AMELOBLASTOMA: A REVIEW

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INTRODUCTION

Ameloblastoma is a slow growing, benign tumor of the jaws which exhibit a locally destructive nature with unlimited growth potential. The tumor was first termed Adamantinoma by Malassez in 1885[1] and later given the name ameloblastoma by Ivy and Churchill in 1930.[2] Since the publication of the first edition of the World Health Organization (WHO) classification of head and neck tumors in 1971, it has been officially recognized as its own disease process. Primary treatment of this benign tumor is surgery with wide margins due to its aggressive nature and high propensity to recur. Traditionally, this was a disease entity that could be quite troublesome for the maxillofacial surgeon to treat, but, thanks to advancements in surgical technique, it can be adeptly managed with minimal patient morbidity.

CLINICAL CHARACTERISTICS

Ameloblastoma is a benign neoplasm of the oral cavity which arises from the odontogenic epithelium. It exhibits slow growth but carries a high recurrence rate of almost 10%.[3] Although its growth can be slower in comparison to other jaw tumors, it is locally aggressive, infiltrative, and has unlimited growth potential if left untreated. A conventional and unicystic ameloblastoma presents as a bony tumor while the peripheral ameloblastoma presents as a soft tissue tumor, most commonly of the posterior gingiva and almost always in the mandible.

Ameloblastoma accounts for approximately 1% of tumors of the jaw and 10% of tumors of dental origin.[4] It has no sex predilection and are generally diagnosed in the 3rd through 6th decades of life.[5] Although they are most commonly found in the posterior mandible, namely the angle and ascending ramus, they can be found anywhere in the jaws with a distribution of 80% occurring in the mandible and 20% occurring in the maxilla. The tumor itself is usually asymptomatic and presents as a slowly enlarging facial swelling or, as is most often the case, found as an incidental finding on routine dental x-rays. They can become quite large prior to diagnosis as they are most often not painful.

It is a tumor that is locally destructive and can cause bony expansion and erosion, displacement and mobility of teeth, erosion of tooth roots, and even paresthesia if the inferior alveolar nerve is intimately involved. It has an aggressive nature and a propensity to recur if not completely excised due to invaginations in surrounding bone or through tight adhesion to surrounding soft tissue following cortical perforation. In the Western

Hemisphere, ameloblastoma is the second most common odontogenic tumor following an odontoma.[6] While both conventional and unicystic ameloblastoma are often quite similar, both clinically and radiographically, unicystic ameloblastoma is often found in a younger population with the average age of diagnosis being 26.1 years old and often resembles a dentigerous cyst as it is most commonly associated with an unerupted tooth.[7]

Although this tumor has been extensively studied in the past, there has been significant progress made in the field of molecular genetics providing crucial information as to the behavior of this disease. In 2014, Wright et. al., published work vital to understanding in that dysregulation of mitogen-activated protein kinase (MAPK) and the sonic hedgehog signaling pathways were instrumental in the unrestricted growth of this neoplasm.[3] The most common MAPK mutations found were in BRAF, KRAS, and FGFR2. Coincidentally, both of these pathways are active during tooth development.

TERMINOLOGY

With the publication of the 4th edition of the *World Health Organizations Classification of Head and Neck Tumors* in January 2017, small but important distinctions have been made in classification when describing ameloblastomas. The change in nomenclature was aimed to avoid confusion of the differing as well as streamlining treatment options for each. In the previous classification published in 2005, ameloblastoma could be described as solid/mulitcystic, desmoplastic, unicystic, and extraosseous/peripheral. In the updated classification, solid/multicystic has been changed to conventional ameloblastoma. This was done in an attempt to streamline treatment rationale. Desmoplastic ameloblastoma now is a histologic subtype of conventional ameloblastoma and not its own entity as, although it can have some unique clinical and radiographic features, its behavior is that of a conventional ameloblastoma. Other subtypes of conventional ameloblastoma include follicular, plexiform, acanthomatous, and granular cell.

Since it is amenable to more conservative surgical approaches, unicystic ameloblastoma remains its own entity. There are three subtypes of unicystic ameloblastoma: luminal, intraluminal, and mural. Both luminal and intraluminal unicystic ameloblastoma act similar to traditional unicystic ameloblastoma, showing a low recurrence following conservative surgical treatment namely via enucleation and curettage with small peripheral ostectomy. However, mural ameloblastoma has a high recurrence similar to that of conventional ameloblastoma and should be treated similarly. Lastly, peripheral ameloblastoma also remains its own distinct entity.[3]

The conventional ameloblastoma is by far the most common representing over 85% of ameloblastoma. Unicystic is second at 10-15% and peripheral ameloblastoma being quite rare as it accounts for approximately 1% of tumor occurrence.

As a malignant entity, the ameloblastoma has previously been classified into three malignant subtypes: primary and secondary intraosseous tumors and secondary peripheral tumors. Now, all three of these are simply classified as ameloblastic carcinoma. Finally, metastatic ameloblastoma refers to a lesion which metastasizes, but the histology of both primary and metastatic tissues is benign. The difference in the two is that the ameloblastomic carcinoma has malignant features on histology, where metastatic ameloblastoma has benign features but has a secondary site where it is not usually found, such as in the neck or lung.

HISTOLOGY

Histologically, ameloblastomas are comprised of neoplastic ameloblastic cells which resemble the enamel organ. The epithelium is composed of a mature fibrous stroma that is devoid of odontogenic mesenchyme. The stroma can include the remnants of reduced enamel epithelium found in the crown of an erupted tooth. It also can include remnants of Hertwig's epithelial root sheath, known as the Rests of Malassez, which are found throughout the periodontal ligament, or composed of epithelial remnants of dental lamina, the Rests of Serres, which are found throughout the jaw or gingival connective tissue.

Although there are numerous subtypes of ameloblastoma, the common finding is well-differentiated, palisading cells with reverse polarity and surrounding nests and strands of epithelial stroma. Budding of epithelium from these nests can also be seen. This is a pattern which closely resembles the enamel organ during tooth development.

It was observed that the most common pattern of conventional ameloblastoma is the follicular subtype (**Figure 1**), representing 64.9% of the cases studied.

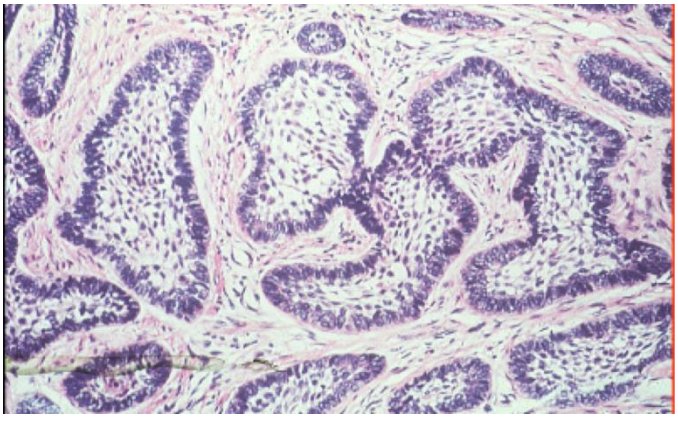


***Figure 1**: Follicular ameloblastoma shows islands of epithelial cells with a central mass of polyhedral cells or loosely arranged angular cells resembling stellate reticulum. These are surrounded by a well-organized single layer of cuboidal or tall columnar cells with nuclei placed at the opposite pole of basement membrane. This peripheral cell layer tends to show cytoplasmic vacuolization. Cystic formation is often seen in the center of the epithelial islands due to degeneration of stellate reticulum like cells.*

The second most common is the plexiform type (**Figure 2**), representing 13% of cases. The follicular subtype displays proliferating odontogenic epithelial cells arranged in islands while the plexiform subtype shows epithelial cells arranged in continuous anastomosing strands.

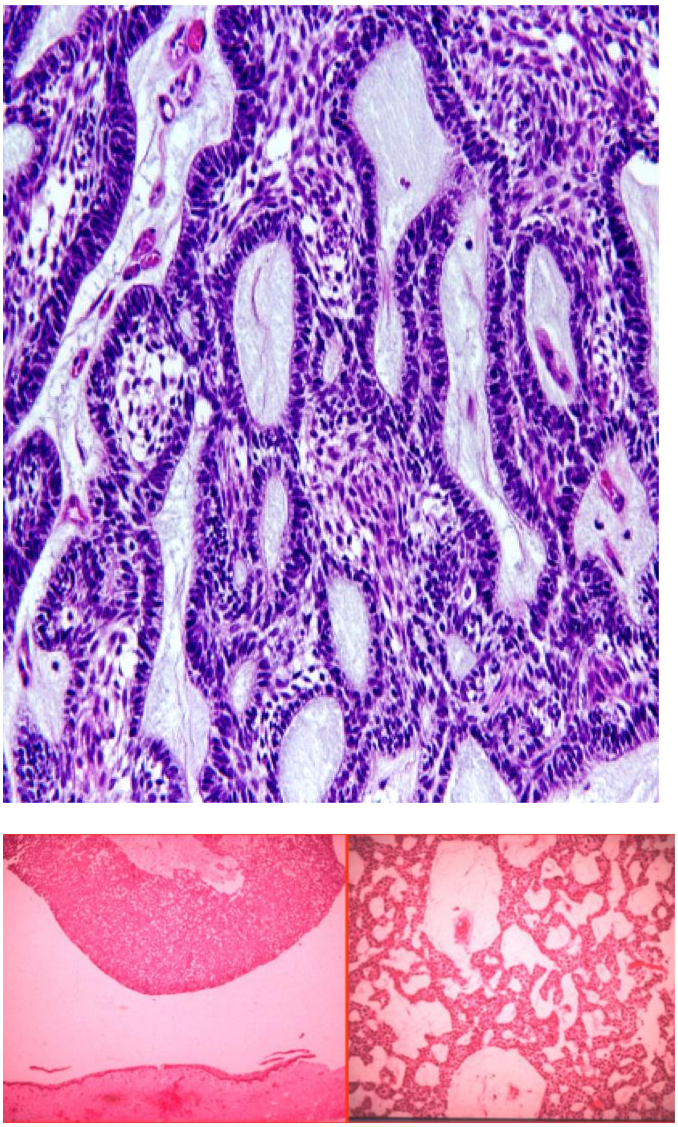


***Figure 2**: Plexiform ameloblastoma is arranged in form of trabeculae which is bound by a layer of cuboidal or columnar cells and stellate reticulum like areas are usually minimal. Cyst formation occurs but is usually due to stromal degeneration rather than cystic change in the epithelium. The stroma consists of loose, vascular sparsely cellular connective tissue.*

Much rarer, the desmoplastic subtype (**Figure 3**) presenting at 5.2%, and lastly, the acanthomatous subtype (**Figure 4**) at 3.9%. It is worth noting that, although these have differing characteristics histologically, this does not influence the clinical or biological behavior of the lesion. Thus, they are all under the classification of conventional ameloblastoma.

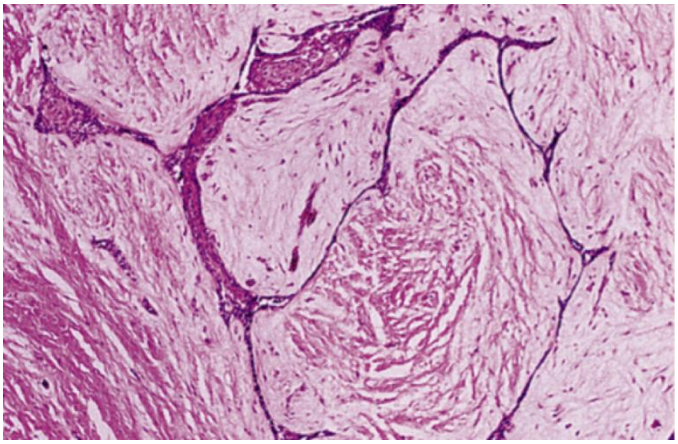


***Figure 3**: Desmoplastic ameloblastoma is characterized by extensive stromal collagenization or desmoplasia surrounding compressed small/irregular islands of odontogenic epithelium, making it a distinct entity.*

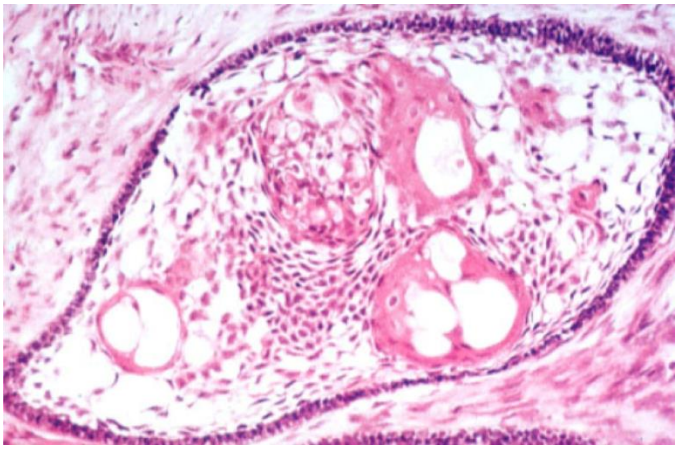


***Figure 4**: Acanthomatous ameloblastoma resembles a typical follicular ameloblastoma except it shows extensive squamous metaplasia, sometimes with keratin formation within the epithelial islands.*

Unicystic ameloblastoma consists of a single cyst lined by ameloblastic epithelium. Intraluminal unicycstic ameloblastoma is a cystic lesion lined by epithelium which exhibits columnar differentiation and reverse polarization of the basal cell layer. (**Figure 5**)

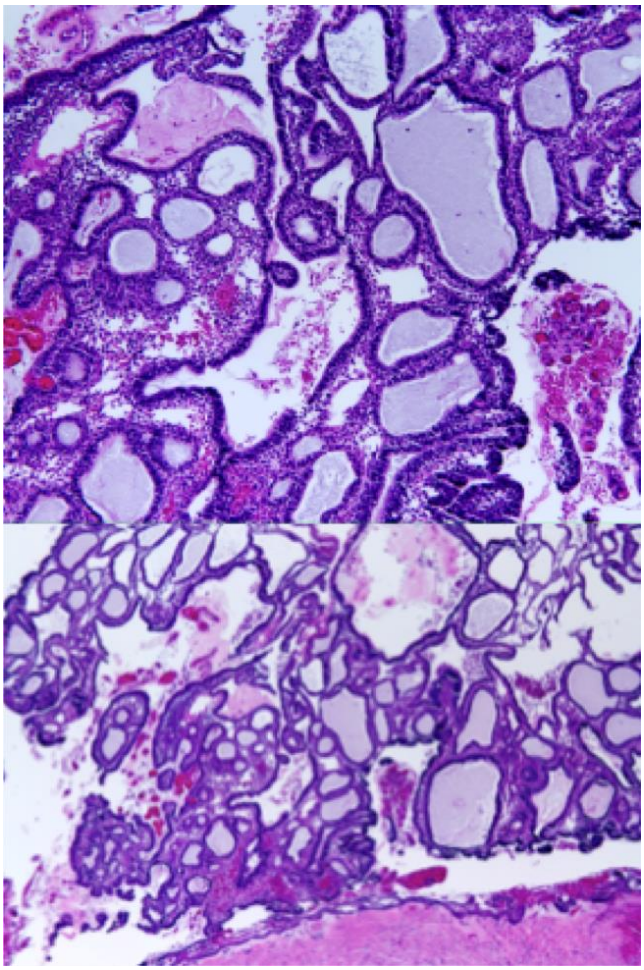


***Figure 5**: Intraluminal unicystic ameloblastoma exhibiting columnar differentiation and reverse polarization of the basal cell layer.*

The connective tissue adjacent to the epithelium often exhibits a uniform, thin band-like area of hyalinization. Mural unicystic ameloblastoma (**Figure 6**) exhibits invasion into the cystic lining and mural exhibits projection through the cystic lining into surrounding connective tissue.

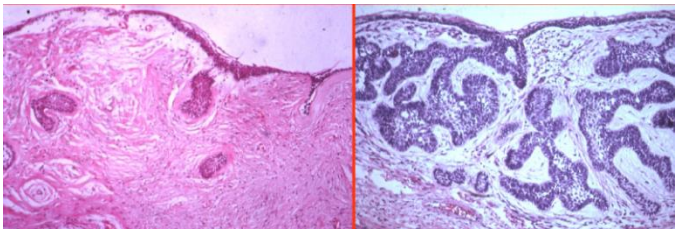


***Figure 6**: Mural, unicystic ameloblastoma tissue may be seen as an infiltration from the cyst lining or as free islands of follicular ameloblastoma.*

Peripheral ameloblastoma consists of islands of ameloblastic epithelium similar to the conventional ameloblastoma. It is differentiated by its location in the soft tissue of the jaws versus intrabony locations, as seen in conventional ameloblastoma.

There are two very rare subtypes which are malignant in nature. The first malignant, or metastatic, ameloblastoma is a previously benign ameloblastoma that has metastasized to a secondary site, usually the lungs. The second type, termed ameloblastic carcinoma, microscopically resembles a well differentiated ameloblastoma along with characteristics of malignant neoplasia. This cytologic atypia includes abnormal mitotic activity, cellular and nuclear hyperchromatism, and focal necrosis. It can develop de novo, or alternatively, it may develop from an initially benign ameloblastoma that loses differentiation. Again, although these subtypes are quite rare, the lung is by far the most common site of metastasis. Thus, any patient exhibiting pulmonary nodules following treatment of ameloblastoma warrants investigation.

RADIOGRAPHIC FEATURES

Conventional ameloblastoma classically present as "soap bubble" or "honey comb" lesions on CT and plain film, namely orthopantogram imaging. They are multiloculated with well-demarcated borders and no matrix calcification. Resorption of adjacent teeth and "root blunting" may often be seen as well as erosion through the cortex into adjacent soft tissues.

Unicystic ameloblastomas are well demarcated radiographically and appear without septation. They often are found in the posterior mandible, commonly associated with the crown of unerupted teeth.

DIFFERENTIAL DIAGNOSIS

Differential diagnosis based on clinical and radiographic examinations can include a wide variety of jaw tumors. Ameloblastoma is often indistinguishable from a dentigerous cyst, a keratocystic odontogenic tumor, or an odontogenic myxoma on clinical and radiologic examination alone. Other differentials include a central giant cell lesion or an adenomatoid odontogenic tumor with the latter being much more common in children than ameloblastoma. Other entities that are similar but have markedly different histologic and biologic features are the ameloblastic fibroma, ameloblastic fibro-odontoma, and an aneurysmal bone cyst.

TREATMENT AND PROGNOSIS

Management of ameloblastoma is challenging in that it requires definitive treatment and acceptable reconstruction in a tumor that is often quite large on initial presentation. At this time, surgical excision is the only effective treatment and recurrence of the tumor is seen as a direct result of inadequate removal during the primary intervention. In 2006, Carlson et. al., reported on the resistance of ameloblastoma to treatment with both chemotherapy and radiotherapy.[8] This is compounded by the fact that radiotherapy can lead to secondary tumors, such as sarcomas, or significantly increases the patient's risk of developing osteoradionecrosis later in life.[9] Surgical treatment can be classified as either "conservative" or "radical". The former involves enucleation with peripheral ostectomy and the latter involves either marginal or en bloc resection with wide margins. [12] Based on his review of the literature, Carlson advocates 1 to 1.5cm margins in resection of conventional ameloblastoma in order to provide a curative

surgery.[8] This is to ensure that all daughter cysts are removed.

As the unicystic ameloblastoma is less aggressive than the conventional type, a more conservative approach can be taken in certain scenarios. This treatment is usually employed in situations in which the tumor is quite large or is nearing vital structures and radical resection would result in significant morbidity. Recurrence rate in conservative treatment, namely enucleation and curettage, carries with it a 60-80% recurrence rate of conventional ameloblastoma versus approximately 30% in unicystic cases[10] so patient selection and proper education is key. It also can be used as a strategy to shrink the tumor prior to surgical excision, similar to treatment used in treatment of less aggressive benign entities. Some of the high recurrence rate with conservative treatment of unicystic ameloblastoma can be accounted for by treating mural unicystic ameloblastomas conservatively. However, it is important to remember that they act similar to conventional ameloblastoma, so resection of these is the recommended treatment modality. Of course, resection is the preferred modality of choice if surgically attainable. The systematic review by Lau and Samman found that resection of a unicystic ameloblastoma carries the lowest recurrence rate at 3.8% whereas enucleation alone has a recurrence rate of 30.5%.[11] Recurrence in conventional ameloblastoma following resection is noted at roughly 10%.

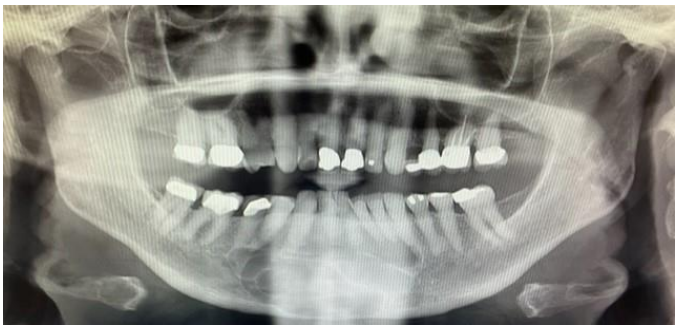
Most authors recommend a follow up for five years at a minimum, although there are case reports of recurrence at the initial site up to 21 years following resection. Thus, long-term patient follow-up is necessary.[11]

As ameloblastomas are benign tumors with late recurrence, immediate reconstruction of the defect is almost always employed. Bony reconstruction, as always, should be appropriate for the defect created as well as to the surgeon's level of expertise. These defects can be treated with allogenic grafts, autogenous grafts most commonly harvested from the iliac crest or free fibula grafts in large segmental defects, or other alloplastic means, such as temporomandibular joint replacement in large tumors of the ascending ramus or the condyle.

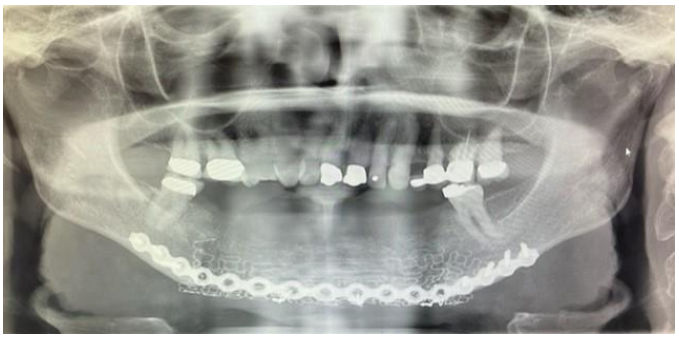
One last consideration in treatment is the anatomic site. Though less frequent, maxillary ameloblastomas are more aggressive and carry with them a more unfavorable prognosis in addition to a greater difficulty in treatment. Unlike the generally thick cortical bone found in the mandible, the maxilla has a much thinner cortex, which facilitates faster spread of the lesion into adjacent structures. Also, due to the complex anatomy, bony reconstruction of the maxilla is intrinsically more difficult than it is in the mandible.

One revolution in treatment of large segmental defects often found in these patients is the role of tissue engineering first described by Marx[6] and expounded upon by numerous authors since. Traditionally, patients with large resections would, at minimum, end up with titanium plate reconstruction or choose to undergo the morbidity of free flap reconstruction. Now, these patients can be treated with combination of allogenic graft material, rh-BMP2, and bone marrow aspirate concentrate held by a titanium plate and crib that can often be done via a transoral approach or a small neck incision that heals predictably and affords minimal morbidity to the patient. As shown in **Figure 7A**, an 82-year-old female patient had a large ameloblastoma. She refused reconstruction with fibula free flap or use of a conventional block hip graft. She underwent resection with oncologic margins, reconstruction with plate and titanium mesh and grafting with a combination of allogeneic

bone, rh-BMP2, and bone marrow aspirate from the hip. This was done solely via a transoral approach, excepting a trochar incision on either side of the mandible to place the screws. Following this, the patient only stayed one night in the hospital and had no post-operative morbidities. The follow up panoramic radiograph at 6 weeks shows adequate reconstruction with beginning bone fill that is even with her native mandible (**Figure 7B**). This technique can be employed in treatment of all benign tumors as it allows adequate recreation of both form and function of the ablative defect with minimal morbidity to the patient. This technique is a great change from the traditional approaches taken to reconstruct large defects, namely with fibula free flap, and the significant morbidity and burden it imposes on the patient.



A)



B)

Figure 7: ***A****, Large lesion in anterior mandible.* ***B****, Reconstruction 6 months following surgery showing bone fill up to height of native mandible.*

As in treatment of all head and neck pathology, treatment of ameloblastoma should be based on the correct histopathologic diagnosis, as well as appropriate patient selection to achieve optimal outcomes.

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