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ORIGINAL ARTICLE

Analysis of demographic differences according to histomorphological subtypes of 1312 cases of ameloblastoma

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Abstract

Introduction: Ameloblastoma is a benign but locally aggressive odontogenic tumour broadly divided into conventional, unicystic, peripheral, adenoid and metastasising types. The first three entities compose the majority and especially the conventional type which has different histopathological subtypes such as follicular, plexiform, acanthomatous, granular cell, basal cell and desmoplastic have been described. We report the largest series of ameloblastoma in a single study to analyse the demographic characteristics according to histopathological subtypes of ameloblastoma. *Materials and Methods:* 1,312 cases of ameloblastoma reported from two centres in Sri Lanka and Malaysia were analysed according to age, site and histopathological subtype. *Results:* Of the total of 1,312 cases, the mean age for conventional ameloblastoma (excluding desmolastic subtype) was 36.82±16.57. It was 46.3±15.21 for categorisewhile peripheral and unicystic ameloblastoma occurred at 40.77±16.35 and 31.00±17.37, respectively. Ninety percent of the cases were in the mandible (p=0.00001) with significant predilection for the right side. Unicystic and plexiform subtypes were mostly seen in the 11-20 age group while the desmoplastic subtype was seen in the 51-60 age group. The commonest histological subtype was follicular subtype and acanthomatous changes were observed predominately in combination with follicular subtype. Majority of the acanthomatous subtype was observed in posterior mandible (p=0.00001). The frequency of luminal (243) and mural (246) subtypes were almost similar. *Conclusion:* This study provides a comprehensive demographic detail of different histological subtypes of ameloblastoma using the largest sample in the literature. The present findings will be helpful in classification and understanding of different subtypes of the tumours.

Keywords: Ameloblastoma, benign, histomorphology, demographic

INTRODUCTION

Ameloblastoma is a benign epithelial odontogenic tumour approximately comprised of 1% of all cysts and tumours of the jaws.[1] Although this is a benign tumour, it behaves as a locally invasive tumour causing expansion and deforming the facial skeleton, tooth displacement, high rate of recurrences and rarely with metastasis. Radiologically, except the peripheral type, ameloblastoma can present as unilocular or multilocular radiolucent lesions. However, desmoplastic ameloblastoma (DA) may show mixed radio-dense lesions mimicking the appearances of different entities of fibro-osseous category.

The conventional ameloblastoma has many histopathological variants. They are broadly divided into follicular, plexiform, acanthomatous, desmoplastic, granular cell, and basal cell subtypes. These subtypes are present either in isolation or in combination with different histological subtypes in the same lesion. Rarely, they can present as hybrid tumours with other odontogenic tumours. For example, some tumours have both follicular and plexiform patterns, and some other tumours may contain follicular and granular/acanthomatous changes.[2] In addition, rare cases have been reported together with adenomatoid odontogenic tumour and calcifying epithelial odontogenic tumour.

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The 4th edition of WHO classification of Head and Neck tumours in 2017 has introduced some changes to 2005 manual especially with regards to ameloblastoma. The 2017 classification has categorised them into ameloblastoma, unicystic ameloblastoma and extraosseous/peripheral types. DA has been named as a histological subtype but not as a clinicopathologic entity. Furthermore, malignant ameloblastoma (metastasising ameloblastoma) is also classified under ameloblastoma leading to a significant controversy.[2,3] The 5th edition of WHO classification of Head and Neck tumour in 2022 has classified ameloblastoma into five clinicopathological variants, namely conventional, unicystic, extraosseous/peripheral, adenoid and metastasising ameloblastoma. The adenoid ameloblastoma has been recognised as a distinctive clinicopathologic entity in the latest WHO classification.[4]

Prevalence of ameloblastoma is more in Asian and African populations, whilst it is low in North American and European countries.[5-12] Several studies analysing odontogenic tumours (OTs) in Sri Lanka and Malaysia are also available in the English literature.[13-17] However, there are only a few studies analysing histological subtypes of ameloblastoma in relation to demographic factors using a large sample in the literature.[18,19] Although there were several studies on OTs in South and Southeast Asia, collective data has not been analysed as a large sample. Hence this effort is to analyse the largest sample in the literature from two centres in two Asian countries focusing mainly on histological subtypes of conventional, unicystic and peripheral ameloblastoma in order to analyse the relationship with demographic variables.

MATERIALS AND METHODS

This retrospective cross-sectional study was undertaken and documented in alignment with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines. Ethical approval was obtained from the Universiti Malaya Faculty of Dentistry Medical Ethics Committee (FDMEC) with the code number DFOS1905/0017(U).

Cases diagnosed as Conventional ameloblastoma (follicular, plexiform, granular cell, acanthomatous, desmoplastic, basal cell subtypes), unicystic, peripheral and metastasising were retrieved from the Oral Pathology data bases from two centres. Cases were selected from 1999-2019 from the Department of Oral Pathology, Faculty of Dental Sciences, University of Peradeniya, Sri Lanka and from 1982-2018 from the Faculty of Dentistry, Universiti Malaya, Malaysia. Demographic data and histological subtypes were gathered. Cases with inadequate data were excluded and cases with multiple biopsies were considered as a single case.

Histologically, all tumours were sub-grouped as follicular, plexiform, mixed (combination of both follicular and plexiform patterns), desmoplastic, peripheral and unicystic. Furthermore, all the cases belonging to follicular, plexiform, mixed and unicystic were further investigated for any evidence of acanthomatous changes, presence of granular cells or basal cell changes. Unicystic ameloblastoma were further subcategorised into luminal, intraluminal and mural subtypes.

Gathered data were entered into a Microsoft Excel worksheet. Collected information was categorised according to the age categories to identify the frequency according to the age. Site of occurrence was also categorised as anterior (from midline to distal surface of canine), middle (mesial surface of premolar to distal surface of 1st molar) and posterior (from mesial surface of 2nd molar towards most posterior) in both jaws. In addition, occurrence according to right and left side of jaws were also recorded for analysis. In child patients' midline to B as anterior, CD middle and from E backwards as posterior were considered for distribution according to site. Large lesions affecting entire left or right side of either the mandible or maxilla were taken as a separate group. The tumours that crossed the midline were also categorised separately.

Chi-square test was used to determine the association. Each variable with different combinations was analysed to identify whether there is any statistically significant relationship. The level of significance was set at ($P < 0.05$) throughout the study.

RESULTS

A total of 1,332 cases of different types of ameloblastoma were identified. There were 681 males and 651 females with the ratio of 1.04:1. Age ranged from 3 - 86 years with the overall average age being 35.19 years. However, the total sample was reduced to 1312 due to inadequate details in 17 cases. Furthermore, 3 cases of metastasising ameloblastoma were also excluded. Overall, 1,009 cases from Sri Lanka and 303 cases from Malaysia of different subtypes were included in the analysis. Out of the total sample,

60.33% were conventional ameloblastoma. Within that, 24.5%, 16.92%, 11.67%, 7.24% were follicular, plexiform, mixed and desmoplastic subtypes, respectively. Unicystic type accounted for 38.64% and peripheral ameloblastoma was the least, amounting to approximately 1%.

The mean age for conventional ameloblastoma (excluding desmoplastic) was 36.82±16.57 with a median of 34 years. For desmoplastic ameloblastoma, it was 46.3±15.21 with a median of 47 years. The values for peripheral and unicystic ameloblastoma were 40.77±16.35 and 47 years, 31.00±17.37 and 28 years, respectively. When the conventional group was classified histologically, the mean age of occurrence for mixed subtype was 36 years (36.85±15.5, 34), follicular type 39 years (39.15±16.44, 38) and plexiform type 33 years (33.58±17.02, 29.5). Overall, the age range for conventional ameloblastoma was 7-86 years, desmoplastic 12-80 years, peripheral 8-68 years and unicystic 3-88 years, respectively.

The samples were divided into 9 categories according to age groups. Distribution of ameloblastoma in relation to age groups is illustrated in FIG. 1. The peak occurrence of conventional ameloblastoma was 21-30 years old, whilst it was 11-20 years old for unicystic ameloblastoma. Furthermore, the prevalence of follicular and plexiform types gradually decreased with the advancement of age and the mixed type appeared to follow the same trend (FIG. 2). The results were statistically significant with regards to age groups and histological type of ameloblastoma (p=0.00001).

It was interesting to note that different histological subtypes predominate in different age groups, except plexiform and unicystic, which were commonly seen in the 11-20 age group (27% and 30.6%, respectively). The follicular type was mainly in the 21-30 years old group, mixed histological in the 31-40 age group, peripheral in the 31-40 years old group and desmoplastic in the 51-60 age group (FIG 2).

Histologically, some conventional ameloblastoma showed acanthomatous change whilst some others showed granular cell change within the tumours with plexiform, follicular or mixed appearance. A few other conventional ameloblastoma showed basal cell changes, and 2 cases showed clear cell changes within follicles. It was noteworthy to highlight that most acanthomatous and granular cell changes were identified in the follicular type. However, basal cell appearance was noted mainly in mixed histological subtypes (TABLE 1). Analysis of acanthomatous changes in conventional ameloblastoma showed the highest prevalence in the 31-40 age group (FIG 3).

The majority of ameloblastoma were found affecting the mandible (1142, 90.35%) with mandible to maxilla (122, 9.65%) ratio of 9.4:1 and the results were significant statistically (p=0.002128) (from the total sample, 48 cases

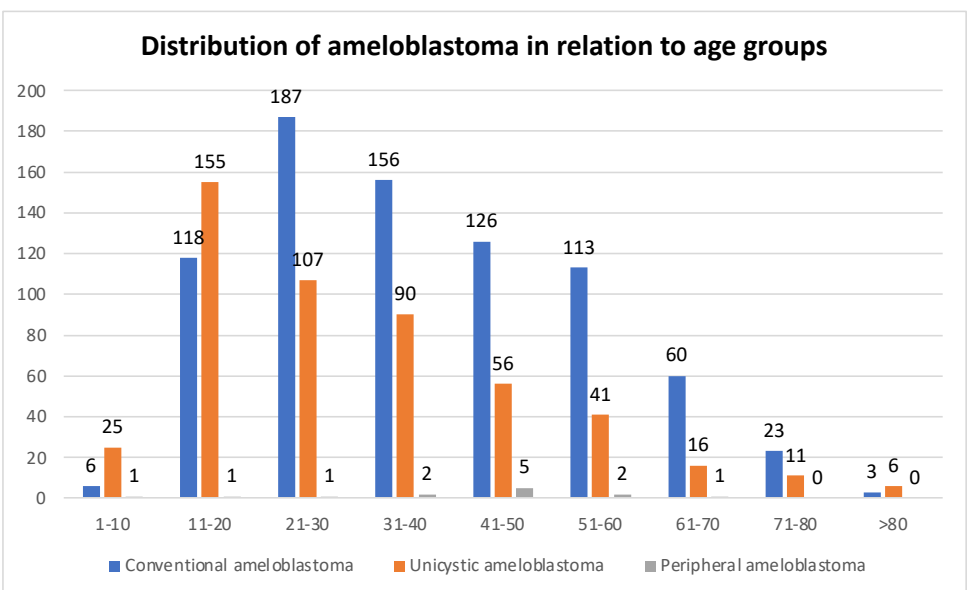

FIG.1: Distribution of ameloblastoma in relation to age groups

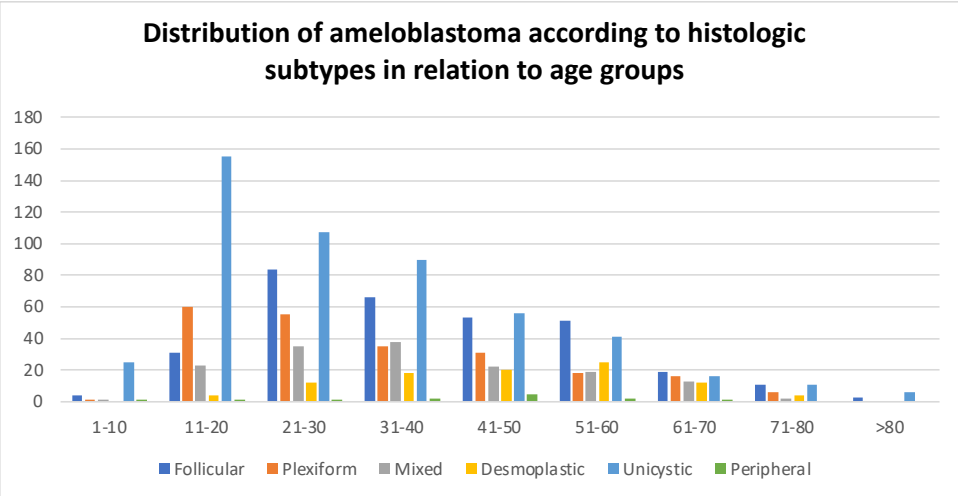

FIG. 2: Distribution of ameloblastoma according to histologic subtypes in relation to age groups

were without sites). The right side of the mandible is more frequently affected (548) out of four quadrants followed by left mandible (488; p=0.00001). Furthermore, in both jaws posterior region was the most affected site (p=0.00001) (TABLE 2).

Distribution of conventional ameloblastoma with acanthomatous changes within the jaws is demonstrated in FIG 4. Accordingly, the most prevalent site of occurrence was in the mandible and mainly towards the posterior part and the findings were statistically significant (p=0.00001). Furthermore, out of the 40 cases with granular cell changes, only a single case was in the maxillary bone which was in the left middle region.

There were 243, 246 and 18 cases of luminal, mural and intraluminal subtypes of unicystic ameloblastoma, respectively. All intraluminal subtypes were found in the mandible. Similarly, 91% of mural and 88.6% of luminal subtypes also occurred in the mandible (TABLE 2).

Demographic analysis according to geographical variation showed that the male-to-female ratios were 1.03:1 and 1.09:1 in Sri Lanka and Malaysia, respectively. The commonest histological subtype was follicular in both countries; however, mixed variant is common than plexiform in Malaysian samples while plexiform is common than mixed type in Sri Lanka. DA was commonly seen in the 31-40 age group (57.1%) in Malaysia whilst it was 51-60 age group (28.4%) in the Sri Lankan sample. Furthermore, both countries showed mandibular predominance for DA (TABLE 3).

DISCUSSION

Ameloblastoma is a benign but locally aggressive tumour. This study analysed the largest series of

TABLE 1: **Metaplastic changes within conventional ameloblastoma**

Histological subtype	Number of cases
Mixed subtype with acanthomatous changes	63
Plexiform subtype with acanthomatous changes	22
Follicular subtype with acanthomatous changes	115
Mixed subtype with granular cell changes	10
Plexiform subtype with granular cell changes	6
Follicular subtype with granular cell changes	24
Mixed subtype with basal cell changes	7
Plexiform subtype with basal cell changes	3
Follicular subtype with basal cell changes	3

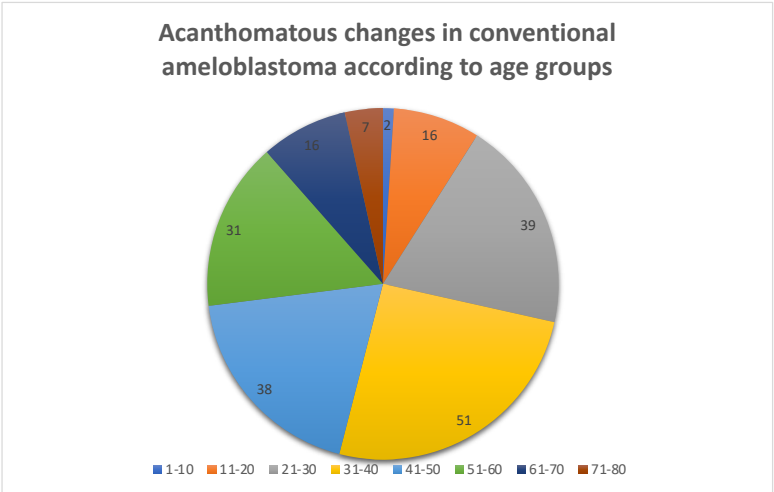

FIG. 3: Acanthomatous changes in conventional ameloblastoma according to age groups

ameloblastoma in the literature reported from two centres. Reichart and his group analysed 3677 published cases in the English literature and after excluding all benign and malignant tumours other than ameloblastoma the total was 1564.[1] Accordingly, the mean age was 36 years with equal gender distribution. Confirming the same fact in the present study after analysing 1312 cases, the mean age was 35.19 and male to female ratio was 1.04:1. It also falls within the range of other published studies.[14,20] However, some studies show slight male predominance.[19,21]

Ameloblastoma is ranked as the commonest odontogenic tumour in some countries,[14,22] whilst according to others, it was the second most common odontogenic tumour after odontoma.[2] This group of benign odontogenic tumours mostly seen in the 2nd and 3rd decades of life in the present study. Results of the present study concurred with previous analysis that unicystic variant occurs in younger patients than conventional.[1,19] The present study further provides evidence to support the previous finding of mainly occurring in older patients.[2,19]

In agreement with the literature, in this study, 90% of ameloblastoma occurred in the mandible mainly in the body and posterior region.[1,19] Although some studies indicated

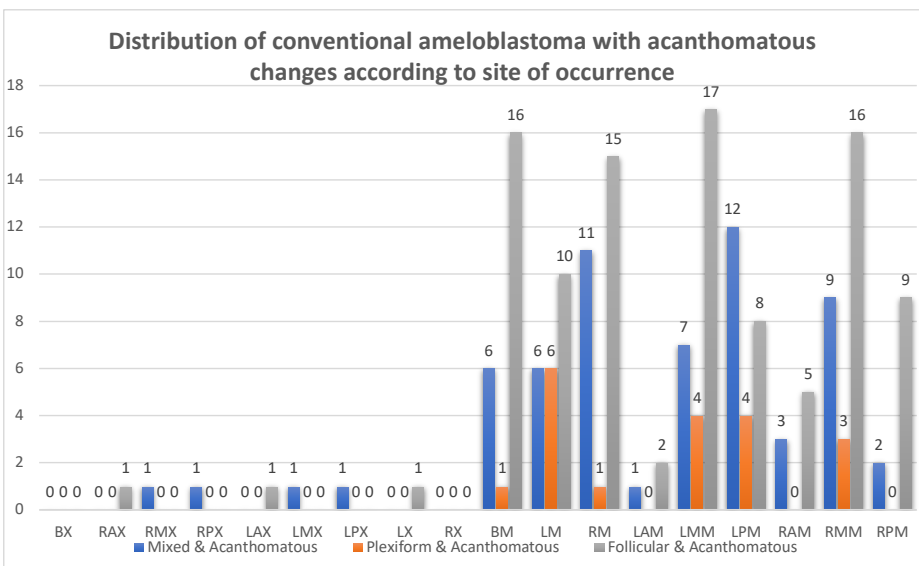

FIG. 4: Distribution of conventional ameloblastoma with acanthomatous changes according to site of occurrence

TABLE 2: **Distribution of ameloblastoma according to site of occurrence**

	Peripheral	Desmoplastic	Plexiform	Follicular	Mixed	Unicystic (Accumulative)	Mural	Intraluminal	Luminal
BX	0	3	0	1	0	5	1	0	4
RAX	2	5	0	2	0	6	5	0	1
RMX	0	3	3	0	1	11	4	0	7
RPX	0	0	0	0	1	2	1	0	1
LAX	1	5	1	1	1	9	4	0	5
LMX	0	3	1	2	3	7	4	0	3
LPX	0	0	2	0	2	3	0	0	3
LX	0	8	1	4	0	6	3	0	3
RX	1	8	1	5	2	0	0	0	0
BM	0	11	18	37	12	28	15	0	13
LM	1	4	46	55	19	52	26	4	22
RM	0	9	42	57	29	38	21	2	15
LAM	2	3	5	4	2	8	2	1	5
LMM	0	11	20	35	19	70	38	0	32
LPM	1	2	28	25	17	59	25	5	29
RAM	1	3	8	9	5	13	1	1	11
RMM	1	6	19	36	18	119	58	3	58
RPM	2	5	22	37	13	56	31	1	24
*Data missing	1	6	5	12	9	15	7	0	7
Total	13	95	222	322	153	507	**246**	**18**	**243**

RPM-right posterior mandible, RMM-right mid mandible, RAM- right anterior mandible, LPM-left posterior mandible, LMM-left mid mandible, LAM- left anterior mandible, RM-right mandible, LM- left mandible, BM- bilateral mandible, RX- right maxilla, LX-left maxilla, LPX-left posterior maxilla, LMX-left mid maxilla, LAX- left anterior maxilla, RPX-right posterior maxilla, RMX-right mid maxilla, RAX- right anterior maxilla, BX-bilateral maxilla.

that desmoplastic variant is mostly found in the maxilla, the present study revealed no such predominance (39.3% occurred in maxilla).[16] However, DA was mostly found in 51-60 years' age group in this study similar to other studies with no gender predilection.[23] The same study showed mandibular predominance analysing 114 reported cases of DA.[23]

Analysis of various histological subtypes are sparse in the literature.[24,25] As the present sample is a large sample, we were able to include all different subtypes for more reliable analysis. Most common subtype was the follicular subtype (40.5% out of all ameloblastoma excluding unicystic and peripheral) followed by plexiform and mixed subtype. According to the available reports some showed similar results after analysing 76, 182 and 50 cases, respectively.[26-28] In contrast, plexiform variant was common in another study analysing a small sample of 30 cases.[20] In agreement with the literature least common was peripheral type.[1] Most common metaplastic change was acanthomatous and mainly found in the follicular variant. Interestingly, basal cell histological appearance was mostly associated with plexiform type. However, the results were not statistically significant. To support these, there are no studies available in the literature and the clinical significance has not been evaluated. Plexiform type was seen in younger age groups and a study done in India analysing 50 cases also showed the same.[28] Furthermore, clear cell differentiation was observed in two cases of follicular type which seems to be a rare occurrence in ameloblastoma. We found that with increasing age, there is a tendency to undergo more metaplastic changes. This is a novel finding in relation to ameloblastoma as it has not been reported in the literature. Although there were cases reported as acanthomatous ameloblastoma, no comparative analysis related to other histological subtypes, demography, and prognosis is available. It is difficult to comment on the frequency of histological subtypes in a global scale due to the lack of studies containing large number of cases. The present study provides evidence to support that the follicular type is the commonest. In addition, granular cell changes and acanthomatous changes occur more frequently in follicular type than in plexiform type.

According to Reichart *et al*.[1], relative frequency of unicystic ameloblastoma has been reported as 5% - 22% out of all subtypes of ameloblastoma and for Li *et al*.[29] it was 18.9%. Although our previous study showed that 31% of ameloblastoma were of unicystic type, it has increased to 38% in the present study may be due to the large sample size with a better representation. No other large series similar to the present one are available in relation to prevalence and incidence of unicystic ameloblastoma. Luminal (47.9%) and mural (48.5%) types of unicystic ameloblastoma were the frequent types and they mainly occur in the mandible. Intraluminal type was very few in number and almost all of them were in the mandible. A systematic review indicated after analysing 513 published cases that 31.4% are luminal and intraluminal, 7.8% were mural and 60.8% without information on the type.[29] This shows that the information on unicystic ameloblastoma is not adequately reported in the literature.

Peripheral ameloblastoma is rare and in our series the youngest is 8 years old. In contrast with the literature, peripheral ameloblastoma in this study showed female predilection (M-5, F-8).[30,31] The limitation of this study is incomplete data extraction from laboratory request form and histopathological reports. A multi-centre study of the same geographical zone involving more diagnostic centres would provide a more representative and better understanding of ameloblastoma.

CONCLUSION

In conclusion, the present series is the largest analysis of ameloblastoma with adequate information in the world literature. This provides significant new information on demographic details in relation to various histological subtypes of ameloblastoma. Posterior mandible is the most frequently affected site. Most common histological subtype is the follicular subtype. Peripheral ameloblastoma are rare. Mural and luminal types are the main subgroups of unicystic ameloblastoma.

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Authors' contributions: BSMSS and YCG- data collection, formal analysis, writing, review and editing; WMT- conceptualisation, review and editing, final approval of the manuscript. All

authors have read and agreed to the published version of the manuscript.

Conflicts of Interest: The authors declare no conflict of interest.

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