CASE REPORT

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Malignant ameloblastoma in an 8-year-old child with metastasis to the lung: case report with a clinicopathologic analysis

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Abstract

Ameloblastomas are rare tumors of odontogenic origin, accounting for 1% of all oral tumors. They are benign, but locally highly aggressive tumors. We report here the unusual case of an 8-year-old patient with multicystic mandibular ameloblastoma, who was submitted to surgery for two relapses in six years and metastasized to the lung two years after initial surgery. The first lesion, diagnosed as follicular ameloblastoma, was treated conservatively with enucleation and curettage. Two years later the tumor relapsed into multicystic granular form. A marginal conservative resection was performed, keeping the basilar contour of the mandible, due to the age of the patient. Three months later, on a routine follow-up examination, a lung metastasis was detected with no signs of tumor in the mandibular bone and the patient was submitted to upper right lobectomy. Three years later a new recurrent tumor was detected in the alveolar process and another marginal resection was performed. Histologically, the tumor showed the follicular growth pattern. After a disease-free period of over five years, the patient was again submitted to surgery for mandibular reconstruction. The mandibular bony defect was filled with iliac bone blocks and four dental implants. He underwent oral rehabilitation with an implant-supported overdenture. With a follow-up period of 22 years since first surgery, the patient is currently free of disease.

Keywords: follicular ameloblastoma, marginal resection, oral rehabilitation.

Introduction

Ameloblastoma is a rare tumor of the jaws originating from odontogenic epithelium. It accounts for 14% of all odontogenic tumors [1]. It is usually a benign, but locally invasive tumor with a high tendency for local recurrence after conservative surgical removal: 50% to 72% of cases [2, 3].

Ameloblastomas can arise from the developing enamel organ, during the stage of tooth formation. In the adult, they may also arise from remnants of the enamel organ in bone, from the epithelial lining of odontogenic cysts or the basal cells of the oral mucosa [4, 5]. When the odontogenic rests are located in the soft tissue of gingiva or alveolar mucosa, they can give rise to peripheral or extraosseous ameloblastoma, an uncommon entity accounting for 1–2% of all ameloblastoma [2, 6].

Ameloblastoma occurs in a wide range of age groups with a mean age of 36 years [6] and equally among the sexes [7, 8]. It is a slow growing, often-asymptomatic tumor, arising in the mandible in over 80% of cases [6, 7]. The posterior region and the ascendant ramus are the most involved areas [2, 6].

According to the *2005 World Health Organization Classification* [9], the benign ameloblastomas are divided into four subtypes based on their clinical behavior, radiographic appearance and histological features: solid (multicystic), unicystic, desmoplastic and peripheral. Solid/multicystic ameloblastoma contains multiple cystic spaces. It accounts for approximately 86% of all ameloblastomas [2], is more aggressive and recurs more often than unicystic ameloblastoma in the absence of radical treatment. It exhibits diverse histopathological subtypes like follicular, plexiform, acanthomatous, basaloid and granular cell variants, which can occur either singly or in mixtures of different patterns. In the last case, the tumor is classified based on the predominant pattern. Follicular and plexiform ameloblastomas are the most common, with incidence rates of 27.7% and 21.1% respectively [7], followed by acanthomatous and the desmoplastic types. The most unusual histological subtypes include granular cell and basal cell ameloblastoma.

Regional and distant metastases are uncommon in ameloblastomas (2%) and have a distinct predilection for the lung, which is involved in 71–80% of cases [3, 8].

We report below an unusual case of multi-recurrent mandibular ameloblastoma in a pediatric patient developing pulmonary metastases 2.3 years after the initial diagnosis, who was submitted to repeated conservative procedures for the primary and recurrent tumors and to an upper right lobectomy for the lung metastasis, achieving actually a 12 years free-disease period.

Patient, Methods and Results

An 8-year-old patient presented 22 years ago with a deformity in the inferior right vestibule, the panoramic radiography showing a multilocular radiolucency in the right mandibular body from tooth 26 to 30 (27, 28, 29 in the area) (Figure 1A). After detecting the biological constants, curettage of the lesion was performed. Histopathological examination of Hematoxylin–Eosin (HE) stained sections showed a well-differentiated proliferation of odontogenic epithelium in the form of islands and follicles. The islands were lined by tall columnar cells arranged in palisade, showing hyperchromatic nuclei with subnuclear vacuolizations and reverse polarity. In the center of the islands and follicles loosely arranged stellate-reticulum like cells were found. The tumoral stroma was dense, collagenous, infiltrated by chronic inflammatory cells. Several areas contained cystic spaces lined by palisaded basophilic cells depicting reverse polarity (Figure 1C). In conclusion, the histological finding was consistent with follicular multicystic ameloblastoma.

The patient was held under observation for two years and a half, when a relapse, which involved the anterior process was noted. The X-ray demonstrated a multilocular radiolucency both in the right mandibular body and in the mandibular arch up to tooth 19 (Figure 1B). The patient was once again submitted to surgery. Due to his age (10 years and a half), a marginal resection was preferred with a 1.5 cm safety margin preserving the basilar outline of the mandible. Microscopic examination revealed that the tumor contained large granular cells replacing the stellate reticulum-like cells in the center of the follicles and islands. The granular cells showed polygonal contour and abundant cytoplasm filled with coarse eosinophilic granules. The connective tissue stroma was loose. Thus, a diagnosis of granular ameloblastoma was established.

Three months later, on a routine check-up, a solitary lung metastasis was detected in the upper right pulmonary lobe (Figure 2A). The patient was submitted to a lobectomy. Microscopic examination of the removed lung metastasis revealed a well-differentiated proliferation of deeply staining basophilic cells showing features similar to those of the primary tumor. The solid tumoral nests were lined by ameloblastic epithelium with no morphological signs of malignancy (Figure 2B). Finally, a diagnosis of malignant ameloblastoma was rendered, based on the clinic and histological features.

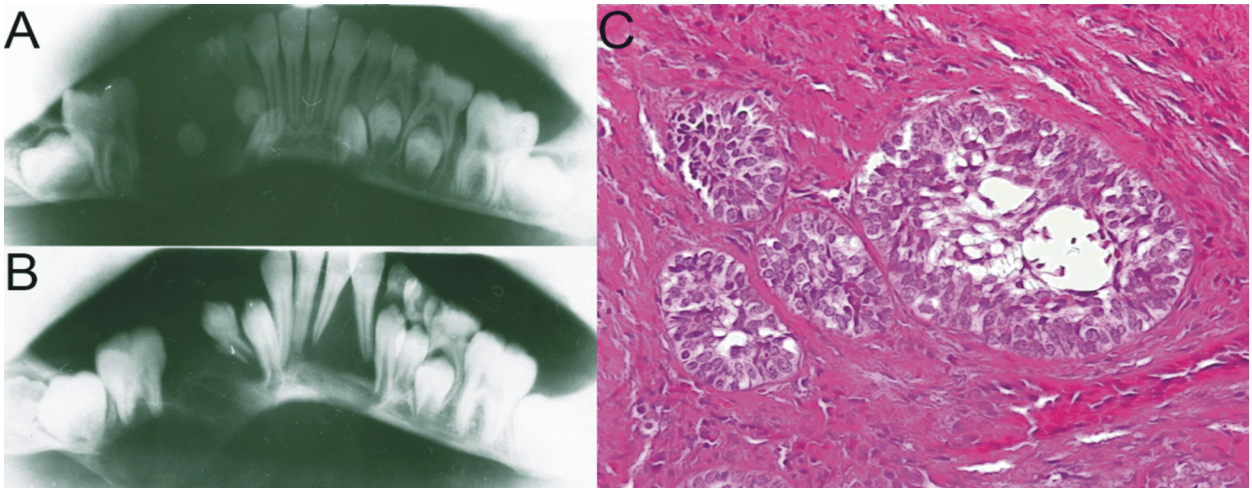

Figure 1 – ***(A) Panoramic radiograph – initial consult. (B) Panoramic radiograph – relapse after curettage. (C) Islands of odontogenic epithelium lying in a fibrous stroma. The islands show tall columnar peripheral cells arranged in palisade with nuclear hyperchromatism and reversed polarity. In the center of the islands, loosely arranged stellate-reticulum like cells were found. Areas of microcystic degeneration in the center of the follicles. HE staining, 200×.***

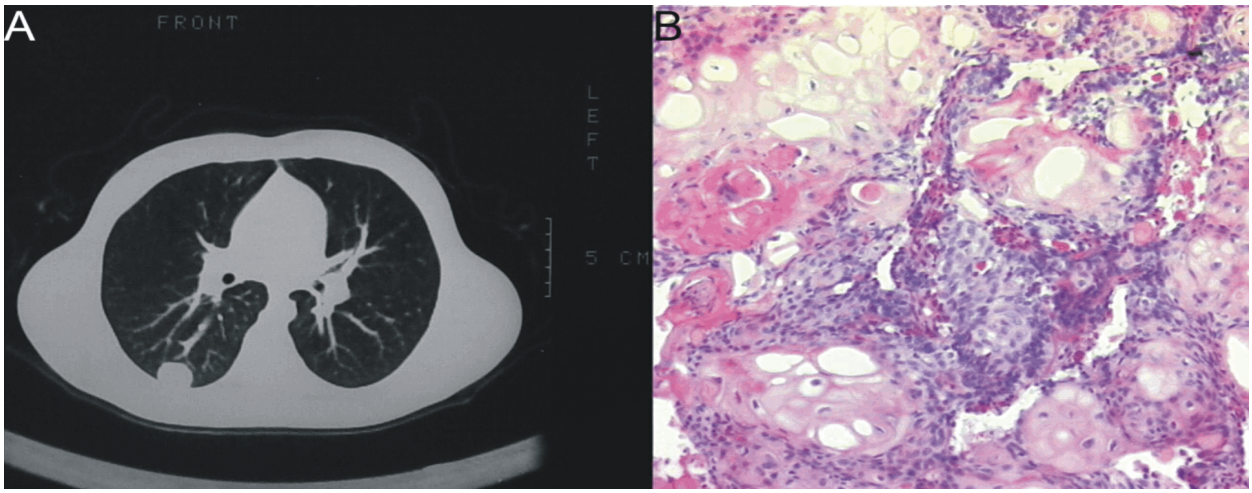

Figure 2 – ***(A) MRI showing right lung tumor. (B) Histopathology of the removed pulmonary metastasis showing solid tumor nests lined by columnar cells with hyperchromatic palisaded nuclei. HE staining, 200×.***

After three years, on a routine follow-up examination, a relapse was noted in the left alveolar process at the level of teeth 20–18. He was planned for surgery; the decision was a marginal resection at this level. Microscopic examination revealed a follicular ameloblastoma containing epithelial cells arranged in nests and follicles within a fibrous stroma. The tumoral nests were lined by columnar palisading cells with hyperchromatic nuclei (Figure 3). In some areas, cystic spaces appeared to be lined by ameloblastomatous epithelium (Figure 4). No signs of cytological malignancy were detected.

The patient was once again held under observation and after a favorable evolution of five years, at the age of 19 years, the remaining bone defect was filled with self-transplanted iliac crest bone (Figure 5C). At the same time, he was fitted with four dental implants. After six months, he was prosthetically rehabilitated with an implant-supported overdenture (Figure 5D). Recent evaluation of the patient, 12 years after the mandibular reconstruction, found no signs of local relapse or remote metastasis.

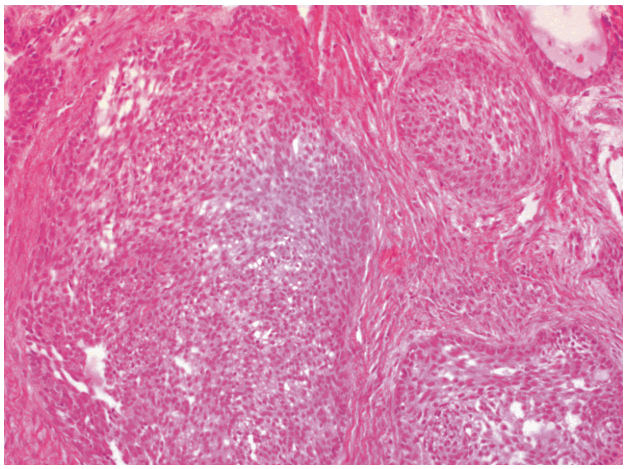

Figure 3 – ***Epithelial islands with central stellate-reticulum like cells surrounded by a peripheral layer of columnar cells lined up in a palisaded pattern. Some islands show central cystic degeneration. HE staining, 100×.***

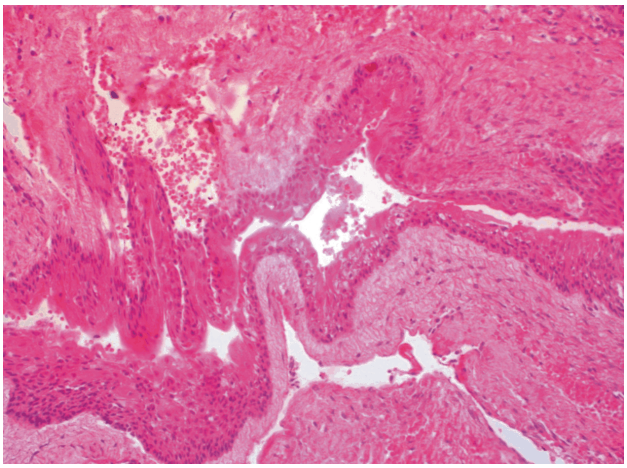

Figure 4 – ***Ameloblastomatous epithelium with palisading cells lining a cystic space. The epithelial cells exhibit inverted nuclear polarity. HE staining, 100×.***

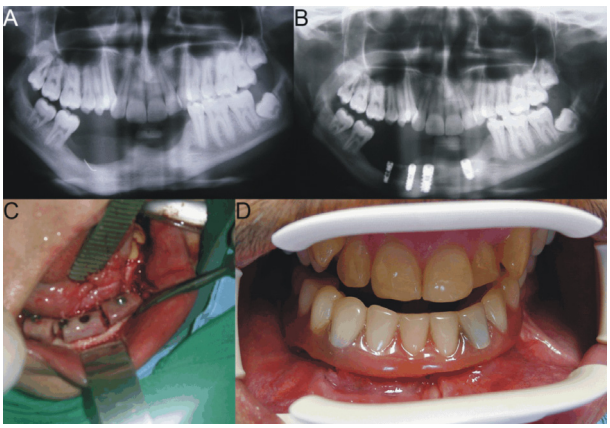

Figure 5 – ***(A) Panoramic radiograph at 10 years follow-up. (B) Final panoramic film after implant osteointegration. (C) Intra-oral image showing iliac bone blocks. (D) Final prosthetic rehabilitation.***

Discussion

Ameloblastoma is a rare entity in children and adolescents, with an incidence rate of 10–15% of all ameloblastoma [10, 11].

Most ameloblastomas in children occur between 4–20 years, with a mean age of 14.5 years [11, 12]. Less than 10% of cases occur in children under 10 years [12]. There is no gender predilection [11]. Approximately 96.6% of them arise in the mandible [10, 11, 13] and frequently affects its posterior area [10, 13, 14].

Ameloblastoma in children differs from adults by prevalence of the unicystic type over the solid type in up to 95% of cases [15]. In our patient, the tumor was a multycistic ameloblastoma, in contrast to the literature data.

An unusual feature of our case is the presence of two different histological tumor types during the follow-up period: follicular pattern in the primary lesion, changing to granular pattern in the first recurrent tumor. The granular cell ameloblastoma is an uncommon histological subtype, representing less than 5% of all ameloblastomas [6] and occurs more often in combination with other histological types, particularly the follicular pattern [16]. The granular cell ameloblastoma is essentially characterized by the transformation of the reticulum-like cells usually seen in center the islands in large granular cells with coarse eosinophilic granules filling their cytoplasm. The cytoplasmic granules are lysosomal aggregates, as demonstrated by ultrastructural and immunohistochemical studies [17]. It was initially thought that the lysosomal aggregates within cytoplasm were due to degenerative changes. Immunohistochemical studies have revealed that the granular transformation might be caused by increased apoptotic cell death of the lesional cells with subsequent phagocytosis by neighboring tumoral cells [17].

The recurrence rate of ameloblastoma is high and it has been linked to the histological variant and the type of surgery performed. In children, it has been reported to range from 20 to 40% after conservative operations [10, 12]. Follicular amelobastomas tends to recur more

frequently than the plexiform type and the solid type more often than the unicystic type [6, 18]. The recurrence rate in adults is 90–100% after enucleation and curettage and only 5% after resection [19]. Our patient experienced two relapses in six years. He underwent conservative surgery: enucleation with bone curettage of the first lesion, followed by two marginal bone resections for the recurrent tumors.

Metastases have rarely been reported. They usually occur in approximately 2–5% of cases and most often involve the lungs (71–80%) [3, 8], followed by cervical lymph node metastases [19], vertebrae [8, 20, 21] and occasionally skull, pleura, diaphragm, parotid gland and liver [22]. The interval from initial diagnosis to the appearance of pulmonary metastases ranges from 0.3 to 31 years with a mean period of 14.3 years [23]. In most cases, there is a recurrence of the primary tumor before metastases appear in the lung. In our patient, the lung metastasis was noted 2.3 years after initial presentation and three months after the first recurrence. He underwent an upper right lobectomy in an oncological pediatric clinic and actually is alive 20 years after removal of metastasis.

According to some authors, patients with multiple relapses and repeated surgical procedures have a tendency to develop metastases [3, 23–25]. Therefore, adequate resection of the primary tumor is needed to avoid multiple surgical procedures and tumor dissemination. Extensive local tumors tend also to be associated with a higher risk of developing metastases [22]. The mechanism of metastatic spread to the lung in malignant ameloblastoma is not yet clear. It may occur by three possible routes: hematogenous, lymphatic and by aspiration [2, 26]. Some pulmonary metastases are peripherally located, suggesting dissemination *via* hematogenous or lymphatic route rather than aspiration.

Classification of ameloblastoma is still a controversial subject. Our case illustrates the distinction that is to be made between classic ameloblastoma, metastatic (malignant) ameloblastoma and ameloblastic carcinoma in order to avoid confusion about the terminology which can lead to falsification of the data regarding the incidence of these tumors. Both clinical behavior and histopathological features have to be considered when establishing the diagnostic. According to the 2005 *WHO Classification* [9], ameloblastoma and metastatic ameloblastoma are two different clinico-morphologic entities. Ameloblastoma is defined as a localized tumor with benign histological features. Malignant (metastatic) ameloblastoma is a tumor that has developed metastases despite benign histological features, similar to those of classic ameloblastoma in both the primary and metastatic sites. Thus, the diagnostic of malignant ameloblastoma is based on clinical behavior and not on histological appearance.

Malignant ameloblastoma must also be clearly distinguished from ameloblastic carcinoma, which carries a worse prognosis [27] and shows malignant histological features including cytological atypia, cellular pleomorphism, mitotic activity, focal necrosis, vascular invasion. The tumoral cells lack the characteristic arrangement noted in ameloblastoma [27]. The term "ameloblastic carcinoma" should be confined to those tumors that combine histological features of an ameloblastoma with cytological atypia, irrespective of the presence of metastases.

Surgery is the treatment of choice in ameloblastoma. Due to the prevalence of the solid type in adult patients, marginal resection approximately 1–1.5 cm past the radiographic boundary is preferred [16, 28]. Ameloblastoma treatment in children is still open to discussion. Good results can be achieved in the treatment of unicystic tumors using conservative procedures (enucleation and curettage) [13, 29, 30], but the solid/multicystic or recurrent lesions should be treated in a way similar to the adults: resections with safety margin of 1 cm [11, 12, 28]. However, there is still a question when dealing with the mandible at the growth age [10, 31, 32]. Surgical removal is the treatment of choice for metastasis too [25]. The role of chemotherapy and radiotherapy is controversial. Chemotherapy is often reserved for palliative purposes when surgery is not feasible [33]. Our patient underwent conservative methods: enucleation and curettage of the initial lesion and then bone marginal resections for the recurrent tumors and was submitted to upper right lobectomy for the lung metastasis. On the last follow-up examination, the patient had no signs of recurrence or metastatic spread, achieving a 12 years disease-free period.

Because of high recurrence rates, post-operatory follow-up is mandatory in managing ameloblastoma and close periodic reassessments must be done on all patients. More than 50% of all relapses occur within the first five years postoperatively [6, 28]. Long-term surveillance is essential since recurrences have been noticed beyond 10 years after primary surgery [34] and metastasis 29 years after primary tumor removal [22]. It is recommended to extent the follow-up period beyond five years from the initial presentation [32].

Conclusions

Metastatic ameloblastoma is a rare entity in pediatric patients and its management remains controversial. In the case presented in order to reduce the impact on facial growth and development, conservative treatment was preferred initially. Despite the multi-recurrent and metastatic character of the tumor, the patient has survived 20 years after metastases removal, with a disease-free period of 12 years.

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