

**Clinical and Histopathological Implications of Unicystic Ameloblastoma – An Overview**

<sup>1</sup>Dr. Syeda Neelam Afroze, Sr. Lecturer, Department of Oral Pathology, Mamata Institute of Dental Sciences. Bachupally, Hyderabad

<sup>2</sup>Dr. Surekha R, Professor and HOD, Department of Oral Pathology, Mamata Institute of Dental Sciences, Hyderabad

<sup>3</sup>Dr. Karanam Sri Varalakshmi, Sr. Lecturer, Department of Oral Pathology, Mamata Institute of Dental Sciences, Bachupally, Hyderabad

**Corresponding Author:** Dr. Syeda Neelam Afroze, Sr. Lecturer, Department of Oral Pathology, Mamata Institute of Dental Sciences. Bachupally, Hyderabad

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**Abstract****Introduction**

Ameloblastoma is a local invasive tumor which originates from remnants of the dental lamina and odontogenic epithelium and it accounts for only 1 % of all oral tumors.

<sup>1</sup>The first time this pathology was described was in the study of Robinson and Martinez in 1977, defining it as unicentric, non-functional, intermittent growth, of a tumor nature, benign, clinically persistent and of conservative treatment.<sup>2</sup> The current classification given by WHO in 2017 is simplified into: Conventional ameloblastoma, Unicystic Ameloblastoma (UA). and the Extrasosseous/Peripheral type<sup>3</sup>. Among the three variants, the conventional type is the most common variety and UA is a comparatively rare type

**Terminology**

The term unicystic is derived from the macroscopic and microscopic appearance, the lesion being essentially a well-defined, often large monocystic cavity with a lining, focally but rarely entirely composed of odontogenic (ameloblastomatous) epithelium.<sup>4</sup> UA differs considerably from the conventional type by presenting at a relatively younger age group, being typically unilocular on radiographs, appearing cystic macroscopically and also by responding better to conservative treatment modalities.<sup>5</sup>

**Clinical Profile**

UA accounts for about 6% of ameloblastomas and occurs in younger age group with about 50% of the patients presenting in the second decade of life.<sup>5</sup> UA has a male predilection with a 1.6:1 ratio to female sex.<sup>2</sup> It is seen more commonly in the posterior mandible than in the

maxilla in the ratio of 13:1.<sup>1</sup> They are characterized as a slow growing and relatively locally aggressive cystic lesion. Radiographically, the lesions commonly show expansive unilocular radiolucencies with a well-demarcated border.<sup>6</sup>

Approximately 50 - 80% of cases are associated with an impacted or unerupted tooth. Therefore, the clinical and radiographic presentations of unicystic ameloblastoma are sometimes indistinguishable from those of dentigerous cysts.<sup>7</sup>

Among the 176 reported cases with detailed radiographic description, 63 cases (35.8%) appeared to be related to the crown of an unerupted tooth. This specific feature has led some authors to argue the possibility that unicystic ameloblastoma arises from a pre-existing dentigerous cyst.<sup>8</sup>

The biological behavior of unicystic ameloblastoma is arguably the most significant factor to account for. Gupta has highlighted the biological differences between lesions that are just cystic or show intraluminal proliferation and those in which the epithelium has penetrated the fibrous wall and can permeate the cancellous bone. Compared to the mandible, the maxilla exhibits greater aggression. Ameloblastomas can also develop into malignant entities, such as ameloblastic carcinoma and metastatic ameloblastoma, with a mere 2% prevalence rate.<sup>9</sup>

### **Etiopathogenesis**

The pathophysiology of UA is uncertain. However three mechanisms have been documented for its pathogenesis

1. Basal cells of reduced enamel epithelium of developing tooth, remains of Malassez from Hertwigs lamina, heterotopic epithelials in extraoral sites, which undergo an ameloblastic transformation to give genesis to a unicystic cavity
2. Alteration of epithelium of odontogenic cysts like Dentigerous Cysts, in which the neoplastic tissue of

ameloblastic epithelium is preceded by a non-neoplastic stratified squamous epithelial lining.

3. UAs can also arise from solid ameloblastomas undergoing cystic degeneration that forms multiple cysts which fuse to form single unicystic lesion.<sup>2</sup>

The reason why some ameloblastomas become completely cystic may be related to epithelial dysadhesion (e.g., defective desmosomes) or, more likely, to the intrinsic production of proteinases enzymes that normally degrade the central zone of the enamel organ after tooth development. (e.g., metalloproteinases and serine proteinases).<sup>4</sup>

### **Histological Features**

To diagnose a lesion as UA, the minimum criteria is the demonstration of presence of a single cystic sac lined by odontogenic (ameloblastomatous) epithelium often seen only in focal areas.<sup>1</sup> Microscopically, the odontogenic epithelium lining the cyst lumen is seen in UA. Its thickness varies, ranging from a few layers to multiple cell layers, and it exhibits the typical cytomorphic features of ameloblastoma as described by Vickers and Gorlin. These features include a basal cell layer made up of columnar cells that exhibit hyperchromatism, palisaded nuclei, reverse polarity, and subnuclear vacuoles. Also visible is a thin layer of cells that resemble stellate reticulum on top.<sup>9</sup>

Ackermann<sup>10</sup> classified UA into three histological groups:

Group I: luminal UA (tumor confined to the luminal surface of the cyst); (FIGURE 1)

Group II: intraluminal/plexiform UA (nodular proliferation into lumen without infiltration of tumor cells into connective tissue wall); and

Group III: mural UA (invasive islands of ameloblastomatous epithelium in the connective tissue wall not involving the entire epithelium) (FIGURE 2)

Another classification proposed by Philipsen and Reichart<sup>11</sup> is as follows:

Subgroup 1, luminal UA; Subgroup 1.2, luminal and intraluminal;

Subgroup 1.2.3, luminal, intraluminal, and intramural; and

Subgroup 1.3, luminal and intramural.

At the microscopic level, UA demonstrates some typical features like tightly cohesive groups of neoplastic epithelial cells with basaloid appearance and scanty or moderate amount of cytoplasm. The centrally located nuclei were round to oval and squamous metaplastic changes may be present. Multinuclear foreign body type giant cells in the background might be seen and believed to belong to the surrounding granulation tissue.<sup>12</sup>

The term, 'plexiform unicystic ameloblastoma' refers to a pattern of epithelial proliferation that has been described in cystic lesions of the jaws. It has been considered as a hyperplastic epithelium, rather than an ameloblastoma by some pathologists, because it does not exhibit histological criteria which were previously accepted for ameloblastomas.<sup>13</sup> Gardner et al., in their study, provided histological evidence that plexiform unicystic ameloblastomas were in fact, variants of conventional unicystic ameloblastomas. Further evidence of the ameloblastomatous nature of plexiform unicystic ameloblastomas is that their biological behaviour, even when this pattern occurs alone, is similar to that of conventional unicystic ameloblastomas.<sup>14</sup>

### **Immune Profile**

Sometimes histopathological features of unicystic ameloblastoma and Dentigerous cysts (DC) overlap leading to misdiagnosis of the lesion. So it is advisable to use advanced diagnostic techniques such as immunohistochemistry. It has been proposed that the calcium-binding protein calretinin serves as a unique immunohistochemistry marker for ameloblastic tissues.

Anandani et al. observed calretinin expression in 50% of cases of unicystic ameloblastomas. Furthermore, 100% of unicystic ameloblastomas had a positive expression of calretinin, according to studies by DeVilliers et al. and Sundaragiri et al.<sup>9</sup>

Research suggests that BRAF V600E biomarker is present in 94% of UA's when compared with solid Ameloblastoma (74%) and it can be used as a biomarker to detect the lesion.<sup>15</sup> Differentiating UA's from other cyst immunocytochemical markers for lectins and proliferating cells may be helpful. Various immunomarkers like Ki-67, CD34, Matrix metalloproteinase-2, MMP -9 show high expression in mural variant of UA and can be used to differentiate the variants. Therefore. Immunomarkers are helpful to predict aggressiveness, which further helps to determine the diagnosis protocol and treatment of the patient.<sup>16</sup>

### **Diagnostic Dilemma**

The diagnosis of Unicystic Ameloblastoma can be challenging, particularly because it may present as a multilocular lesion on radiograph, despite its name suggesting a unilocular appearance. Clinically, an expansile unilocular radiolucency—especially when associated with an impacted mandibular third molar or root resorption in a teenager or young adult—should raise suspicion for Unicystic Ameloblastoma.<sup>8</sup>

Biopsies of a large pericoronal cystic lesion is usually necessary as it may represent Dentigerous Cyst, Odontogenic Keratocyst, Unicystic or Conventional Ameloblastoma, Adenomatoid Odontogenic Tumor. The cystic cavities of Unicystic Ameloblastomas are not always characteristic and are often partly lined by a nonspecific epithelium similar to the lining of Dentigerous Cysts.<sup>11, 17</sup> A biopsy that samples only this nonspecific lining may fail to reveal the true nature of the lesion,

potentially leading to a misdiagnosis and inadequate treatment.<sup>6</sup>

The true nature of the lesion may only become evident when the entire specimen is available for pathological examination. Furthermore, it is crucial for pathologists to carefully examine all biopsy specimen and take multiple sections to detect ameloblastomatous components, particularly to identify the presence of invading tumour islands within the cyst walls.<sup>8</sup>

### **Treatment**

UA is considered to be a less aggressive form of ameloblastomas that can be successfully treated by simple enucleation or other less aggressive surgery.<sup>18</sup> Unicystic ameloblastomas compare favorably with their solid counterparts in terms of clinical behavior and response to treatment. Accordingly, conservative treatment is suggested, especially in younger populations, in light of the devastating impacts on the developing jaw, masticatory function, facial growth, and psychosocial aspects. Porgrel et al advocated that enucleation followed by curettage and liquid nitrogen cryospray or Carnoy's solution cauterization would be appropriate for Unicystic Ameloblastomas. In extensive lesions, marsupialization may be an alternative treatment, because it is easy to perform and safe, and can reduce the size of the lesion.<sup>19</sup> However, once the tumour has breached the periphery of the fibrous tissue wall such as in intraluminal variant, it can behave like a solid or multicystic ameloblastoma and accordingly treated with aggressive radical resection.<sup>8</sup>

### **Recurrence**

Unicystic ameloblastomas have a variable recurrence rate depending on the histologic subtype. The recurrence rate after treatment of UA ranges from 10%-25%.<sup>5</sup> Among the three subtypes, the mural type has the highest recurrence rate since the epithelium penetrates and breaches the

fibrous wall with a high potential to invade the adjacent cancellous bone.

Long-term post-operative follow-up is required because recurrence for UA may be long delayed. Particularly lesions of mural subtype should be reviewed for recurrence.<sup>18</sup>

### **Conclusion**

Unicystic Ameloblastoma is an unique entity and diagnosis relies on identifying ameloblastomatous lining the cyst wall. Unicystic Ameloblastoma shares significant clinical and radiological similarities with other odontogenic cysts and tumors. Hence, a thorough examination of tissue is obligatory to determine the proper diagnosis. The pathologist should thoroughly examine the entire tissue in an attempt to determine various subtype of ameloblastoma. As mural subtype may exhibit more aggressive behaviour and risk for recurrence thus requiring more extensive treatment. Conservative treatment approaches, such as marsupialization and enucleation are often considered for luminal and extraluminal subtypes.

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#### Legends Figures

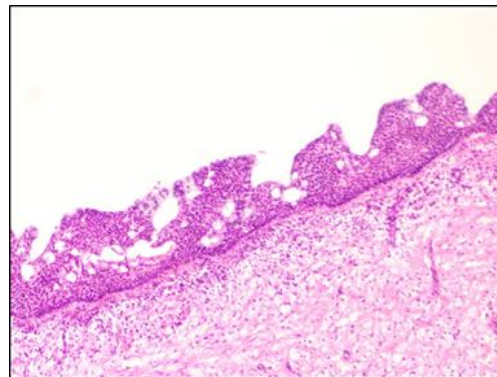


Figure 1: Microscopic examination showing cystic cavity lined by ameloblastomatous epithelium with typical

peripheral tall columnar ameloblast like cells and hyperchromatic polarized nuclei (40X)

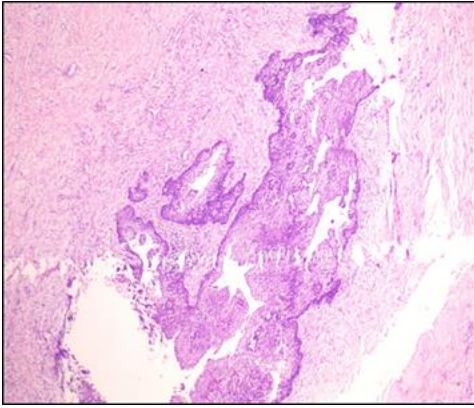


Figure 2: Focal areas show multiple odontogenic island inclusions infiltrating into the connective tissue wall (40X)