Ameloblastic Carcinoma of the Maxillary Sinus

FRANCESCA ANGIERO 1, ROBERTO BORLONI 1, MAURIZIA MACCHI 2 and MICHELE STEFANI 3

1 Università degli Studi di Milano-Bicocca, Facoltà di Medicina e Chirurgia
Sezione Anatomia Patologica Ospedale San Gerardo, Monza (Mi);
2 Istituto Stomatologico Italiano, Maxillo facciale, Milano;
3 Università degli Studi di Milano Statale, Istituto di Anatomia Patologica Sezione Patologia Orale, Italy

Abstract. Ameloblastic carcinoma is a very rare malignant odontogenic neoplasm of the mandible and maxilla, accounting for some 66 reported cases. The case of a 68-year-old man who presented a fistula with orosinus communication of 14-year duration that, after anti-aggregant therapy, began bleeding is reported. The initial microscopic evaluation of the biopsy and radiographic findings were consistent with benign peripheral ameloblastoma without cellular atypia and extensive fields of acanthomatous pattern, but immunohistochemical investigation found strong positivity for Bcl-2, cytokeratins CAM 5 and 6, and for Ki-67/MIB-1, changing our diagnosis. The treatment consisted of left maxillary resection followed by reconstruction. Cellular features of malignancy in the surgical specimen confirmed the diagnosis of ameloblastic carcinoma. This case of an aggressive ameloblastic carcinoma of the maxillary gingiva that presented with an unusual histological pattern illustrates that these tumors can create a diagnostic challenge that may require extensive surgical sampling and/or removal to establish the diagnosis. Immunohistochemically analyzed expression of bcl-2 protein, cytokeratins CAM 5 and 6, and Ki-67/MIB-1 antigen serve to characterize the cyto-differentiation and cellular activity of ameloblastic carcinoma.

Ameloblastoma is the commonest benign odontogenic tumor of the jaw, whereas ameloblastic carcinoma is a rare lesion, with fewer than 66 cases reported in the English-language literature to date (1), characteristic histological features and clinically aggressive behavior.

Malignancy in ameloblastomas has been the subject of controversy for a number of years, in part because of its rarity, complicated by the confusion in terminology. In 1972, the World Health Organization published its classification of odontogenic carcinomas, which included malignant ameloblastoma (2). In the updated World Health Organization (WHO) classification (3), odontogenic carcinomas include metastasizing ameloblastoma, ameloblastic carcinoma, primary intraosseous carcinoma, ghost cell odontogenic carcinoma, and clear cell odontogenic carcinoma. The term ameloblastic carcinoma was introduced by Elzay (4). Ameloblastic carcinomas meeting the WHO criteria may arise as a result of malignant changes in a preexisting benign ameloblastoma (carcinoma ex ameloblastoma, secondary type) or may develop de novo as a primary ameloblastic carcinoma not preceded by a simple ameloblastoma. It is defined as a rare odontogenic malignancy that combines the histological features of ameloblastoma with cytological atypia, even in the absence of metastases.

Histologically, ameloblastic carcinoma can be considered a form of ameloblastoma that has lost most of its recognizable microscopic features. Despite areas or foci that resemble ameloblastoma, ameloblastic carcinoma shows changed patterns and cytological features. The presence of sheets, islands, or trabeculae of epithelium and the absence or rare presence of stellate reticulum-like areas should alert the pathologist to the possibility of ameloblastic carcinoma. Round to spindle-shaped epithelial cells with little or no differentiation toward the columnar cells of ameloblastoma further suggest this malignant process. Other features of malignancy include hyperchromatism, large or atypical nuclei, increased mitotic index, necrosis, and calcification, and particularly neural and vascular invasion. Calcifications are rare in ameloblastoma, so the presence of calcifications should be carefully evaluated. The presence of many clear cells (>15% of tumor cells) strongly suggests an ameloblastic carcinoma. A single definitive microscopic criterion for ameloblastic carcinoma is elusive. The histological features may vary, and in order to ascertain a diagnosis of ameloblastic carcinoma, it is necessary to make a careful examination of the submitted tissues, especially in cases in which there is limited material. Other aspects are also necessary to distinguish between benign and malignant lesions; these include occasional mitoses, keratin production, and the formation of hyaline material adjacent to
the epithelial portion of the tumor (induction of the fibrous connective tissue). The histological features of benign ameloblastoma may be found in ameloblastic carcinoma arising from ameloblastoma (3).

The clinical presentation of ameloblastic carcinoma is variable; it may arise in the form of a cystic lesion with benign clinical features, or as a large tissue mass with ulceration, bone resorption and tooth mobility. Ameloblastic carcinoma appears most commonly in the posterior mandible (5), with about one third of the reported cases being in the maxilla (5-8). Ameloblastic carcinoma does not seem to show any age-group predilection. An age range of 15 to 84 years has been reported, the average age being approximately 30 years (5-7, 9, 10).

Swelling is the commonest clinical sign, but pain, rapid growth, and trismus may also be presenting symptoms.

Radiographic findings include poorly defined radiolucency, sometimes with focal radiopacities (5, 7). This finding, which is very unusual in ameloblastoma, may result from necrosis with dystrophic calcification, which has been reported in ameloblastic carcinoma (6, 11).

The clinical course is reported as typically aggressive, with extensive local destruction and distant metastatic spread. This criterion seems to be the major factor determining prognosis, with preferentially hematogenetic spread. However, metastatic lymph nodes have also been described. The most involved site of metastasis is the lung, but brain and bony locations have also been reported (12, 13).

The clinical, histological, immunohistochemical and therapeutic details of a case of ameloblastic carcinoma, are reported.

**Case Report**

A 68-year-old man presented at the Oral and Maxillofacial Surgery Institute. He had been under observation elsewhere for a sinus fistula, for which he had been wearing an obturator prosthesis for some 14 years. The patient had a history of dental problems, particularly in the left maxillary area and reported that for two weeks, for systemic problems of coagulation, he had been taking anti-aggregant medication and that the gingiva around the fistula had started to bleed; he was alarmed and thus reported to our center. At objective examination, the gingiva appeared to be characterized by expansion and overlying mucosal erythema. A biopsy was taken because of the suspicion of other diseases. Soft tissue from this area was evaluated, with a preliminary diagnosis of peripheral odontogenic ameloblastoma with an acanthomatous pattern (Figure 1A). However, at immunohistochemical investigation it was observed that MIB-1, a proliferative index, was very high. A second biopsy of the sinus mass was taken via the nasal cavity shortly thereafter and a diagnosis of ameloblastic carcinoma was rendered. A panoramic radiograph and a CT scan were performed (Figure 1B), showing a mass measuring approximately 2.4×2.8 cm occupying the left maxillary sinus, extending beyond the confines of the maxillary sinus inferiorly but not involving the hard palate or the maxillary alveolus and with no extension posterolaterally into the region of the pterygopalatine fossa. The orbital tissues also appeared to be free of tumor invasion and no visual disturbances were noted. The medical history was unremarkable. The patient was referred to the Maxillofacial Surgery Department for definitive treatment and was subsequently treated with a wide local excision with 1.5 cm margins in all directions.

The surgical pathology report confirmed the diagnosis of ameloblastic carcinoma.

**Materials and Methods**

The surgical specimens were fixed in 10% buffered formalin and embedded in paraffin. The tissue blocks were sliced into 3-μm-thick sections for routine histological and subsequent immunohistochemical examinations. For the immunohistochemical analysis, three 3-μm sections were incubated using the avidin-biotin-peroxidase complex. The tissue sections were dewaxed and rehydrated following standard protocols. Table I provides the details of the antibodies used.

The immunohistochemical reactivity for Bcl-2, CAM 5 and 6, and MIB-1 was evaluated and classified into: −, negative; +, slightly positive for a limited number of cells; ++ intensely positive for numerous cells.

**Results**

The tumor consisted of a highly pleomorphic odontogenic epithelial population with permissive features in a minimally fibroblastic stroma. This pattern was characterized by islands, nests, and anastomosing strands of odontogenic cells within a collagenous stroma (Figure 2). The tumor cell nests showed
peripheral palisading of columnar cells with a vacuolated cytoplasm and reverse polarized nuclei, displaced away from the basement membrane. In some areas, the squamous central cells were loosely arranged in an acanthomatous pattern. In other areas, the epithelial component exhibited cytological malignancy, characterized by nuclear pleomorphism, increased nucleus-to-cytoplasm ratio, hyperchromatic nuclei and a high mitotic rate (Figure 3). The rapid proliferation was confirmed

Figure 1. A, Photomicrograph shows features of benign peripheral ameloblastoma (hematoxylin and eosin; original magnification ×100). B, Coronal CT scan demonstrating the presence of a soft tissue mass filling the left maxillary sinus with lateral, medial, superior and inferior extension.
Figure 2. Photomicrograph showing the characteristic squamous differentiation in an acanthomatous ameloblastic carcinoma with keratin production. (hematoxylin and eosin; original magnification ×100).

Figure 3. A peripheral palisading of columnar cells with a vacuolated cytoplasm and reverse polarized nuclei, displaced away from the basement membrane and rare cells with pleomorphic, enlarged and hyperchromatic nuclei are present (hematoxylin-eosin, original magnification ×200).
Figure 4. Photomicrograph showing plexiform and follicular pattern in focal areas (hematoxylin-eosin, original magnification ×200).

Figure 5. Immunohistochemically, the ameloblastic cells showed strong reactivity for Bcl-2 (original magnification ×100).
Figure 6. Immunohistochemically strong positive reactivity limited exclusively to the squamous epithelium for CAM 5 and 6 (original magnification ×100).

Figure 7. Immunohistochemically moderately positive reactivity for MIB-1 (original magnification ×100).
by immunohistochemistry, as shown by the MIB-1/Ki-67 index. Focal areas of keratinizing metaplasia, a follicular and a plexiform pattern were also present (Figure 4). The tumor infiltrated the maxillary bone, invading and filling the inferior portion of the maxillary sinus. The margins were reported to be tumor free.

Immunohistochemically, the squamous epithelial and the basal areas and those within the neoplasia were strongly positively stained by Bcl-2 (Figure 5). Cytokeratin 5 and 6 protein was expressed in the cytoplasm in all the squamous cells (Figure 6). The MIB-1/Ki-67 protein was expressed in the cytoplasm of the basal epithelial cells and in the tumor cells (Figure 7).

The site healed uneventfully and was ultimately reconstructed with a partial denture. The patient has now been under observation for six months, with serial examinations, chest x-rays and CT scanning, without any evidence of recurrent disease.

**Discussion**

Differential diagnosis is rather complex in this type of tumor and there are various aspects that should be considered. Metastases in the jaws from visceral neoplasms must be ruled out (5, 11) including the invasion of bone by a tumor from adjacent soft tissue or paranasal sinus (14). Squamous cell carcinoma, basal cell carcinoma and primary intra-alveolar epidermoid carcinoma have to be considered; in the latter case it is possible that this tumor may represent simply a less-differentiated, usually non-keratinizing, form of ameloblastic carcinoma, both lesions being derived from odontogenic remnants (5). Kerato-ameloblastoma, a rare variant of ameloblastoma that contains prominent keratinizing cysts, could also distract the pathologist from otherwise clear ameloblastomatous features (5). Acanthomatous ameloblastoma may require differential diagnosis with the benign variant, as in the present case, varying degrees of squamous metaplasia and even keratinization of the stellate-reticulum portion of the tumor islands may be exhibited, however, peripheral palisading is maintained and no cytological features of malignancy are found in the benign form (5, 11).

A squamous odontogenic tumor may also be mistaken for ameloblastic carcinoma (15). It is composed of islands of squamous epithelium that lack stellate-reticulum-like zones and peripheral palisading. In addition, microcystic changes and dystrophic calcifications are occasionally seen in this lesion. However, the epithelium of the squamous odontogenic tumor lacks any cytological evidence of malignancy (5).

An additional possibility in differential diagnosis is that of squamous cell carcinoma arising in the lining of an odontogenic cyst (11, 16). Histologically, however, this tumor tends to more closely resemble oral squamous cell carcinoma than the description of ameloblastic carcinoma (5).

The present case was initially diagnosed as a peripheral ameloblastoma. The first biopsy sampled only a small part of the tumor, probably in the part exhibiting the peripheral epithelial component as compared to the surgical specimen. The cytokeratins (CKs), intermediate filaments that function as epithelial skeletons (17), were evaluated, in particular cytokeratin CAM 5 and 6, which is expressed in squamous epithelial cells, was evaluated immunohistochemically. CKs 5, 7, 8, 13, 14, 17 and 19 have been detected in the human enamel organ and ameloblastoma cells have been reported to react with CKs 5, 8, 13, 14 and 19 (17). The Bcl-2 protein, product of a proto-oncogene and one of the regulators of apoptosis associated with odontogenesis and growth in odontogenic tumors, was also evaluated (18-21). The MIB-1/Ki-67 antigen is a reliable marker of cellular proliferation, normally expressed in proliferative cells through the G1-, S-, G2- and M-phases (22, 23); it has been used to study various types of tumor and cystic lesions (12, 22, 23). Positive expression of bcl-2 was found in the squamous cells and in the odontogenic cells; positive expression of CAM 5 and 6 in the basal epithelial cells and in all the squamous cells was found, but was absent from almost all the ameloblastic cells, and MIB-1/Ki-67 protein expression in the cytoplasm of basal epithelial cells and in the tumor cells was found. Thus immunohistochemistry confirmed a high degree of proliferation, as shown by the positivity of the MIB-1/Ki-67.

With regard to recurrence, numerous instances have been reported, and thus a long follow-up is necessary for these tumors (24-27). For the same reason a wide local excision is the treatment of choice and 2- or 3-cm bony margins have been advocated, which in many cases implies en bloc removal (14, 28). Cervical lymph node dissection should also be considered when there is obvious lymphadenopathy.

Radiotherapy and chemotherapy appear to be of limited value; however, these methods should be considered when there is a locally advanced or metastatic disease that is not amenable to surgical resection (24). Apart from the radiosensitivity of these tumors, which has not been clearly documented, the use of radiotherapy brings the traditional risk of osseous complications, in the form of osteonecrosis and induced sarcoma. Ramadas et al. (23) found cisplatin, adriamycin, and cyclophosphamide of benefit in malignant ameloblastoma metastasizing to the lung. Close-periodic reassessment with a long period of follow-up (at least 10 years) is mandatory.

**Conclusion**

Ameloblastic carcinoma is a rare type of odontogenic tumor that exhibits malignant histological features in primary and secondary tumors. Its histological characterization is difficult, and many differential diagnoses must be excluded. These tumors must be removed with wide margins to avoid local...
recurrence, which occurs frequently after minimal surgical treatment. Neck lymph node involvement has not been clearly documented, and the mechanism of metastatic spread appears to follow a hematogen route. Thus, if there is no evidence of lymphatic metastasis, systematic neck dissection is not recommended. No conclusion is possible concerning the utility of adjuvant therapies such as radiotherapy or chemotherapy, which appear to possess limited value. The prognosis is dominated by the risk of local recurrence, including after a long relapse, and by distant metastases. These generally occur in the lung, but also in the bones and brain. Systematic assessment of the chest through periodic imaging is recommended.

References


