Ameloblastoma

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INTRODUCTION

Ameloblastoma is a noncancerous tumor that originates from epithelial tissue in the oral cavity. It exhibits strong local invasiveness and the ability to grow without limits, and there is a significant risk of it transforming into a malignant form and potentially spreading to other parts of the body.1 If left untreated, they can grow to be quite big, causing facial disfigurement and functional issues.2 When left undetected and untreated, it can cause symptoms like alterations in the position of adjoining teeth, shifting and/or looseness of next teeth, root resorption, and even paresthesia. The syndrome can cause bone tissue disintegration, invasion into soft tissues, and finally cortical bone enlargement.3

The world health organization (WHO) considers ameloblastoma to be the quintessential example of odontogenic cancers that arise from epithelial tissue. Ameloblastoma is also defined by the WHO as a benign, slow-growing, locally invasive epithelial odontogenic tumor with a probable genesis in enamel. The WHO categorizes ameloblastoma into three clinicopathological types: conventional ameloblastoma (CA), unicystic ameloblastoma (UA), and peripheral ameloblastoma (PA).4

Ameloblastoma occasionally exhibits metastasis despite having benign histological characteristics. This particular variant is referred to as metastasizing ameloblastoma (METAM).5

HISTORY

Ameloblastoma is a kind of tumor that develops from the dental lamina epithelium and is distinguished by its local aggressiveness and proclivity to recur. The term "ameloblastoma" is a combination of the words "amel," which means "enamel," and "blastos," which means "germ" in Greek. It was first described in 1827 by Cusack, then as "adamantinoma" by Malassez in 1885, and finally as "ameloblastoma" by Ivey and Churchill in 1930, which is the largely recognized word today. This tumor is quite similar to the cells of the enamel-forming organ. Robinson defined it as a benign tumor that is often seen in a single area, is nonfunctional, grows sporadically, is physically benign, and is clinically persistent in 1937. The WHO classified ameloblastoma as a benign but locally aggressive tumor with a high...
Ameloblastoma is regarded as one of the most aggressive OT in several nations throughout the world. It is a circumscribed tumor that arises from the odontogenic epithelium but lacks odontogenic ectomesenchyme. Approximately 70% of instances eventually progress to malignant transformation, and the tumor can spread to other parts of the body in up to 2% of cases. Ameloblastoma accounts for around 1% of all OT. This illness is far more common in underdeveloped nations, where the chance of recurrence is greater. Ameloblastoma occurs around five times more frequently in the lower jaw (mandible) than in the upper jaw (maxilla). There is no predilection for sex, and it is most common in the third and fourth decades of life. Despite histologically benign findings, 2-4.5% of all cases have malignant potential and spread, most often to the lung. The average age at which this occurred in METAM was 42.71 years, with a slight predilection for men.

Ameloblastoma tends to be more prevalent in developing nations, such as India, where cancer strikes at a younger age. This disparity in ameloblastoma demographic distribution may be connected to an accelerated aging process caused by poor nutrition and limited access to healthcare services. Males were more affected than females in terms of gender distribution, which is consistent with previous research from throughout the world. However, an increase in females was documented in the literature, which aligned to the findings of our study. Biologically, ameloblastomas can develop into malignant forms such as ameloblastic carcinoma and metastatic ameloblastoma, however this transformation happens seldom, with a prevalence rate of about 2%. Metastatic ameloblastoma often has well-differentiated benign histology, comparable to the main variety of ameloblastoma. However, other patches of benign histology are detected far from the main site and are considered metastatic occurrences.

**CLASSIFICATION**

According to the WHO and the international agency for research on cancer's 2003 classification, ameloblastoma is a benign tumor characterized by odontogenic epithelium, a mature fibrous stroma, and the lack of odontogenic ectomesenchyme. Ameloblastoma is further classified into four types: solid/multicystic, extrasosseous/peripheral, desmoplastic, and unicystic. The new method categorizes ameloblastoma into three types: conventional, unicystic, and peripheral. The phrase "solid/multicystic" has been dropped since it might be mistaken with unicystic. Desmoplastic ameloblastoma was also classified as a histological subtype rather than a separate clinical-pathological entity. This is predicated on the finding that, while having distinct clinical and radiographic features, desmoplastic ameloblastoma behaves similarly to conventional ameloblastoma. The term ‘solid/multicystic’ to define conventional ameloblastoma has been dropped since it has no predictive value and can cause confusion when distinguishing it from unicystic ameloblastoma. Despite having different clinical and occasionally radiographic features, desmoplastic ameloblastoma is currently regarded a histological variant of conventional ameloblastoma.

It often manifests clinically as a tumor that develops slowly without generating symptoms and exhibits a variety of radiological and clinical characteristics. Although ameloblastoma is a benign tumor, it has an invasive growth pattern and a significant risk of recurrence if not treated effectively.

**Unicystic**

Unicystic ameloblastomas (UA) are neoplastic entities with a cystic morphology covered by an ameloblastic epithelium that might offer tumor development to the lumen and fibrous connective tissue. AU is classified into three histological categories depending on the proliferation pattern of the epithelial component: luminal, intraluminal, and mural. Conservative surgical approaches often work well for luminal and intraluminal variations. The mural form, on the other hand, has a greater recurrence rate and is treated similarly to normal ameloblastomas.
There is significant evidence that unicystic ameloblastoma has different behavioral and clinicopathological features, and it is treated as a separate category. The luminal type is distinguished by a simple cyst bordered with ameloblastic epithelium, whereas the intraluminal type is distinguished by proliferations of ameloblastic epithelium, frequently in a plexiform pattern, within the cyst's lumen. Mural type has ameloblastic epithelial growth in the cyst wall.  

Ameloblastoma that is seen in the gingival or alveolar mucosa. It infiltrates the surrounding tissues, most notably the gingival connective tissue, but has little effect on the underlying bone. The PA is formed by remains of the dental lamina, known as "glands of Serres," as well as vestibular lamina odontogenic remnants, versatile cells in the mucosal epithelium's basal cell layer, and pluripotent cells from minor salivary glands. 

The peripheral ameloblastoma is the least common variety, accounting for just 1% of cases. It primarily affects those over the age of 52 and is most usually discovered in the gingiva of the mandible. Even when conservative therapy is used, this variation seldom recurs. Histopathologically, it shows islands of ameloblastic epithelium in a manner similar to the usual form. 

Conventional ameloblastoma

There are six histological variants of the conventional type: plexiform, follicular, acanthomatous, desmoplastic, granular, and basal cell type. Notably, the follicular pattern has the highest recurrence rate at 29.5%, while the acanthomatous pattern has the lowest at 4.5%. The recurrence rate varies according on histologic subtype. The follicular type is made up of multiple tiny islands that are surrounded by a layer of cuboidal or columnar cells with reversely polarized nuclei. The production of cysts is rather prevalent in this kind. The emergence of anastomosing islands of odontogenic epithelium with two rows of columnar cells placed back to back is referred to as "plexiform." 

The cells that would typically form the stellate reticulum undergo squamous metaplasia in the acanthomatous type, resulting in the creation of keratin pearls in the center of tumor islands. The cytoplasm of stellate reticulum-like cells in granular cell ameloblastoma appears coarse and granular, with an eosinophilic appearance. The epithelial tumor cells of the basal cell type are less columnar and organized in sheets. A thick collagen stroma that appears hypocellular and hyalinized characterizes the desmoplastic variation.

STAGING

Yang and colleagues used clinicopathological criteria to divide ameloblastomas into three phases. Tumors in stage I had a maximum diameter of 6 cm or less. Tumors in stage II were larger than 6 cm in diameter or had penetrated the maxillary sinus or orbital floor. Tumor invasion of the skull base or metastases to regional lymph nodes were symptoms of stage III. Their findings demonstrated a significant relationship between the period of recurrence and the tumor stage, with stage III tumors having the earliest recurrence.

ETHIOPATHOGENESIS

A big change occurred in understanding of the etiology and progression of ameloblastoma in 2014, when critical research articles on the genetics of this tumor were released. These findings demonstrated the presence of frequently occurring somatic mutations that activate
signaling pathways in ameloblastoma, notably the MAPK and Hedgehog pathways. These two pathways are known to be active during tooth growth. Through genomic analysis of archival data, oncogenic mutations in the Hedgehog and mitogen-activated protein kinase (MAPK) pathways were revealed in more than 80% of ameloblastomas, which are locally aggressive OT located in the jaw. Mutations in SMO (encoding Smoothened, SMO) were often detected in instances of maxillary ameloblastomas, whereas tumors in the mandible were characterized by prevalent BRAF mutations. BRAFV600E-activating mutations are frequent in ameloblastomas and can be found regardless of the tumor's location or histological type. This mutation has also been reported in certain cases of odontogenic carcinoma.

BRAF is a serine/threonine protein kinase within MAPK that activates downstream signaling pathways, resulting in increased cell proliferation and survival as well as the onset of neoplastic (cancerous) transformation. This mutation is critical in the formation of OT with an ameloblastomatous component, strongly contributing to their etiology. Typically, the BRAF protein is activated by interacting with the G-protein RAS. RAS mutations have been discovered in around 20% of ameloblastomas, including mutations in KRAS, NRAS, and HRAS. These RAS mutations often occur at locations (codons 12 and 61) that are frequently mutated in other types of cancers, resulting in persistent RAS signalling activation. RAS and the remainder of the MAPK pathway are normally activated by the activation of a growth factor receptor in response to a growth factor.

**CLINICAL PRESENTATION**

Ameloblastoma normally has a limited clinical presentation and vague symptoms. It generally manifests as painless swelling in the afflicted jaw region. Pain is frequently connected with bleeding in the surrounding soft tissues. It usually appears as a solid, painless intraoral enlargement or as an unintentional finding during normal dental imaging. Conventional ameloblastomas normally enlarge gradually and painlessly. The posterior portion of the mandible is the most common location for their occurrence. They have a tendency to grow buccolingually, resulting in significant expansion. On the other hand, ameloblastic carcinomas are more usually linked with symptoms such as pain, paresthesia, trismus, dysphonia, and ulceration due to perineural tumor development.

**TREATMENT**

The current standard of care for ameloblastoma is radical excision with a margin of at least 1 cm. Recurrence rates might range from 0% to 15%. Even broader resection margins may be required in the event of more aggressive kinds of ameloblastoma, such as the granular cell type. The traditional technique to treating a single metastasis in
order to reduce the chance of recurrence is radical surgery. This surgical approach frequently compromises the stomatognathic system’s function. It involves removing a section of bone with a 1-to-2-cm margin and resecting the periosteum with a 1 mm margin.

Conservative treatments, such as curettage followed by further therapies (such as Carnoy's solution, cryotherapy, or peripheral ostectomy), on the other hand, may allow for more successful postoperative activities such as chewing, swallowing, and speaking. A less intrusive therapeutic technique, on the other hand, is often associated with a higher chance of recurrence.23

CONCLUSION
Ameloblastoma is one of the most aggressive OT in several nations throughout the world. Mutations affecting several genes within the MAPK pathway are now known to occur in a large majority of cases. The current standard of care for ameloblastoma is radical excision with a margin of at least 1 cm.

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