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Ameloblastic carcinoma of the mandible: A case report and literature review

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ABSTRACT

Ameloblastic carcinoma is a rare malignant odontogenic tumor. Here we present a case of malignant transformation of ameloblastoma into ameloblastic carcinoma over a period of eight years. A cystic lesion in the left mandible was initially identified histopathologically as ameloblastoma, and curettage of the lesion was performed. Recurrence occurred 7 years later, and was treated with a second enucleation and curettage of the tumor. The second histopathological diagnosis was also ameloblastoma. One year later the patient presented with a swelling on the left side of the retromolar triangle. An incisional biopsy detected cytological atypia, and the histopathological features met the criteria for diagnosis of ameloblastic carcinoma. Surgical treatment with segmental mandibulectomy and reconstruction with a free vascularized fibula bone graft was performed. A literature review was performed identifying a total of 234 cases of ameloblastic carcinoma reported. The median age of onset was 47 years, with a peak incidence during the third- and sixth decades. A predominance of men was found, with a male-female ratio of 2,21:1. The tumor was more frequently reported in the mandible, with a mandible-to- maxilla ratio of 1,96:1, and the most common tumor site was the posterior mandible. Surgical treatment was the primary treatment modality and was performed in 87,2% of the patients. Recurrence was reported in 22,2% of the patients, and metastasis in 18,8%. The most common sites for metastasis were the lungs, followed by regional lymph nodes and the brain.

1. Background

Ameloblastic carcinoma (AC) is a rare malignant neoplasm arising from odontogenic epithelium. AC may arise *de novo*, from transformation of a long-standing primary benign lesion, or from benign lesions that have undergone several surgical excisions. The clinical features and histopathological characteristics of AC are comparable to those of ameloblastoma [1]. Radiologically, a radiolucent uni- or multilocular lesion with destruction of alveolar bone is typically found, and in some cases focal radiopacity may also be detected [2]. AC combines the histopathological features of ameloblastoma with focal areas of cytological atypia [3]. This report presents a case of AC, which arose from a previously diagnosed ameloblastoma that underwent malignant transformation over a period of 8 years. Clinical and histopathological features are described, and treatment modalities are discussed. Also, a literature review was

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performed, comprising the reported data of AC in the English language literature.

2. Presentation of case

A healthy 36- year old female was referred in May 2019 for assessment of a swelling on the left side of the mandible. Her chief complaint was tenderness in the area and total anesthesia of the inferior alveolar nerve (IAN) after previous surgery. A minor facial asymmetry was found in the mandibular angle. The oral mucosa was intact, but a poorly demarcated swelling was observed. It was mildly tender, hard in consistency and with diffuse margins. She had been treated abroad in 2011 with enucleation of a cystic lesion histologically diagnosed as a follicular type ameloblastoma (Fig. 1). A recurrence had occurred in 2018, and a second enucleation performed. A panoramic radiograph showed a radiolucent lesion on the left posterior alveolar ridge of the mandible (Fig. 2). A 3 x 2,5 cm tumor with resorption and expansion of the lingual cortex extending into the soft tissue was found on CT and MRI. Cervical lymph

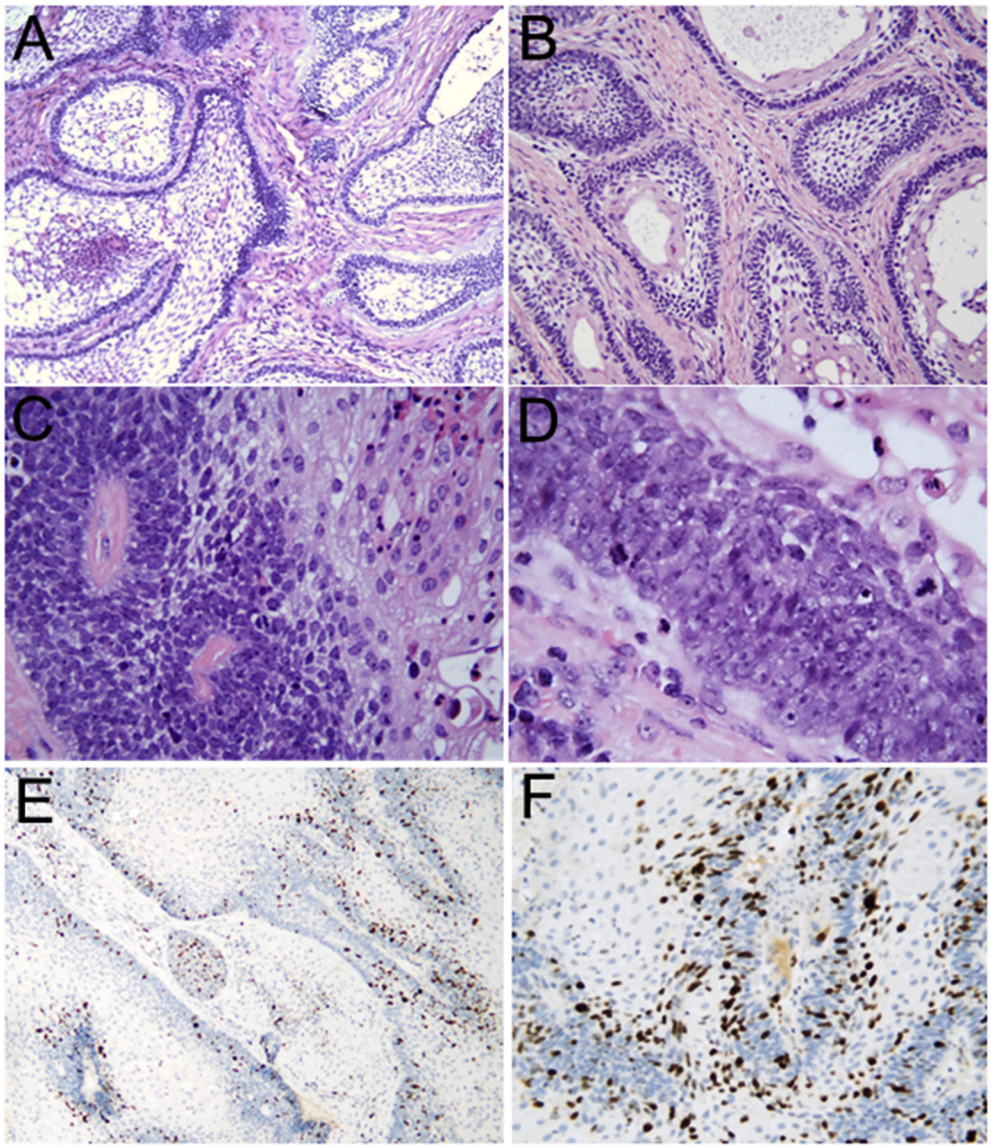

Fig. 1. A) Histopathological examination from the first operation in 2011 showing typical features of ameloblastoma with peripheral palisaded ameloblasts, stellate reticulum and central cystic or acanthomatous changes. B–F) Biopsy prior to resection of tumor in 2019. B) Low magnification shows a tumor comprised of sheets and variably sized islands of ameloblastoma-like appearance. C) and D) Other areas with higher magnification show basal nuclei with a speckled chromatin pattern, marked expansion of the basal compartment and loss of typical stellate reticulum features The basal cells have large and crowded nuclei with speckled chromatin and up to 3 small nucleoli. Several mitoses and scattered abnormal mitoses can be found in focal areas. E) and F) The proliferation marker Ki-67 showed higher proliferation index than normally seen in benign ameloblastomas, mainly limited to the basal compartment.

nodes showed no enlargement or change in size, and no metastatic lesions were found in the lungs or mediastinum. Based on the clinical and radiological findings, a recurrent ameloblastoma was suspected, and an incisional biopsy was performed under local anesthesia. The histopathological examination showed a tumor with poorly defined periphery with sheets and variably sized islands of ameloblastoma-like appearance. Some of the smaller islands had architectural features of benign ameloblastoma. However, the basal nuclei showed a speckled chromatin pattern even in the most highly differentiated areas. The islands retained ameloblastoma-type architecture, but there was a marked expansion of the basal compartment, loss of typical stellate reticulum features and central keratinization. A few islands showed loss of organization with basaloid cells seen centrally. The basal cells had large and very crowded nuclei with speckled chromatin and up to 3 small nucleoli. Mitoses were fairly frequent and occasionally abnormal, and some were found in the stellate reticulum areas. The larger sheets showed central necrosis with peripheral apoptotic degeneration (Fig. 1). The margins were poorly defined with islands showing genuine invasion between the pre-existing collagen bundles and not limited by the periosteum. The proliferation marker Ki-67 showed higher proliferation index than normally seen in benign ameloblastomas, mainly limited to the basal compartment (Fig. 1). A BRAF V600E mutation was detected identical to those seen in benign ameloblastomas. Based on the histopathological findings, the diagnosis of AC was made. Established protocol for surgical treatment of carcinoma of the mandible with segmental resection including the mandibular canal was followed. A segmental mandibulectomy and supraomohyoid lymph node dissection were performed. The tumor was removed with approximately 1 cm margin and the mandible was reconstructed with a free vascularized fibula flap (Fig. 3). The histopathological features of the resected tumor were similar to the incisional biopsy and resection margins were free of tumor cells. Chemotherapy or radiation therapy was not performed. The patient made an uneventful recovery. There were no signs of recurrence 6 months after surgery, and the patient is satisfied with the functional and esthetic outcome (Fig. 4).

3. Literature review

A search in the NCBI database was performed using the keywords: “ameloblastic carcinoma” or “ameloblastic carcinoma treatment”. Publications in English language from 1980 until February 1st, 2020 were included. The majority of the publications were case reports or small case series, and only one review article was identified. Only full-length articles were included. Studies of malignant ameloblastoma were excluded. The search revealed 234 eligible cases of AC from 118 publications. A total of 159 males and 72 female patients were identified, corresponding to a male-female ratio of 2,2:1. The males affected by AC were slightly older than females, having a mean age of 48,6 compared to a mean age of 43,1 in females. The median age of all patients was 47,2 years, ranging from 7 to 90 years, with a peak incidence during the third- and the sixth decades (Table 1). A higher predilection of AC in the mandible was found, accounting for 155 (66,2%) of the cases. In total 79 cases (33,8%) were found in the maxilla, with a mandible-maxilla ratio of 1,96:1. The majority of the lesions (60,3%) developed in the posterior region of the mandible, and no predilection was seen for any sides of the jaws. Recurrence was reported in 52 patients (22,2%), and metastasis in 44 patients (18,8%). The most common sites for metastasis were lung, lymph nodes and brain. Surgery was the most common treatment modality and was performed in 87,2% of the patients. A combination of surgery and radiotherapy was performed in 21,4% of the patients.

4. Discussion

The majority of AC presented arise *de novo*, whereas only few malignant transformations of pre-existing ameloblastomas are described [4–7]. A clear distinction between a primary malignant ameloblastoma and one arising from a benign ameloblastoma is difficult to obtain. For the latter, the entire first lesion needs to be examined without histological signs of carcinoma. In addition, the combination of radiological features and presence for some time could suggest a diagnosis of malignant transformation of benign ameloblastoma. In the present case, we cannot exclude that earlier lesions could have displayed focal areas with features of AC, since a retrospective re-analysis of the tissue from abroad was not possible. Distinguishing AC from benign ameloblastomas can also be

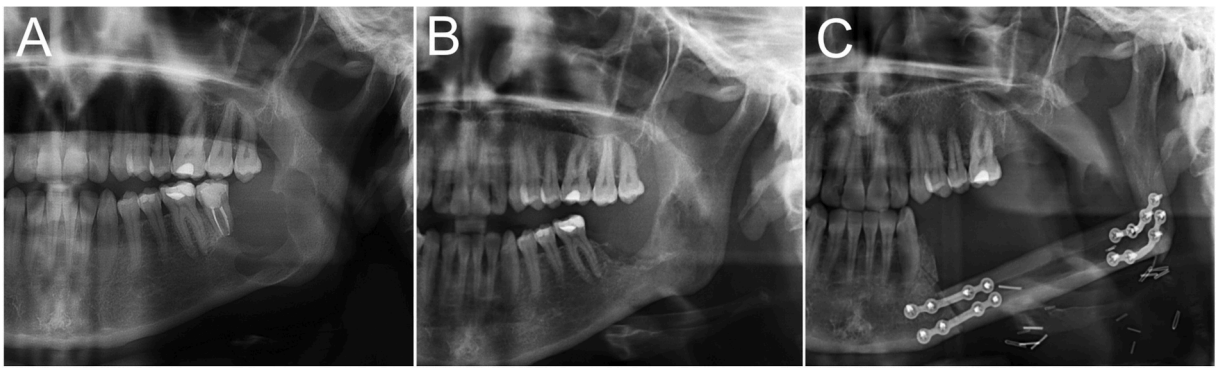

Fig. 2. Panoramic radiographs from A) 2018 before the second enucleation showing a multilocular radiolucency in the left angle of the mandible. B) 2019 before resection. Some bone ingrowth is seen despite the growing soft tissue mass. C) After resection and reconstruction with a free vascularized fibula flap.

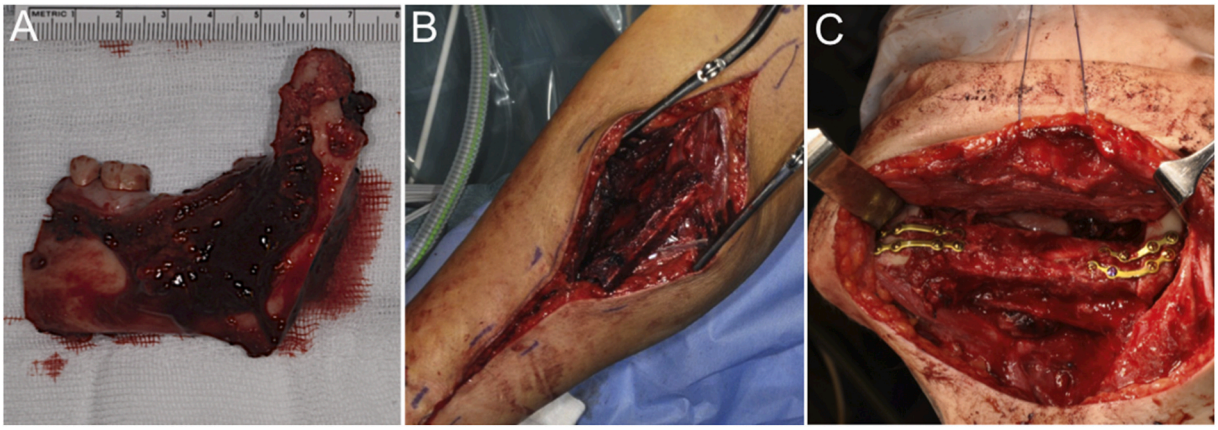

Fig. 3. A) Surgical specimen following segmental mandibulectomy. B) Donor site of the free vascularized fibula flap after preparation of the bone segment. C) After anastomosis and fixation to the mandible.

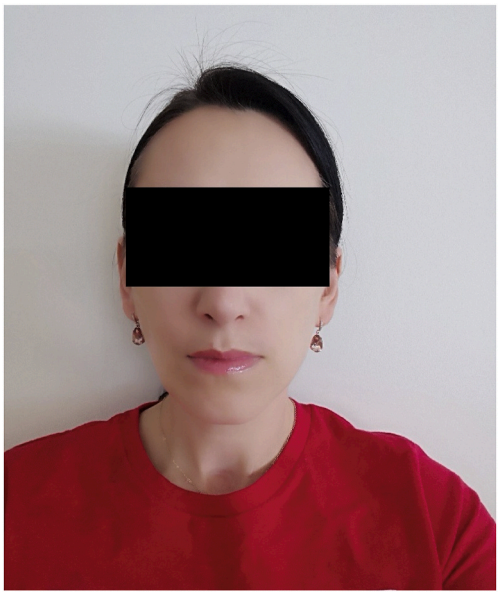

Fig. 4. Photo of the patient after treatment. Facial symmetry was maintained with intact facial nerve function.

Table 1
Age and localization of ameloblastic carcinoma.

	Age distribution					Localization		
	Female	Male	No data	Total		Mandible	Maxilla	Total
0–9yrs	2	0		2	Right side	40 (17,1%)	19 (8,1%)	59 (25,2%)
10–19yrs	4	13		17	Left side	42 (17,9%)	31 (13,2%)	73 (31,1%)
20–29yrs	17	21		38	Anterior	14 (5,9%)	6 (2,6%)	20 (8,5%)
30–39 yrs	11	27		38	No data	59 (25,2%)	23 (9,8%)	82 (35%)
40–49 yrs	10	17		27	Total	155 (66,2%)	79 (33,8%)	234 (100%)
50–59 yrs	6	17	1	24				
60–69 yrs	13	34		47				
70–79 yrs	5	22	2	29				
80–89 yrs	4	7		11				
90–99 yrs	0	1		1				
Total	72	159	3	234				
Average age (yrs)	43,1	48,6		47,2				

challenging. Histologically, benign and malignant features can present in the same tumor, and AC may show only focal areas of malignant morphology [8]. The presence of sheets, islands or trabeculae of epithelium, minimal presence or absence of stellate reticulum-like areas, epithelial cells with little or no differentiation towards the columnar cells, should alert the pathologist of a potential malignant transformation. Furthermore, cellular and nuclear pleomorphism, hyperchromatism, basilar hyperplasia, increased or abnormal mitotic activity, central keratinization, necrosis and presence of many clear cells can justify the diagnosis of AC [6–8]. Borderline lesions may however not be confidently diagnosed histologically, and its correlation to clinical and radiological findings is therefore important for the final diagnosis.

Because of the rarity of the disease, evidence-based treatment guidelines are not established, but protocols for other head and neck carcinomas are commonly used. Based on the available information, surgical treatment with segmental resection and wide surgical margins is the safest modality to ensure recurrence-free survival [3–5,9,10]. Maxillary ACs may in particular need radical treatment because of the tendency to invade adjacent structures. Cervical lymph node dissection is not routinely performed without evidence of metastatic involvement [4–6]. AC reported to have a higher proliferation index may be more radiosensitive than benign ameloblastomas, but based on available data, adjuvant radiation and/or chemotherapy appear to have limited effect. In cases where complete resection is impossible or in patients where surgery is contraindicated, this treatment modality may however be considered [5,11]. Recurrence of ameloblastoma after technically competent curettage suggests infiltration of medullary spaces. In order to eradicate the benign lesion, a wider resection with 1 cm margins should therefore be considered in such cases. In the present case, adequate treatment of the initial ameloblastomas might have prevented development of the malignant neoplasm.

5. Conclusions

Reported literature on ameloblastic carcinoma is mostly limited to case series and case reports. It is more frequently found in male patients, with a peak incidence during the third- and sixth decades. The most common tumor site is the posterior mandible. The histopathological diagnosis can be challenging, as benign and malignant features can be present in the same tumor. Surgical treatment with wide margins is performed in majority of cases, and is rarely combined with radiation therapy. The most common sites for metastasis are the lungs, followed by regional lymph nodes and the brain.

Credit author statement

Mindaugas Brukas: Conceptualization, Writing - original draft, Writing - review & editing. **Torbjørn Ø. Pedersen:** Visualization, Writing - original draft, Writing - review & editing, Supervision, Project administration. **Stein Lybak:** Visualization, Writing - review & editing. **Kathrine Skarstein:** Visualization, Writing - review & editing. **Sigbjørn Løes:** Conceptualization, Writing - review & editing, Supervision, Project administration.

Declaration of competing interest

None.

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