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Exploring Ameloblastoma – A Literature Review

[1] Dr.Archana Muthukrishnan, [2]Dr.K.Balasankari, [3]Dr.G. Keerthana, [4]Dr.M.Arunachalam, [5]Dr.M.Sathish kumar

[1]CRI, [2,3]Postgraduate, [4]Reader, [5]Head of the Department

Karpaga Vinayaga Institute of Dental Sciences, Chengalpet, India

ABSTRACT

Ameloblastoma is a group of odontogenic tumors of the jaws that arise from ectomesenchyme or epithelial remnants associated with tooth development. The majority of them speculate that the tumor's growth and development may be connected to the intricate process known as the epithelium-mesenchymal transition (EMT), which allows cells to dynamically change from having a mesodermal shape to a morphological one. The etiopathogenesis of these tumors is still incompletely understood. The most common site of the lesion is the mandibular premolar area, which accounts for 32.6% of cases. The lesion's histological subtype and the existence of mural invasion are two important variables to take into account when evaluating the histopathological features of atypical lesions. This article gives a complete review of ameloblastoma, pathophysiology, clinical features and its management.

Keywords: ameloblastoma, aggressive, odontogenic tumor

INTRODUCTION

A group of cancers known as odontogenic tumors of the jaw arises from ectomesenchyme or epithelial remnants associated with tooth development [1]. It is a heterogenous group of lesions consisting of hamartomatous, benign, or malignant neoplasms. There have been significant recent developments in our understanding of the genetic basis of certain odontogenic tumors, even though the etiopathogenesis of the majority of odontogenic tumors is still unknown. The regulation of crucial cellular processes is closely linked to the mitogen-activated protein kinases/extracellular signal-regulated kinases (MAPK/ERK) pathway, which is frequently dysregulated in a number of human neoplasms [2].

According to WHO classification of odontogenic tumors,2022 [4,5]

BENIGN EPITHELIAL ODONTOGENIC TUMOURS	BENIGN MIXED EPITHELIAL AND MESENCHYMAL ODONTOGENIC TUMORS	BENIGN MESENCHYMAL ODONTOGENIC TUMORS	MALIGNANT ODONTOGENIC TUMOURS
Adenomatoid odontogenic tumour	Odontoma	Odontogenic fibroma	Sclerosing odontogenic carcinoma
Squamous odontogenic tumour	Primordial odontogenic tumour	Cementoblastoma	Ameloblastic carcinoma
Calcifying epithelial odontogenic tumour	Ameloblastic fibroma	Cemento-ossifying fibroma	Clear cell odontogenic carcinoma
Ameloblastoma, unicystic	Dentinogenic ghost cell tumour	Odontogenic myxoma	Ghost cell odontogenic carcinoma
Ameloblastoma, conventional			Primary intraosseous carcinoma, NOS
Adenoid ameloblastoma			Odontogenic carcinosarcoma
Metastasizing ameloblastoma			Odontogenic sarcomas

HISTORY:

Cusack published the first description of ameloblastoma in 1827[11,12]. Malassez coined the term "adamantinoma" in 1885, and it is currently used to describe a rare type of bone cancer that Fisher reported in 1913[11,13]. Falkson presented the first full description of it in 1879. Ivey and Churchill first used the term "ameloblastoma" in 1930[11,14,15].

Ameloblastoma is an odontogenic epithelial tumor that mostly consists of enamel organ-type tissue that has not reached differentiation to the stage of tooth formation. It is the second most prevalent odontogenic neoplasm. It frequently manifests as a slowly expanding, painless swelling that causes the lingual and/or buccal plates to perforate, the cortical bone to expand, and soft tissue to infiltrate. Due to its gradual growth, the diagnosis is sometimes delayed [26,27]. The male to female ratio is 1:1, and its peak incidence occurs in the third and fourth decades of life. Its incidence was 0.6 cases/million overall [11,16,17].

The fourth version of the WHO Classification of Head and Neck Tumors was published in 2017.The four types of ameloblastoma described by this most recent categorization are as follows, and it is a simplification of the prior versions [29,30]

WHO CLASSIFICATION OF AMELOBLASTOMA (2017)
Ameloblastoma
Unicystic ameloblastoma
Extraosseous / peripheral ameloblastoma
Metastasizing ameloblastoma

For traditional ameloblastoma, the term "solid/multicystic" was eliminated because it has little bearing on prognosis and can be mistaken for unicystic ameloblastoma [29,31].

PATHOPHYSIOLOGY:

Ameloblastoma arises from epithelial tissues associated with tooth formation, such as the lining of odontogenic cysts, the enamel organ, the Malassez epithelial cell resting, and the decreased enamel epithelium [6,32]. Ameloblastoma etiology has been explained by a number of concepts. The majority of

them speculate that the tumor's growth and development may be connected to the intricate process known as the epithelial-mesenchymal transition (EMT), which allows cells to dynamically change from having an epithelial to a mesenchymal shape. Research indicates that EMT mediates the migratory and invasive potential of several tumor cell types and induces transcriptional alterations in genes [6,33,34]. The importance of the MAPK/ERK signaling system in the molecular pathogenesis of some odontogenic cancers is known, despite the fact that the molecular pathogenesis of these tumors remains incompletely understood. Ameloblastoma has been linked to mutations in the genes involved in the MAPK/ERK pathway [2,3]

The initial investigation by the Heikinheimo group revealed recurring activating BRAF p.V600E mutations in ameloblastomas in 2014 [2,3] . Given that transmembrane receptors, such as EGFR, can activate MAPK/ERK signaling and that EGFR overexpression has been linked to ameloblastomas in the past, the researchers screened ameloblastoma cultured cells which showed resistance to EGFR-targeted inhibition cells for the mutant BRAF p.V600E. Following the discovery of the mutation in this index instance, Kurppa et al. said that BRAF p.V600E mutation was identified in 62.5% (15/24) of cases of samples with ameloblastoma using Sanger sequencing. In additionally, these writers' analysis showed the usefulness of the monoclonal antibody VE1 that is specific to BRAF p.V600E to identify ameloblastomas with the BRAF p.V600E mutation by Histopathology and immunohistochemistry [2,3].

CONVENTIONAL AMELOBLASTOMA

Eighty-six percent of all ameloblastomas are conventional. It occurs as growths arising from the remains of the odontogenic epithelium, exclusively rests of dental lamina [11] Neoplastic alterations in the wall or lining of a non-neoplastic odontogenic cyst, specifically dentigerous and odontogenic keratocysts, can also result in SMAs [11]

CLINICAL FEATURES:

They often develop in the third and fourth decades of life. It begins slowly but aggressively, destroying the cortical bone and then leaking into adjacent tissue [6,11]. Majority of cases occurs between the age group of 33-39 years and 10% of cases are reported in children. There is no sex predilection. Although ameloblastoma can occur anywhere in the jaws, it most frequently affects the mandible. Compared to the premolar and anterior regions combined, the molar angle-ramus area is affected three times more frequently [23]

RADIOGRAPHIC FEATURES:

Ameloblastoma has been described classically as a multilocular cyst like lesion of the jaw. The tumour appears compartmentalized,With bone septa extending into the radiolucent tumor mass. However, the lesion is frequently unilocular and lacks any pathognomonic or distinctive characteristics[23]. Conventional ameloblastoma appears radiographically as large, radiolucent, multilocular images that resemble soap bubbles or honey comb pattern. The associated non-erupted tooth gets displaced as the cortical plate thins, enlarges, and occasionally erodes. There is a pronounced resorption of the neighbouring teeth' roots [6,7].

HISTOLOGICAL FEATURES:

Conventional ameloblastoma can be distinguished into various subgroups, based on cell morphological patterns. Vickers and Gorlin's description of the characteristic histological pattern of ameloblastoma is distinguished by:

- peripheral layer of tall columnar cells
- palisaded and hyperchromatic nuclei
- reversal polarity of nuclei
- subnuclear vacuole formation
- stroma - moderate to dense collagenized
- connective tissue. [11,23]

HISTOLOGICAL VARIANTS OF AMELOBLASTOMA
Follicular ameloblastoma
Plexiform ameloblastoma
Acanthomatous ameloblastoma
Granular ameloblastoma
Basal cell ameloblastoma
Desmoplastic ameloblastoma

Of all the subtypes, plexiform and follicular have the highest occurrence [6,8,9].

FOLLICULAR AMELOBLASTOMA:

The follicular form is the most common variant of ameloblastoma. It consists of several little islands with a reversely polarized nucleus in a cuboidal or columnar call periphery layer. These cells enclose a centre mass of polyhedral, loosely distributed cells that resemble the stellate reticulum, and they have a strong resemblance to ameloblasts or pre-ameloblasts. Clinically, in certain cases, there are microscopic cysts visible with close examination and removal of the lesion. Peripheral columnar cells in these cases frequently flatten to resemble low cuboidal or even squamous cells. In these cases, the stellate reticulum-like tissues have experienced full collapse or cystic degeneration.
In this type, cyst development is comparatively common [23]

PLEXIFORM AMELOBLASTOMA:

The tumor cells that resemble ameloblasts are grouped as asymmetrical masses or, more commonly, into a web of interconnected cell strands. Stellate reticulum-like cells can be found in between the columnar cell layers that encircle each of these masses or threads. The development of anastomosing islands of odontogenic epithelium with double rows of columnar cells are arranged back-to-back. The plexiform variety of ameloblastoma has a far less noticeable stellate reticulum-like tissue than the follicular variant. Cystic stromal degeneration is very frequently observed in these areas.[23]

ACANTHOMATOUS AMELOBLASTOMA:

The cells that make up the stellate reticulum undergo squamous metaplasia, and at the centre of the tumor islands, keratin production can occasionally occur. This typically happens in ameloblastoma that are of the follicular variety. Sometimes epithelial or keratin pearls are even visible.[23]

GRANULAR CELL AMELOBLASTOMA:

there is a noticeable change in the cytoplasm, often of the cells that resemble stellate reticulum, giving it a rough, granular, and eosinophilic look. This frequently encompasses the periphery cuboidal or columnar cells as well. Ultrastructural studies, like as that of Tandler and Rossi, have established that these cytoplasmic granules comprise lysosomal aggregates with no noticeable cellular components. Granular cell ameloblastoma is a form of lesion that appears to be aggressive and has a notable proclivity for recurrence unless adequate surgical procedures are adopted at the time of the initial operation. Hartman has documented a series of 20 examples of this condition. Furthermore, a few of these kinds of cases have been documented as metastasizing [23]

BASAL CELL AMELOBLASTOMA:

exhibits profound resemblances to skin basal cell carcinoma. The epithelial tumor cells of this subtype are thought to be the rarest histologic subtype; they are typically organized in sheets and exhibit more primitive and less columnar characteristics than those in other tumor kinds [23]

DESMOPLASTIC AMELOBLASTOMA:

found in a thick collagen stroma that might be a hypocellular, hyalinized appearance. The desmoplastic ameloblastoma has a greater tendency to grow in thin strands and cords of epithelium rather than in an island like pattern. The thick hyalinized stroma nearly looks to squeeze and fragment the epithelial growth. In epithelial proliferation, central cells are often scant, while the cells that make up the strands and cords' periphery frequently have a cuboidal or flattened appearance as opposed to a tall, columnar one. Reversible polarity of subnuclear vacuoles and nuclei formation could be hard to recognize. [11,23].

TREATMENT:

In cases of solid/multicystic ameloblastoma, enucleation has to be carried out. However, the guideline recommends a drastic course of action with 1.5–2 cm security margins in the event of recurrence. The first five years of post-operative follow-up should involve annual assessments, and the next ten years should see biannual assessments [28,48]. According to certain research, the best course of action for the small lesions associated with multicystic ameloblastoma is marginal excision. However, in about 15% of the cases, there are reports of recurrence [28,46].

PERIPHERAL AMELOBLASTOMA

Peripheral ameloblastoma (PA) is an ameloblastoma that is restricted to the gingival or alveolar mucosa. It infiltrates the surrounding tissues, mainly the gingival connective tissue, instead of penetrating the underlying bone [11,18]. The so-called "glands of Serres," vestiges of the dental lamina, odontogenic remains of the vestibular lamina, pluripotent cells from minor salivary glands, and pluripotent cells in the basal cell layer of the mucosal epithelium are the sources of the PA [11,19]. Fibrous epulis is frequently first confused with an exophytic development, which is restricted to the soft tissues covering the tooth-bearing regions of the jaws. Surgery may show superficial bone degeneration known as cupping or saucerization, even if radiographic evidence of bone involvement is typically lacking.
With a slight gender gap, the population's average age is 52.1 years. The male to female ratio is 1.9:1 in comparison to the solid variety. The mandible to maxilla ratio is 1:2.6. The mandibular premolar region is the most frequent location, making for 32.6% of instances. [11, 20]. A broad local excision is the most popular treatment for peripheral amelablastoma. Despite the rarity of malignant transformation, metastasis and a 9% recurrence following treatment have been documented [11,21,22].

HISTOLOGICAL FEATURES:
Peripheral Ameloblastoma can have a variety of histological features, similar to conventional ameloblastoma. As seen in our instance, it has a noticeable propensity to be acanthomatous. However, granular cell [51,52] and desmoplastic variants [51,53] . Greer and Hampton examined the ultrastructural features of their case and discovered that the electron microscopic appearance resembled that of cutaneous basal cell carcinoma and intraosseous ameloblastoma [23]

TREATMENT:

Conservative supraperiosteal surgical excision with sufficient disease-free margins is currently the preferred course of treatment [51,20]. Since late recurrences are recorded, continuous monitoring is required.

UNICYSTIC AMELOBLASTOMA

Robinson and Martinez coined the term "Unicystic Ameloblastoma" in 1977[11,24] although the World Health Organization referred to it as "cystogenic ameloblastoma" in the second edition of their worldwide histologic categorization of odontogenic tumors. Five to fifteen percent of ameloblastomas are unicystic in nature [11,25].

CLINICAL FEATURES:

It is a less aggressive variant of intraosseous ameloblastomas with a low recurrence rate. It accounts for 15% of all ameloblastomas and is more common in the second or third decade. It is similar to an odontogenic cyst both clinically and radiologically [6,11].

HISTOLOGICAL FEATURES:

According to the degree of tumor cell proliferation inside the cyst wall, unicystic ameloblastomas can be classified histopathologically into three categories [6,8,10]

Ackermann [42] classified this entity into the following three histologic groups:

HISTOLOGIC TYPE	DESCRIPTION
Luminal	Tumour confined to luminal surface of the cyst
Intraluminal /plexiform	Nodular proliferation into the lumen without infiltration of tumour cells into the connective tissue wall
Mural	Invasive islands of ameloblastomatous epithelium in the connective tissue wall not involving the entire epithelium

TREATMENT:

According to the 2010 management strategy, unicystic ameloblastomas should be treated with marsupialization at first, and then a careful radiological evaluation should be performed to see if the lesion is shrinking[28,48] Several publications state that curettage and enucleation are effective treatments for smaller, unicystic lesions. These operations can also be combined with other auxiliary procedures including cryotherapy, peripheral osteotomy, and the use of Carnoy's solution[28,50]

METASTASIZING AMELOBLASTOMA

Metastasizing ameloblastoma is an uncommon tumour with a 1% incidence rate.15% of the cases are diagnosed as metastatic at the time of the primary lesion, but a large percentage of cases of this variant are diagnosed between three months and 24 years after the primary tumour, with an average latency time of 8.23 years [40,41]

CLINICAL FEATURES:

It is more prevalent in male [35-38]. initial tumour originated in the mandible. The lung followed by cervical lymph nodes were the preferred locations for metastasis[35,39]

While 33% of patients are less than 20 years old, the average age of patients upon presentation is 30 years old. Metastatic nodules appear in the lung (80%), cervical lymph nodes (15%), or extragnathic bones after an average of roughly 11 years. Pulmonary metastases usually affect both lungs and are multifocal. Following the identification of the metastatic lesion, the median survival is roughly two years. Quiet metastases may be concealed by benign lung "granulomas" that appear on routine chest images in ameloblastoma patients [23]

Usually, there is no increased cytologic atypia or mitotic activity in the metastatic ameloblastoma compared to the primary. Ameloblastoma that metastasizes, officially known as "malignant ameloblastoma," unmistakably exhibits the biological characteristics of a well-differentiated low-grade carcinoma [23]

It was obvious that radiolucent/hypodense multiloculated radiographic presentation and/or irregular borders dominated the initial lesion's radiographic appearance[35,39]

TREATMENT:

Metastatic ameloblastoma is managed best by surgery. Neck dissection is the treatment for the metastases of cervical lymph node. Lobectomy is an option for removing lung metastases if sufficient lung function can be maintained. During surgery, it is common to find more pulmonary metastatic deposits than what the diagnostic imaging scans showed. Chemotherapy has often been ineffective, yet there may be a temporary partial response[23]

CONCLUSION:

Selecting the optimal course of treatment is a crucial decision that should always be focussed on the removal of the lesion, taking into consideration the potential morbidity associated with the chosen approach as well as its impact on the patients' quality of life and ability to recover [28,43]

The lesion's histological subtype and the existence of mural invasion are two important variables to take into account. [28,44,45].

More invasive techniques are required when the ameloblastoma grows to a bigger volume and compromises a significant amount of cortical bone and anatomical structures. These procedures incorporate segmental extraction with the brokenness of the bone piece, indeed expelling the periosteum and covering delicate tissue[28,47].

Certain procedures can be incorporated into the final resolutive procedure to minimize the extent of the surgery required to remove the lesion and lower the chance of a recurrence[28,49]. One method that has been applied in certain extensive ameloblastomas is marsupialization. This operation is aimed at minimizing the size of the lesion and ensuring a second surgical procedure which will be safe for anatomical structures.

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