GIANT AMELOBLASTOMAS: CLINICO-PATHOLOGICAL REVIEW OF IMPLICATIONS OF TUMOR GROWTH RATE

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ABSTRACT

INTRODUCTION: Limited number of publications describe the influence of tumor growth rate on clinicopathologic features of giant (extreme or gigantic) forms of ameloblastoma (GA). This paper explores the relationship between these two factors.

OBJECTIVES: To determine the relationship between tumor growth rate of GA and clinico-pathologic factors such as age, gender and histopathologic subtype.

MATERIAL AND METHODS: GA cases were selected from the published literature based on the criteria described by Kanoi et al., availability of clinical data, such as age and gender of patient, duration of lesion, and three-dimensional size (volume) of specimen after surgical resection. Data collected were used to calculate individual tumor growth rate using modified formula of Merhara et al. Clinico-pathological features and calculated tumor growth rates were compared with other publications.

RESULTS: In total, 18 reviewed patients were included into this study, from sixteen publications with 17 patients who fitted the selection criteria and one case of GA from our center. There was gender balance (male : female ratio, 1 : 1), with age ranging 19-73 years (mean, 44.2 ± 15.6 years). Mean age of patients with GA was much higher than in non-GA cases, with statistically significant difference (p = 0.02). There was mild positive correlation (r = 0.219) between surgical volume and duration of tumor, but it was not statistically significant (p = 0.382). Mean specific growth rate was 85% ± 40.1%/year (range, 19.9-170%/year). Comparison of SGR with other clinico-pathological parameters of GA revealed no statistical significance.

CONCLUSIONS: GA occurred at a higher mean age than other forms, and the mean tumor growth rate was 85% per year. This had no statistical relationship to clinico-pathological characteristics studied.

KEY WORDS: ameloblastoma, giant lesion, specific tumor growth rate, poverty, surgery.

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INTRODUCTION

The recent histological classification of odontogenic tumors perceives ameloblastoma as a histologically benign, locally invasive neoplasm of epithelial odontogenic origin, which occurs in conventional, unicystic, and extraosseous/peripheral types [1]. The tumor is rare, accounting for 1% of all jaw cysts and tumors [2]. Most cases arise from the mandible and maxilla, and involve persons between the third and fourth decades of life, but without a clear sexual predilec-
Tumor growth rate of giant ameloblastoma

OBJECTIVES

To determine the relationship between tumor growth rate of GA and clinico-pathologic factors such as age, gender and histopathologic subtype.

MATERIAL AND METHODS

SEARCH STRATEGY AND SELECTION CRITERIA

The current study was a review of published literature on GA cases. Using PubMed, Google scholar, and Web of Science, studies in English on extreme, gigantic, neglect behaviors, it is important to differentiate types of tumor in order to deliver patient-specific treatment [5].

As reported in the literature, only some ameloblastoma grow to be huge, massive, neglected, extreme, giant, or gigantic. These are described as giant ameloblastoma (GA), which cause poor facial esthetics [6], metabolic derangement like hypoproteinemia [7], hypercalcemia, leukocytosis, elevated tumor markers via production of parathyroid hormone, and granulocyte colony-stimulating factor [8]. Moreover, GAs are more difficult to manage apart from other cases of ameloblastoma [9-11]. Establishing the growth rate of GA and its relationships could assist in the management of these lesions and prognosing the outcomes.

The hypothesis of this study was that specific growth rate (SGR) of GA has a relationship to gender, age of occurrence, and histopathologic subtype. Therefore, the purpose of this study was to test the hypothesis that SGR of GA is associated with gender, age, and histopathologic type.

RESULTS

They were 17 patients from 16 publications [6-8,14-27] selected, with post-surgical specimen volume dimensions and duration of symptoms recorded. One case was added from own center, making 18 GA patients for this study. SGR was calculated for each patient. Table 1 shows the data abstracted from included studies [7, 13-27]. GA occurred equally in males and females (ratio, 1:1), while the age ranged from 19 to 73 years (mean, 44.2 ± 15.6 years). As compared to the mean age of 35.9 years reported by Reichart et al. [3], the mean age of GA from the present study was higher with statistically significant difference (p = 0.02). There was no statistically significant difference (p = 0.21, df = 16) between the mean ages of males (48.9 ± 17.0 years; 95% CI: 35.8-61.9) and females (39.6 ± 13.4 years; 95% CI: 29.3-49.8). Various age groups included patients with 0-20 years (1; 5.6%), 21-40 years (6; 44.4%), and > 40 years (9; 50%). Mean
tumor volume was 3624.4 ± 6294.4 cm$^3$ (range, 288-27778 cm$^3$). There was no statistically significant difference ($p = 0.72$) in the mean surgical specimen volumes of males (4776.4 ± 8701.3 cm$^3$) and females (2472.4 ± 2343.7 cm$^3$). The mean tumor duration for the 18 patients included was 12.5 years. There was a mild positive correlation ($r = 0.219$) between surgical volume and duration of tumor, but it was not statistically significant ($p = 0.382$). The range of SGR was 19.9-170% per year (mean, 85% ± 40.1%/year). Comparison of SGR versus gender, age group, and histological growth pattern of GA did not yield any statistical significance. Summary of the comparison is presented in Table 2.

### DISCUSSION

There is controversy about the definition of GA. Chaine et al. [9] characterized GA as mandibular lesions of a large size (> 5 cm in length). However, this definition did not clarify whether the measurement was based on clinical, radiological findings, or the post-surgical specimen. Also, the basis for this length was not stated.

**TABLE 1.** Determination of specific growth rate (SGR) of some giant ameloblastoma

<table>
<thead>
<tr>
<th>Serial No.</th>
<th>Author(s), year of publication</th>
<th>Gender/age (years)</th>
<th>Dimensions of surgical specimen (cm$^3$)</th>
<th>Duration of lesion (years)</th>
<th>SGR (% per year)</th>
<th>Location*</th>
<th>Histologic subtype</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Rambo et al., 1977 [14]</td>
<td>F/41</td>
<td>21 × 15 × 10</td>
<td>14</td>
<td>57.6</td>
<td>Posterior/anterior/posterior mandible</td>
<td>N/A</td>
</tr>
<tr>
<td>3</td>
<td>Ueyama et al., 1995 [16]</td>
<td>M/73</td>
<td>10 × 9 × 7.5</td>
<td>10</td>
<td>65.1</td>
<td>Posterior/anterior/posterior mandible</td>
<td>Plexiform</td>
</tr>
<tr>
<td>4</td>
<td>Gordy et al., 1996 [17]</td>
<td>F/19</td>
<td>8 × 6 × 6</td>
<td>5</td>
<td>113.3</td>
<td>Posterior mandible</td>
<td>Follicular</td>
</tr>
<tr>
<td>5</td>
<td>Hughes et al., 1999 [18]</td>
<td>F/53</td>
<td>15.2 × 11.4 × 12</td>
<td>6</td>
<td>127.3</td>
<td>Posterior/anterior mandible</td>
<td>Plexiform</td>
</tr>
<tr>
<td>6</td>
<td>Mukhopadhyay et al., 2005 [19]</td>
<td>M/32</td>
<td>25 × 15 × 10</td>
<td>7</td>
<td>117.5</td>
<td>Posterior/anterior/posterior mandible</td>
<td>Acanthomatous</td>
</tr>
<tr>
<td>7</td>
<td>Kasbeka et al., 2011 [20]</td>
<td>M/30</td>
<td>12 × 8 × 6</td>
<td>5</td>
<td>127.2</td>
<td>Posterior/anterior mandible</td>
<td>Follicular/acanthomatous</td>
</tr>
<tr>
<td>8</td>
<td>Acharya et al., 2011 [7]</td>
<td>F/35</td>
<td>15 × 12 × 10</td>
<td>10</td>
<td>74.9</td>
<td>Posterior/anterior/posterior mandible</td>
<td>Plexiform</td>
</tr>
<tr>
<td>10</td>
<td>Ota et al., 2012 [8]</td>
<td>F/32</td>
<td>27.2 × 20.3 × 15.1</td>
<td>10</td>
<td>90.3</td>
<td>Posterior/anterior mandible</td>
<td>Acanthomatous</td>
</tr>
<tr>
<td>11</td>
<td>Hunasgi et al., 2013 [22]</td>
<td>F/39</td>
<td>12 × 9 × 10</td>
<td>10</td>
<td>69.8</td>
<td>Posterior/anterior mandible</td>
<td>Granular cell</td>
</tr>
<tr>
<td>12</td>
<td>Choudhary et al., 2014 [23]</td>
<td>F/65</td>
<td>14 × 11 × 8</td>
<td>10</td>
<td>71.2</td>
<td>Posterior/anterior/posterior mandible</td>
<td>Follicular/acanthomatous</td>
</tr>
<tr>
<td>15</td>
<td>Duc et al., 2018 [26]</td>
<td>M/67</td>
<td>19 × 12 × 13</td>
<td>40</td>
<td>19.9</td>
<td>Posterior/anterior/posterior mandible</td>
<td>N/A</td>
</tr>
<tr>
<td>16</td>
<td>Duc et al., 2018 [26]</td>
<td>M/48</td>
<td>10 × 12 × 12</td>
<td>30</td>
<td>65.1</td>
<td>Posterior/anterior/posterior maxilla</td>
<td>N/A</td>
</tr>
<tr>
<td>17</td>
<td>Nariai et al., 2019 [27]</td>
<td>M/62</td>
<td>13.5 × 9 × 8</td>
<td>7</td>
<td>98.3</td>
<td>Posterior mandible</td>
<td>Follicular/Desmoplastic</td>
</tr>
<tr>
<td>18</td>
<td>Own case, 2020</td>
<td>M/30</td>
<td>43 × 38 × 17</td>
<td>10</td>
<td>102.3</td>
<td>Posterior/anterior/posterior mandible</td>
<td>Follicular</td>
</tr>
</tbody>
</table>

*Posterior was behind the canine teeth, anterior was between the canine teeth
In another study, Kanoi et al. [11] described GA resulting in a post-surgical defect > 7 cm in length after segmental resection and the bone defect involving central mandibular segment. The bases for their definition were clinical objectivity and simplicity in better doctors’ communication, having a direct influence on decision-making and GA management. The present study selected GA cases based on the criteria of Kanoi et al. [11], and cases after 1970 were chosen for evaluation because the earliest World Health Organization classification of odontogenic tumors was published in 1971.

In the literature, GA dimensions have been given from clinical, radiological, and post-surgical measurements. However, these dimensions could vary even for the same patient. Raghunath et al. [25] reported a patient whose GA measured 18 cm × 12 cm × 11 cm clinically, while the post-surgical specimen was 17 cm × 11 cm × 9 cm. In another paper, Gupta et al. [28] described a patient whose GA measured 16 cm × 13 cm × 12.5 cm clinically, 20 cm × 13 cm × 13 cm on a CT, and 12 cm × 10 cm from the post-surgical specimen. Based on these differences between various modalities of measurement, only publications with three dimensional post-surgical measurements were evaluated to ensure uniformity. The range of volumes recorded for various cases of GA in this study were 288 cm³ to 27778 cm³ (mean, 3624.4 ± 6294.4 cm³). There was no comparable literature on mean volumes for resected GA; hence, there is a need for future reports of GA to provide three-dimensional measurements of post-surgical specimens to improve comparability of these rare lesions.

In a study of 100 cases of ameloblastoma, Effiom and Odukoya [5] reported almost equal gender ratio (male : female ratio, 1 : 0.9) for ameloblastoma. In a smaller sample consisting of 16 cases of GA, Chae et al. [13] observed more females than males (ratio, 2.2 : 1). The present study showed no sexual predilection for GA, which was similar to other conventional (formerly called “solid- multicystic”) ameloblastoma [1, 3]. Ameloblastoma is known to occur at any age, rarely at the extremes of life, but mostly between the third and fourth decades of life [3]. The 18 patients reviewed in Table 1 had a mean age of 44.2 years, with 50% (9) of cases aged above 40 years of age. On statistical analysis, the mean age of patients with GA was much higher than those described by Reichart et al. [3], with statistically significant difference (p = 0.02). Therefore, GA appears to occur in an older age group than other forms of ameloblastoma.

Despite significant morbidity and mortality associated with these neoplasms, there are very few reports on the growth rate of ameloblastomas. Effiom and Odukoya [5] evaluated monthly growth rate of solid, multicystic (now described as “conventional”) ameloblastoma to be 0.81 cm per month, which was higher than that for the peripheral type (0.17 cm per month). They also found that tumor growth was slower in males than females, while the latter presented lower tumor volumes.

However, their results lacked clarity on study sample collection criteria; it was based on mixture of clinical and radiological measurements and assumed that ameloblastoma followed a linear growth pattern [13].

Available evidence shows that ameloblastoma initially exhibits slow growth, which later accelerates in weeks [29, 30] or in years [15]. Chae et al. [13] systematically reviewed natural history and growth pattern of 16 cases of ameloblastoma. Using a natural exponential growth formula for carcinomas proposed by Mehrara et al. [12], they obtained the mean SGR of ameloblastoma to be 87.84% per year (range, 37.37-169.68). An important drawback of Chae et al. [13] findings was using a combination of clinical, radiological, and surgical specimen sizes of ameloblastoma. It had been previously observed that there could be differences in the measured sizes using these modalities even for the same lesion, as reported by Raghunath et al. [25] and Gupta et al. [28]. The mean SGR from our study was 85% per year, which was close to the 87.84% per year reported by Chae et al. [13]. However, our finding was more representative of the SGR of GA due to better sampling criteria.

In our study, there was no statistically significant association between SGR and gender and age group (Table 2). Chae et al. [13] found the most statistical significance (p = 0.14) in cases when ameloblastoma of the plexiform/follicular histologic subtypes compared to other subtypes of ameloblastoma were analyzed in association with SGR (as a categorical variable). However, they noted that the results could be due to a low sample size. In Table 2, the most statistically significant difference (p = 0.15) was shown when tumors exhibiting follicular and plexiform patterns were compared based on SGR as a categorical variable. It is known that ameloblastomas are mostly (66.6%) of follicular or plexiform histopathologic subtypes, while the rest (33.3%) are acanthomatous, granular cell, basaloid, and desmoplastic subtypes [1].

GAs present as large, gigantic, or extreme swellings [6-11, 14-27]. They can occur in jaw, but are more frequent in the mandible than the maxilla [1, 3]. In this study, most GAs (94.4%) occurred in the mandible (Table 1). Due to their large sizes, GAs causes loss of occlusal function, and mastication, speech, and breathing difficulties [6]. There is also an increased risk of hemorrhage from skin ulceration and symptoms of anemia [7]. As found in this review, GAs present as solid, multicystic lesions in radiologic appearance, with fenestration of cortical bone in multiple places [7, 19, 21].

**TABLE 2.** Summary of SGR versus gender, age group, and tumor subtype

<table>
<thead>
<tr>
<th>P-value</th>
<th>Gender</th>
<th>Age group</th>
<th>Growth pattern</th>
</tr>
</thead>
<tbody>
<tr>
<td>SGR</td>
<td>0.16</td>
<td>0.43</td>
<td>0.38</td>
</tr>
<tr>
<td>SGR (2)</td>
<td>0.63</td>
<td>0.22</td>
<td>0.15</td>
</tr>
</tbody>
</table>

SGR (2) is SGR as a categorical variable.
In spite of large sizes of GA, the treatment goal aims at complete tumor removal, and functions and appearance restoration. In order to remove the tumor completely, a surgical resection with 1.0-1.5 cm of normal bone margin is used to ensure adequate tumor removal, as the tumor infiltrates cancellous bone beyond the radiological margins [31, 32].

Early radical resection is especially important in the maxilla because of its more aggressive behavior. Anatomically, the maxilla has thinner cortical plates and abundant cancellous bone, while the thick cortical bone in the mandible decelerates tumor growth. Furthermore, maxillary ameloblastoma can invade the central nervous system [33, 34].

Jawbone resection for GA can cause dysfunctions in appearance, speech and swallowing mastication with saliva drooling. These can severely reduce the post-surgical quality of life of patients [11, 32]. To decrease these sequelae, immediate or delayed reconstruction are necessary. While an immediate reconstruction is favored by many [7, 9, 11], it is not always possible due to patient and technical factors [35]. Immediate reconstruction reduces costs, decreases number of surgeries, and allows earlier prosthetic rehabilitation [36]. However, treatment of GA need an individualized, systematic, and multidisciplinary approach, with an involvement of related fields, such as maxillofacial surgery, ENT, oral implantology, prosthodontics, and radiology [32]. The ideal reconstruction is observed with a bone graft or flap, distraction osteogenesis, and dental prosthesis for rehabilitation [37].

There are some challenges in the surgical management of GA. These include the risk of airway compromise, possibility of severe hemorrhage from the external carotid artery and pterygoid plexus of veins, post-operative infections, and death. To reduce the risk to the airway, suturing the muscles of tongue to a Kirschner wire or leaving the nasotracheal tube in a position for 36 hours [38] as well as preoperative tracheostomy [7] have been utilized. The use of a tongue stitch to secure the tongue either on an artery clip or on a syringe has also been described [39]. To prevent severe hemorrhage, ligation of the external carotid arteries has been suggested, but Acharya et al. [7] did not support this technique due to risk of cutaneous necrosis.

The technical challenge associated with surgical management of GA requires mandatory follow-up of treated patients for a prolonged period, possibly for life. More than 50% of ameloblastoma recurrences are observed within 5 years of treatment [3, 40]. However, life-long review of treated patients is advisable, as a recurrence after 20, 30, or 49 years have been reported in bone or surrounding soft tissues [39-42]. Granular and follicular variants of the tumor have been reported to exhibit higher recurrence rate [41, 42]. To a large extent, a recurrence occurs due to inadequate tumor clearance at primary surgery. A recurrence rate of 4.5% after segmental jaw resection has been reported [43]. However, in the present study, no recurrence after the treatment of GAs lesions was reported (Table 1).

CONCLUSIONS

GAs are rare conventional ameloblastoma that are extremely big and disfigure the patient's appearance. Most cases of GA present at 44 years of age, unlike other forms of conventional ameloblastoma, which occur about 10 years earlier. The specific tumor growth rate is 85% per year, and this shows mild correlation with duration before presentation. The management of GA is challenging due to various difficulties, including the control of airway, risk of intra-operative bleeding, reconstruction of the jawbone, and lost dentition to restore function and appearance. Surgical resection and immediate reconstruction is the ideal treatment, and life-long follow-up needs to be maintained in order to detect a recurrence.

CONFLICT OF INTEREST

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

References

10. Li X, Zhu K, Liu F, Li H. Assessment of quality of life in giant ameloblastoma adolescent patients who have had mandible defects.