

Jowl cysts, multiplicity and taxonomy: ameloblastoma.

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Short Communication

Elaborated from “amel” (implying enamel) and “blastos” (connoting a germ) and initially chronicled in 1827 by Cusack, Ameloblastoma is a rare, benign, slow-growing, locally invasive neoplasm of odontogenic origin, affecting mandible (80%) and maxilla necessitating conservative therapy and elucidating considerable recurrences. Substitute terminologies are cystosarcoma, adamantine epithelioma, adamantinoma and ameloblastoma. The worldwide prevalence is of 0.5 cases per million persons, a range of presentation between 30 to 60 years and a median at 40 years. The tumor classically manifests as a painless lump in the maxilla or mandible. Malignant metamorphosis is heralded by a painful, accelerated growth. Tooth displacement, root resorption, paraesthesia are infrequent. Mandibular lesions (80%) are predominate in the posterior mandibular zone and exceptionally in the sinonasal cavities. Maxillary ameloblastoma, in conjunction, may preponderate the posterior molar region. Ameloblastic carcinoma preferentially has a maxillary localization. Non-specific irritation from tooth extraction, dental caries, trauma, inflammation, nutritional deficiencies are factors which predispose to the genesis of ameloblastoma.

Diagnostic Approbation is with imaging and biopsy. The tumor arises in the bone and is incidentally discovered on dental or

plain x-rays delineating a lytic lesion with scalloped boundaries, resorption of tooth roots, impacted molars (the unicystic variant) and the classic soap bubble occurrence (characteristic of the multilocular /solid variant). Computerized tomography (CT) is beneficial - a well delineated radiolucence (unilocular/ multilocular), an expansive lesion with cortical destruction or soft tissue extension. CT can be utilized for computation of a planned surgery. Magnetic Resonance Imaging (MRI) assists in the identification of a soft tissue / marrow extension besides the classic, lytic bony participation. It expedites the detection of a typical lesion arising from the maxilla and extending to the orbit, paranasal sinuses, and base of the skull [1]. Positron Emission Tomography (PET-CT) is a method to evaluate the staging and distant metastasis in metastatic ameloblastoma. Resection biopsy at the site of cortical destruction (an aperture for biopsy sampling) is essential for preventing unnecessary surgery. Surrogate diagnoses are osteomyelitis, cystic fibrous dysplasia, and giant cell tumor, ossifying fibroma, multiple myeloma and rare sarcomas. Fine needle aspiration cytology (FNAC) is suitable for localized lesions displaying cortical erosions/ in a dental socket. Incisional biopsy is precise but necessitates mucosal disruption. The specific locus is subsequently surgically eliminated. Peripheral ameloblastoma lacks a bony envelope and is successfully biopsied (Table 1).

Table 1. Histology with ancillaries.

Epithelium of Origin	Odontogenic /Enamel	Cell rests of Malassez Sheets of Hertwig	Epithelium of Dentigerous Cyst	Basal Layer of Oral Mucosa
WHO(2005) Classification	Solid Multicystic	Extraosseous Peripheral	Desmoplastic	Unicystic
Microscopic Patterns	Follicular, Acanthomatous	Spindle, Granular	Basal Cell like	Plexiform
Microscopic Features	Stellate Reticulum	Peripheral Palisading	Reverse Polarization Columnar Epithelium	Basal Layer
Clinical Subtypes	Central- Osseous	Peripheral- Extra osseous		
Malignant Subtypes	Metastatic Ameloblastoma	Ameloblastic carcinoma		
IHC staining	CK5, CK6	CK13, CK14	CK 19, CD56	Calretinin
Molecular features	SMO mutations	BRAF mutations	KRAS	FGFR2
Electron Microscopy	Epithelial Differentiation	Tonofilament	Desmosome	

Supplementary Aspects the ectomesenchyme or the heterotopic epithelial rests from body components such as the pituitary are implicated in the tumor ancestry. Clinico-pathological elements demonstrate that the solid/multicystic variant of ameloblastoma is extremely common (91%) and locally destructive. Unicystic type is an infrequent (6%), benign version, demarcated into the intraluminal or intramural subdivisions. The intraluminal

subtype has a lower reoccurrence rate, minimal stromal invasion and is amenable to conservative management. Solid/ Multicystic/ Desmoplastic variant has the highest reappearance rate (90% with enucleation/curettage), can be centralized in the bone marrow and illustrates a bony circumscription, hence it is also designated as Central ameloblastoma. Peripheral ameloblastoma is extra-osseous (2%), may classically present

as s gingival pedunculated/ exophytic lesions. Desmoplastic variant is the least common (1%). Cellular atypia and mitosis is infrequent, an augmentation of these parameters is a harbinger of neoplastic conversion. Ameloblastic carcinoma/odontogenic sarcoma are malignant subtypes (excluded from the WHO classification) commencing de novo or from benign ameliorations. Metastatic ameloblastoma may display well differentiated benign histology similar to the preponderant solid/multicystic type but adjunctive, similar benign foci are recognized at a distant location from the initial primary focus, thus it is labelled as discussed. Ameloblastic carcinoma may delineate a malignant outcome featuring atypical mitosis, cytological atypia or invasiveness which are detectable at the primary locus. Distant metastasis are discerned at the lungs, bones, liver and brain. Provocation for a malignant transformation are observed with lengthy duration of the tumor, numerous reoccurrences after conventional treatment and delayed metastasis (Figures 1-9).

Histological Variants

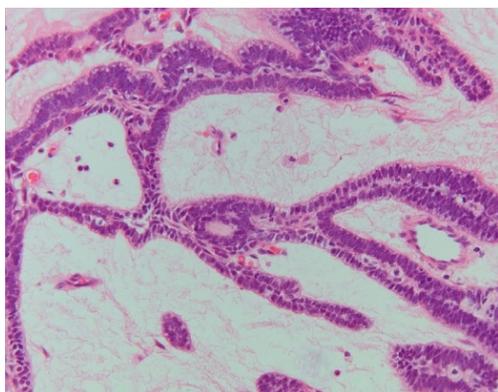


Figure 1. *Plexiform ameloblastoma.*

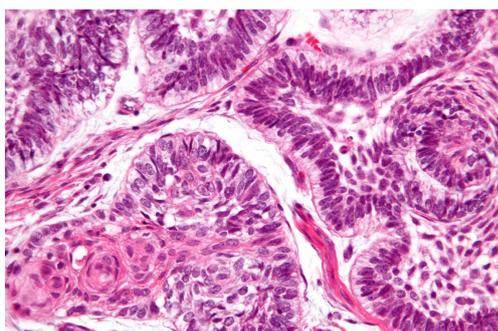


Figure 2. *Highly Magnified Odontogenic Epithelium with reverse polarization and stellate reticulum.*

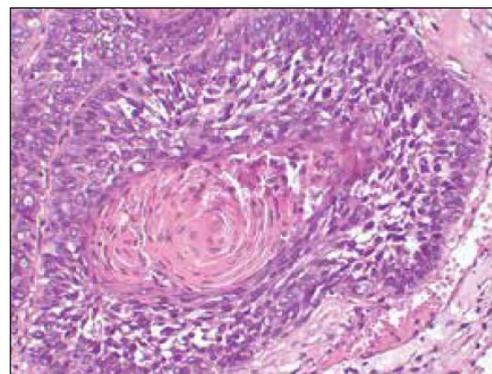


Figure 3. *Acanthomatous Ameloblastoma with squamoid nests [2].*

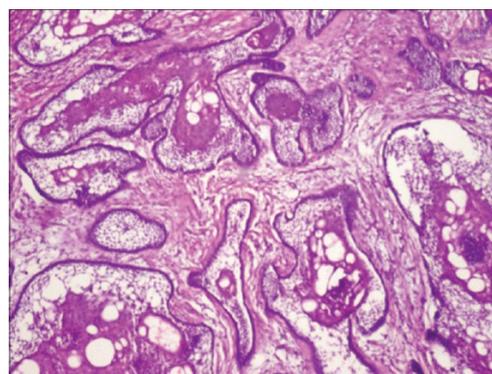


Figure 4. *Hybrid Ameloblastoma [3].*

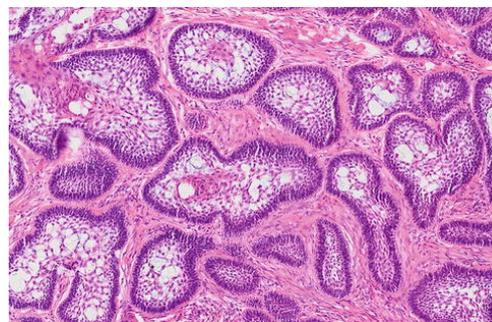


Figure 5. *Follicular Ameloblastoma in a fibrous stroma [4].*

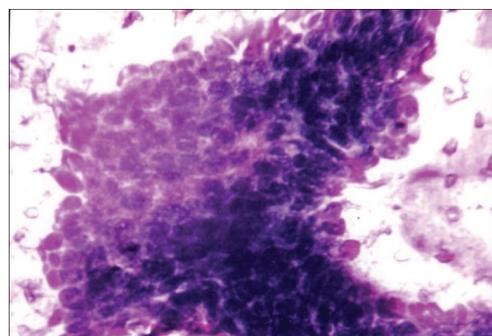


Figure 6. *Cystic Ameloblastoma with peripheral palisading and basaloid cells- aspiration cytology.*

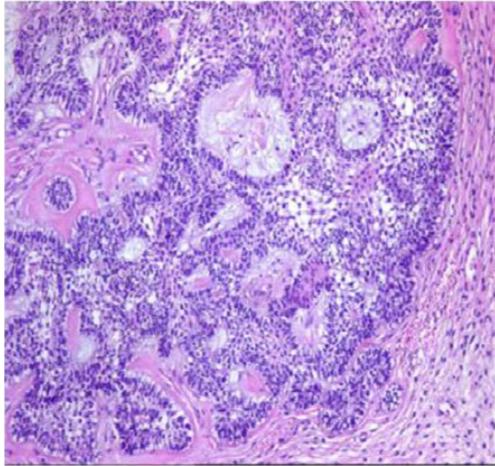


Figure 7. Ameloblastic Carcinoma with basaloid edges and infiltrative pattern.

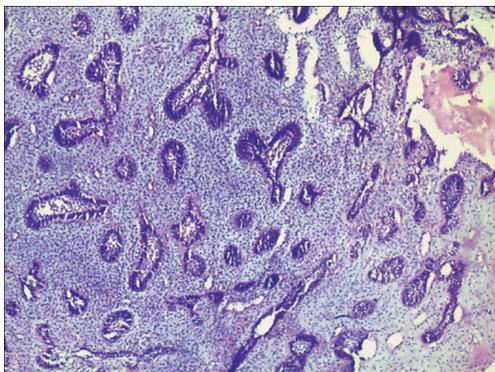


Figure 8. Ameloblastic Fibroma with characteristic stroma [5].

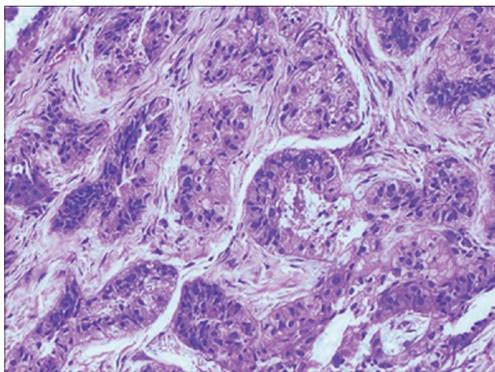


Figure 9. Granular Cell Ameloblastoma [6].

Molecular Referendums: Somatic mutations precipitate the mitogen signalling pathway (MAPK i.e. FGFR2 –RAS-BRAF) that contain the cell proliferation. Abundant BRAF-V600E (Valine to glutamic acid) amino acid substitutions develop at amino acid 600 and activate the mutations. BRAF mutated lesions are preponderantly localized in the mandible. BRAF – V600E mutations are simply established by immunohistochemistry. BRAF negative maxillary ameloblastoma harbours mutations in the sonic hedgehog pathway (SHH), apparently evoking mutations in the smoothened (SMO). Stimulated SMO mutations can be restricted by inhibitors of SHH signals (arsenic trioxide). SMO

mutated ameloblastomas harbour anomalies in the Fibroblastic growth factor receptors (FGFR2) or RAS (KRAS, NRAS or HRAS). SMO mutations are commonplace in maxillary ameloblastomas whereas BRAF mutations are preponderant in mandibular lesions. Exceptionally, mutations are illustrated in PIK3CA (PI3 kinase network which regulate cell survival) CTNNB1 (Beta catenin in the Wnt signaling circuit) and SMARCB1 (chromatin remodeling) [7-10]. Deprivation of SHH signal induces imperceptible growth and morphogenesis but does not thwart differentiation and enamel/dentin secretion in the tooth. Loss of heterozygosity (LOH) in the PTCH gene ensues in 40% cases. Tumor obliteration and anti-apoptotic networks are implicated in the development of ameloblastomas. Significant are p53 and MDM2 evident in the majority of the ameloblastomas as demonstrated on immunohistochemistry.

Therapeutic Surgical Interventions surgical resection is the preferred therapy. A conservative regimen is enucleation/curettage of the bony crater with minimal reconstruction and is an outpatient procedure. Simple enucleation ensures a recurrence of 60 to 90%. It is currently believed to have no role in the management of multicystic ameloblastoma. To curb reoccurrences, oral surgeons have expanded this technique to accommodate intra operative adjuvant therapy of the bony circumference besides maneuvers such as cryotherapy, cautery, drilling, tissue fixation with e.g. carnoy's solution etc. For radical surgery a definitive methodology is en bloc resection with 1 to 2 cm tumor free bone perimeter [11-16]. Bone remodelling is also advocated to correct speech and swallowing deformities. Bony margin is defined as the distance away from the radiographic margin anticipated to be exempt of disease and oncologically secure to accomplish osteotomies. Elective node dissection is discouraged particularly in maxillary tumors. Pre-operative imaging, CT and intra-operative diagnostic assistance with plain radiography have been the recourse for co-relating the tumor boundaries with palpable surgical landmarks. Frozen section of soft tissue (overlying the cortical perforation) and bone marrow margins are favored sites for inspection. The precision of frozen section is 95-98%. For peripheral ameloblastoma, excision of a 1 cm soft tissue margin and a cuff of uninvolved alveolar bone (marginal mandibulectomy) are advisable. Segmental defects of the mandible are generally restored with vascularised free bone grafts. Maxillary lesions are amputated utilizing diverse approaches beneficial for partial maxillectomy. Radiotherapy ameloblastoma is practically radio resistant, adjuvant radiotherapy is proposed for definitely involved tumor margins (gross and microscopic), for recurrent and un-respectable ameloblastomas, tumors with unsatisfactory outcomes [17-19]. Ramifications of prospective radiation induced malignancies and accessory sequelae of extended radiation therapy must be recognized. Systemic chemotherapy is executed with platinum based agents and is seen to ameliorate clinical symptoms in patients abstaining from a surgical intervention.

Prognosis is contingent to determinants such as the age of the patient, tumor size, extent of disease, location of the tumor and histological category. Recurrences are directed by components

such as competent surgical margins and extension of a maxillary ameloblastoma into the vital structures (base of the skull, orbit, paranasal sinuses). Recurrence originates from the persistent microscopic disease. For extended follow up, a post-operative base line CT, annual clinical exams and an increasing interval of CT for the first five years in asymptomatic patients is counselled. Recurrence in multicystic tumors is 25 to 50% and in unicystic tumors is 5 to 10%.

Perplexities in diagnosing the neoplasm are large size of untreated tumors jeopardizing the airway, metabolic abnormalities, and for metastatic ameloblastoma with pulmonary extension, a paraneoplastic syndrome with hypercalcaemia.

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