Review of metastasizing (malignant) ameloblastoma (METAM): pattern of metastasis and treatment

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Objectives. The rare malignant odontogenic tumor, metastasizing (malignant) ameloblastoma (METAM) is reviewed with the aim of analyzing the pattern of disease and treatment of cervical metastasis based on the 2005 World Health Organization classification.

Study design. A total of 65 cases, including reported cases from 1923 to 2009 compatible with the current classification and a new case are reviewed.

Results. METAM occurred mostly in lungs (71%), followed by cervical lymph nodes (28%). Female-to-male ratio was 1:1.1. Primary tumor was diagnosed in 28% of cases at ages ≤20 years, and maxilla-to-mandible ratio was 1:5.2. The mean disease-free interval and survival for pulmonary metastasis were 14.37 years and 3 years, respectively, and 12.96 years and 6 years for cervical METAM. Five-year survival rate for cervical metastasis treated purely surgically was 71.43%.


Ameloblastoma is a slow growing odontogenic tumor which infiltrates to surrounding tissues, but rarely metastasizes. In this context it has been consistently listed as a benign odontogenic tumor and is defined in the most recent (2005) World Health Organization (WHO) classification of odontogenic tumors as a “slow-growing locally invasive epithelial odontogenic tumor of the jaws with a high rate of recurrence if not removed adequately, but with virtually no tendency to metastasize.”

Although histologically benign and slow growing, ameloblastoma has the ability to develop metastasis in regional lymph nodes and distant sites. Incidence of malignancy/metastasis in relation to ameloblastoma was earlier reported as 2%, but more realistically is far less. Only 1 case (0.3%) was found after long-term follow up of 305 ameloblastomas with recurrences. This behavior of ameloblastoma, though very rare, led Kunze et al. to propose ameloblastoma to be “a potentially malignant neoplasm.” Malignant ameloblastoma has been listed as an odontogenic carcinoma in WHO classifications of odontogenic tumors in the past from 1971 as well as the classification systems proposed by Elzay in 1982 and Slootweg and Müller in 1984. Considerable variations were seen in the criteria used in each of these to define the entity, causing confusion in identifying and differentiating between malignant ameloblastoma and ameloblastic carcinoma. This complicated the reviewing of literature and accurate comparison of reported cases, because both entities were sometimes grouped and reported as metastatic/malignant ameloblastoma. In contrast, a clear distinc-
tion between malignant ameloblastoma and ameloblastic carcinoma was made in the current WHO classification system of 2005, considering both clinical behavior of metastasis and histopathologic features. In this classification, metastasizing (malignant) ameloblastoma (METAM) is defined as “an ameloblastoma that metastasizes in spite of a benign histologic appearance. It does not show any features that can be distinguished from ameloblastoma that does not metastasize and is reclassified as such only in retrospect when metastasis occurs. Ameloblastic carcinoma has combined histologic features of ameloblastoma with cytologic atypia with or without metastasis.”

The new case we report is a METAM of multiple cervical lymph nodes that occurred after 23 uneventful years after treatment for the primary tumor of the right-side of the mandible and treated solely surgically with hemimandibulectomy but not having multiple recurrences or repeated surgeries. The present review is based on 65 cases of METAM, including cases reported from 1923 to 2009 and the single new case we report. To the best of our knowledge, this is the first comprehensive review since the clarification offered by the 2005 WHO classification of odontogenic tumors between METAM and ameloblastic carcinoma.

MATERIAL AND METHODS

This review includes a total of 65 cases with a single new case and 64 cases from published literature in the English language from 1923 to 2009, including 8 reviews.2,4,6,8,29 METAM was found to be reported as metastasizing, metastatic, or malignant ameloblastoma. An attempt was made to exclude those cases with features of ameloblastic carcinoma reported as malignant ameloblastoma in the past, and only 64 cases were found to be compatible with the current WHO classification of odontogenic tumors. All details were not available in some publications, especially in review articles. Site of primary tumor, gender, site of metastasis, age at diagnosis of primary tumor, disease-free interval or time between primary tumor and first metastasis (excluding patients presenting with metastasis simultaneously with the primary tumor), and patient survival were studied for overall cases of METAM and separately for lung METAM (patients with only lung metastasis or with first site of metastasis confirmed as lung) and cervical METAM (patients with only cervical lymph node metastasis or with first site of metastasis confirmed as cervical lymph nodes). Patient survival/outcome in relation to treatment modality for cases of cervical METAM were also evaluated.

RESULTS

Site distribution of metastasis

Site distribution for the 65 cases of METAM is given in Table 1. Of these patients, 48 had metastasis in a single site, 10 had METAM in 2 sites, and 7 had metastasis in >2 sites. Metastasis occurred mostly in lungs, including pleura and hilar nodes in 46 of the cases (71%), and 18 cases (28%) had cervical lymph node METAM. Bones, including spine, skull, vertebrae, femur and iliac bone were affected in 8 cases (12%). One patient had 2 bone sites affected, resulting in a total of 9 sites of METAM in bone. Six patients

### Table 1. Site distribution of metastasizing ameloblastoma (METAM)

<table>
<thead>
<tr>
<th>Site(s)</th>
<th>Number of sites affected (n = 92)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 site (n = 48)</td>
<td></td>
</tr>
<tr>
<td>Lung only</td>
<td>30</td>
</tr>
<tr>
<td>Cervical LN only</td>
<td>13</td>
</tr>
<tr>
<td>Distant site only</td>
<td>5</td>
</tr>
<tr>
<td>2 sites (n = 10)</td>
<td></td>
</tr>
<tr>
<td>Lung + cervical LN</td>
<td>2</td>
</tr>
<tr>
<td>Lung + 1 distant site</td>
<td>7</td>
</tr>
<tr>
<td>Cervical LN + 1 distant site</td>
<td>1</td>
</tr>
<tr>
<td>&gt;2 sites (n = 7)</td>
<td></td>
</tr>
<tr>
<td>Lung + distant sites</td>
<td>5</td>
</tr>
<tr>
<td>lung + distant sites + cervical LN</td>
<td>2</td>
</tr>
<tr>
<td>Total sites</td>
<td>46</td>
</tr>
<tr>
<td>Percentage (n) of cases affected with each site</td>
<td>71 (46) 28 (18) 12 (8) 9 (6) 8 (5) 3 (2) 3 (2) 3 (2) 1.5 (1) 1.5 (1)</td>
</tr>
</tbody>
</table>

LN, lymph node.

*Two bone sites were affected in 1 of the 8 patients with METAM in bone.
(9%) had metastases in intracranial tissues, including brain. Liver was affected in 5 cases (8%). Metastases were reported in the kidneys, spleen, and diaphragm in 2 cases (3%) each. Heart and skin were also affected in 1 case (1.5%) each. Of the cases affected by cervical lymph node METAM, specific information regarding affected levels was not available for 4 cases. However, multiple levels were affected in 2 cases17 and the present case, whereas a single level was affected in 12 cases.2,9,10,14,15,18,21,23-26,28

Gender distribution

Information regarding gender of patients affected was available for 63 cases (Table II). Thirty were female and 33 were male.

Site of primary tumor

Information for the site of primary tumor was available for 63 cases, and of these cases, 52 had primary tumor in the mandible and 10 in the maxilla. One case was a peripheral ameloblastoma (Table II).

Age at presentation of the primary tumor

Of the 63 cases for whom these data were available, the mean age of diagnosis of the primary tumor was 33.85 years, with the age range 6 to 83 years (Table II). The mean age for lung METAM was 31.6 years and for cervical lymph node METAM was 38.6 years. Twenty-eight percent of patients were found to be ≤20 years old when the primary tumor was diagnosed. Approximately 8% were <10 years old.

Disease-free interval (time from primary to first metastasis)

In the cases reviewed, the overall disease-free intervals ranged from 2 months to 42 years, with a median of 14 years and mean of 14.33 years (Table II).

Survival from time of first metastasis

The survival after development metastasis had a range of 0 to 37 years with a mean of 6.7 years and 5-year survival of 44% (Table II).
Patient survival/outcome related to treatment for cervical METAM

Survival of patients with cervical METAM related to the treatment modality is indicated in Table III. Five-year survival rate for cervical metastasis treated only with surgery was 71.43% (mean survival of 9.58 years) and when radiotherapy was added it was 66% (mean survival of 9 years).

CASE REPORT

In May 2009, a 43-year-old female patient presented to the oral-maxillofacial surgical unit of the Dental Institute, Colombo, Sri Lanka, complaining of a small lump at the right-side submandibular region of ~6-8 months’ duration. Though asymptomatic for the past 23 years, she had been treated for ameloblastoma in 1986 after presenting with a bony hard lump of the right-side body of the mandible. Further reviewing her previous clinical notes and diagnostic card, it was revealed that she had undergone right-side hemimandibulectomy and reconstruction with a rib graft. The extent of the primary lesion or the type of ameloblastoma was not specified, and the presurgical radiographs were not available.

Clinical examination of the neck after the present complaint revealed 2 lumps in the right-side submandibular region and another 1 in the right-side submental region. Nodules were soft in consistency. The lumps were excised and sent for histopathology with a clinical impression of tuberculosis.

Macroscopically, the submandibular specimen consisted of 2 soft tissue nodules measuring $1.6 \times 1.1 \times 0.8$ cm and $2.0 \times 0.8 \times 0.6$ cm each. The specimen from the submental region consisted of 1 soft tissue nodule measuring $2.0 \times 1.3 \times 1.3$ cm. Histopathologically submandibular lymph nodes were mostly replaced by cystic tumor with basal cells showing reversed polarity (Figs. 1 and 2). Few areas also showed marked stellate reticulum–like cells and ameloblast-like cells showing reversed polarity.

Table III. Treatment for cervical metastasizing ameloblastoma (METAM) versus patient outcome

<table>
<thead>
<tr>
<th>Treatment for cervical METAM</th>
<th>Total no. of cases</th>
<th>No. of cases with follow-up*†</th>
<th>Mean survival, y</th>
<th>5-y survival rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery only</td>
<td>9</td>
<td>6-7,14,19,24,25, present case</td>
<td>9.58</td>
<td>71.43%</td>
</tr>
<tr>
<td>Surgery and radiotherapy</td>
<td>4</td>
<td>12,17,26,28</td>
<td>3</td>
<td>66%</td>
</tr>
<tr>
<td>Surgery and chemotherapy‡</td>
<td>1</td>
<td>21</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Surgery, radiotherapy, and chemotherapy‡</td>
<td>2</td>
<td>10,15</td>
<td>6</td>
<td>50%</td>
</tr>
<tr>
<td>No treatment</td>
<td>1</td>
<td>23</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No data on treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Patients followed up for >1 year.
†Excluding the patient with simultaneous thyroid carcinoma.
‡Patients also had metastasis in lungs.
ture could not be identified, and evidence to suggest that the tumor was within a node was seen only in a single focus, and therefore reticulin stain had to be used additionally. No cytologic atypia was found in the tumor. Thus, the diagnosis was consistent with METAM of lymph nodes.

After the initial diagnosis, the patient underwent a series of investigations to exclude recurrence at primary site and other metastatic lesions in the neck, lung, or other distant sites. Ultrasound scans (USSs) of neck and abdomen, radiographs of jaws, including postero-anterior, lateral oblique, and othopantamographic views, chest x-ray, and computerized tomographic (CT) scan of neck and brain were done. USS and CT scan of neck revealed a possible enlarged lymph node of digastric triangle and a soft tissue lesion of ill-defined margins anterior-medial to the right-side parotid gland. A fine-needle aspiration biopsy of the lymph node in the jugular digastric region gave inconclusive results, and no recurrences were found in radiographs of the mandible. Chest x-rays did not show evidence of lung metastasis. USS of abdomen and CT of brain were also negative.

With these findings, patient was managed surgically with a right-side selective suprahyoid neck dissection. Histopathologic diagnosis of the digastric lymph node was consistent with the earlier diagnosis of METAM showing plexiform and follicular areas. Other lymph nodes did not show evidence of tumor. The patient is under regular follow-up to detect recurrences at primary site or other tumor metastases that she may subsequently develop.

DISCUSSION

Ameloblastoma is a rare tumor of odontogenic epithelial origin constituting only ~1% of all tumors and cysts of the jaws, but it is the second most common odontogenic tumor. Ameloblastoma affects both genders equally and presents as a painless swelling predominantly in the molar region and ascending ramus. Typically, primary tumor of the mandible appears as a multicocular radiolucency often with buccolingual expansion. Resorption of adjacent teeth and those of unerupted teeth may also be seen. Most cases are reported between 30 and 60 years of age. It is rare before the age of 20 years. Only 1.8% of patients are reported to be <10 years of age. High rate of recurrence of up to 50%-72% is reported depending on the treatment modality.  

The rare occurrence of malignancy with metastasis was first described in regional lymph nodes by Emura in 1923 and distant metastasis was first described by Vorzimer and Perla in 1932. In our review of cases with METAM, it was found that the site of the primary tumor and gender distribution is similar to those reported by Reichart et al. for conventional ameloblastoma. Maxilla-to-mandible ratio for primary tumor is 1:5.2. One case of peripheral ameloblastoma was also reported. The female-to-male ratio is 1:1.1. Men are slightly more commonly affected (52%) with lung metastasis, whereas the same trend is seen for females (56%) in cervical lymph node metastasis. Lung is the commonest site of metastasis, and cervical lymph nodes are the second most frequent site for METAM. Although lung is the commonest site of metastasis, our patient had cervical lymph node involvement only. However, in contrast to most other cases that had a single nodal level affected, our patient was affected with multiple levels of lymph nodes.

Twenty-eight percent of these patients were found to be ≤20 years old when the primary tumor was diagnosed, and 8% of the patients were <10 years old, which is in contrast to conventional ameloblastoma. Our patient was 20 years at the time of the diagnosis of the primary tumor, and had a 23-year disease-free interval between the occurrence of the primary tumor and development of metastasis.

The mean disease-free interval for pulmonary metastasis is 14.37 years and for cervical lymph node metastases is 12.96 years. This indicates that cervical metastasis may precede lung metastasis as seen in 3 of the cases reviewed. Therefore, close follow-up would be prudent in our patient.

Although the longest reported survival after pulmonary metastasis is 37 years, the median survival is 3 years and 5-year survival rate is 37%. Survival after
likely. Eisenberg also argued that most of such metastasis but Kunze et al. considered this as unimportant seeding has been a long-held belief as a cause of cells after repeated surgical procedures causing tumor. They also explained that the low capacity of proliferation of tumor cells is the cause for the prolonged latency period for the metastasis to manifest to a clinically significant size. Implantation of tumor cells after repeated surgical procedures causing tumor seeding has been a long-held belief as a cause of metastasis but Kunze et al. considered this as unlikely. Eisenberg also argued that most of such tumor foci should be destroyed by natural defenses or fail to attain significant size or biochemical capacity to produce metastatic tumor and therefore should not be considered to be a possible mechanism of metastasis. Eisenberg explains the occurrence of ameloblastoma in regional lymph nodes by the biologic process of heterotopy: Ectopic odontogenic epithelial rests entrapped in lymph nodes during embryogenesis would undergo benign neoplastic transformation independent from the tumor of the jaws. She explains that metastasis via lymphatics should first develop at the site of entry, i.e., at the subcapsular space. However, supporting her view, she observed that the subcapsular space in METAM of lymph nodes is free of tumor. Most ameloblastomas metastasize from solid/multicystic type ameloblastomas of mixed or pure plexiform pattern.

There are no reports of metastasis from desmoplastic or unicystic ameloblastomas. One case of peripheral ameloblastoma that resulted in a metastasis has been reported. Although metastasis was found to occur mostly from plexiform type, histologically the primary tumor of METAM is the same as any other nonmetastatic ameloblastoma showing no cytologic atypia. Therefore, it is not possible to predict the behavior of a solid/multicystic ameloblastoma in respect to its ability to metastasize.

Route of metastasis could be via lymphatics or hematogenous spread through blood circulation to regional lymph nodes, distant organs, viscera, and bone. Implantation and growing directly on surfaces and body cavities, as in aspiration, is also implicated. Vorzimer and Perla in 1932 proposed that pulmonary metastasis is due to aspiration of tumor cells during surgery. This was supported by Yonemoto in 1959 by observing the presence of tumor within the bronchi and bronchioles. In addition, the tumor was found either bilaterally or mostly in the right lung. However, presence of tumor foci found diffusely scattered in both lungs as well as in surrounding blood vessels should be the result of hematogenous spread.

Laughlin advocates that the best method of dealing with metastasis from ameloblastoma is by prevention of recurrences. This is achieved by appropriate and adequate treatment of primary tumor. Treatment for primary solid/multicystic ameloblastoma is by excision with adequate margin of uninvolved tissue. Long-term follow-up is recommended, owing to the slow and constant growth of recurrent as well as metastatic tumor. Inquiring about pulmonary and musculoskeletal complaints, annual radiographs of the primary site for possible recurrences and chest radiographs to detect lung metastasis together with evaluation of the neck is recommended. If there is any suspicion, further investigations, such as additional radiographs, CT/bone scans, and lymph node biopsy, should be done where appropriate.

METAM has been treated in various ways depending on the location and extent at the time of presentation. Complete surgical resection should be the accepted first line of treatment. For pulmonary metastasis significant resection with as much preservation of viable lung tissue as possible has been the treatment of choice for operable lesions. Cervical lymph node metastasis is to be treated by some type of a neck dissection. Functional neck dissections to identify and treat occult metastasis has also been advocated when one unsuspecting node with metastasis is identified histologically or if there is clinical or radiologic evidence of lymph node involvement. However, the rationale of this type of elective neck dissection is questioned owing to the unpredictability of its results. Even though some report favorable results from radiation, it may also
cause high recurrence rates and resistance to therapy.\textsuperscript{9,11} Furthermore, caution is advised by Becker and Pertl, because 25% of their patients developed postradiation sarcomas.\textsuperscript{28} Chemotherapy is not curative, but varying combinations of cisplatin, adriamycin, cyclophosphamide, doxorubicin, vinblastine sulfate, and bleomycin are reported to have reduced the tumor size and improved symptoms.\textsuperscript{11} Radiotherapy and chemotherapy are reserved to offer palliative cure for those lesions that are inoperable or for those where tumor-free margins cannot be achieved by resection.\textsuperscript{14,22}

Because METAM is a rare event, the numbers of reported cases are inadequate to develop treatment protocols with randomized studies. We reviewed the available data of treatment with patient outcome for 13 cases of METAM in cervical lymph nodes having >1 year of follow-up and excluding the patient with simultaneous thyroid carcinoma. For those who were treated purely surgically, the mean survival period is 9.58 years and 5-year survival rate is 71.43%. For those whom radiotherapy was added the figures were 9 years and 66%, respectively. These results may reflect the small sample size. Only 1 case was treated with chemotherapy and survived 3 years.\textsuperscript{15} Two patients had both radiotherapy and chemotherapy in addition to surgery and had a mean survival of 6 years. All patients who had chemotherapy were those with metastasis in the lungs. Radiotherapy and chemotherapy failed to show significant improvement in patient survival. Four patients out of the 5 who were given radiotherapy developed further metastases in the neck or other distant sites after therapy.\textsuperscript{10,21,26,28}

From these findings, we conclude that, in the absence of properly developed treatment protocols, cervical METAM should be treated by neck dissection preceded by adequate investigations to detect all levels of involved nodes. Considering all treatment options, the present case was treated only surgically with a right-side selective suprathyroid neck dissection after investigations to detect all possible metastases. The patient is also under close follow-up to detect further metastases. Owing to inconclusive evidence of the benefits of either radiotherapy or chemotherapy, these treatment modalities were not used for our patient after surgery.

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