

Management of Ameloblastoma

Dr. Anuj Sharma¹, Dr. Puja Bansal², Dr. Deepak Bhargav³

School of Dental Sciences,
Sharda University, Greater Noida, UP., India

Abstract: Ameloblastoma is a benign odontogenic tumor generally present in the jaw bone. The tumor originates from the residual epithelium of the tooth germ, epithelium of odontogenic cysts stratified squamous epithelium and the epithelium of enamel organ. It represents approximately 1% of oral tumors. About 80% of ameloblastomas occur in mandible mainly in the third molar region and the remaining of the 20% in the upper jaw region. Ameloblastoma clinically appears as an aggressive odontogenic tumor, often asymptomatic and slow-growing, with no evidence of swelling. The diagnosis of ameloblastoma requires computerized tomography (CT) imaging as well as biopsy. A biopsy is helpful in differentiating ameloblastoma from ossifying fibroma, osteomyelitis, giant cell tumor, cystic fibrous dysplasia, myeloma, sarcoma. The high recurrence rate and large tissue defects have been long standing issue in the treatment of ameloblastoma. Recent molecular developments strongly suggest the possibility of targeted therapy with better outcomes in ameloblastomas. This article discusses the types of ameloblastoma, pathogenesis, clinical and radiographic, histopathology, differential diagnosis and management of Ameloblastoma.

Keywords: Ameloblastoma, mandible, odontogenic tumor, maxillary neoplasm, jaw neoplasm, adamantinoma.

Introduction

Synonyms: Adamantinoma; Adamantoblastoma, Multilocular cyst.

The ameloblastoma is a true neoplasm of enamel organ type tissue which does not undergo differentiation to the point of enamel formation. According to Robinson “usually unicentric, nonfunctional, intermittent in growth, anatomical benign and clinically persistent”. First recognized by Cuzack in 1827. Later on Falksson in 1879 as ‘Follicular cystoid tumor’.[1] The term ‘Adamantinoma’ used by Malassez in 1885. Ivy and Churchill coined the term “Ameloblastoma” in 1934. It is the second most common neoplasm with odontoma outnumbering it in reported frequency of occurrence. Excluding odontoma, incidence of ameloblastoma is at least equal to the incidence of all other odontogenic neoplasm combined.[2] However, sriram and shetty, based on an Indian institutional study, reported it to most common odontogenic neoplasm in india. Its incidence, combined with its clinical behavior, makes ameloblastoma the most significant odontogenic neoplasm of concern to oral and maxillofacial surgeon. The ameloblastoma has a relatively low incidence, encompassing only 1% of maxilla and mandible tumors, most of the cases being diagnosed between third and fifth decade of life.[3] It is a slow growth tumor with only few symptoms in initial stages. Despite being benign, it has an invasive behavior with a high recurrence rate if not treated properly. The goal of present paper is to do descriptive review of ameloblastoma cause admitted in a reference head and neck cancer treatment center.[4]

Types

The WHO in 1971 had included odontogenic tumor in its first histological classification and provided the clinicopathological criteria necessary for diagnosis. The fourth edition of WHO classification of head and neck tumor was published in 2017. This latest classification is simplified from the previous version and described ameloblastomas is of four types: ameloblastoma multicystic, ameloblastoma unicystic type, ameloblastoma peripheral types, ameloblastoma metastasizing (table no. 1).[5] desmoplastic ameloblastoma which had been sub-categorized under ameloblastoma in the previous 2005 WHO classification, was also removed, as it was considered merely a histological variant of conventional ameloblastoma, despite its unique clinical and radiographical features.[6]

Recently there has been an effort for the inclusion of adenoid ameloblastoma as a sub type of ameloblastoma in the next revision of the WHO odontogenic tumor classification. Adenoid ameloblastoma is a hybrid odontogenic tumor showing histopathological features of the both ameloblastoma and adenomatoid odontogenic tumor.[7]

Pathogenesis

It is noted that the resemblance of ameloblastoma with epithelial component of the developing tooth germ and suggested that neoplasm was derived from a portion of this apparatus or from cells potentially capable of forming dental tissues. However, Heikinheimo and coworkers suggested that differentiation of the ameloblastoma cells remain at the cap/bell stage of tooth development.[8] Malassez described the small collection of epithelial cells adjacent to the the root of the tooth 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 varied origin, although the stimulus initiating the process is unknown. Thus, the tumor convievably derived from

>cell rest of dental organ, other remnants of dental lamina (cell rest of serres) or remnants of heartwig’s sheath (epithelia rest of malassez).

>Epithelium of odontogenic cysts, particularly the dentigerous cyst, and odontomas.

>Disturbances of developing enamel organ.

>Basal cells of the surface epithelium of the jaws.

>Heterotropic epithelium in the other parts of the the body especially the pituitary gland.[9]

However at present, it is likely thought due to alterations or mutations in the genetic material of cells that are embryologically preprogrammed of tooth development. Environmental factors and individual patient variables (eg. General health status, nutritional status) are also likely to have role in modulating the incidence of the disease.[10]

Epidemiology of Ameloblastoma

Ameloblastoma shows a variable geographic prevalence with a global incidence of 0.92 cases per- million persons-year. Most epidemiological studies have revealed that ameloblastoma is either the most common or second most common benign odontogenic tumor. In Brazilian study of 6231 oral lesions, 185 (3%) were odontogenic tumor, all benign. Of these the most frequent lesions are ameloblastomas (29%), followed by keratocystic odontogenic tumor (28%) and odontomas (19%)[11]. Similarly two large series on odontogenic tumor from china, one comprising 759 cases based on the 1992 WHO classification and other comprising 1642 cases and based on the 2005 WHO classification had, revealed that ameloblastoma was the most frequent odontogenic tumor (59% and 40% respectively). However in other Chinese series of 1309 odontogenic tumors, the most frequent was the keratocystic odontogenic tumor (39%), followed by ameloblastoma (37%) and odontomas (6%).[12] In the united states and Canada also, ameloblastoma is the second most common odontogenic tumor next to odontoma.

Among the Indian studies, most it was carried out in the maharashtra region, where histopathology records from 1992 to 2012 were reviewed. Of the benign odontogenic tumors, the most common was the keratocystic odontogenic tumor (45%) followed by ameloblastoma (35%), odontoma (7%) and adenomatoid odontogenic tumor (5%).[13]

Clinical presentation

A wide range of occurrence of the tumor from 10 years through 90 years has been reported. Most cases cluster between the ages of 20 and 60 years with 30 to 39 years being the average age at diagnosis. Only 10% of cases are reported in childrens and less one – third of cases occur in children younger than 10 years. Slight seen in male as compare to female. occur in posterior region of mandible.[14] It is slow growing, but local invasive tumor with high rate of recurrence. In later stages there will be gradually increase in swelling will lead to facial deformity and surrounding bone become thin that **crepitation and egg-shell crackling** occurs. The desmoplastic variant of ameloblastoma often occurs in anterior part of maxilla or mandible. The growth of ameloblastoma occurs in buccolingual direction, resulting in a significant expansion. The mean size of ameloblastoma at presentation is approximately 4 cm. pain is uncommon symptom of ameloblastoma but can occur because of hemorrhage inside or adjacent to the tumor. Malocclusion, facial deformity, soft tissue invasion, or loosening of teeth are other signs and symptoms of ameloblastoma.[15]

The unicystic variant of ameloblastoma presents commonly in the pediatric age group. It is possibly arises from pre-existing dentigerous cyst or from a dental follicle because of its frequent dentigerous relationship with an un-erupted tooth. Thus, third molar is the region where frequent location of unicystic ameloblastoma seen.[16]

The mean age of occurrence of metastasizing ameloblastoma is 16 to 43 years, with slight male predilection. The mandibular cases showed more metastasis than maxillary cases, and lungs, followed by lymph nodes, are the most commonly affected secondary sites.[17]

Radiographic features

The radiographic features of ameloblastoma has been described clinically as a multilocular cyst like lesion of the jaw exhibiting a **soap bubble appearance**. this is especially true in advanced cases of ameloblastoma. The tumor exhibited the compartmented appearance with the septa of bone extending into radiolucent tumor mass. In many cases however lesion is unilocular one and present no characteristics or pathognomic features.[18] The periphery of the lesion is smooth and thinning of the cortical plates is seen in jaw expanding advanced lesion. sometimes displacement of impacted third molar can also be seen in panoramic radiograph. However, desmoplastic ameloblastomas in contrast to conventional tend to occur more commonly anterior to the molar region in both the jaws. In addition to that desmoplastic ameloblastomas often shows areas of radiopacity and radiolucency with ill defined borders mimicking fibro-osseous lesion.[19]

“cystic ameloblastoma“ is a term frequently used in referring to some of these neoplasms. However, there is no correlation between the term used clinically and the appearance of the tumor on the radiograph. The radiographic film does nothing more than indicate the relative presence or absence of calcified tissues and variety of lesion may manifest themselves in manner similar to that of ameloblastoma.[20]

Histopathological Findings

Histologically ameloblastoma contains two types of cells: peripherally situated ‘basal cells’ that resemble ameloblasts and centrally situated suprabasal ‘epithelial cells’ that resemble stellate reticulum. The basal cells are hyperchromatic, columnar in shape with a palisaded arrangement, vacuolated cytoplasm, and the nuclei displaced away from the basement membrane (reversal of polarity). The epithelial cells have bland cytological appearance with sparse mitotic figures in keeping with slow rate of growth.[21]

In classical ameloblastoma (previously labeled as solid ameloblastoma or multicystic), these basal cells and epithelial cells turned are arranged in two characteristics pattern: follicular and plexiform type. In the follicular pattern epithelial cells are arranged in island or follicles surrounded by connective tissues; while in flexiform these cells are arranged in a form of network surround the connective tissues. Various other histological variants of multicystic ameloblastoma have been described such as desmoplastic, acanthomatous, basal cell, granular cell and keratopapillary ameloblastomas.[22] These variants are often superimposed of the two main characteristics features except desmoplastic ameloblastoma, which may be more aggressive. In peripheral ameloblastoma, the stellate reticulum is seldom conspicuous and most of the epithelial islands exhibit palisading of columnar basal cells. Bone or periosteum is not involved, though the tumor may produce a superficial impression on the underlying bone.[23]

Metastasizing ameloblastoma also has typical well differentiating benign histology of the solid/multicystic type at the primary site, but in addition, similar to foci of benign histology are also seen in location remote from primary site, considered to be metastases. Since histological differentiation from the non-metastasizing ameloblastoma which is not possible, the diagnosis of metastasizing ameloblastoma can be made only respectively, when metastasis has occurred. Where as follicular ameloblastoma was most frequently encountered at the secondary site followed by plexiform type. Lungs were the most commonly affected secondary sites.[24]

Management

The treatment modality of choice for ameloblastoma is surgical approach and conservative approach-

Surgery

The goal of surgical treatment of ameloblastoma is to minimize recurrences and restore good function and aesthetics with minimum morbidity in donor area. The currently recommended surgery for classic ameloblastoma (multicystic) is complete en bloc resection (radical surgery) with an adequate margin of safety, which is classified as segmental or marginal osteotomy for the mandible and partial or total maxillectomy for the maxilla.[25] Due to high recurrence rate after the conservative surgery, particularly for multicystic ameloblastoma, a wide resection with a 1 to 1.5 cm bony margin is recommended. However, a recent meta-analysis could not prove the superiority of radical surgery over conservative surgery. Recurrence is attributed to the infiltration of tumor cells into cancellous bone beyond the periphery of radiographic margin. Immediate or delayed bone reconstruction and dental rehabilitation have to be ensured to help with speech and swallowing and improve patient outcomes.[26]

However radical surgery leads to aesthetics deformities, functional impairments and psychological distress. To avoid these complications, conservative surgery has also been tried, which includes marsuplization, enucleation, curettage, enucleation combined with Carnoy's solution, enucleation combined with curettage, enucleation combined with cryotherapy.[27] However these conservative approaches lead to a high recurrence rate, which has been reported to be 40% in a recent meta-analysis. For the treatment of primary multicystic ameloblastoma when conservative treatment was performed, the relative risk of recurrence was three-fold higher in comparison to radical treatment. Similarly in another meta-analysis that included four studies on radical versus conservative treatment approach for ameloblastoma, a higher recurrence rate after a conservative approach compared to surgical approach was documented. Thus, the treatment of primary multicystic ameloblastoma with bone resection is justified.[28]

For mandibular reconstruction, vascularization free bone grafts (from the fibula, ilium, scapula or radius) are the standard flap of the choice is the fibular free flap, which has the added advantage of reconstructing long mandibular defects.[29]

Reconstruction of maxillary defects is done using bone grafts to line the cavity. An obturator is fitted through allowing easy access to resection bed during surveillance. The cortical bone of the maxilla offers less resistance to tumor invasion as compared to the mandible and therefore ameloblastoma of the maxilla has a higher local recurrence rate after surgical procedure. Hence, free flaps are not used for maxillary defects to avoid covering a potential recurrence site.[30]

For unicystic ameloblastomas, both radical as well as conservative approach, including excision, marsuplization, chemical electrocautery, curettage, radiation therapy or combined surgery and radiation may be employed. The peripheral ameloblastoma is mostly treated with wide local excision, and a recurrence rate of 9% to 20% following treatment has been reported.[31]

Non-Surgical Treatment

Systemic chemotherapy has no role in the treatment of localized ameloblastoma, however in metastatic settings, chemotherapy is a choice of treatment. Numerous agents and combination have been employed using cyclophosphamide, methotrexate, 5-fluorouracil, vinblastine, cisplatin, bleomycin, adriamycin, paclitaxel-carboplatin, doxorubicin and gemcitabine. Ameloblastoma may be sensitive to platinum based anticancer agents.[32]

Recently with elucidation of molecular markers of ameloblastoma, there have attempts for the treatment of ameloblastoma with molecular targeted therapy. These tumors have highly recurrent somatic mutation in the signaling pathway of mitogen-activated protein kinase (MAPK) and sonic hedgehog (SHH) which are known to be activated during tooth development.[33]

Conclusion

The ameloblastoma is usually of late diagnosis because its poor symptoms and low prevalence. Its treatment preferably includes the resection with safety margins and immediate reconstruction whenever possible. Routine histological classification of the ameloblastoma is mandatory for its morphological characterization and, thus, a better treatment definition. The main success factor associated with the treatment is the early diagnosis and to correlate the findings with clinical and radiographic features to achieve a corrective definitive diagnosis as all such lesions might have prognostically different biologic behaviors and the final diagnosis may alter the therapeutic decision significantly. Recent molecular developments strongly suggest the possibility of targeted therapy with better outcomes in ameloblastomas.

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