

Ameloblastic carcinoma in a young patient

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Owing to the rarity of publications describing ameloblastic carcinoma, little is known about this entity in pediatric patients. To our knowledge, malignant transformation from an odontogenic cyst into an ameloblastic carcinoma in a pediatric patient has not been documented to date. We present the case of a 14-year-old boy in whom a large osteolytic lesion associated with an impacted right maxillary third molar germ was fortuitously detected by orthopantomographic radiography. With a preoperative clinical-radiographic diagnosis of odontogenic cyst, the patient underwent surgical enucleation of the lesion. Histologic evaluation rendered a diagnosis of follicular cyst with a focal area of ameloblastic carcinoma. The literature addressing ameloblastic carcinoma is reviewed. (*Oral Surg Oral Med Oral Pathol Oral Radiol* 2014;117:e396-e402)

Odontogenic tumors originate from epithelial, ectomesenchymal, or mesenchymal tissues that are, or have been, part of the tooth-forming apparatus. Such tumors are thus exclusively found within the maxillofacial skeleton (intraosseous or centrally located), in the soft tissue overlying tooth-bearing areas, or in the alveolar mucosa in edentulous regions (extraosseous or peripherally located). Onset may be at any age.¹

Odontogenic malignancies are 1% of all cysts and tumors occurring in the jaws.^{2,3,4} In the 2005 World Health Organization classification (Table I), the ameloblastic carcinoma is defined as a rare primary odontogenic malignancy that combines the histologic features of ameloblastoma with cytologic atypia. This definition applies even in the absence of metastasis.¹

Microscopically, ameloblastic carcinoma shows characteristics of ameloblastic differentiation, cellular nests with peripheral palisading of basaloid cells, associated with a central discohesive component, forming stellate reticulum-like areas. The malignant nature of the lesion is revealed by marked nuclear atypia, mitotic figures, an infiltrative growth pattern, and association with the presence of disordered sheets and islands of epithelium.

We present a case of pediatric ameloblastic carcinoma arising in a follicular cyst. The literature addressing the ameloblastic carcinoma is reviewed and discussed.

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Table I. World Health Organization classification of odontogenic malignancies (2005)

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| a. Metastasizing (malignant) ameloblastoma |
| b. Ameloblastic carcinoma—primary type |
| c. Ameloblastic carcinoma—secondary type (dedifferentiated), intraosseous |
| d. Ameloblastic carcinoma—secondary type (dedifferentiated), peripheral |
| e. Primary intraosseous squamous cell carcinoma—solid type |
| f. Primary intraosseous squamous cell carcinoma derived from keratocystic odontogenic tumor |
| g. Primary intraosseous squamous cell carcinoma derived from odontogenic cysts |
| h. Clear cell odontogenic carcinoma |
| i. Ghost cell odontogenic carcinoma |



Fig. 1. Orthopantomographic radiography revealed a large osteolytic lesion within an impacted right maxillary third molar germ.

CASE REPORT

In September 2010, during routine orthopantomographic radiography, a large osteolytic lesion associated with an impacted right maxillary third molar was detected in a 14-year-old boy (Figure 1). The patient was referred to the Maxillo-Facial Surgery Department, Monza San Gerardo Hospital, University of Milan-Bicocca School of Medicine, for evaluation and treatment. On examination, the patient's general health was good. Intraoral examination revealed a right maxillary swelling with intact overlying mucosa. No trigeminal paresthesia was noted. The right maxillary first and second molars

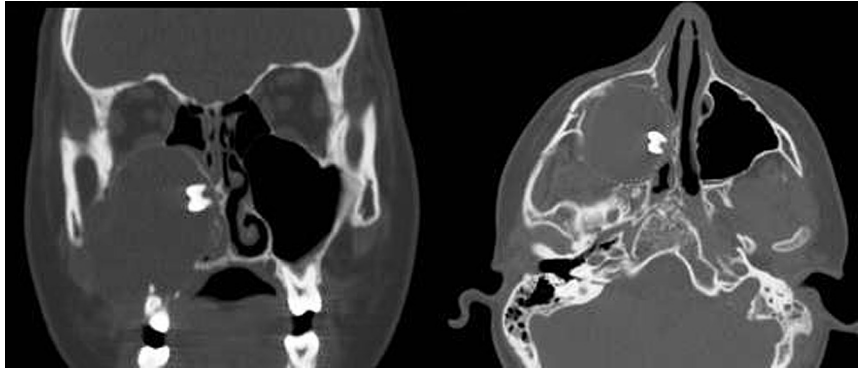


Fig. 2. Computed tomography. Coronal section (*right*) shows a large cystic lesion of the maxilla. Axial section (*left*) shows a radiolucent area occupying a large portion of the right maxillary sinus, extending into the nasal cavity.



Fig. 3. At macroscopic examination, the tumor comprised a cystic mass containing within it an impacted tooth and considerable cellular debris, with vegetation adherent to the inner surface.

were mobile. Computed tomography (CT) scanning revealed a large maxillary cystic lesion, involving the alveolar bone, maxillary sinus and nasal cavity, with no soft tissue extension, containing the right maxillary third molar germ medially (Figure 2). The clinical and radiologic presentation and the patient's age were suggestive of a follicular cyst.

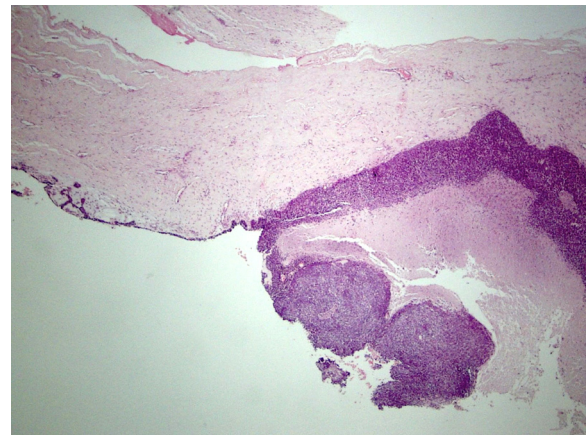


Fig. 4. Photomicrograph showing the transition from conventional bland-appearing cystic epithelium (consistent with dentigerous cyst) to an area which exhibits ameloblastomatous features (hematoxylin-eosin, original magnification $\times 10$).

Intraoral surgical enucleation was performed. Parts of the cortical bone were removed where they were very thin. The third-molar germ was contained within the cystic lesion.

The surgical material was sent to the Oral Pathology Department. The tumor comprised a cystic mass with adherent thin bony plates, containing within it an impacted tooth and considerable cellular debris. Vegetations adherent to the inner surface were present (Figure 3). Microscopically, on hematoxylin-eosin staining, the histologic sections revealed a cystic structure lined with odontogenic epithelium of variable thickness, composing a focal odontogenic tumor of epithelial origin made up of cellular elements resembling ameloblasts (Figures 4 to 6). These cellular elements, medium-sized to large, had voluminous and hyperchromatic nuclei and clear cytoplasm arranged in nests, with central areas of necrosis and peripheral areas of odontogenic epithelium. Cells showed marked cytologic atypia and loss of normal nuclear polarization (Figure 7). Five mitotic figures per 10 high-power fields were noted. The immunohistochemical (IHC) profile showed a positive reaction for cytokeratin AE1/AE3, smooth muscle actin, and Ki-67 proteins

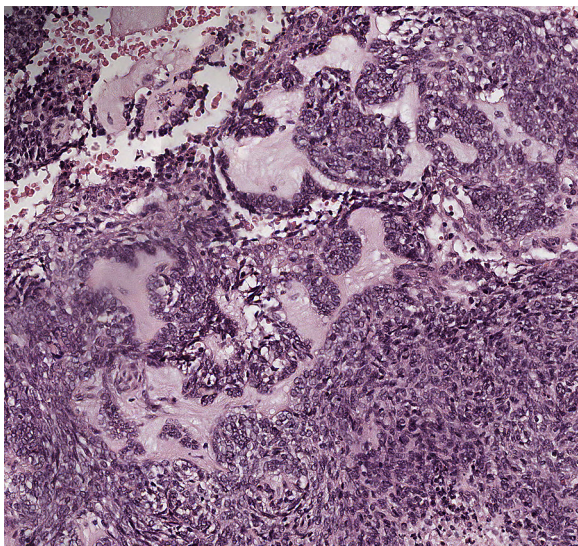


Fig. 5. Photomicrograph showing follicular growth pattern with stellate reticulum-like structure and central necrosis. Peripheral columnar cells are palisaded in the follicular islands (hematoxylin-eosin, original magnification $\times 20$).

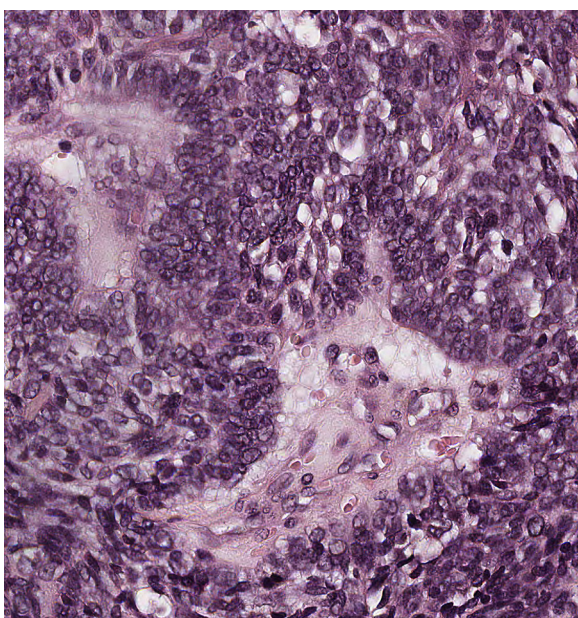


Fig. 6. Photomicrograph showing tumor cells with hyperchromatism, nuclear pleomorphism, and mitotic figures. Central necrosis is also visible (hematoxylin-eosin, original magnification $\times 10$).

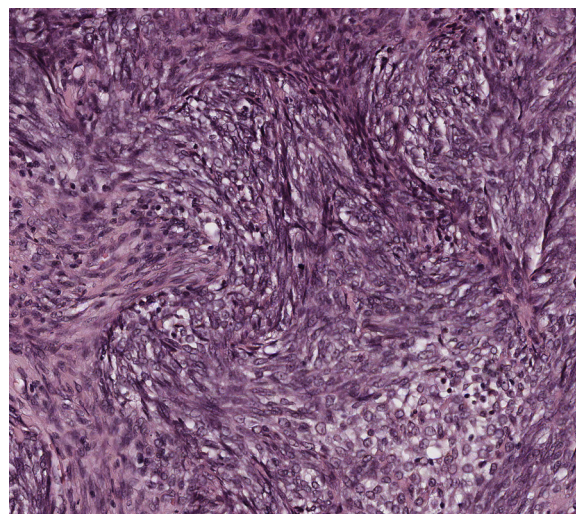


Fig. 7. Photomicrograph showing a proliferative area characterized by hypercellular nests of epithelial cells. Mitotic activity is apparent (hematoxylin-eosin, original magnification $\times 40$).

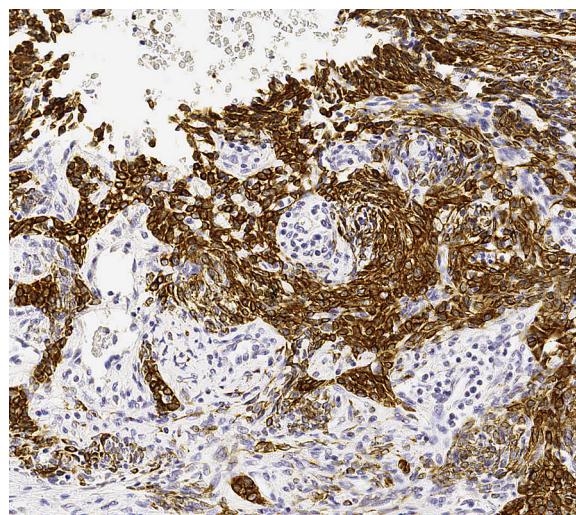


Fig. 8. Photomicrograph showing positive membrane immunohistochemical expression of cytokeratin AE1/AE3 in the ameloblastic epithelium (original magnification $\times 20$).

(Figures 8 to 10). Focal positivity was found for calponin. IHC was negative for S-100, p53, and vimentin proteins.

The final diagnosis was follicular cyst with a focal area of ameloblastic carcinoma.

Based on this diagnosis, the patient was scheduled for head and neck CT, chest radiography, bone scintigraphy, and abdominal ultrasonography to rule out metastases. Based on

the negative findings from these tests, together with the histologic finding of a focal ameloblastic carcinoma surrounded by considerable nonmalignant tissue, and in agreement with the wishes of the patient's parents, a "wait and see" approach was taken. The patient was followed up every 3 months. After 2 years, there were no clinical or radiologic signs of recurrence or metastasis.

DISCUSSION AND CONCLUSIONS

Ameloblastic carcinoma is a rare malignant odontogenic tumor that can develop *de novo* (primary type) or by malignant transformation of an intraosseous or peripheral ameloblastoma (secondary type).⁵ There is as

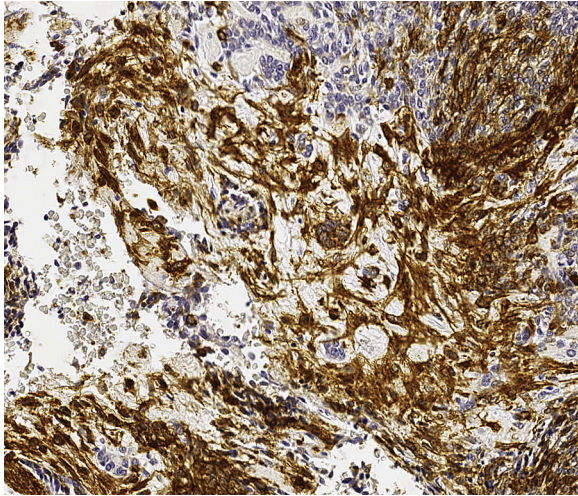


Fig. 9. Positive immunohistochemical reactivity for smooth muscle actin (original magnification $\times 20$).

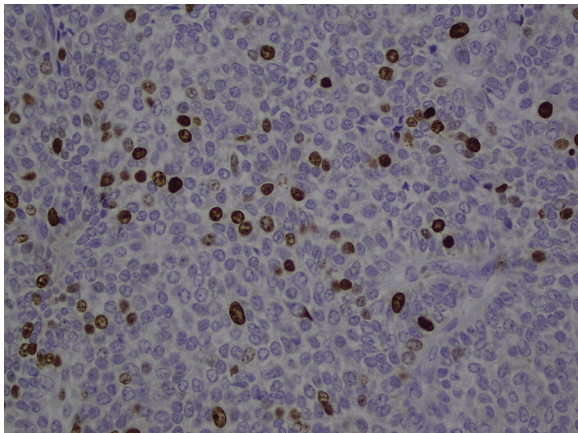


Fig. 10. Focal immunohistochemical reactivity for Ki-67 protein (original magnification $\times 20$).

of yet no agreement on whether odontogenic carcinoma can develop from a preexisting odontogenic cyst. In 1984, Slootweg et al⁶ presented a case that had probably originated from a keratocyst. In a 2009 review, Yoon et al⁷ reported 6 cases, none originating from a follicular cyst. In 2012, Pirklbauer et al.⁸ reported an 86-year-old man in whom an ameloblastic carcinoma had appeared at the site from which an odontogenic cyst had been enucleated 10 years previously. A review of the literature in English from 1932 to 2012 found 18 pediatric cases,^{4,15-26} none reportedly originating from a follicular cyst.

Approximately two-thirds of ameloblastic carcinomas involve the mandible. The posterior segments of the jaws are the most frequently affected site.⁴ There is no gender difference in frequency of occurrence. Radiologically, the lesion generally presents as a poorly defined radiolucent lesion with irregular margins.^{9,10}

The typical clinical presentation includes expansion of the jaw, rapid tumor growth, pain, paresthesia, perforation of the cortical plate, extension into surrounding soft tissues, and tooth mobility.¹¹ The typical clinical course is reported to be aggressive, with extensive local destruction and distant metastatic spread. Metastases preferentially spread via the hematogenous route, but metastatic lymph node involvement has also been reported. The most frequently involved site of metastasis is the lung, although brain and skeletal metastases may also occur. The ameloblastic carcinoma is predisposed to repeated recurrence and thus requires long-term follow-up.³

The diagnostic criteria of an ameloblastic carcinoma that has dedifferentiated from ameloblastoma (carcinoma ex ameloblastoma) are based on cytologic atypia and increased mitotic index. Histologic changes include (1) elevated proliferative index (emphasized by high mitotic activity), elevated proliferating cell nuclear antigen expression, and elevated Ki-67 expression; (2) atypia, including nuclear pleomorphism and basilar hyperplasia; (3) hyperchromatism of the nuclei of basaloid cells; and (4) other features of malignancy, such as perineural or perivascular invasion. According to Akrish et al.,¹² histologic findings should be correlated with clinical and biologic features.

In our case, the clinical and histopathologic features were suggestive of an ameloblastic carcinoma. Focal necrosis and atypical mitosis were noted. Irregular islands of odontogenic epithelium were also visible, which aided the diagnosis. There is as yet no general agreement concerning the reactivity of IHC markers as it relates to ameloblastic carcinoma, and findings are discordant.^{13,14} Of interest in this case was the positivity for smooth muscle actin. Recently, Bello et al.¹³ and Kamath et al.¹⁴ reported on the utility of various epithelial and stromal markers in differentiating ameloblastic carcinoma from ameloblastoma. They noted positive expression of α -smooth muscle actin in epithelial islands and stroma, suggesting that the presence of α -smooth muscle actin within epithelial islands is highly predictive of ameloblastic carcinoma. However, too few positive cases were reported to reliably use actin in the differential diagnosis.

On conventional radiographs, these lesions present as a poorly defined radiolucent area, similar to an ameloblastoma, but with dispersed radiopacities, apparently due to areas of dystrophic mineralization, which are uncommon in conventional ameloblastoma.¹³

Little is known about the natural history of ameloblastic carcinoma in pediatric patients. Treatment guidelines are not based on results obtained from long-term follow-up, because most case reports cover a period of fewer than 5 years after initial surgical treatment.¹⁴ A review of the literature published in

Table II. Published cases of ameloblastic carcinoma in pediatric patients (1932-2013)

Case	Year	Study (authors, reference No.)	Age (y)	Site	Gender	Treatment	Metastases/ Recurrence	Follow-up (mo)	Death/Alive
1	1932	Spring ¹⁷	5	Mandible	Male	Not mentioned	Bone	168	Death
2	1958	Villa ¹⁸	17	Mandible	Male	Not mentioned		0	Alive
3	1971	Herceg et al. ¹⁹	9	Mandible	Male	Not mentioned	Multiple	121	Death
4	1977	Höltje et al. ²⁰	4	Mandible	Male	Not mentioned		36	Death
5	1979	Krempien et al. ²¹	5.5	Maxilla	Male	Surgical (not specified)	Lung	144	Alive
6	1986	Nadimi et al. ²²	15	Maxilla	Female	Surgical (not specified)		0	Alive
7	1987	Corio et al. ²³	15	Maxilla	Male	Surgical (not specified)		12	Alive
8	1987	Corio et al. ²³	17	Mandible	Male	Surgical (resection)	Recurrence	12	Alive
9	2007	Hall et al. ⁴	15	Maxilla	Male	Surgical (enucleated)	Recurrence	196	Alive
10	2007	Hall et al. ⁴	16	Maxilla	Male	Surgical (resection)		288	Alive
11	2007	Hall et al. ⁴	7	Maxilla	Female	Surgical (enucleated)	Recurrence	119	Alive
12	2007	Hall et al. ⁴	17	Mandible	Female	Surgical (not specified)	Recurrence	122	Death
13	2008	Yazici et al. ²⁴	10	Maxilla	Male	Surgical (resection + radiotherapy)		6	Alive
14	2009	Reid-Nicholson et al. ²⁵	15	Mandible	Male	Surgical (resection)	Lymph node	Not specified	Not specified
15	2010	Ndukwe et al. ²⁶	16	Mandible	Male	Surgical (resection)		Not specified	Not specified
16	2010	Ndukwe et al. ²⁶	16	Mandible	Female	Surgical (resection)		Not specified	Not specified
17	2012	Horváth et al. ²⁷	8	Mandible	Female	Chemotherapy	Multiple	8	Death
18	2013	Yoshioka et al. ²⁸	17	Mandible	Male	Surgical (enucleation)	Lung/Recurrence	39	Death

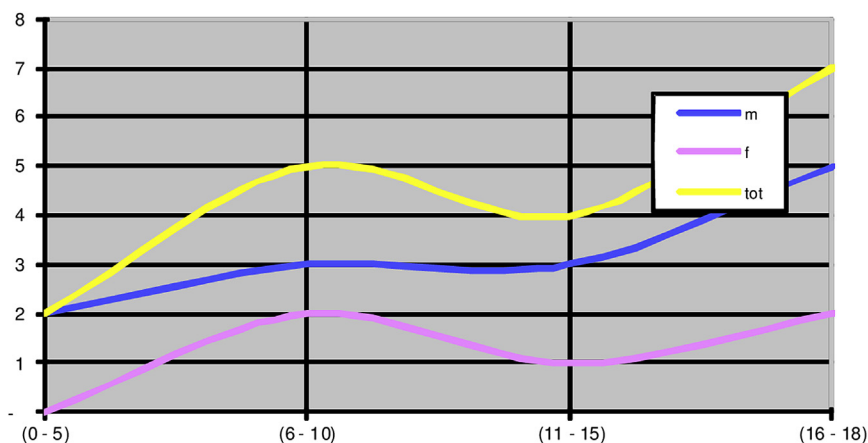


Fig. 11. Age and gender distribution.

English from 1932 to 2012 found 18 pediatric cases of ameloblastic carcinoma.¹⁵ Data reported included gender, age, location, clinical signs, treatment, follow-up, recurrence, and metastasis, although not all details were available for every case (Table II). The mean age was 12.6 years, with a wide age range (4 to 17 years). The female-to-male ratio was 1:3 (Figure 11). In 50% of cases, the first clinical sign was swelling. Other initial signs were pain in 5%, in 5% it was pain, 6% dysphonia, and the remaining 39% unknown or not given (Figure 12). Of all cases, 53% were in the mandible (Figure 13). During follow-up (mean duration, 7.8 years), local recurrences were detected in 4 of the 18 pediatric patients, and metastasis (both hematogenous and lymphatic) was detected in 4 patients (1 bone, 1 lung, 1 lymph node, and 1 case with multiple metastases). Local recurrences occurred after periods

ranging from 1 to 16.3 years, suggesting that long-term follow-up is mandatory.

Since 1979, all cases reported in the literature have been treated surgically. In only 1 case did the patient receive radiotherapy because of the involvement of surgical margins. In another case, chemotherapy was administered.

In contrast to the presentation of ameloblastic carcinoma in the adult, in pediatric patients there is no jaw predilection (53% mandible). Gender predilection has been reported to be limited in the adult,^{3,5,12} although in our examination of the available literature concerning pediatric patients, we found a male predilection (female-to-male ratio, 1:3). Clinical presentation in pediatric patients is the same as in adults (see Figure 12).

When ameloblastic carcinoma is diagnosed, nodal and distant metastases must be carefully investigated.

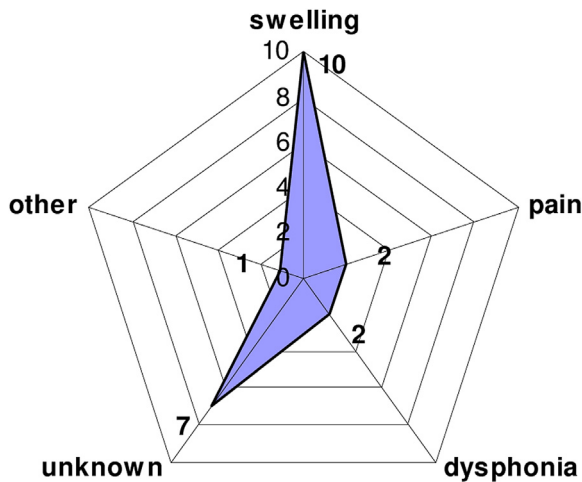


Fig. 12. Distribution of first symptoms.

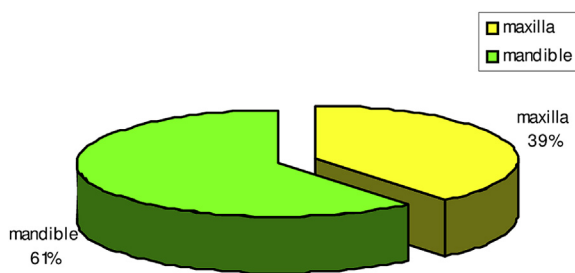


Fig. 13. Primary tumor sites.

Staged work-up comprises a neck examination, head and neck CT scan, chest radiography, and abdominal ultrasonography. Total body CT scanning has also been recommended.

Preoperative radiotherapy has been suggested to decrease tumor size and may be used to treat some rapidly growing tumors before surgery. The radiosensitivity of these tumors has not been investigated in depth, and adjuvant radiation may or may not be indicated. There are few reports on chemotherapy regimens for ameloblastic carcinoma.²⁸ However, the role of chemotherapy has not yet been proven.²⁹ Avon et al.¹¹ suggested both prophylactic and therapeutic contiguous neck dissection. In the case reported here, we adopted a “wait and see” approach, considering the absence of infiltration into the cyst wall, the absence of lymph node metastasis, and the fact that the ameloblastic carcinoma was only present focally, embedded within a larger cyst.

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