



# Considerations on a long-term course of a plexiform ameloblastoma with a recurrence in the soft tissue

Adorján Kovács,\* Mathias Wagner,\*\* Mostafa Ghahremani\*

## ABSTRACT

Ameloblastomas (ICD-DA-213.XI) are unicentric, nonfunctional, and clinically persistent benign tumors, intermittent in growth. The following histologic patterns may be distinguished: spindle cell, acanthomatous, granular cell, follicular (simple), basal cell type, and plexiform. Clinical features (even if combined with radiology or histology findings) are not useful when trying to determine the biological behaviour and therefore the prognosis of an individual ameloblastoma. A long-term course of a plexiform ameloblastoma (ICD-O-9310.0), well documented over 20 years with special regard to its recurrence in the soft tissue of the left cheek, is presented in this paper. Important questions on pathology, molecular biology, and therapy are discussed. In conclusion, a close cooperation of clinicians and surgical pathologists is necessary over a long period of time for the best management of each individual case.

**Key words:** Plexiform ameloblastoma, soft tissue recurrence.

## RESUMEN

*Los ameloblastomas (ICD-DA-213.XI) son tumores unicéntricos, no funcionales, clínicamente persistentes y benignos, intermitentes en su crecimiento. Desde el punto de vista histológico se pueden distinguir los siguientes patrones: espinocelular, acantomatoso, granular, folicular (simple), basocelular y plexiforme. Hasta ahora no es aún posible determinar los factores pronósticos para el comportamiento de los ameloblastomas. Esto no se puede hacer ni por la clínica, radiología o histología. Sólo los métodos biológicos moleculares, inmunohistoquímicos pueden enfrentar el problema como se muestra durante el curso de un ameloblastoma plexiforme (ICD-O-9310.0) muy bien documentado durante 20 años con especial atención a su recidiva en tejidos blandos de la mejilla izquierda. Se discuten puntos importantes de la patología y terapéutica. Se requiere de amplia cooperación de las secciones de clínica y patología durante un largo lapso de tiempo en cada caso individual.*

**Palabras clave:** Ameloblastoma, patología, recidiva.

## INTRODUCTION

Ameloblastomas (syn.: Adamantinoma, Adamantoblastoma, Multilocular Cyst, ICD-DA-213.XI) are benign odontogenic tumors with high a probability of recurrence. These true neoplasms are discussed to

derive from Serré's epithelial cell rest's, the epithelial cell nest's of Malassez, the epithelial of odontogenic cysts and the basal cell layer of the gingiva or the oral mucosa. The term "ameloblastoma" was suggested by Churchill<sup>1</sup> (1934), because the old term ("adamantinoma", coined by Malassez in 1885)

\* Department of Maxillofacial Plastic Surgery (Head: Professor Klaus Bitter, MD, DMD). Johann Wolfgang Goethe-University Medical School, Frankfurt am Main, Germany.

+ Institute for Pathology (Head: Professor G. Zieger, MD), Stadtkrankenhaus Hanau, Hanau, Germany.

Dedicated to Professor Dr. Dr. Gerhard Frenkel, Frankfurt am Main, Germany.

erroneously implied the formation of hard tissue. Since the enamel organ-type tissue does not undergo differentiation to the point of malformation, no such material is present in ameloblastomas. As a very rare tumor ameloblastomas account for about 1 % of all neoplasms of mandible and maxilla.<sup>2,3</sup> With the majority of patients in their 4th decade, the lesion can be found in any age group including children.<sup>4-5</sup> Men are affected slightly more often than women with particularly elevated an incidence in Eastern Africa.<sup>6</sup> More than 80 % of the ameloblastomas are observed in the mandible (mostly angle or ramus<sup>2,7</sup>). Peripheral ameloblastomas are rare:<sup>8</sup> they are either primary or secondary soft tissue tumors, the latter appearing after operations. Radiologically, they present with unilocular or multilocular to polycystic translucences without clear-cut diagnostic features. Since the histologic pattern of this lesion varies greatly, a number of subtypes can be distinguished:<sup>9</sup> spindle cell, acanthomatous, plexiform, follicular (simple), basal cell type and granular cell ameloblastoma, again of doubtful prognostic value. Attempts are made to reduce the number of subtypes by clinical separation in solid or multicystic, unicystic and peripheral ameloblastomas.<sup>10</sup> Some authors concede prognostic value to histological, as well as radiological features and age.<sup>11</sup> Maxillary ameloblastomas are reported to be more aggressive and have a poorer prognosis,<sup>12</sup> while unicystic ameloblastomas are believed to be less aggressive.<sup>13</sup>

Yet, differential therapy is not advisable. The best treatment is an initial extensive surgical excision. Conservative treatment leads to high a rate of



**Figure 1.** Oblique x-ray of the mandible at the time of first diagnosis (1976). The alteration is tublike in the region of the corpus and sinuated in the region of the ramus.

recurrence (up to 90 %<sup>14</sup>). Reviewing literature, one can find various concepts of ameloblastoma therapy more or less subtype-specific. Olaitan and Adekeye<sup>13</sup> as well as Gardner and Corio<sup>15</sup> for instance state curettage to be sufficient for treatment of unicystic plexiform ameloblastomas provided that the tumor did not invade the peripheral connective tissue. Curi et al.<sup>16</sup> suggested that management of solid or multicystic ameloblastomas of the jaws with curettage followed by liquid nitrogen spray cryosurgery may decrease the local recurrence rate and reduce the initial indication of radical resection.

A patient with recurrent plexiform ameloblastoma (ICD-O-9310.0) with a clinical course over 20 years was our motive to discuss radiological and histological views, radicality of therapy, and their prognostically relevant interrelations.

#### CASE REPORT

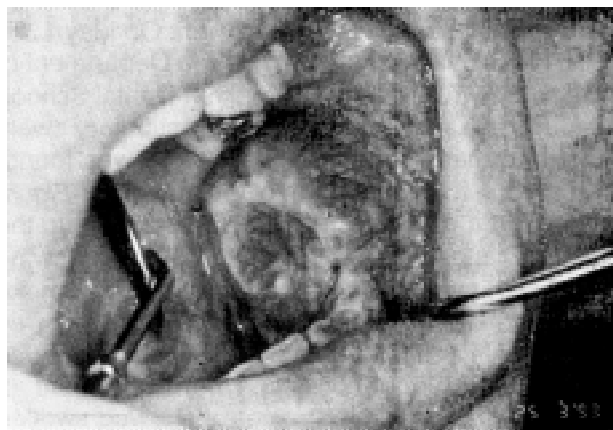
For reasons unknown, the left inferior wisdom tooth was extracted from a 56 year old otherwise healthy caucasian male for reasons unknown in December 1975. The patient had an inferior partial denture which he refused to wear since then. On May 12th, 1976 his dentist assigned him to the Department of Oral surgery (University of Frankfurt Dental School) suspecting a mandibular cyst. A vestibular swelling of the mandible in region 36 to 38 was found. The oblique roentgenogram of the mandible (*Figure 1*) showed a cystic alteration of region 36 up to the ramus. Cystostomy was carried out the following day. The diagnosis based on histology was ameloblastoma. Thereupon, extended curettage followed by conservative treatment of the cavity was carried out until early January, 1978, when the patient alleged chronic pain. X-ray control showed swollen cystic structures reaching from corpus to ramus of the left mandible. The patient was hospitalized. On January 20th, 1978, continuity resection of the mandible (with the tumor reaching from the first molar to the semilunar incision) was carried out at the Department of Maxillofacial Surgery (University of Frankfurt Medical School). The resection was confined by region 34 to the base of the collum including the inferior alveolar nerve. A plastic interponate was brought in by means of plate fixation. Two more surgical interventions took place in this anatomical region: May 1982 (removal of the metal plate, mandibular reconstruction with a free autologous iliac bone graft along with a reconstruction plate, removal of the collum due to dislocation) and March 1983

(removal of the reconstruction plate). All this time and for the next ten years, the patient showed no clinical signs of recurrence of the ameloblastoma.

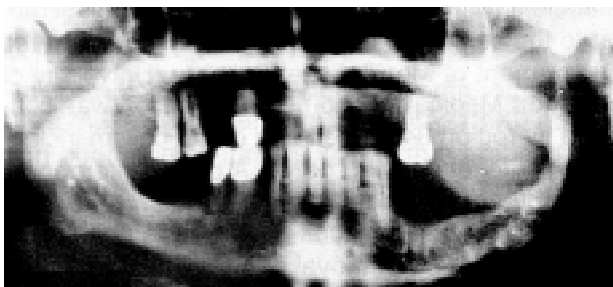
In January 1993, the patient noticed a slight protrusion of the left cheek. In March the same year, the swelling was about 4 cm in diameter, making him come to our clinic for treatment. Unlike the rather inconspicuous and movable skin of the cheek, the oral mucosa covering central parts of the tumor was fixed and ulcerated (*Figure 2*). Lymph nodes were not palpable. Roentgenograms showed a partly resorbed yet inconspicuous bone graft with a large intermaxillary shadow. There were no signs of tumor-induced bone absorption (*Figure 3*). On April 29th, 1993 the tumor was resected via enoral access. The defect was closed by anterior rotation of the mucosa.

The patient is without recurrence up to date (1998).

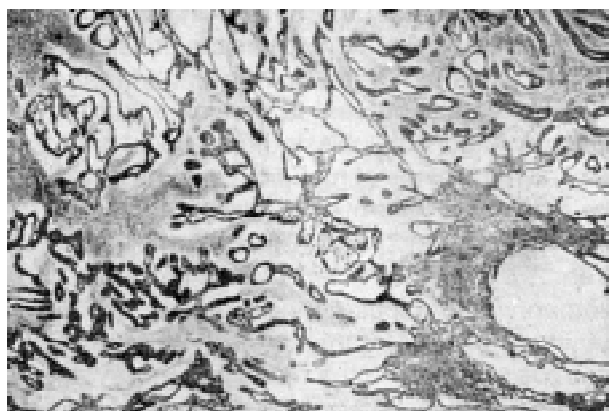
**Radiology:** The oblique roentgenogram of the mandible (*Figure 1*), dated the day of first medical evidence (May 12th, 1976), shows an expanded unicystic translucence of the bone structure on the left



**Figure 2.** Intraoral view of the tumor of the left cheek (1993).



**Figure 3.** Orthopantomography at the time of soft tissue recurrence (1993). Tumor is not adherent to the bone.



**Figure 4.** Predominant histological aspect in the ameloblastoma in 1976 (x 50).

side with clear delimitation. No specific diagnostic signs are presented. In the orthopantomography from April 1st, 1993 (*Figure 3*) a soft tissue shadow between maxilla and mandible can be seen at the level of the ramus, whilst the iliac bone graft is inconspicuous.

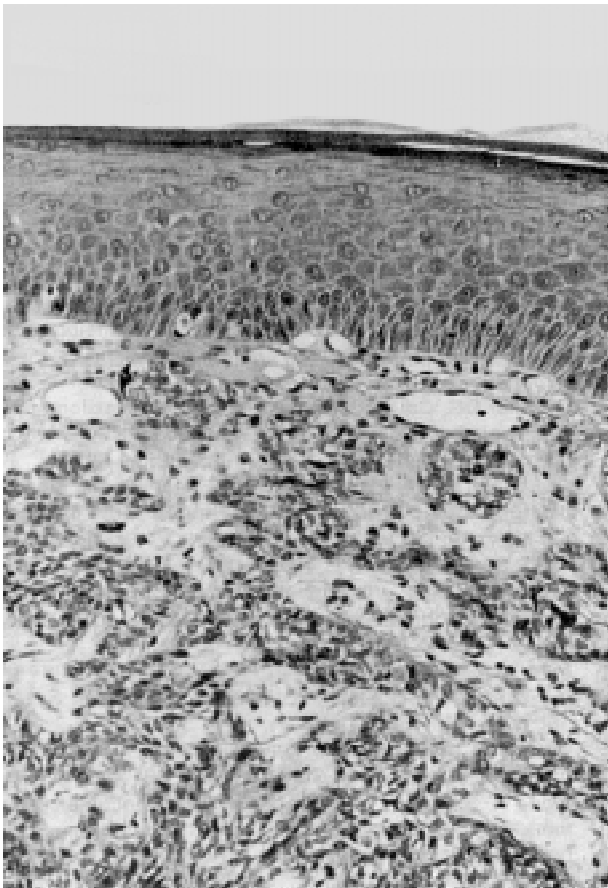
**Surgical pathology:** A piece from the jaw (2 x 3 x 5 cm in size) was extirpated. The histopathological processing of the tumor revealed a plexiform ameloblastoma predominantly composed of epithelium arranged as a tangled network of anastomosing strands enclosing cysts of various size here and there (*Figure 4*). The lesion also presented irregular masses each of which show cell layers formed by angular cells resembling the stellate reticulum of the normal enamel organ. These areas were surrounded by a layer of columnar or cuboidal cells resembling ameloblasts. The nuclei were regular and the tumor showed no mitotic activity elevated. The fraction of tumor penetrating the left cheek's soft tissue presents with more solid aspects composed of the cells already described above (*Figure 5*). Cystic areas were not as predominant as in the mandibular bone. In the soft tissue the cells were either lying in strands or in more or less medium sized to large heaps of irregular shape.

Histomorphological features of the excisions were the same in 1976, 1978 and 1993.

## DISCUSSION

The ameloblastoma is a locally invasive neoplasm derived from odontogenic epithelium. Possible origins of the neoplastic epithelium are discussed to be either disturbances of the developing enamel or-

gan or the epithelial lining of odontogenic cysts, particularly the dentigerous cyst, and odontomas or cell rests of the enamel organ, namely either remnants of the dental lamina or remnants of Hertwig's root sheath (epithelial cell rests of Malassez) or the basal layer of the oral surface epithelium (epithelium of the jaws) or heterotopic epithelium in other parts of the body. This distinctive semimalignant, unicentric, nonfunctional, persistent odontogenic neoplasm shows intermittent or slow growth. The proliferating tumor may infiltrate the cancellous marrow spaces without causing bone destruction. It tends to expand the bone rather than perforate it. Occasionally patients allow an ameloblastoma to persist for many years without treatment and though the expansion may become extremely disfiguring the tumor does not break through the bone. But for reasons unknown some ameloblastomas manage to penetrate the bone and extend into the surrounding soft tissues. A



**Figure 5.** The ameloblastoma infiltrating the soft tissue of the left cheek 15 years after continuity resection of the mandible (x 25).

breakdown of the skin or the oral mucosa is hardly to be observed. Local extension to the base of the skull is life-threatening.<sup>17</sup> Very rarely ameloblastomas develop distant metastases.

The tumor found in our patient was an ameloblastoma of the plexiform type. The term "plexiform" refers to the appearance of anastomosing islands of odontogenic epithelium in contrast to a follicular pattern. Due to invasiveness and a rare chance of metastases of ameloblastomas, the tumor has been subject to definition from a benign odontogenic epithelial tumor<sup>18</sup> to a slow-growing malignant tumor.<sup>19</sup> If ever metastases were delivered by an ameloblastoma, the most common sites are lung (76.7 %), followed by regional lymph nodes (37,8 %), pleura (16,2 %), vertebrae (13,5 %), skull (10,8 %), diaphragm (8,1 %), liver and parotid (5,4 %) and, even more rarely, the spleen and the kidney.<sup>20</sup> Hematogenous<sup>21,22</sup> and lymphatic<sup>23</sup> spread of the tumor are discussed, whilst pulmonary metastasis are probably a result of aspiration of tumor cells associated with surgery, particularly in cases having undergone multiple operations due to recurrences.<sup>24-25</sup> Some patients with metastases of an ameloblastoma develop hypercalcemia.<sup>20</sup> Neither any of these routes of tumor spread nor hypercalcemia applies to our case. Originating from the left mandible, the tumor directly infiltrated the soft tissue of the cheek. Despite the long period of time the tumor persisted in our patient no metastasis has yet been found. Major histomorphological changes were not seen throughout the years in our case. The rate of mitosis and dysplasia did not vary significantly.

The observation of Ueno et al.<sup>7</sup> and El-Mofty et al.,<sup>26</sup> that most peripheral ameloblastomas are plexiform, is supported by our case.

Major histomorphological changes were not seen throughout the years in our case. Rates of mitosis and dysplasia did not vary significantly during this period of time. Authors dispute to which extent the various histological patterns of simple ameloblastoma accompany distinctive variations in clinical behaviour.<sup>11, 27,28</sup> Immunohistochemical staining for various keratins is positive in all ameloblastomas but positivity for different keratin subtypes does not correlate with the biological behavior of the tumor. The labelling index expressing the percentage of Ki-67 positive cells showed no significant correlation with clinical features like age, sex or tumor size.<sup>29</sup>

The expression of proliferating cell nuclear antigen (PCNA) indicated differences in proliferating potential between different areas of unicystic

ameloblastoma and between unicystic and solid lesions and may be related to recurrence after conservative treatment.<sup>30</sup> But biopsies generally are taken from the best accessible area of a tumor which may not be the one with the highest proliferating potential.

Some odontogenic tumors like odontogenic myxomas and ameloblastic fibromas show an overexpression of p21<sup>RAS</sup> compared to normal human developing teeth (cells of ectodermal origin in the fetal tooth germ). The highest expression was seen in recurrent plexiform ameloblastomas and a granular cell ameloblastoma.<sup>31</sup> For prognostic reasons future studies should reveal whether high p21<sup>RAS</sup> expression levels in solely recurrent ameloblastomas correlate with chromosome 8 rearrangements<sup>32</sup> and if the pattern in chromosomal rearrangements differs in ameloblastomas delivering metastases. This may be a future tool to estimate an individual risk for the (rare) development of metastases, since neither light nor transmission electron microscopy are helpful in identifying the primary tumor as a malignant ameloblastoma.<sup>28</sup>

In our case the ameloblastoma was treated radically in 1978. It is difficult to say whether the time between first medical evidence and radical resection was responsible for the recurrence clinically observed 15 years later. The tumor in the cheek was no metastasis. Nevertheless the case shows, that radicality is absolutely indispensable and discussions about its necessity are detrimental for the patient. This seems even clearer when findings of Ueno et al.<sup>11</sup> are taken into consideration that recurrences appear more often in follicular than in plexiform, more often in polycystic than in unicystic ameloblastomas and more often in younger people than in older ones. Neither of these parameters are found in our case, and still there was a recurrence notwithstanding high radicality. Segmental resection for the mandible therefore should be the primary treatment, marginal resection is appropriate only for small primary tumors.<sup>33</sup>

Although it is not possible to exclude later metastasis histologically,<sup>28</sup> the long course (over 20 years) of our case shows the relative benignity of this ameloblastoma. A higher regularity of recall is necessary even over such a long time.

Surgical pathologists should preserve at least the paraffin-blocks for more than 25 years for comparative immunohistochemical and molecular biological longitudinal studies.

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*Address for correspondence:*

**Dr. med. Dr. med. dent. Adorján Kovács**  
Klinik und Poliklinik für Kiefer- und Plastische Gesichtschirurgie  
Klinikum der Johann Wolfgang Goethe-Universität,  
Haus 21  
Theodor-Stern-Kai 7  
D - 60590 Frankfurt am Main  
Germany  
Tel.: +49 - 69 - 6301 5876  
Fax: +49 - 69 - 6301 5644