ORIGINAL ARTICLE

Ameloblastoma in Siriraj Hospital: A 14-Year Retrospective Analysis of Clinicopathological Characteristics Correlating to the WHO 2017 Classification

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Background: Ameloblastoma is a benign, locally aggressive neoplasm eliciting frequent relapse and morbidity. Based on many updates, there is an introduction of the World Health Organization (WHO) 2017 Classification in which the terminology has been modified and re-categorized.

Objective: To study natural courses, the clinicopathological characteristics, and rate of recurrence of ameloblastoma patients in Siriraj Hospital.

Materials and Methods: The H&E stained slides of 122 patients diagnosed with ameloblastoma between 2006 and 2019 at Siriraj Hospital were reviewed and re-classified according to the WHO 2017 Classification. The natural course of disease and the clinicopathological characteristics were analyzed. A descriptive statistical analysis was used to calculate the frequency and percentages of different variables.

Results: There were 86.9% of the cases being conventional ameloblastomas, whilst the predominant histologic pattern being the follicular pattern. The treatment of choice is excision. Recurrence of ameloblastoma is thought to be the consequence of several risk factors, clinicoradiological characteristics of the tumor, anatomical locations, treatments of choice, tumoral behavior, and tumor subtypes in particular. Thirty cases presented with recurrence, of which 83.3% were conventional ameloblastomas. Most of the cases were treated with radical treatment and have free surgical resection margins.

Conclusion: The clinicopathological characteristics and natural course of ameloblastoma patients in Siriraj Hospital corresponds to the WHO Classification. The present study demonstrated a high recurrence rate in patients treated with conservative surgery. Thus, the authors agree with the WHO 2017 Classification that radical surgery is recommended for patients with a history of recurrence and some specific subtypes of ameloblastomas.

Keywords: Ameloblastoma; Mandible; Neoplasm; Odontogenic tumors; Oral pathology

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Ameloblastoma is a benign neoplastic lesion of the odontogenic epithelium, primarily of the enamel organ-type tissue that has not gone through differentiation into hard tissue formation[1]. It is typically a slow-growing, otherwise locally aggressive tumor and is capable of reaching an enormous size[2,3].

In 2014, important studies on the genetics of ameloblastomas were published. They found that the mutually exclusive mutations in BRAF and SMO constitutively activate mitogen-activated protein kinase (MAPK) and sonic hedgehog (SHH) signaling pathways[4-7].

Ameloblastoma was previously classified, according to the World Health Organization (WHO) and the Internal Agency for Research on Cancer, 2003, as a benign odontogenic neoplasm comprising odontogenic epithelium and mature fibrous stroma with the lack of odontogenic ectomesenchyme. Ameloblastoma was then further classified into four types consisting of solid/multicystic, extraosseous/peripheral, desmoplastic, and unicystic types[8].

The recent 2017 WHO Classification of Head and Neck Tumors categorized ameloblastic tumors

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into simply three types comprising conventional, unicystic, and peripheral types. The previous term of solid/multicystic type was discarded because it could be bewildered with the unicystic type. Desmoplastic ameloblastoma, which was previously a clinical-pathologic entity, was also reclassified only as a histological subtype, a subtype in conventional ameloblastoma. This is because they behave in the same way as any other conventional ameloblastoma, albeit the clinical-radiologic features are still questionable and peculiar[9,10]. Moreover, various histologic patterns can be found frequently in the same ameloblastoma. In those cases, the pattern with the highest percentage in the tumor corresponds to the histological classification[10-12].

Conventional ameloblastoma is the most common among these three types, accounting for 85% of all ameloblastoma, which mainly occurs in the third and the fourth decades of life. Due to its higher incidence of recurrence, it is considered more aggressive than others[3,13]. It can be categorized into four common morphological patterns, which are follicular, plexiform, acanthomatous, and granular cells. The less common variants are clear cells and desmoplastic variants. Typically, plexiform and follicular patterns, each representing one-third of the conventional type, while the other patterns correspond to the remaining one-third[10-12].

Four decades ago, unicystic ameloblastoma was considered to be a distinct subtype of ameloblastoma based on clinicoradiologic characteristics along with histopathologic features[14]. Years later, researchers found that it responds satisfactorily to conservative treatment in contrast to its conventional counterpart in which extensive surgery is required. Histologically, unicystic ameloblastoma is categorized into three distinct histological subtypes, characterized by the pattern of proliferation of the epithelial components into luminal, intraluminal, and mural subtypes. The mural variants are reported to have higher recurrent rates and need more extensive surgical approaches similarly to conventional ameloblastomas, whereas the luminal and intraluminal variants respond satisfactorily to conservative surgery[4].

The least common and unusual variant, representing only 1% of the cases, is peripheral ameloblastoma. It is treated in a conservative manner. The recurrence rate is low and is attributed to the completeness of excision, not to the behavior of the disease[3,15,16]. Researchers considered it as a hamartomatous lesion[17]. Histologically, peripheral ameloblastoma is characterized by the presence of islands of ameloblastic epithelium in a dense connective tissue stroma. The histologic patterns of the ameloblastic epithelium are similar to the conventional type[3,18].

The conservative surgical treatment could be in the form of enucleation, curettage, cryotherapy, or marsupialization. It preserves the patient's normal tissues, and minimizes facial disfiguration, but is prone to higher recurrence especially if the ameloblastoma subtype was aggressive. Radical surgical treatment involves en bloc tumor resection with wide bone margin, followed by immediate or delayed bone reconstruction of the surgical defect with tissue grafts and prosthetic rehabilitation[19].

Recurrence of ameloblastoma is thought to be the consequence of several risk factors, clinicoradiological characteristics of the tumor, anatomical locations, treatments of choice, tumoral behavior and tumor subtypes in particular. Unicystic type is typically accepted to be less aggressive than the conventional type[20]. Among all the histologic patterns in conventional ameloblastomas, follicular, granular, and acanthomatous patterns have a high likelihood of recurrence, whereas the least aggressive behavior is plexiform pattern. There is currently no guideline published for follow up or adequate proper surgical resection margin for ameloblastoma[21]. There is no definite recommendation in taking margins of ameloblastoma in pathological gross examination, in which many cases with free all resection margins showed recurrences.

The present study purpose was to assess clinicopathological characteristics of ameloblastoma according to the new WHO criteria and to evaluate the clinicopathological characteristics of cases with recurrence.

Materials and Methods

The present study was approved by the Research Ethics Committee of the Institution, under protocol number 435/2562 (EC3) approval Si 567/2019.

According to the new WHO classification, which was published in 2017, and other literatures, the authors made a retrospective analysis about the clinical, demographic, and histopathologic characteristics, including the following variables as age, gender, tumor location, type of operation, histologic subtype, and recurrence. All patients admitted to the Siriraj Hospital, Thailand for ameloblastoma between 2006 and 2019 were retrospectively included, comprising 134 cases, where 12 cases were excluded due to missing H&E-

stained slides.

All the tissue sections were then fixed in formalin, embedded in paraffin, and stained with hematoxylin and eosin. Soon, they were re-examined using an optical microscope (Nikon Cover) to ascertain the ameloblastoma types and classify them according to the new WHO classification (2017). Two independent evaluators analyzed the slides, while a third evaluator was called upon when there were disagreements, and the results were established in consensus. Considering that if there were cases with more than one histologic subtype observed, the histologic classification of the lesions was based on the most predominant subtype. The clinical and histopathologic information was retrieved from the hospital database. Primary and recurrent ameloblastoma cases were counted as one single patient. The present study used a descriptive statistical analysis to calculate the frequency and percentages of different variables. Data analyses were conducted using IBM SPSS Statistics, version 22.0 (IBM Corp., Armonk, NY, USA).

Results

Clinical findings

One hundred twenty-two patients were included into this present study. Most of which were Thai (99.2%). The mean age was 39.1 years, ranging from 9 to 92 years. The majority of patients were male, with 68 men (55.7%) and 54 women (44.3%).

Most cases had lesions in the mandible at 76.2% and were treated with excision for 36.8%, segmental resection for 27.8%, total resection for 13%, curettage alone for 13%, excision and curettage for 8%, enucleation for 6%, and enucleation with curettage for 3%.

Table 1 gives further characteristic information of each variable as to the distribution of all cases in the present study.

Table 1. Clinical and histopathologic features of 122 lesions

Variable	Total; n (%)
Age	
0 to 29 years	28 (22.9)
30 to 59 years	77 (63.1)
60 to 99 years	17 (8.9)
Sex	
Male	68 (55.7)
Female	54 (44.3)
Location	
Mandible	93 (76.2)
Maxilla	29 (23.8)
Operation	
Radical surgery	47 (38.5)
Conservative surgery	75 (61.5)
Follow-up (months) (n=99); median (P25, P75)	26 (4, 54)

Pathological findings

According to the new WHO classification (2017) by Wright and Vered (2017), the study sample was divided into 106 conventional (86.9%) and 16 unicystic (13.1%). No peripheral ameloblastoma was observed in the present study.

Conventional ameloblastomas in the present study represented the highest percentage of these tumors. Most of them were diagnosed in the late third decade of life with a slight male predilection and were located predominantly in the mandible at 72.6%. Among the conventional histological variants, the follicular pattern was the most represented at 41.8%, followed by plexiform at 28.7%, and the other subtypes at 16.4%, with acanthomatous at 15.6% and desmoplastic at 0.8%.

Unicystic ameloblastomas were diagnostically confirmed in 16 cases (13.1%). They mainly occurred in young patients, with a mean age in the second decade of life. The mandible was the most common location presented in this type of lesion. Fourteen cases were classified in the mural subtype, whereas two cases were classified as intraluminal subtype.

Recurrence rate

Thirty patients presented with recurrence. All of the cases were Thai with a slight male predilection, comprising 17 male cases (6.7%) and 13 female cases or (43.3%). The mean age of the patients in this group was 34.5 years, ranging from 18 to 57 years of age. Most of the lesions were located in the mandible for 27 cases (90%), with only three cases presented at the maxilla (10%).

For the type of operation, the majority of patients had excision, accounting for 40% of the cases, followed by curettage alone for 26.7% and segmental resection for 16.7%. Enucleation and excision with curettage were equally presented at 6.7% each, whereas one case had enucleation and curettage, accounting for only 3.2% of the cases.

Histologically, 25 cases out of 30 cases had conventional ameloblastoma, accounting for 83.3%, most of which had follicular variant in 18 cases followed by acanthomatous variant in seven cases. The remaining five cases (16.5%) presenting with recurrence had unicystic type, all of which were mural variants.

Table 2. Clinical and histopathologic features of 30 cases with recurrence

Variable	Total; n (%)
Age	
0 to 29 years	12 (40.0)
30 to 59 years	18 (60.0)
60 to 99 years	0 (0.0)
Sex	
Male	17 (56.7)
Female	13 (43.3)
Location	
Mandible	27 (90.0)
Maxilla	3 (10.0)
Operation	
Radical surgery	5 (16.7)
Conservative surgery	25 (83.3)
Histologic type	
Conventional	25 (83.3)
• Follicular	18 (60.0)
• Acanthomatous	7 (23.3)
Unicystic	5 (16.7)
• Mural	5 (16.7)

Table 2 gives further characteristic information of cases presented with recurrence of each variable as to the distribution of all cases in the present study.

Discussion

Demographic findings

Although ameloblastoma may be associated with local morbidity, mortality is rare. There is still controversy discussing the terminology, classification, morphology, etiology, diagnosis, treatment of choice, appropriate resection margin, and guideline for follow up cases[4,12,18,22,23]. Currently, only few studies have evaluated the clinicopathological characteristics of these lesions in Southeast Asia, especially in Thailand. Therefore, it makes the present study of great importance in the context of clinicopathological characteristics of each ameloblastoma subtype correlating to the new WHO 2017 classification.

A recent study by Intapa[24] investigated the prevalence and clinical features of ameloblastoma and its histopathological subtypes in Southeast Myanmar and Lower Northern Thailand populations. This 13-year retrospective study highlighted the predominance of mandibular distribution in 86.7%, particularly in the posterior body-ramus-angle region. The majority of cases were asymptomatic, with swelling being the most common clinical manifestation. The present study identified three subtypes of ameloblastomas, unicystic ameloblastoma at 20%, conventional solid/multicystic ameloblastoma at 70%, and desmoplastic ameloblastoma at 10%[24].

Studies have described the etiology of ameloblastoma as having factors related to the onset of the lesion after local trauma, inflammation, nutritional status, genetic mutations and/or molecular alterations, in which various signaling pathways participate[18].

Considering that ameloblastoma is the second most common odontogenic neoplasm after odontomas is important. It represented 11% to 18% of all odontogenic tumors. It should be kept in mind that there may have been a difference in prevalence, depending on where the studies took place, as hospital studies showed higher prevalence compared to those of universities[22,25]. This aspect highlights the underestimation of odontomas in certain regions, particularly in Asia and Africa, and provides insights into the factors contributing to the potential under detection of odontomas[12,22,26]. Limited access to routine dental check-ups and the asymptomatic nature of odontomas may lead to their underestimation, as patients may not seek medical attention due to the absence of pain or noticeable disfigurement. Furthermore, the diagnosis of odontomas based solely on radiographic appearance without histopathological examination can also contribute to their underestimation. This valuable comment emphasizes the importance of considering these factors when interpreting the prevalence of ameloblastoma, and it enriches the understanding of the topic.

Moving on to gender, studies have reported that there is no gender predilection in ameloblastoma[24,27]. However, others revealed predominance in men[12,22,26]; which corresponded to the result of the present studies, stating 55.7% of the patients were male (Table 1).

Histopathologic findings

The lesions of ameloblastoma could be intraosseous or extraosseous, with the mandible being predominantly affected, accounting for 80% to 85%[3,28]. The mandible to maxilla ratio varies from 5:1 to 90:1[29,30]. In the present study, 76.2% of the lesions were in the mandible and 23.8% were in the maxilla.

In the present study, the distribution of histologic subtypes corresponded to that reported in the literature and agreed with studies in which follicular and plexiform patterns were the two most common

patterns observed[13,22,29,30]. For the present study, the two most common patterns were the follicular and plexiform patterns, accounting for 41.8% and 28.7%, respectively. As for unicystic ameloblastomas, all of the cases were classified into the mural subtype, a finding similar as compared to other studies, where age, location, and subtype corresponded likewise.

Management

The management of ameloblastoma is still controversial as it is a benign, locally aggressive tumor with a high rate of recurrence. In the planning of surgery, it is crucial to acknowledge whether it is a primary or recurrent tumor along with the age, size, location, and duration of the lesion. The presence of cortical bone rupture and the involvement of soft tissue may also be beneficial in surgical planning. The treatment of choice for ameloblastoma can be either conservative or radical[31,32]. Conservative treatments in these tumors include enucleation, enucleation associated with curettage, and the use of adjuvant therapies such as Carnoy's solution and cryotherapy. Radical treatment of ameloblastoma comprises marginal or block resection of 1- to 2-cm margins and immediate bone reconstruction[3,31,33]. Facial reconstruction procedures with iliac crest graft or microvascular fibula flaps may be needed[2,28,34]. In the present study, the treatment for most conventional ameloblastoma cases was excision in 36.8%, followed by segmental resection, total resection and curettage, excision associated with curettage, enucleation, and lastly, enucleation associated with curettage. All cases of unicystic ameloblastoma were treated conservatively.

The optimal surgical margin for the treatment of ameloblastoma remains a topic of discussion among clinicians and researchers. While there is no definitive consensus, recent studies have shed light on the appropriate surgical approach for this aggressive benign tumor. There is emerging evidence suggesting that a 2-cm margin may be sufficient for the management of ameloblastoma in certain cases, particularly for small and non-aggressive lesions. It is important to note that the decision regarding margin width should be made on a case-by-case basis, considering factors such as tumor size, radiographic features, histological subtype, and the patient's overall health. Close postoperative follow-up and long-term monitoring are also crucial in detecting and managing any potential recurrence[18].

Recurrence rate

There is currently no guideline published for follow up after treatment in ameloblastoma patients, and in the authors' hospital, routine follow-ups were appointed to these patients. Meanwhile, some patients often return only when the recurring symptoms can be detected by themselves. The median follow-up duration for ameloblastoma patients in the authors' hospital was 26 months. Studies have revealed that there is a higher rate of recurrence after conservative treatment compared to radical treatment[19].

The prognosis of ameloblastoma is usually favorable, even though it may cause facial deformity[2,28]. It was observed that patients treated with conservative surgery had a significantly higher rate of recurrence when compared to cases treated with segmental resection[27]. In the present study, 30 patients presented with recurrence after treatment. Most of the cases were male in the third decade of life and up to 90% of the lesions were located in the mandible. The majority of the cases with recurrence were previously treated with radical treatment for 56.7%. The odds ratio of association between recurrence and the type of surgery showed that the conservative surgery group had an odds to recurrence of 2.42 compared to the radical surgery group. Moreover, it is surprising that all of the cases treated with radical treatment had free surgical resection margins on pathological reports. Histologically, most of the cases were conventional variants with the follicular subtype being the most predominant pattern, followed by the acanthomatous pattern. All unicystic type cases presented with recurrence had been treated with conservative treatment.

Conclusion

According to the clinicopathological aspect of the present study, a vast number of ameloblastoma patients had lesions located in the mandible, with conventional ameloblastomas being the majority. Although the prognosis of ameloblastoma is usually favorable, a significantly higher rate of recurrence was presented in patients who received conservative treatment. Nevertheless, the treatment of ameloblastoma should be based upon its histological subtype, size, extent of the lesion, location, and type of bone involvements to best suit one's requirements.

What is already known on this topic?

Ameloblastoma was recently re-categorized according to the new WHO 2017 classification. However, due to controversial conception, information about its clinico-pathological aspect and rate of recurrence is still to be determined.

What does this study add?

The clinicopathological aspect of ameloblastoma in this study demonstrated that conventional ameloblastomas were the vast majority with the mandible being predominantly affected. The rate of recurrence of ameloblastoma is significantly higher in patients receiving conservative treatment. This study in Thailand correlates to the current guideline, therefore, each patient must be treated accordingly based upon the guideline and each patient's status prior to treatment.

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Conflicts of interest

The authors declare no conflict of interest.

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