CASE REPORT

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Malignant ameloblastoma metastasis to the neck – radiological and pathohistological dilemma

Metastaza malignog ameloblastoma na vratu – radiološka i patohistološka dilema

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Abstract

Introduction. Ameloblastomas are odontogenic epithelial, locally invasive tumors of slow growth and mostly of benign behavior. Their frequency is low (they account for 1% of all head and neck tumors and about 11% of tumors of dental origin). Malignant variations of ameloblastoma are malignant ameloblastoma and ameloblastic carcinoma. They constitute less than 1% of all ameloblastomas. We presented a case of malignant ameloblastoma of the mandible with neck metastasis. **Case report.** A patient, aged 72, presented with the following symptoms: pain in the lower jaw, swelling in the left submandibular area and difficult mouth opening. The patient was admitted to the Department of Oral and Maxillofacial Surgery, Clinical Center of Montenegro, two months after he had noticed the symptoms. Panoramic radiography (OPG) showed that both jaws were partially toothless with terminal stage of periodontitis of the remaining teeth. Also, OPG showed sharply limited semicircular defect in the retromolar region and along the front edge of the mandible rami. Conventional histopathologic examination of the neck masses showed malignant ameloblastoma which contained central fields of squamous differentiation. Immunoreactivity of several markers was determined using immunohistochemical analyses. After these diagnostic methods a definite histopathology diagnosis was made: *Ameloblastoma metastaticum in textus fibroadiposus regio colli (typus acanthomatosus)*. **Conclusion.** It is not possible to distinguish conventional, *ie* intraosseous, ameloblastoma from malignant ameloblastoma according to histopathologic features. It is necessary to pay special attention, especially in elderly patients, and to carry out further clinical, radiological and pathohistological diagnostic procedures, such as immunohistochemical analysis. A timely and correct diagnosis and treatment of malignant ameloblastoma require a multidisciplinary approach.

Key words:
ameloblastoma; neoplasm metastasis; diagnosis, differential; immunohistochemistry.

Apstrakt

Uvod. Ameloblastomi su odontogeni epitelni tumori, lokalno invazivni, sporog rasta, i u većini slučajeva pokazuju benigno ponašanje. Veoma su rijetki. Njihova učestalost je 1% u grupi tumora glave i vrata, kao i 11% kod tumora koji potiču od zubnih tkiva. Maligne varijante ameloblastoma su maligni ameloblastom i ameloblastički karcinom. Oni čine manje od 1% svih ameloblastoma. U radu je prikazan bolesnik sa malignim ameloblastomom donje vilice sa metastazom na vratu. **Prikaz bolesnika.** Prve subjektivne tegobe bolesnika, starog 72 godine, manifestovale su se kao bolovi u predelu donje vilice, otok u podviličnom predelu sa leve strane i otežano otvaranje usta. Bolesnik je primljen u Odeljenje oralne i maksilofacijalne hirurgije Kliničkog centra Crne Gore dva meseca nakon što je primetio prve tegobe. Ortopantomografski snimak pokazao je suptotalnu bezubost obeju vilica sa terminalnim stadijumom parodontopatije na preostalim zubima. U retromolarnoj regiji i duž prednje ivice ramusa donje vilice, uočen je jasno ograničen polukružni defekt. Biopsija promene na vratu pokazala je metastazu malignog ameloblastoma, sa prisutnim centralnim poljima skvamozne diferencijacije. Imunohistohemijskom analizom određivana je imunoreaktivnost više markera. Nakon ovih dijagnostičkih metoda postavljena je definitivna patohistološka dijagnoza: *Ameloblastoma metastaticum in textus fibroadiposus regio colli (typus acanthomatosus)*. **Zaključak.** Na osnovu histopatološkog nalaza nije moguće razlikovati konvencionalni, tj. intraosealni, ameloblastom od malignog ameloblastoma. Zbog toga je potrebno obratiti posebnu pažnju, naročito kod bolesnika starijeg životnog doba, i sprovesti sve dodatne kliničke, radiološke i histopatološke, ali i imunohistohemijske dijagnostičke procedure. Za postavljanje blagovremene i tačne dijagnoze, kao i sprovođenje adekvatnog terapijskog tretmana malignog ameloblastoma, neophodan je multidisciplinarni pristup.

Ključne reči:
ameloblastom; neoplazme, metastaze; dijagnoza, diferencijalna; imunohistohemija.

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Introduction

Odontogenic tumors are mostly benign lesions (97% of cases) [1], which are predominantly developed in the mandible [1,2].

Ameloblastoma is an odontogenic epithelial tumor. It derives from odontogenic epithelium of *lamina dentalis* (from which during embryogenesis enamel organ arises), or from odontogenic cyst epithelium, or epithelial rests of Malassez, and from the basal cells of oral mucous membrane or enamel organ [3].

Ameloblastomas are locally invasive tumors of slow growth and in most cases they have a benign behavior. Despite their low frequency (they account for 1% of all head and neck tumors and about 11% of tumors of dental origin) [4], they are a subject of continuous interest because of their diversity of microscopic – histopathologic features, as well as difficulties in radical surgical therapy. The most frequent localization of the tumor is the lower molar region [5], and it rarely occurs in the upper jaw or maxillary sinus [4]. There are three clinical pathologic types of ameloblastoma: a conventional solid or multicystic (present in about 85% of cases), unicystic (present in about 15%) and peripheral ameloblastoma (extraosseous) – present in about 1% of cases.

Malignant variations of ameloblastoma represent a separate entity because of their clinical characteristics and pathohistologic features.

According to the World Health Organization (WHO) histological classification of odontogenic tumors published in 2005 there are: metastasizing (malignant) ameloblastoma; ameloblastic carcinoma – primary type; ameloblastic carcinoma – secondary type (dedifferentiated), intraosseous; ameloblastic carcinoma – secondary type (dedifferentiated) [6]. Peripheral malignant ameloblastoma is a neoplasm that shows histopathologic features of ameloblastoma in the primary tumor and metastatic deposits (cell signs of malignancy are absent). They constitute less than 1% of all ameloblastomas and are characterized by the aggressive growth and metastasis ability. It is not possible to distinguish conventional (intraosseous) ameloblastoma from malignant ameloblastoma, based on histopathologic findings. The diagnosis of malignant ameloblastoma is usually made *post festum* and based on the findings of metastasis of the same microscopic characteristics as the intraosseous ameloblastoma. Because of that reason, the clinical (not histological) finding could be of great importance for diagnosis of metastasizing ameloblastoma. The appearance of metastasis is a paradox considering that intraosseous conventional ameloblastoma is characterized by benign microscopic features.

Ameloblastic carcinoma is an ameloblastoma that demonstrates all the classic features of cancer including cytological atypia, recurrence and metastatic spread into the lymph nodes and the lungs [7].

A meloblastoma may be present radiographically as unilocular (often even lobular in appearance) or multilocular [8]. There are, however, several radiographic features which make one suspicious of the diagnosis. As it begins within the jaw and grows slowly, it expands the lingual cortex. Radiographically, this translates to a radiolucency which when unilocular is difficult to distinguish from a simple odontogenic cyst. Nearly one-half of all ameloblastomas exhibit an overlapping multilocular soap-bubble or honeycomb appearance. The margins of the defect are scalloped and well-defined in the majority of cases. When the tumor occurs adjacent to a tooth, the root of the tooth is typically eroded whereas displacement of teeth is more common in association with simple dentigerous cysts. The differential diagnosis of a multilocular radiolucency in the jaw includes cherubism, giant cell granuloma, odontogenic myxoma, aneurysmal bone cysts, odontogenic keratocysts, and others, and often the diagnosis is not made until the patient undergoes diagnostic biopsy.

Microscopic findings of conventional or classic intraosseous ameloblastoma show numerous variations, which are not associated with the biological behavior of tumors. The most common forms are follicular and plexiform ameloblastoma and much less frequent acanthomatous variation [9,10]. Microscopically, ameloblastoma is composed of nests, strands, and cords of ameloblastic epithelium, all separated by relatively small amounts of fibrous connective tissue stroma. In the follicular form, the epithelial islands contain central portions that are composed of a loose network resembling that of the enamel organ. The epithelium at the periphery is composed of tall columnar cells with polarized nuclei. In the plexiform type, the epithelium is arranged in anastomosing strands and cords. Epithelial cells are closely apposed and with basaloid or cuboidal appearance [3].

Case report

The patient, aged 72, was treated for 10 years in Neuropsychiatry Department due to dementia and Alzheimer's disease. The disease gradually progressed, and it was manifested by obliviousness to daily things. At the time of first examination by the dentist the patient was completely disoriented, could not recognize his family members, and was occasionally aggressive. Cooperation with the patient was extremely difficult.

The patient noticed the first symptoms, such as pain in the lower jaw, swelling in the left submandibular area and difficulty opening mouth, two months before the visit to the dentist. The dentist prescribed him an antibiotic therapy for 10 days because of the limited mouth opening (first degree trismus – mouth opening about 25 mm).

As there was no improvement after the implementation of oral therapy, the antibiotic therapy was given intravenously (*iv*) for a period of 10 days. Ten days after the patient stopped using antibiotics, the patient was unable to open the mouth (third degree trismus).

After a month of antibiotic therapy prescribed by his dentist the patient was admitted to the Department of Oral and Maxillofacial Surgery, Clinical Center of Montenegro. Heteroanamnesis revealed that the patient had lower left wisdom tooth extracted 3 years ago. This was confirmed by the patient's daughter. Clinical examination established changes in the upper neck area of approximately $30 \times 30 \times 25$ mm in size, of irregular shape, clearly limited, that erected the surrounding

skin by about 10 mm. Palpation revealed painless, hard elastic, mobile lesion that mostly looked like conglomerate of enlarged lymph nodes.

Panoramic radiography (OPG) showed that both jaws were partially toothless with terminal stage of periodontitis of the remaining teeth (Figure 1). Also, OPG showed sharply limited semicircular radiolucency of the osseous tissue in the retromolar region and along the front edge of the mandible rami. This radiolucency extended up till almost half of the front edge of the ramus and its posterior wall was very close to the mandibular channel. The dimension of bone lesion was approximately 25 × 25 mm. The defect was relatively homogenous and it spreaded over the distal root of the second molar. From the mesial side of that tooth there was also a defect of alveolar ridge, which reached half of the length of a mesial root and probably corresponded to advanced stages of periodontitis (less probable connection with retromolar defect).

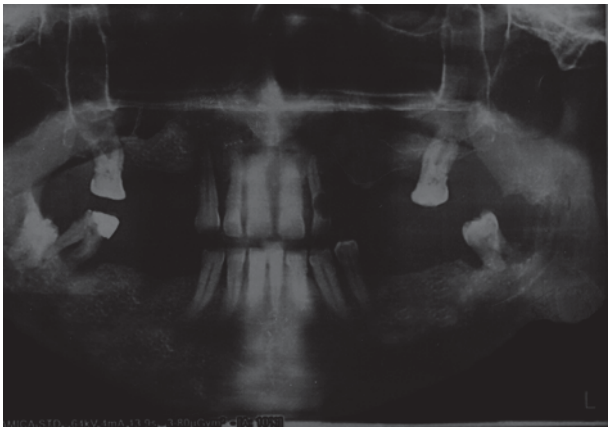


Fig. 1 – Radiological appearance of malignant ameloblastoma on the left side of the mandible

Computerized tomography (CT) examination of the neck region (made in 5 mm axial sections, native and postcontrast series) revealed in the left submandibular region, below the mandibular angle, a differentiated oval tumor formation, predominantly soft tissue density, relatively clearly designated, 38 × 35 mm in size, that did not intensify after *iv* application of contrast (Figure 2). CT also showed two to three lymphatic nodes, which were located anteriorly – medially and distally to the formation described before, up to 15 mm and 23 mm in size.

Bioptic material was sent to the Center of Pathology, Clinical Center of Montenegro. Biopsy (conventional histopathological finding) of the neck masses showed malignant ameloblastoma that contained central fields of squamous differentiation (Figure 3). After histomorphologic analysis of the

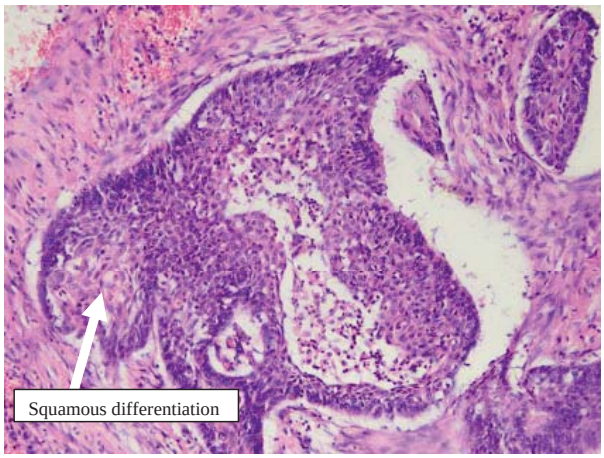


Fig. 3 – *Ameloblastoma metastaticum in textus fibroadiposus regio colli – typus acanthomatosus*
(H/E – hematoxylin – eosine, ×100)
The arrow shows fields of squamous differentiation with keratin formation in central parts of tumor tissue.

tumor tissue in the standard hematoxylin-eosine (H&E) products, the immunohistochemical analysis was done. Using this method, immunoreactivity of several markers was analyzed: epithelial membrane antigen (EMA, Figure 4a), pancytokeratin (PCK, Figure 4b) and vimentin (Figure 4c). The following results were obtained: EMA and PCK showed focal, medium immunohistochemical positivity, while vimentin gave a negative result. After these diagnostic methods definite histopathology diagnosis was made: *Ameloblastoma metastaticum in textus fibroadiposus regio colli (typus acanthomatosus*).

The patient was presented in the consilium of medical doctors for malignant tumors of the head and neck of the Clinical Center of Montenegro. Having in mind general

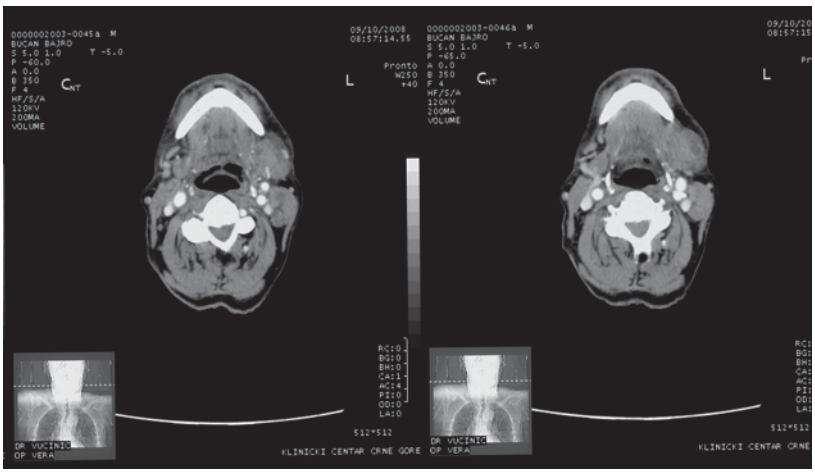
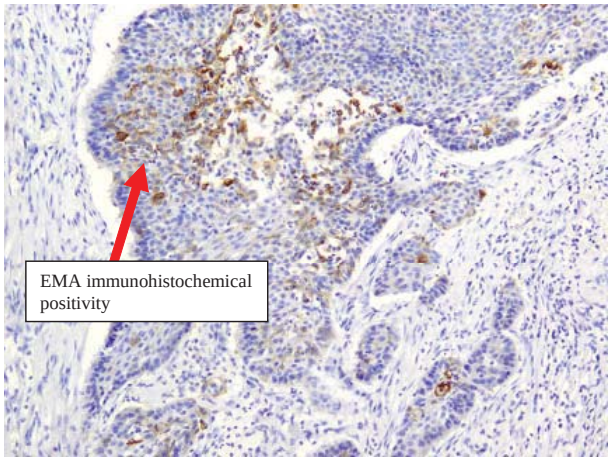
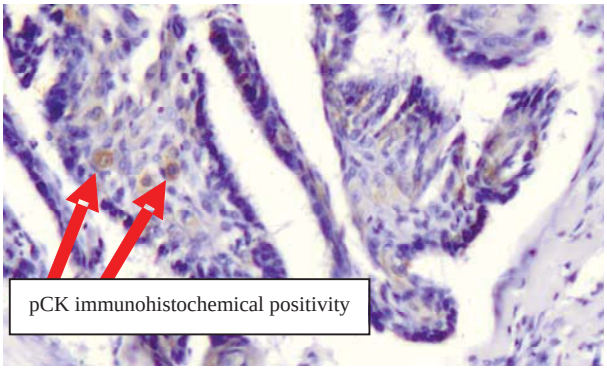


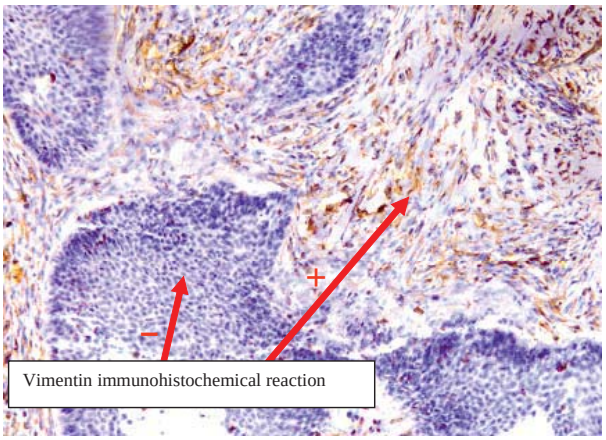
Fig. 2 – Computerized tomography of the neck shows oval tumor formation in the left submandibular region



a) The arrow indicates tumor cells with focal, middle immunohistochemical positivity (epithelial membrane antigen, ×100).



b) The arrow indicates tumor cells with focal, middle immunohistochemical positivity (pancytokeratin, ×200)



c) The arrow indicates tumor cells with focal, middle immunohistochemical positivity (vimentin, ×100)

Fig. 4 – *Ameloblastoma metastaticum in textus fibroadiposus regio colli – typus acanthomatosus*

health status and the primary illness of the patient, it was decided that symptomatic therapy should be administered. Surgery was not possible in this case.

Discussion

Malignant ameloblastomas occur in patients aged between 4 and 75 years [11]. The etiology of ameloblastoma is unknown. Some authors consider that the lesion arises in association with the difficult eruption of a third molar, or in association with previous infection or cyst, while the others suggest that trauma and inflammation are common etiologic agents [3].

Radiographic image of ameloblastoma in this case was atypical, and therefore the diagnosis of ameloblastoma could not be made by radiography alone.

In this case, the acanthomatous variation of malignant ameloblastoma was represented, showing strong squamous metaplasia (Figure 4). There have been some cases with microscopic features of ameloblastoma represented by the three previous types of ameloblastoma [12].

Only recently malignant potential for ameloblastoma has been described [13, 14]. Metastatic deposits of ameloblastomas are frequently developed in the lungs but have also been reported at other sites [15–17]. Verneuil et al. [13] have described malignant ameloblastoma of the mandible with metastasis in submandibular region.

Ciment et al. [14] described metastasis of malignant ameloblastoma in the lung 29 years after the excision of the primary tumor. Hayakawa et al. [18] described a case of metastatic ameloblastic carcinoma in both kidneys while Hayashi et al. [19] described the case of mandibular ameloblastoma metastasis to the orbit.

Some authors have described metastasis of malignant ameloblastoma to the lungs seven years after removal of the primary tumor in the lower jaw [20] and that metastatic ameloblastoma in the region of the lung and pleura responded well to hemiotherapy [21].

Histologically, ameloblastomas that may metastasize cannot always be differentiated from the more classic benign ameloblastoma. It appears that inadequate surgical resection and a long duration of the tumor have a significant relationship with metastatic disease appearance [3].

Conclusion

Considering that it is not possible to distinguish conventional, *ie* intraosseous ameloblastoma from malignant ameloblastoma, according to the histopathologic features it is necessary to pay attention, especially to elderly patients, and carry out all clinical, radiological and pathohistologic procedures including immunohistochemical ones. Complete radical excision of the primary tumor with jaw resection and radical neck dissection is recommended as the method of choice in the surgical treatment of this disease. Regular postoperative clinical control should certainly be implemented as a form of local control and disease prevention. A timely and correct diagnosis and treatment of malignant ameloblastoma require a multidisciplinary approach.

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