

MINOR SALIVARY GLAND MUCINOUS ADENOCARCINOMA OF BUCCAL MUCOSA – CASE REPORT AND REVIEW OF THE LITERATURE

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Mucinous adenocarcinoma (MAC) is commonly found in the gastrointestinal tract but head and neck localisations are very rare. This article presents the case of a 67-year-old patient suffering from a minor salivary gland MAC of the left buccal mucosa, who was treated in the Department of Cranio-Maxillofacial Surgery in Krakow due to multiple recurrences of the tumour. The results of immunohistochemical staining, the course of surgical treatment and follow-up, as well as a review of literature are also discussed.

Key words: mucinous adenocarcinoma, minor salivary glands, immunohistochemistry, radiography.

Introduction

Mucinous adenocarcinoma (MAC) is most frequently observed in the digestive organs. The most common localisation is the large intestine (colon), and it is estimated that MAC constitutes 10-20% of colorectal cancers, followed by the pancreas, ovary, lung, prostate, and breast [1]. The primary head and neck localisation of MAC is very rare and accounts for about 3% of salivary gland tumours. Salivary gland MACs are characterised by high aggressiveness due to a high rate of local recurrences and nodal metastasis [1-3].

The tumour is composed of large extracellular mucin pools and irregular-shaped neoplastic epithelial cells surrounded by numerous cystic cavities, separated by fibrous strands. The cancer cells have clear cytoplasm and small, round, darkly-stained nuclei. The tumour cells form nests embedded in the extracellular mucin pools [3-7]. According to some authors the histological features are so characteristic that differential diagnosis from other malignant salivary gland tumours is straightforward [5]. On the other hand, there are au-

thors who regard MAC's recognition criteria as controversial and inconclusive [3, 6, 8]. According to the WHO, the microscopic image is dominated by small foci of cancer cells or even single cells surrounded by large areas of extracellular mucin separated by connective fibrous strands. In addition, at least half of the tumour cells should produce mucus [8]. Histologically, MAC may be confusingly similar to the mucinous eccrine carcinoma of the skin, mucinous carcinoma of the breast and colloid carcinoma of the bowel [7]. An important feature of MAC are mucus-producing cells which show positive staining for mucicarmine and Alcian blue. However, these cells are also characteristic for other salivary gland tumours; hence immunohistochemical (IHC) staining is helpful in differential diagnosis. Typical for MAC is a strongly positive reaction for cytokeratins (CK) AE1/AE3,7, intermediate or strong reaction for CK 8, 18, 19, positive reaction for epithelial membrane antigen (EMA), vimentin, carcinoembryonic antigen (CEA), and varied reaction with α -SMA (smooth muscle actin), α -amylase and calcitonin. Cytokeratins, vimentin, S-100 protein, and α -SMA pos-

itive staining is characteristic for most salivary gland tumours [3, 4, 6]. Some authors believe that the positive reaction for neuron specific enolase (NSE), calcitonin and somatostatin may be the evidence of neuroendocrine differentiation, but the exact significance of this expression is unknown [8]. Primary minor salivary gland MAC requires exclusion of metastatic nature of the tumour. An important feature of salivary gland MACs is a clear difference in the number of chromosomal aberrations in comparison with MAC of digestive organs [1].

Case report

A 67-year-old patient reported to the Outpatient Unit of the Department of Cranio-Maxillofacial Surgery due to a large tumour involving the left half of the face. The lesion had been observed by the patient for about 12 years, originally removed as an epidermal cyst of the left cheek in the regional hospital. Three years later a recurrent tumour in the postoperative scar was removed. The histological examination revealed gelatinous adenocarcinoma, most likely arising from a minor salivary gland of the oral mucosa; the lesion was excised without adequate margins. The patient was consulted in the Department of Oncology but due to the radioresistance of the tumour he was disqualified from

adjuvant radiotherapy and was admitted to our department in order to extend the surgical resection. In 1997 the excision of the tumour of the left infraorbital area with resection of the underlying bone was performed; the defect was reconstructed by the frontal flap. The margins of resection were positive; thus an additional extended excision of the postoperative scar was carried out. This time there were no signs of the tumour in the histopathological examination. In 1999 the next excision of the local recurrence was carried out, and the histological examination indicated radical excision. In 2007 the patient reported again to our department with the suspicion of local recurrence in the left cheek but did not consent to the proposed surgery and avoided follow-up examination until 2012, when the patient reappeared, presenting an extensive tumour involving the whole left half of the face infiltrating the orbit, infraorbital area, left cheek as well as masseteric area and submandibular region on the left side (Fig. 1, 2). The range of the tumour was confirmed in CT of the facial part of the skull (Fig. 3, 4). Diagnostic biopsy was performed. During collection of the diagnostic material, a jelly-like consistency of the tumour could be observed with an abundant outflow of mucus. The results of basic blood tests revealed no abnormalities. The ultrasound examination of the abdomen and



Fig. 1. The patient with minor salivary gland MAC of the buccal mucosa infiltrating the left half of the face

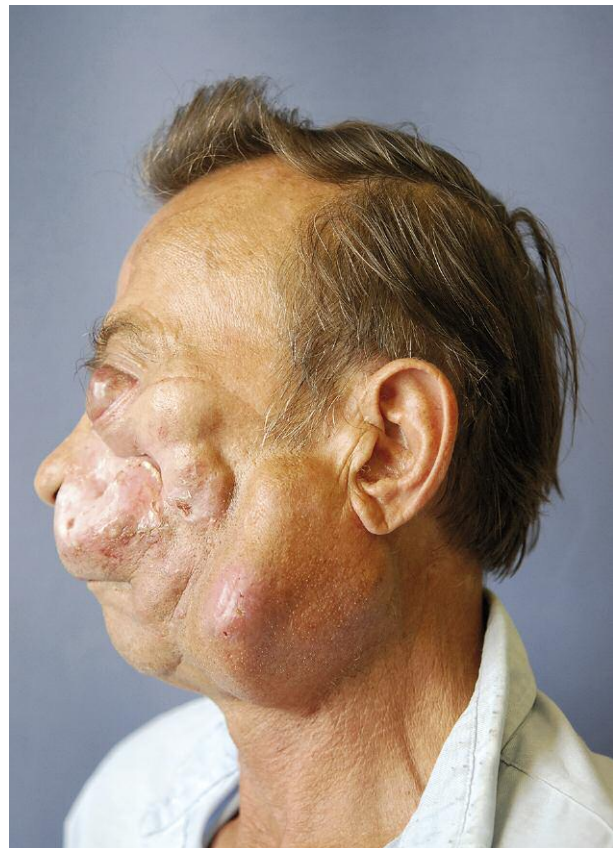


Fig. 2. The same patient – lateral view

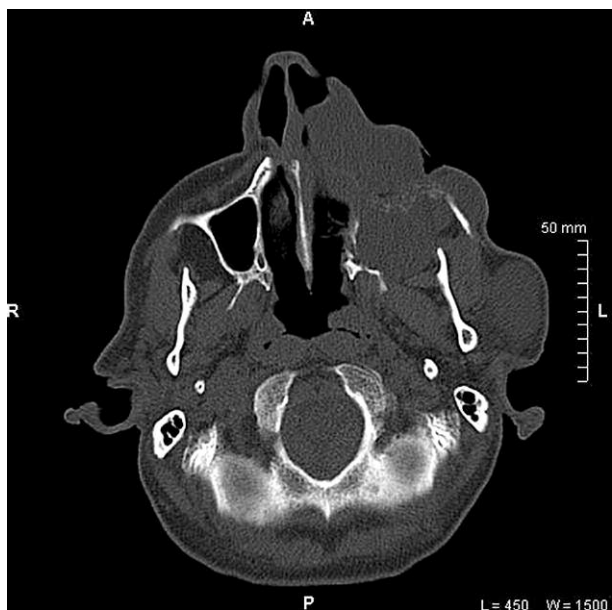


Fig. 3. The same patient – CT scan showing extension of the tumour (horizontal view)

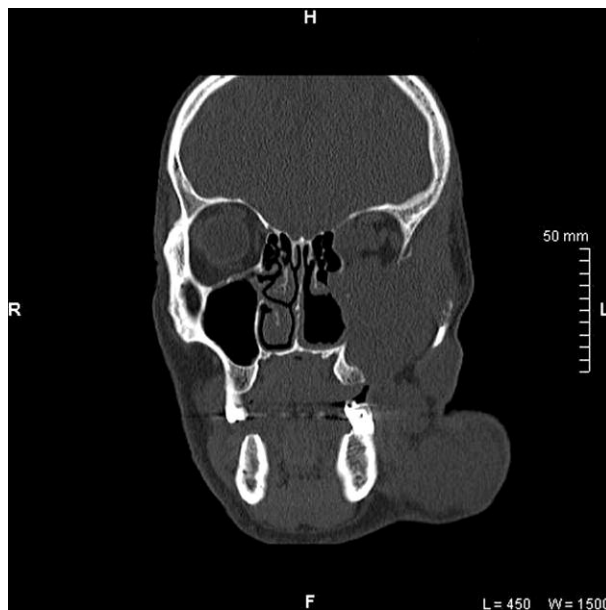


Fig. 4. The same patient – CT scan showing extension of the tumour (frontal view)

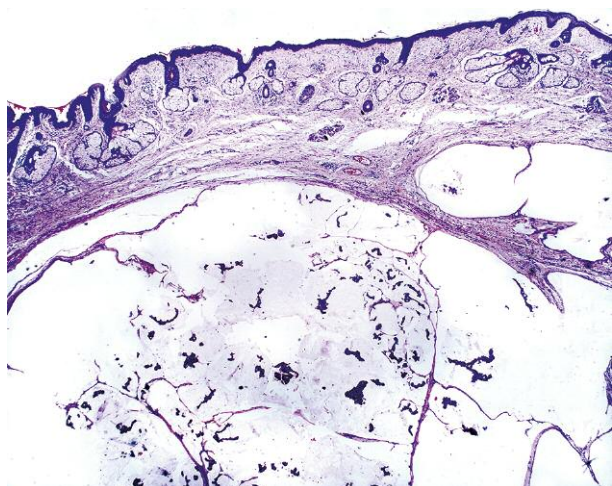


Fig. 5. MAC nests within dermis. HE staining, magnification 25×

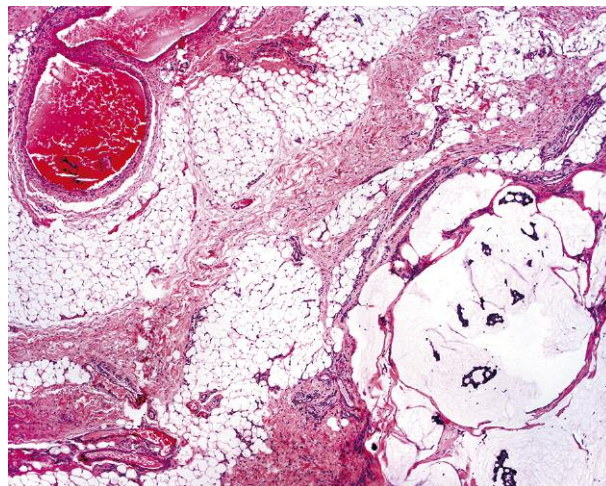


Fig. 6. MAC cells in deep subcutaneous fat tissue. HE staining, magnification 50×

X-ray image of the chest revealed no distant metastases. The histological result of the biopsy of the tumour of the left cheek revealed recurrent mucinous adenocarcinoma G1 with cancer cells of medium size, with a slightly basophilic cytoplasm and oval nuclei. The cancer cells were arranged in small concentrations and patches embedded in mucus, divided into small cavities (Fig. 5, 6). The cells presented the following pattern of IHC reactivity: CK: AE1/AE3, CK19 positive reactions in the cancer cells; in contrast, CK5/6, CK5/6/18, and SMA were negative. Histochemical reactions – PAS, Alcian blue, mucicarmine – were positive in the cancer stroma (Fig. 7, 8). The tumour originated from a small salivary gland. Due to the severity and advancement of the disease the patient was dis-

qualified from surgical treatment, reconsulted in the Department of Oncology and qualified for palliative chemotherapy.

Discussion

As a rare tumour, MAC causes difficulties in diagnosis [3, 5, 6, 8]. Clinical symptoms of the head and neck MAC are uncharacteristic and diagnosis is based on the histopathological and immunohistochemical examination. In the available literature (PubMed 1973-2012) we have found 21 published cases of MAC arising from minor salivary glands localised in the palate (9 cases), buccal mucosa (4 cases), floor of the mouth (3 cases), lips (3 cases) and tongue (2 cases) [3, 6, 7, 9].

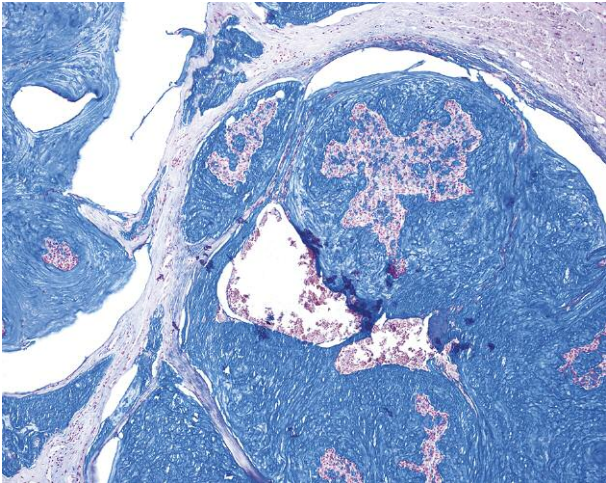


Fig. 7. MAC cells embedded in mucus – in Alcian blue staining, magnification 50×

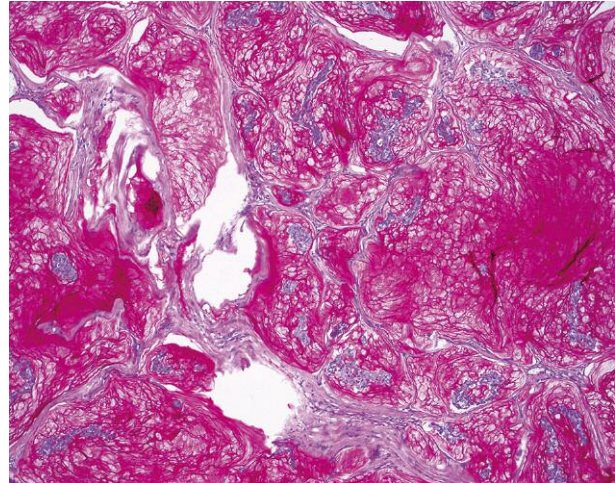


Fig. 8. PAS staining (mucus in pink, cell structures of the cancer in blue), magnification 100×

Table I. Reported cases of MAC arising from minor salivary glands

REFERENCES	LOCAL APPEARANCE	AGE	SEX	LOCALISATION	CERVICAL LYMPH NODE METASTASIS	TREATMENT	FOLLOW-UP
Shumway	greyish tumour	72	male	palate	no	excision + RT	8 months
Notani	ulcerated tumour	64	male	palate	yes	RT + maxillectomy + ND	6 months
Gao	ulcerated tumour	50	male	palate	yes	not mentioned	not mentioned
Gao	ulcerated tumour	51	male	palate	yes	not mentioned	not mentioned
Gao	exophytic tumour	58	female	palate	no	not mentioned	not mentioned
Gao	ulcerated tumour	48	female	palate	yes	not mentioned	not mentioned
Gao	tumour	70	male	floor of the mouth	not mentioned	not mentioned	10 months
Mano	ulcerated tumour	70	male	palate	yes	excision+ ND+ chemotherapy	cervical lymph node metastasis after 9 months, cervical skin metastasis after 20 months
Seoane	exophytic fibroma-like tumour	47	male	palate	no	excision	not mentioned
Aydin	tumour	80	male	lip	not mentioned	excision	6 months
Uchida	tumour	65	male	ventral part of the tongue	no	glossectomy	6 years
Ide	tumour 1 cm	76	female	lower lip	no	excision	distant metastasis after 6 years
Ide	tumour 1.4 cm	82	female	upper lip	no	excision	local and nodal recurrence after 3 years
Barbosa	tumour	52	male	floor of the mouth	no	RTGTH + excision + ND	11 months
Current case	primarily tumour of the cheek	67 (43)	male	cheek	yes	multiple excision	24 years

RT – radiotherapy, NP – neck dissection

The data of 13 patients (reported in English-language literature only) are presented in Table I. In the oral cavity MAC appears as an exophytic, painless tumour of various morphology which clinically may imitate adenoma, fibroma or pyogenic granuloma. MAC of the floor of the mouth resembles calculus of the salivary duct. In differential diagnosis all neoplasms with cells producing mucus should be taken into consideration, e.g. mucoepidermoid carcinoma, mucinous cystadenocarcinoma, mucin-rich salivary duct carcinoma and signet-ring cell adenocarcinoma. An analysis of the reported cases of MAC arising from minor salivary glands revealed that the disease was characteristic for older adults (average age 57 years) with male to female ratio 2 : 1. Cervical lymph node involvement at the time of initial diagnosis of MAC was observed in 12 patients (57.1%).

Major salivary gland MAC was reported in 9 to 14 patients (some cases might be doubled). In 5 cases the primary tumour was localised in the submandibular gland, in 3 to 8 cases in the parotid gland and in 1 in the sublingual gland. The data concerning the frequency of MAC occurrence in minor and major salivary glands are ambiguous and indicate predominance of MAC arising from minor salivary glands (2 : 1) [3-8]. Other atypical localisations of MAC include the nasal cavity, paranasal sinuses and one case of a tumour of the mandibular ramus [8].

In the currently reported case, we believe that the tumour arising from the minor salivary gland of the buccal mucosa was initially misdiagnosed as an epidermal cyst. In our patient immunohistochemical staining revealed positive reaction for CK AE1/AE3 as well as CK19, and negative for CK5/6, CK5/6/18 and SMA. Also positive staining for PAS, Alcian blue and mucicarmine was obtained in mucin stroma of the cancer. These findings correspond with the results presented by other authors [4, 5, 7, 8].

In commonly observed cases of MAC of the digestive organs well-established algorithms of therapy are available. In the treatment of patients in stage I surgery is the method of choice, in stages II and III surgery combined with chemotherapy, whereas in stage IV surgery combined with chemo/radiotherapy is indicated [10-13]. Based on the current literature, we conclude that the best treatment modality in patients with MAC of the head and neck region is surgery, comprising wide excision of the tumour with concomitant neck dissection. Some authors stress the necessity of adjuvant radiotherapy in these patients. As limited clinical data are not sufficient for establishing clear indications for chemotherapy, in patients with head and neck MAC, the decision should be taken after an analysis of each individual case [3, 4, 6, 7].

Conclusions

In the cases reported so far, the aggressive character of salivary gland MAC is proved by a high rate of

cervical lymph node metastases (about 60%) present at the initial diagnosis of the tumour as well as a high rate of local recurrence. Such features of the tumour as well as its radioresistance suggest that extensive excision combined with neck dissection is the optimal treatment modality in patients with MAC of the head and neck region. We can hypothesize that in the presented patient exceptionally long follow-up might have been related to unique different chromosomal aberrations in the cancer cells. Appropriate immunohistochemical profiling is mandatory for the proper histopathological diagnosis of MAC.

The authors declare no conflict of interests.

References

1. Uchida K, Oga A, Mano T, et al. Screening for DNA copy number aberrations in mucinous adenocarcinoma arising from the minor salivary gland: two case reports. *Cancer Genet Cytogenet* 2010; 203: 324-7.
2. Spiro RH, Koss LG, Hajdu SI, et al. Tumors of minor salivary origin. A clinicopathologic study of 492 cases. *Cancer* 1973; 31: 117-29.
3. Ide F, Mishima K, Tanaka A, Saito I, et al. Mucinous adenocarcinoma of minor salivary glands: a high-grade malignancy prone to lymph node metastasis. *Virchows Arch* 2009; 454: 55-60.
4. Osaki T, Hirota J, Ohno A, et al. Mucinous adenocarcinoma of the submandibular gland. *Cancer* 1990; 66: 1796-801.
5. Krogdahl AS, Schou C. Mucinous adenocarcinoma of the sublingual gland. *J Oral Pathol Med* 1997; 26: 198-200.
6. Seoane J, Varela-Centelles P, López-Niño J, et al. Gingival mucinous adenocarcinoma of a minor salivary gland. *J Periodontol* 2010; 81: 626-31.
7. Notani K, Iizuka T, Yamazaki Y, et al. Mucinous adenocarcinoma of probable minor salivary gland origin. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2002; 94: 738-40.
8. Hashitani S, Sakurai K, Noguchi K, et al. Mucinous adenocarcinoma with neuroendocrine differentiation of the mandibular ramus: report of a case. *J Oral Pathol Med* 2004; 33: 59-63.
9. Gao Y, Di P, Peng X, et al. Mucinous adenocarcinoma of salivary. *Zhonghua Kou Qiang Yi Xue Za Zhi* 2002; 37: 356-8.
10. Safae A, Moghimi-Dehkordi B, Fatemi SR, et al. Characteristics of colorectal mucinous adenocarcinoma in Iran. *Asian Pac J Cancer* 2010; 11: 1373-5.
11. Komm M, Kronawitter-Fesl M, Kremer M, et al. Primary mucinous adenocarcinoma of the vermiform appendix with high grade microsatellite instability. *J Cancer* 2011; 2: 302-6.
12. Chung MY, Park YS, Ryu SR, et al. A case of colonic mucinous adenocarcinoma in 19-year-old male patient. *Clin Endosc* 2012; 45: 103-7.
13. Ionila M, Margaritescu C, Pirici D, et al. Mucinous adenocarcinoma of the colon - a histochemical study. *Rom J Morphol Embryol* 2011; 52: 783-90

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