Ameloblastoma - A brief Review

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Abstract: Ameloblastoma is a benign odontogenic tumour generally present in the jaw bone. The tumour originates from the residual epithelium of the tooth germ, epithelium of odontogenic cysts stratified squamous epithelium and epithelium of the enamel organ. It represents approximately 1% of oral tumours. About 80% of ameloblastomas occur in the mandible, mainly the third molar region and the remaining 20% in the upper jaw. Ameloblastoma clinically appears as an aggressive odontogenic tumour, often asymptomatic and slow-growing, with no evidence of swelling.(1)

I. INTRODUCTION
The word ameloblastoma derives from the early English word “amel,” meaning enamel and the Greek word “blastos,” meaning germ. Ameloblastomas represent about 1% of all jaw tumours, but they are the second-most common odontogenic tumour. They are much more common in the lower jaw than in the upper jaw, and more common in the posterior mandible as compared to the anterior.(2)

II. HISTORY
Ameloblastoma, is derived from the English word “amel” which means enamel and the Greek word “blastos” which means the germ.[3] It arises from the epithelium of the dental lamina, and it is characterized by its local aggressive behavior and a high recurrence rate. Ameloblastoma was first described in 1827 by Cusack.[4] In 1885, Malassez introduced the name “adamantinoma,” which is presently used to illustrate a rare form of bone cancer described by Fisher in 1913.[5] It was first detailed and described by Falkson in 1879. The term ameloblastoma was coined by Ivey and Churchill in 1930,[6,7] a currently accepted term. It is considered as a true neoplasm as the name implies it mimics the cells of the enamel-forming organ. It was described by Robinson in 1937, as a benign tumor that is “usually unicentric, nonfunctional, intermittent in growth, anatomically benign and clinically persistent.” The World Health Organization (WHO) (1991) defined ameloblastoma as a benign but locally aggressive tumor with a high tendency to recur, consisting of proliferating odontogenic epithelium lying in a fibrous stroma.[8]

III. PATHOGENESIS
The earlier workers noted the resemblance between the odontogenic apparatus and the ameloblastoma and suggested that the neoplasm was derived from a portion of this apparatus or from cells potentially capable of forming dental tissue. Malassez described small collections of epithelial cells adjacent to the roots of teeth in the periodontal ligament and suggested that the ‘adamantine epithelioma’ was produced by a proliferation of these cell rests. Most authorities consider the ameloblastoma to be of varied origin, although the stimulus initiating the process is unknown. Thus the tumour conceivably may be derived from:
-Cell rests of the enamel organ, either remnants of the dental lamina or remnants of Hertwig’s sheath, the epithelial rests of Malassez.
-Epithelium of odontogenic cysts, particularly the
-Dentigerous cyst, and odontomas.
-Disturbances of the developing enamel organ.
-Basal cells of the surface epithelium of the jaws.
-Heterotrophic epithelium in other parts of the body, especially the pituitary gland.

IV. CLASSIFICATION
Ameloblastoma is classified, according to WHO and the International Agency for Research on Cancer, 2003, as a benign tumor with odontogenic epithelium, mature fibrous stroma and without odontogenic ectomesenchyme. Ameloblastoma is further classified into:

- Solid/multicystic
- Extraosseous/peripheral
- Desmoplastic ameloblastoma
- Unicystic.

IV1 SOLID/MULTICYSTIC AMELOBLASTOMA

The solid or multicystic ameloblastoma is a benign epithelial odontogenic tumor of the jaws.[1] It is slow- growing locally aggressive and accounts for about 10% of all odontogenic tumors in the jaw.[12] Solid multicystic ameloblastoma (SMA) occur as growths arising from remnants of odontogenic epithelium, exclusively from rests of the dental lamina. SMAs may also arise as a result of neoplastic changes in the lining or wall of a nonneoplastic odontogenic cyst, in particular dentigerous and odontogenic keratocysts.[13] Signaling pathway such as WNT, Akt and growth factors like fibroblast growth factor play a pivotal role in the pathogenesis of solid type of ameloblastoma. Proteins mainly bone morphogenic protein ameloblastin, enamel matrix proteins calretinin, syndecan-1 and matrix metalloproteinases also play an important contribution in the etiopathogenesis. Tumor suppressor
genes p53, p63 and p73 bring about molecular changes in the pathogenesis of ameloblastoma. p53 plays an important role in the differentiation and proliferation of odontogenic epithelial cells. Matrix metalloproteases, triggers mitogens to be released, leading to the proliferation of ameloblastomacells.[14]

Mostly this type is diagnosed in young adults, with a median age of 35 years and no gender predilection. About 80% of ameloblastomas occurs in the mandible,[2] frequently in the posterior region.[12] The lesions more often progresses slowly, but are locally invasive and infiltrates through the medullary spaces and erodes cortical bone. If left untreated, they resorb the cortical plate and extend into adjacent tissue. Crepitation or eggshell cracking might be elicited posterior maxillary tumors might obliterate the maxillary sinus and consequently extend intracranial.[15]

Radiographically SMAs show an expansive, radiolucent, multiloculated cystic lesion, with a characteristic “soap bubble-like” appearance. Other findings include cystic areas of low attenuation with scattered regions representing soft tissue components. Thinning and expansion of the cortical plate with erosion through the cortex is elicited, with the associated unerupted tooth displaced and resorption of the roots of adjacent teeth common.[16]

Six histopathologic subtypes of solid ameloblastoma includes follicular, plexiform, acanthomatous, basal cell, granular and DA. Mixtures of different histological patterns are commonly observed, and the lesions are frequently classified based on the predominant pattern present. The follicular pattern type has the highest recurrence rate of 29.5% and acanthomatous type having the least recurrence rate of 4.5%, and the rate of recurrence depends on the histologic subtypes. The epithelial component of the neoplasm proliferates in the form of Islands, strands and cords within the moderately to densely collagenized connective tissue stroma. A prominent budding growth pattern with small, rounded extensions of epithelium projecting from larger islands, recapitulates the various stages of enamel organ formation. The classical histological pattern of ameloblastoma described by Vickers and Gorlin is characterized by peripheral layer of tall columnar cells with hyperchromasia, reverse polarity of the nuclei and subnuclear vacuole formation.[17]

Follicular type is composed of many small islands of peripheral layer of cuboidal or columnar cells with reversely polarized nucleus. Cyst formation is relatively common in follicular type. The term plexiform refers to the appearance of anastomosing islands of odontogenic epithelium, with double rows of columnar cells in back to back arrangement. In acanthomatous type, the cells occupying the position of stellate reticulum undergo squamous metaplasia, with keratin pearl formation in the center of tumor islands. In granular cell ameloblastoma, cytoplasm of stellate reticulum-like cells appear coarse granular and eosinophilic. Basal cell type, the epithelial tumor cells are less columnar and arranged in sheets. Desmoplastic variant is composed of the dense collagen stroma, which appears hypocellular and hyalinized.[17]

Other histological types are papilliferous-keratotic type, clear cell type, and mucous cell differentiation type. SMAs contain clear, periodic-acid Schiff positive cells most often localized to the stellate reticulum-like areas of follicular SMA.[13] Keratoameloblastoma consists partly of keratinizing cysts and partly of tumor islands with papilliferous appearance. Mucous cell type of ameloblastoma shows focal mucous cell differentiation, with vacuolated mucous cells.[18]

The main modality of treatment is surgery, with wide resection recommended due to the high recurrence rate of solid/multicystic ameloblastomas. The recurrence rate after resection is 13-15%, as opposed to 90-100% after curettage.[19] Recommend a margin of 1.5-2 cm beyond the radiological limit is implicated to ensure all microcysts are removed.[20]

### IV. PERIPHERAL AMELOBLASTOMA

The peripheral ameloblastoma (PA) is defined as an ameloblastoma that is confined to the gingival or alveolar mucosa. It infiltrates the surrounding tissues, mostly the gingival connective tissue, but it does not involve the underlying bone.[21] The PA arises from remnants of the dental lamina, the so-called “glands of Serres,” odontogenic remnants of the vestibular lamina, pluripotent cells in the basal cell layer of the mucosal epithelium and pluripotent cells from minor salivary glands.[22]

The PA is an exophytic growth restricted to the soft tissues overlying the tooth-bearing areas of the jaws, the initial diagnosis often mistaken for fibrous epulis. In the majority of cases, there is no radiological evidence of bone involvement, but a superficial bone erosion known as cupping or sauceration may be detected at surgery. The overall average age is 52.1 years, slightly higher for males than for females. The male/female ratio is 1.9 : 1, as opposed to 1.2 : 1 for the solid type. The maxilla/mandible ratio is 1 : 2.6. The mandibular premolar region accounts for 32.6% and is the commonest site.[23] Histologically same patterns are as in solid type, with a common type being acanthomatous.[17] Differential includes peripheral reactive lesions such as pyogenic granuloma, epulis, papilloma, fibroma, peripheral giant-cell granuloma, peripheral odontogenic fibroma, peripheral-ossifying fibroma, Baden's odontogenic gingival epithelial hamartoma, and basal cell carcinoma.[23]

The PA is mostly treated with a wide local excision. 9% of recurrence following treatment has been reported, though malignant transformation is rare, metastasis has also been reported.[24,25]

### V. DESMOPLASTIC AMELOBLASTOMA

Desmoplasic ameloblastoma was first reported by Eversole et al. in 1984 and was recently included in the WHO's classification of head and neck tumors (WHO-2005).[26] This tumor is characterized by an unusual histomorphology, including extensive stromal collagenization or desmoplasia, leading to the proposed term ameloblastoma with pronounced desmoplasia or DA.[27]

Radiographically it produces mixed radiolucent - radioopaque lesion with diffuse border that indicates that the tumor is more aggressive than other variants of ameloblastoma.[28] Mixed radiologic appearance expresses the infiltrative pattern of the tumor and when the DA infiltrates the bone marrow spaces, remnants of the original nonmetaplastic or nonneoplastic bone were found to remain in the tumor tissue. The infiltrative behavior of the DA explains one of the characteristic features of the tumor, the ill-defined border.[13]

The DA also appears as a poorly defined, mixed, radiolucent-radioopaque lesion mimicking a benign fibro-osseous lesion, especially when evaluating panoramic and periapical radiographs.[29,30] Histologically DA appears as irregularly shaped odontogenic
epithelial islands surrounded by a narrow zone of loose-structured connective tissue embedded in desmoplastic stroma.[31]
About 15.9% rate of recurrence has been reported in DA cases treated by enucleation and/or curettage, with an average recurrence period of 36.9 months.[29] The majority of DA cases reported treated by resection, most likely due to ill-defined borders, consequently suggesting an infiltration process and aggressive biological behavior.[32]

IV. UNICYSTIC AMELOBLASTOMA
Unicystic ameloblastoma (UA) represents an ameloblastoma variant, presenting as a cyst that show clinical and radiologic characteristics of an odontogenic cyst. In histologic examination shows a typical ameloblastomatous epithelium lining part of the cyst cavity, with or without luminal and/or mural tumor proliferation. In 1977, Robinson and Martinez first used the term “UA,”[33] but it was also named in the second edition of the international histologic classification of odontogenic tumors by the WHO as “cystogenic ameloblastoma.” 5-15% of all ameloblastomas are of the unicystic type.[15] Five to 15% of all ameloblastomas are of the unicystic type. UA with an unerupted tooth occurs with a mean age of 16 years as opposed to 35 years in the absence of an unerupted tooth. The mean age is considerably lower than that for solid/multicystic ameloblastoma with no gender predilection.[15] UA is a prognostically distinct entity with a recurrence rate of 6.7-35.7%, and the average interval for recurrence is approximately 7 years. Three pathogenic mechanisms for the evolution of UA: Reduced enamel epithelium, from dentigerous cyst and due to cystic degeneration of solid ameloblastoma.[34] Six radiographic patterns are identified for UA, ranging from well-defined unilocular to multilocular ones. Comparing unilocular and multilocular variants, there is an apparent predominance of a unilocular configuration in all studies of UA, especially in cases associated with impacted teeth.[35] UA might mimic other odontogenic cysts clinically and radiographically. Histopathological classification of UAs are:[36]
- Luminal UA
- Luminal and intraluminal UAs
- Luminal, intraluminal, and intramural UAs
- Luminal and intramural UAs.

Treatment of UA includes both radical and conservative surgical excision, curettage, chemical and electrosurgery, radiation therapy or combination of surgery and radiation.

V. HISTOPATHOLOGY- Ameloblastic carcinoma is generally more aggressive and has a worse prognosis in late disease. Ameloblastic carcinoma has certain features of benign ameloblastoma such as reverse polarisation, peripheral palisading, and stellate reticulum-like cells. It has features of malignancy common to many cancers such as high nuclear to cytoplasmic ratio, increased mitoses with atypical forms, cytological atypia, and necrosis. The following are some features of ameloblastic carcinoma.(37)(37.1)

1) High mitotic figure
2) Cellular atypia
3) High proliferative mitotic index
4) Perineural or perivascular invasion
5) Nuclear atypia such as nuclear pleomorphism

Malignant ameloblastoma, on the other hand, has these histological features:

1) Lack of mitotic figure
2) Normal ameloblastic cells
3) Lack of a mitotic index
4) No perineural or perivascular invasion
5) Normal polarized ameloblastic nucleus
VI. RADIOGRAPHIC FEATURES

The ameloblastoma has been described classically as a multilocular cyst like lesion of the jaw. This is especially true in advanced cases of ameloblastoma. Here, the tumour exhibits a compartmented appearance with septa of bone extending into the radiolucent tumour mass. In many cases, however, the lesion is a unilocular one and presents no characteristic or pathognomonic features. The periphery of the lesion on the radiograph is usually smooth, although this regularity may not be borne out at the time of operation. In the advanced lesion producing jaw expansion, thinning of the cortical plate may be seen radiograph. The term cystic ameloblastoma is frequently, referring to certain of these neoplasms. It is important, there is no correlation between the term and the appearance of the tumour on the radiograph. Radiographic film does nothing more than indicate the presence or absence of calcified tissue, and a variety may manifest themselves in manner similar to the Ameloblastoma.

VII. CLINICAL FEATURES

A wide age range of occurrence of the tumor from 10 years through 90 years has been reported. The average age at diagnosis is in the range of 33-39 ears, and most cases cluster between ages 20 and 60 years. Only about 10% cases are reported to arise in children. Then 1/3rd of those occur in children younger than 10 yrs.No significant sex predilection has been reported. There is conflicting evidence on the incidence rates in different races. Although some reports claim an increased incidence of ameloblastoma in black individual. A large study identifies asian as the population with the greatest number of affected patients.

Ameloblastoma occurs in all areas of the jaws but the mandible is the most commonly affected area. (More than 80% of all cases.). Within the mandible the molar angle ramus area is involved three times more commonly than are the premolars and anterior region combined. When comparing large studies, it appears that maxillary tumour tends to occur in slightly older patients than do mandibular lesions. The incidence of occurrence of ameloblastoma in different sites within the jaws has been shown to vary among racial groups.

VIII. TREATMENT AND PROGNOSIS:

There is some differences of opinion about the preferable method of treatment of the ameloblastoma. The only unanimity centre around the fact that complete removal of the neoplasm, regardless of how it is accomplished, will result in a cure of the patient. The types of treatment that have been used include both radical and conservative surgical excision, curettage, chemical and electrocautery, radiation therapy or a combination of surgery and radiation. The majority of workers today prefer some form of surgical excision. Curettage is least desirable. since it is associated with the highest incidence of recurrence, The basic principles of treatment have been discussed in detail by Gardner and Mehlisch and his colleagues. Frissell reviewed the reported cases in which radiation therapy was utilized and found that there was considerable variance of opinion as to its benefit. The report of Kimm supported by study of serial biopsy, on the treatment of the ameloblastoma by radiation indicated that this neoplasm is generally highly radio resistant and that the use of this form therapy is not warranted. Wide clinical experience has show the truth of this finding. Regardless of the form of treatment long-term follow-up of the patient is an absolute necessity Treatment decisions for
ameloblastoma are based on the individual patient situation and the best judgement of it surgeon. The surgical plan should be strongly influenced by whether the lesion involves the mandible Maxillary lesions behave distinctly different from mandibular lesions. For cystic nature - enucleation
For neoplastic nature-no resection required. Good prognosis.(38)

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