tumour growth but also to local invasion, by inducing the production of proteases.[9]

Etiologically, the site of ameloblastomas links them to the dental lamina. The morphologic similarity between the two indicates a causal relationship. The acanthomatous, plexiform and follicular arrangement could reflect an embryonic cellular spectrum with junctional tendencies. This may mimic the surface epithelium from which the dental lamina is derived, the lamina itself or the dental organ that its cells are destined to produce. The multiple finger- like columns of proliferating cells of dental lamina are highly reminiscent of the peripheral invasive expansion seen in association with ameloblastomatous growth. Recently Abdelsayed et al had demonstrated that ameloblastomas express parathyroid hormone related protein (PTHrP). They suggested that PTHrP expression in ameloblastoma plays a role in local bone resorption and may at least in part provide explanation for the infiltrative growth and destructive behaviour of this tumour.[10]

SQUAMOUS ODONTOGENIC TUMOUR (SOT)

SOT is a rare odontogenic tumour consisting of islands of well differentiated Squamous epithelium in a fibrous stroma. The epithelial islands occasionally show foci of central cystic degeneration. The origin of SOT is unclear, although there are indications that it arises from rests of Malassez in the periodontal ligament. Peripheral SOTs may originate in the gingival surface epithelium as a “dropping off” phenomenon or from remnants of the dental lamina. In cases where the origin of the SOTs was supposed to be the surface epithelium, the tumours appeared histologically as pseudoepitheliomatous hyperplasias or peripheral ameloblastoma.[11]

The cases reported in association with embedded teeth indicate that, the tumour may also develop from proliferation of epithelial rests of dental follicle. Pullon et al called attention to the possible hamartomatous nature of SOT, because of multiple site involvement in one of their cases.[12] In fact this provides an illustration of the wide spectrum of differentiation and proliferation of gingival epithelium. A familial pattern was noted by Leider et al.[13] Because the lesion is epithelial in nature and arises in the periodontium, origin from rests of Malassez appears to be reasonable hypothesis.[14]

CALCIFYING EPITHELIAL ODONTOGENIC TUMOUR (CEOT)

This neoplasm, also known as Pindborg’s tumour, clinically resembles ameloblastomas, but microscopically there is no resemblance. CEOT is believed to be odontogenic in origin, although the specific cells from which it is derived and the stimulus for growth is unknown. However stratum intermedium of the enamel organ has been postulated as a source for its origin. The CEOT is a benign neoplasm located either intra- osseously or extra-osseously. However, it is more common in intraosseous location and in premolar to molar region of mandible.

Any attempt to determine the histogenesis of CEOT must be related to its constant association with an unerupted permanent tooth. As no remnants of the enamel organ remain within the tissue of fully erupted tooth the implication is that the reduced enamel epithelium is probably involved in the origin of the tumour. This theory was based on serial sections, which suggested origin from a structure histologically compatible with reduced enamel epithelium.[15] When the enamel has completely matured the ameloblasts degenerate and can no longer be differentiated from the cells of stratum intermedium and the outer enamel epithelium. These cells form the outer

stratified epithelial covering for the enamel.[15]

Johnson and Bevelander showed that prior to the engagement of the erupting tooth with the oral mucosa, the stratum intermedium proliferates into multicellular layer overlaid by degenerating ameloblasts. They concluded that the epithelial attachment of the tooth is a product of the stratum intermedium. It is therefore postulated that this tumour is a rare consequence of continued proliferation by the cells of the reduced enamel epithelium and in particular those of the original stratum intermedium. This is believed to be an attempt to carry out their normal function with the oral epithelium, when the tooth for some reasons fails to erupt.

Another possibility suggested is transformation of the dentigerous cyst lining into CEOT. This is largely based on the fact that some dentigerous cysts can get transformed into ameloblastoma, although incidences of such cases have fallen drastically after establishment of unicystic ameloblastoma as an entity.[16]

Further the appearance of reports of the cases of intraosseous CEOT without an associated unerupted tooth and cases of peripheral CEOT, it became evident that other sources than reduced enamel epithelium should be considered in pathogenesis of CEOT. The peripheral location strongly suggests the possibility that the tumour arises from rests of dental lamina, or from the basal cells of oral epithelium. In order to conceptualize a unified source of origin for the diverse locations of CEOT, one has to look to odontogenic epithelium with widespread occurrence. Disintegration of dental lamina gives rise to a countless number of epithelial remnants persisting in the jaw bones and gingiva after completion of odontogenesis.[5]

The basic histologic pattern of CEOT is an unusual and variable combination of odontogenic epithelium and calcified structures. Four patterns of histologic features of CEOT have been explained[17]:-

Pattern 1- consists of sheets, nests, and masses of polyhedral epithelial cells with deeply eosinophilic cytoplasm. Cellular abnormalities, including bi- or multinucleated cells, giant cells and nuclear pleomorphism are regularly seen. However, the common appearance of two or more nuclei in these cells might in fact represent lobes of a deeply indented nucleus rather than separate nuclei. Calcified corpuscles and confluent calcified masses are seen in fibrous stroma.

Pattern 2- numerous spaces are present in the tumour cell mass, which give it a cribriform appearance. There is less variation in nuclear size and multinuclear cells containing giant nuclei are rare. Some of the eosinophilic, homogeneous material filling the cribriform spaces appears to undergo calcification and becomes concentric corpuscles, which may coalesce to form larger calcified masses with a Leisegang calcification pattern.

Pattern 3- the epithelial tumour cells appear either scattered or arranged in cell dense areas of varying sizes. Cell size varies greatly and multinucleated giant cells are frequently seen. Stroma may contain mucoid matters.

Pattern 4- the tumour consists of nests and chords of epithelial cell. The variable quantity of connective tissue may contain eosinophilic homogeneous material, calcified bodies as well as diffuse dystrophic calcifications.

The true nature of eosinophilic tumour cell product occurring in CEOT is controversial. An origin from light chain fragments of immunoglobulin molecules has been proposed for some forms of systemic amyloid. Another type is probably associated with endocrine tumours, where it is referred as APUD – amyloid.[18] Another theory postulated for the production of amyloid is that the epithelial cells secrete or modify some precursor proteins, which subsequently may become altered extracellularly.[19] In EM studies, these homogeneous substances appear as

either fibrillar or granulo- fibrlillar material. Yamaguchi et al supported the amyloid concept, but also agreed that it is likely that the material having a beta – protein configuration is similar to enamel matrix. In the scant fibrous connective tissue stroma of CEOTs, studies have demonstrated the presence of cementum like components. The mechanism of formation of the cementum like material is still unclear. However majority of the calcifications in CEOT are thought to be dystrophic calcifications. In the study by El- Labban it was found that the outer layer of the calcified lamellar bodies consisted of typical banded calcified collagen with an arrangement like that seen in cemental sharpey fibers. Slootweg suggested that the amyloid like material is an inductive stimulus for the stroma cells to differentiate toward production of a collagenous matrix that is destined to mineralize and resembles cementum. El – Labban noted that the fully calcified amyloid masses consist of calcified collagen. This was clearly demonstrated by Van Gieson stain and the ultrastructural finding of typical banded collagen. This author referred the calcified collagen layer as cementum like material. The use of this term was based on the arrangement of collagen fibers in this layer at right angles to the surface of lamellar bodies into compact calcified layer and relatively loose uncalcified free ends reminiscent of sharpey's fibers of the root cementum.[19] In some cases of, epithelium may show large cells with clear and foamy cytoplasm and distinct cell borders. It has been shown histochemically that these clear cells contain glycogen. Anderson et al interpreted the clear cells as representing a degenerative process. Yamaguchi et al, however, believed that the tumour cells represent the feature of cytodifferentiation rather than that of simple degeneration.

Another variation is presence of Langerhans cells. These cells belong to the mononuclear phagocyte system and are also found in the skin and oral mucosa. Langerhan cells in CEOT may play a role either in antigen presentation or in regression of this tumour.[20] Some studies have reported that CEOT has a dual cell population. In addition to the usual polyhedral cells, peripheral cells with very elongated profiles and juxtaposed to tumour epithelial cells, have been reported. These cells, based on their Ultrastructural properties, resemble myoepithelial cells. This cell type, although found in tumours of glandular origin, have not been described previously in any odontogenic tumours. But its occurrence in CEOT is not yet confirmed by other studies.[21]

Since its recognition as entity, CEOT have been described as epithelial odontogenic tumour. Recently it is believed that the mineralized epithelially derived material appears to stimulate the adjacent stroma. This stroma then deposit the material resembling cementum, by its cellularity and brush borders with radially arranged cells, as well as material recognized as bone by its cellular nature. Based on these facts, authors suggested that CEOT have some characteristics in common to mixed odontogenic tumours.[22] The role of the Sonic hedgehog pathway in the pathogenesis of CEOT has been investigated. Immunoreactivity for Sonic hedgehog pathway proteins was evaluated using antibodies to the receptor PTCH as well as to the transcription factors Gli1 and Gli2. PTCH gene sequencing was completed using PCR. The study implicated that the Sonic hedgehog pathway in the pathogenesis of the CEOT through sequencing. Similar to other odontogenic neoplasms, gene mutations in PTCH1 are present in the CEOT.[23] Studies have suggested that ameloblastin gene alterations may be relevant to the pathogenesis of CEOT. DNA sequencing was modified in an important domain of the ameloblastin in CEOT.

ADENOMATOID ODONTOGENIC TUMOUR

The histology of adenomatoid odontogenic tumour (AOT) is characterized by the

formation of duct like structures and whorl shaped tumour cell nests in which eosinophilic droplets are scattered.[24] Stafne (1948) originally suggested that AOT arises from epithelium entrapped in the lines of embryonic fusion. This theory is unacceptable, as it is unable to explain the occurrence of AOT in mandible. Aisenburg (1953), Cahn (1955), and Oehler (1956) proposed that stem cell was from epithelium that differentiated into glandular epithelium. Spouge (1967) considered AOT to be a benign and orderly proliferation of cells at the enamel organ stage of differentiation, whereas Chambers suggested origin from epithelial cell rests of Malassez around the apex of the deciduous teeth. Most authors support this point of view that the lesion is not a tumour but an overgrowth of odontogenic tissue or more properly hamartoma.

Electron microscopic studies suggest that this tumour is derived from cells of inner enamel epithelium at the pre ameloblastic stage.[25] AOT contains four types of cells, namely, polygonal cells, flat cells, star shaped cells, and cuboidal cells. The order of arrangement of each cell type resembled that of the enamel organ of normal tooth germ, from apically the inner enamel epithelium, stratum intermedium, stellate reticulum and outer enamel epithelium. Further, the presence of fine filamentous layer and finger like cytoplasmic processes in these cells are similar to those in normal tooth germ at the beginning of predentin formation. The tumour cells lining the duct like structures and small eosinophilic areas seem to be comparable to the ameloblasts of differentiating stages. But in this tumour, mesodermal cells, which have the potential to form dentin, are not present. Due to this, the ameloblast like cells could not further differentiate and development is thus arrested at the stage before enamel matrix formation.

In order to conceptualize a unified source of origin for the diverse location of AOT, one has to look to odontogenic epithelium with a widespread occurrence in the jaws. To this requirement, only dental lamina complex and its remnants match.[25]

Disintegration of complex system of dental lamina gives rise to numerous epithelial remnants persisting in the jaw bones and in the gingival after odontogenesis. Significantly these epithelial remnants are not haphazardly distributed, but confined to the soft tissue of gubernaculum dentis (GD). The GD is composed of fibrous connective tissue and runs in intrabony or through gubernacular canals, which connect the bony crypts of the developing permanent teeth with lamina propria of gingiva. GD is believed to guide or direct the course of erupting permanent teeth. Thus epithelial remnants occur like “pearls on a string”, from the dental sac around a developing permanent tooth to the gingival mucosa. What initiates the proliferation of epithelial remnants and gives rise to tumorous/ hamartomatous lesions remain speculative.[25] Prior to the eruption of a permanent tooth, proliferation starts in cell nests of the successional dental lamina remnants located in the GD close to the dental sac. Continued tumour growth possibly combined with initial tooth eruption may lead to contact and later fusion between tumour and the reduced enamel epithelium of the erupting tooth. Sooner or later, the tumour embraces the tooth resulting in characteristic follicular variant of AOT. Although this appears as dentigerous cyst, closer examination of the operation specimen reveals that, AOT often extends laterally from one surface of crown of unerupted tooth. These observations as well as experimental evidences strongly support the envelopmental concept.[25]

Duct like structures has been suggested to be a type of basement membrane, although these structures appear to be “outside – in” forms of the true ductal walls. Such extracellular matrix substances in AOT are believed to be derived from secretions of the tumour cells. AOT specific extra cellular matrices such as luminal contents of duct like structures, eosinophilic hyaline droplets, and small mineralized particles,

have been previously interpreted as a form of enamel, dentin, cementum and dystrophic calcification.[19]

Lee suggested that the nature of the eosinophilic material is heterogeneous and may be comprised of at least three components, namely an amyloid like material, dystrophic calcification of degenerating tumour cells and a dentin like material. He demonstrated the presence of collagen, reticulin and amyloid.[26]

EL- Labban, in addition to collagen and amyloid, also demonstrated fine filamentous layer which is perpendicular to the epithelial basal lamina. This layer resembles to that described in early dentin formation.[19] The presence of collagen masses in this tumour has been interpreted by some authors as representing dentin like material. However, both the thickness and distribution of collagen fibers in these masses is different from those of dentin matrix, which are usually thicker and randomly arranged. Hence these authors do not support the presence of dentin in AOT.

Authors in their ultrastructural studies of CEOT have shown that, amyloid results from degradation of basal lamina material, probably secreted by epithelial cells of this tumour.[27] In AOT, however, such relationship is absent. Lee suggested that in AOT amyloid material is within the stroma of the lesion and not the secretory product of epithelial cells.[26] However Smith et al suggested that it may be of enamel protein origin, which, like amyloid have a β pleated protein configuration.[28] Recently Murata et al immunolocalized enamel proteins in mineralized materials and hyaline in tumour cell nests of AOT. Since it is now evident that the biosynthesis and secretions of enamel proteins and extra cellular matrix molecules by AOT cells are synchronized, which also occurs in normal odontogenesis, the odontogenic characteristics of this tumour can be confirmed functionally.

The simultaneous retention of enamel proteins and basement membrane associated extra cellular matrix molecules in the duct like structures and stromal spaces of AOT suggests that both enamel proteins and extra cellular matrix molecules play an important role in formation of duct like structures. Since the duct like structure retains extra cellular matrix molecules, these authors have proposed them to be a kind of 'stromal cyst'. Murata et al interpreted their results as follows: amelogenin is expressed in AOT cells when they formed solid nests, and some of the synthesized amelogenin was deposited in the extracellular space as eosinophilic hyaline deposits or variously shaped inner stromal space. But the extracellular deposits were soon degraded by AOT cells. Finally no more amelogenin is left in pseudo cystic space. In contrast, enamelin seemed to last longer because it was localized in the cystic spaces.

These authors also noted that the co localization of basement membrane associated macromolecules as type IV collagen, laminin, fibronectin and type V collagen in the luminal space of the pseudocystic structures is basically similar to immunolocalization of above molecules in lamina basalis ameloblastica. This lamina is located beneath the line of preameloblasts and separates them from odontoblasts or predentin of normal tooth germ. This fact suggests that AOT cells have the ability to synthesize molecules, as pre ameloblasts do, although neither odontoblastic nor predentin linings are induced in AOT.[24] The mineralized particles in AOT did not seem to be related to eosinophilic hyaline materials or pseudocystic structures. The immunopositivity for Type I collagen in mineralized particles suggests that mineralization is initiated from the extracellular milieu but not from cellular components, although the mineralized products traced somewhat the tumour cell contour. Therefore mineralization in AOT must take place in a process different from that of AOT specific structure formation.[24]

CONCLUSION

The development and progression of odontogenic tumours are affected by alterations of many kinds of genes and molecules. In particular, the characteristics of odontogenic tumours appear to depend on the molecular mechanisms associated with (i) tooth development, (ii) bone metabolism, and (iii) the malignant potential of tumours. Further molecular studies, including genomic and proteomic based profiling, are required to clarify the etiology and pathogenesis of odontogenic tumours.

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