Original paper

Renal clear cell carcinoma metastasis to salivary glands – a series of 9 cases: clinico-pathological study

Hanna Majewska[1], Alena Skálová[2], Klaudia Radecka[1], Dominik Stodulski[3], Martin Hyrcza[4], Czesław Stankiewicz[3], Wojciech Biernat[1]

[1]Department of Pathomorphology, Medical University of Gdańsk, Poland
[2]Department of Pathology, Charles University in Prague, Medical Faculty in Plzeń, Czech Republic
[3]Department of Otolaryngology, Medical University of Gdańsk, Poland
[4]Department of Pathology, University Health Network, Toronto, ON, Canada

Metastatic tumors involving salivary glands arising from the non-head and neck area are very rare. Renal cell carcinoma (RCC) is known for its high propensity for metastasis to unusual localizations. RCC metastasis to the maxillofacial area is an uncommon event (16%), but metastasis to salivary glands is extremely rare. We report a series of 9 such cases retrieved from two institutions.
The group included 6 females and 3 males. The age at diagnosis ranged from 60 to 97 years (mean 72.6 years). The tumors involved the parotid gland in 7 cases, and the submandibular and small salivary gland of the oral cavity in 1 case each. The size of tumors ranged from 0.4 to 5 cm. Total parotidectomy with selective neck dissection was performed in 4 cases, while superficial parotidectomy was performed in 1 case and simple resection in 3 cases. Histologically, all the tumors were clear cell renal cell carcinomas, and therefore the differential diagnosis mainly included clear cell variants of salivary gland carcinomas.
The parotid gland was the initial manifestation of renal malignancy in 4 of the cases, while in the remaining 5 cases a history of RCC had been known. The salivary gland involvement developed from 11 months to 13 years after the time of diagnosis of the primary tumor. In 2 cases it was the first site of dissemination.
Pathologists need to maintain a high index of suspicion for the possibility of metastasis when confronted with oncocytic or clear cell neoplasms developing in salivary glands. RCC, although rare, should be included in this differential diagnosis.

Key words: metastasis, salivary gland, renal cell carcinoma, clear cell carcinoma, differential diagnosis.

Introduction

Metastatic disease to salivary glands is uncommon representing approximately 5% of all malignant tumors at this site [1, 2]. The parotid gland is most frequently affected, whereas involvement of the submandibular and sublingual glands is less common [1, 3]. Both regional and distant metastatic disease should always be considered in the work-up of these histologically variable and heterogeneous tumors. Metastases to salivary glands most often (in about 80%) originate from squamous cell carcinomas of the head and neck region [4], followed by cutaneous as well as mucosal melanomas [1]. Carcinomas of the breast, lung, kidney and prostate are those prima-

ries that may also potentially metastasize to salivary glands [4, 5, 6, 7, 8].

Renal cell carcinoma (RCC) comprises about 4% of all cancers in the USA and its incidence is still rising [9]. Renal cell carcinoma is known for its high propensity for metastasis to unusual localizations, such that any anatomical site may be affected [10]. About one third of patients with RCC present with metastatic disease [10] and the high metastatic potential accounts for the unpredictable clinical behavior of this malignancy. It is estimated that 30% of organ-confined RCCs will develop metastatic disease after local treatment [11]. Non-central nervous system (non-CNS) head and neck metastases from RCC are uncommon, comprising approximately 15% of tumors [12], but are not infrequently identified in the skin, nasal cavity, lips, hard palate, tongue, sinuses, and tonsils [6, 10, 13, 14]. The thyroid gland is the most common site of head and neck metastasis for RCC [15].

Metastasis of RCC to major salivary glands is extremely rare. Since the initial report of Patey *et al*. [16], 46 cases with a predominance of parotid gland metastases have been published [14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46]. Among them, two reports contained detailed and full reviews of the literature [14, 46]. Renal cell carcinoma metastases to the submandibular gland were reported in seven cases [47, 48, 49, 50, 51, 52]. Only one case of metastasis to the sublingual gland was found in the current literature [52].

We report a series of 9 cases of renal cell carcinoma metastases to salivary glands. Although metastatic spread to salivary glands is uncommon, it should be taken into consideration in the differential diagnosis of salivary gland tumors. To our best knowledge, this is the largest series presenting such a pattern of dissemination. Finally, we consider the differential diagnosis of clear cell variants of primary salivary gland carcinomas with the emphasis on ancillary immunohistochemical and molecular methods.

Material and methods

The material consisted of 9 cases which came from the pathology archives of two institutions. Five cases of metastatic clear RCC were selected from the historic files of salivary gland neoplasms operated on between 1992 and 2015 in the Departments of Otolaryngology and Maxillofacial Surgery, Medical University of Gdańsk, Poland (HM). Four cases were selected from consultation archives from the Department of Pathology, Charles University in Prague, Faculty of Medicine in Plzen, Czech Republic (AS). Clinical data and follow-up were obtained from medical records (DS, CS). Paraffin blocks and recuts were available for histological and immunohistochemical analysis and reclassification in all studied cases.

Clinical data

The group of patients included 6 females and 3 males (Table I). Their age ranged from 60 to 97 years (mean 72.6 years); the age of 3 patients from consultation material was unknown (cases 6-8). All the patients presented with unilateral metastasis: one tumor was found in the submandibular gland, one in the retromolar region of the oral cavity, and the other 7 cases were located in the parotid gland. All the patients presented with a palpable lesion, but only in three cases the lesions were associated with symptoms suggesting malignancy, i.e., palsy of the facial nerve and immobility of the mass. In one case (9) a multinodular palpable mass was found in the scar after prior parotidectomy due to a benign lesion 16 years earlier.

The parotid tumor was the initial manifestation of renal malignancy in 4 cases. The remaining five patients had been diagnosed and treated for RCC prior to salivary gland metastases, which developed in a time interval from 11 months to 13 years after the primary treatment and was the first sign of metastatic disease. Only in one case the dissemination to lungs had developed prior to salivary gland metastasis (case 6).

All patients underwent surgical treatment: total parotidectomy with selective neck dissection (4 cases), superficial parotidectomy (1 case) or simple resection of the tumor (3 cases); the type of surgery in 1 patient is unknown. The size of tumors ranged from 0.4 to 5 cm (unknown in 3 patients).

Histopathological findings

The tumors revealed multinodular arrangement (cases 3 and 4) or constituted a single round nodule with nested or tubular structure (case 5) (Fig. 1A, B). Unless fragmented, as occurred in cases 1 and 2, they were covered with a thin fibrous pseudocapsule. Histologically, all the tumors were composed of clear cells arranged in small nests divided by a regular network of small thin-walled blood vessels (Fig. 2). The capillary network was rich and associated with areas of extravasated erythrocytes and small hemorrhages. In some alveolar structures the lumen was filled with erythrocytes (Fig. 2). Hemosiderophages were found in the stroma at the periphery (Fig. 1A). The clear cytoplasm was surrounded by distinct cell membrane and contained small round or oval nuclei with evenly distributed chromatin or slightly vesicular nuclei. The nucleoli varied from small and inconspicuous to large and prominent. Mitotic figures were absent.

In seven out of nine cases the origin of tumors was confirmed by at least two antibodies: vimentin, CD10, renal cell carcinoma monoclonal antibody

Table I. Clinicopathological data of studied patients

Patient sex and age at diagnosis	year of diagnosis of salivary gland tumor and clinical data	Location	Presenting symptoms	Size of tumor [cm]	Treatment
F/66	1991 as first manifestation of RCC	right parotid	painless, enlarging,hard, immobile mass, facial nerve palsy	5 × 4	total parotidectomy, radiotherapy
F/76	1994 as first manifestation of RCC	right parotid	painless, enlarging, immobile mass	5 × 5	total parotidectomy with N VII
F/97	2007, RCC in anamnesis	right submandibular	hard, cohesive, immobile mass	no data	no data
M/68	2010 as first manifestation of RCC	left parotid gland	growing mass for 4 months, painless, firm	2,6 × 1,8 × 1,3	resection of the tumor
M/69	2013 as first manifestation of RCC	left parotid gland	palpable mass	1,8 × 1,5 × 2	superficial parotidectomy
M	1999, Status post right nephrectomy, metastasis in lungs	right parotid	painless slowly growing mass for 3 months	no data	total parotidectomy
F	1996, RCC in anamnesis	small salivary gland of oral cavity (left retromoral region)	tumor	no data	resection of the tumor
F	2010, 11 month after bilateral RCC in the kidneys	right parotid, deep lobe	palpable tumor	1,5	total parotidectomy
F/60	2010 – as first metastasis after 13 years of right nephrectomy (1997) 1993 – resection of PA	right parotid	multinodular palpable mass in the area of cicatrix	0,4 focus RCC and multifocal recurrence of PA	resection of the tumor

RCC – renal cell carcinoma; PA – pleomorhic adenoma

(RCCma) and paired box gene 8 (PAX8). All the tumor cells were negative for S100, p63, and mucin.

Case 9 presented with a most unusual coincidence of recurrent pleomorphic adenoma and RCC. The former was composed of multiple foci of predominantly myxoid hypocellular tumor permeating the residual tissue of parotid gland and extraglandular tissues. Adjacent to one such nodule, a well-circumscribed, non-encapsulated RCC metastasis was identified (Fig. 3). It co-expressed vimentin, cytokeratin AE1/AE3, EMA, and CD10 and was negative for CK7, CK20, and S100 protein. S100 protein was positive in the pleomorphic adenoma component.

Histologically, all the tumors were diagnosed as clear cell renal carcinoma.

Discussion

Salivary gland involvement by dissemination of renal malignancy is uncommon. However, correct diagnosis in such cases is important since the treatment of primary malignancies of the salivary glands differs from the treatment of metastases.

Parotid metastasis may be the initial sign of malignancy in the kidney, as evidenced in 19 of the historical cases and four patients from our series. A previous history of nephrectomy for RCC was known in 20 and 5 patients, respectively; the time interval of presentation spanned from 2 to 19 years and from 11 months to 13 years, respectively. Therefore, the time lag from the original diagnosis of RCC until salivary gland involvement may appear to be less than one year but it may also take decades. Similarly, the size may vary, and, as shown in our series, it may be found accidentally within the confines of the primary salivary gland tumor such as pleomorphic adenoma.

Epidemiological data show that cases in male patients predominated (2 : 1) in the published cases [14, 46], reflecting the epidemiology of this malignancy

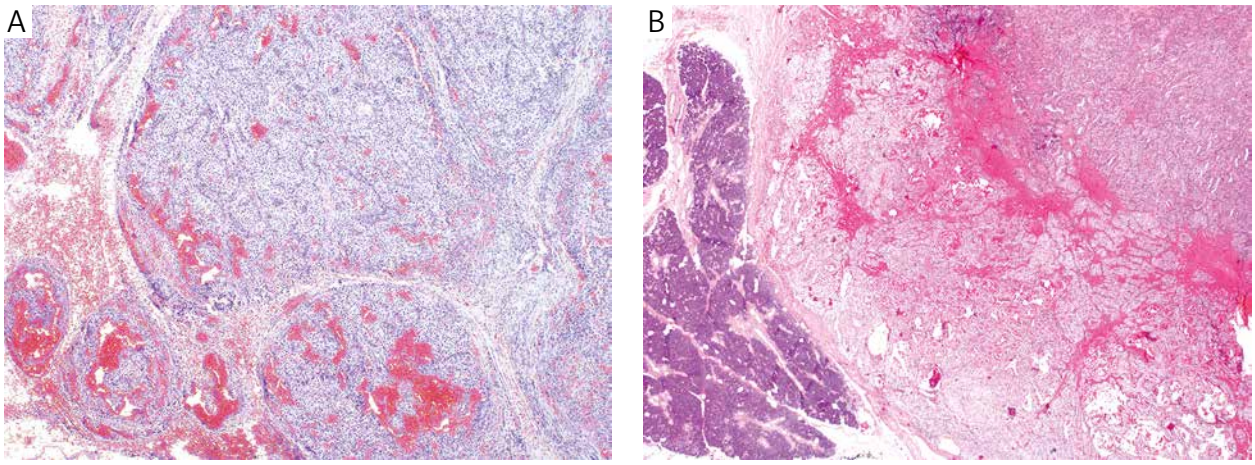

Fig. 1. On small magnification (HE), metastatic renal clear cell carcinoma revealed multinodular structure (A, magnification 40×) or constituted a single round nodule adjacent to parotid gland (B, magnification 20×)

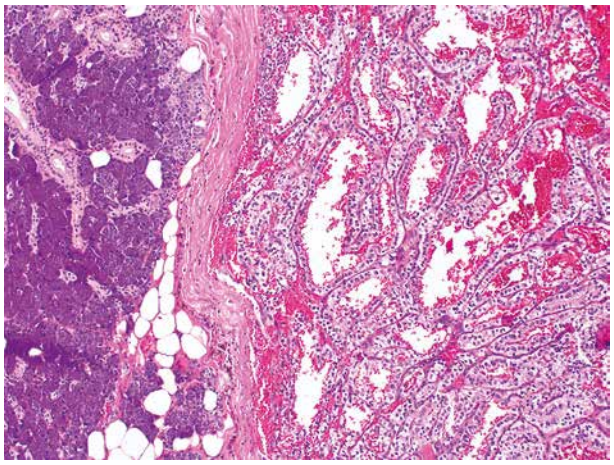

Fig. 2. Metastatic clear cell RCC with typical morphology adjacent to the parotid gland (HE, magnification 100×). Note nests and glandular structures composed of cells with clear cytoplasm and rich capillary network and erythrocytes

[11, 14, 46], whereas in our series the reverse was observed (M : F = 1 : 2). The peak incidence occurs in the 7th to 8th decade. The vast majority of patients in the literature (32/46 cases) presented with unilateral parotid metastasis [46], with similar presentation in our group. All the patients had a palpable mass that was occasionally accompanied by pain, tenderness, pulsation, tinnitus, and/or ipsilateral facial weakness. In our series only one case (1) presented with facial nerve palsy and two others (cases 2 and 3) showed immobility of the mass.

The differential diagnosis of a clear cell neoplasm of the salivary gland includes clear cell myoepithelial tumors, oncocytic lesions, clear cell variants of mucoepidermoid carcinoma, acinic cell carcinoma, epithelial-myoepithelial carcinoma, and hyalinizing clear cell carcinoma. Secondary tumors should always be taken into consideration, as the clinical information may not be available or the underlying cancer may be asymptomatic and salivary gland tumor is the first manifestation of the disease.

It is difficult to separate histologically metastatic RCC from benign and malignant oncocytic lesions. Typically metastatic RCC presents characteristic prominent vascular stroma with erythrocytes in the lumina or between nests formed by clear cells. However, there is a significant morphologic overlap between oncocytic neoplasms and RCC, as 37% of RCC present a predominantly oncocytic component and 26% of oncocytomas and 36% of oncocytosis cases show clear cell areas [2, 53]. As neither vimentin nor CD10 is specific, the immunohistochemical staining for p63 proved to be the most reliable single marker for distinguishing RCC (negative) and oncocytic lesions (positive) [2].

In most instances of primary salivary gland lesions clear or oncocytic cells compromise only a minor cellular component and the diagnosis can be rendered based upon identification of classic histomorphological features. However, in the series presented by Skálová *et. al.* a prominent clear cell component was found in only 39% of *de novo* clear cell myoepithelial carcinomas (CCMC) and in 24% of clear cell myoepithelial carcinomas ex pleomorphic adenoma (CCMCexPA) [54]. This subset of tumors was arranged in nodules composed of compact nests of large polyhedral cells with abundant clear cytoplasm. Moreover, these tumors showed *EWSR1* rearrangement, thus clear cell myoepithelial carcinomas may represent distinctive aggressive variant composed predominantly of clear cells with frequent necrosis [54, 55]. Renal cell carcinoma does not show expression of any myoepithelial markers, e.g., smooth muscle actin (SMA), glial fibrillary acidic protein (GFAP), p63 and S100. On the other hand, CCMCs are usually negative for vimentin and co-express cytokeratin/EMA, S-100 protein and/or at least one other myoepithelial marker: SMA, muscle specific antigen (MSA), calponin, p63, and/or GFAP [54, 55, 56].

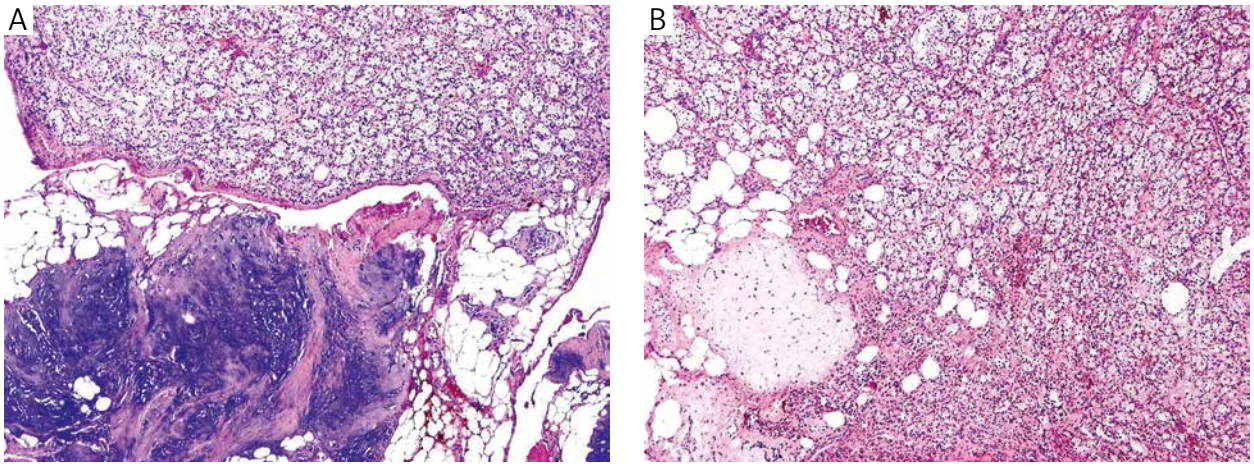

Fig. 3. Well circumscribed unencapsulated RCC metastatic focus composed of cells with clear cytoplasm and round central uniform nuclei adjacent to recurrent pleomorphic adenoma composed of multiple foci of predominantly myxoid hypocellular stroma (case 9) (A, B)

Clear myoepithelial cells may also predominate in epithelial-myoepithelial carcinoma (EMC), thus including it in the group of clear cell tumors. In these cases and in small biopsies immunohistochemistry is extremely helpful in identifying biphasic architecture of EMC: the inner abluminal epithelial cells (CK7+, Cam5.2+) and the outer myoepithelial layer (p63+, calponin+, SMA+) [57, 58, 59].

In mucoepidermoid carcinomas (MEC), clear cells comprise approximately 10% of the tumor cells [59]. However, they may occasionally form large aggregates, as clear morphology may be seen not only in the mucinous but also in the intermediate and epidermoid components [57]. As mucinous cells contain mucin, they stain positively with PASD (PAS with predigestion with diastase), mucicarmine, and alcian blue, contrary to glycogen-rich RCC, which is revealed by PAS staining [55]. Schwartz *et al.* found that the clear cell variant of MEC is the least common pattern [60]. Nevertheless all these cases, like most low-grade MEC, harbored recurrent translocations CRTC1/3-MAML2 [60]. This translocation appears to be specific for MEC and might be helpful in the differential diagnosis.

The historically oldest two cases (no. 1 and 2) in our series had been diagnosed as acinic cell carcinoma (AciCC) and were reclassified retrospectively [61]. Clear cells were found in approximately 6% of AciCC, but in about 1% of cases they predominate [59]. The identification of PAS-positive diastase-resistant zymogen granules in the cytoplasm is crucial for establishing the diagnosis. Positive staining for S-100, CEA, and GFAP in AciCC may prove to be helpful in contrast to vimentin.

Despite minimal morphological similarity [62], hyalinizing clear cell carcinoma (HCCC) must also be taken into account in the differential diagnosis. This unique salivary gland tumor develops predominantly in the minor salivary glands of oral cavity and is composed of nests, cords and trabeculae of clear and eosinophilic cells in a hyalinized stroma [62, 63]. Immunohistochemically, HCCC is diffusely positive for pancytokeratin and p63 but negative for S100, SMA, MSA, calponin, GFAP [2, 62]. Renal cell carcinoma never expresses p63 [2]. Recently, it was demonstrated that more than 80% of HCCC harbor recurrent *EWSR1-ATF1* fusion [63].

As tissue evaluation by light microscopy does not always guarantee proper identification of the tumor type, especially in the overlapping and rare entities, the role of molecular markers is expanding in the diagnostic algorithm. The relatively novel but widely used immunohistochemical markers paired box gene 2 and 8 (PAX2 and PAX8) are promising. PAX8 proved to be very useful in primary and metastatic sites of RCC [64]. Nuclear PAX8 positivity was found in 90% of metastatic clear cell RCC [64], whereas the nuclear positivity of PAX2 was shown in 81% of primary and 85% of metastatic clear cell RCC [65, 66]. However, they are not specific to renal epithelium, as both are positive in cancers of Müllerian (endometrial and ovarian) origin, and PAX8 also in thyroid carcinomas [65, 66].

Conclusions

Distinction between metastasis and primary tumor is crucial as management of metastatic renal cell carcinoma and primary carcinoma of salivary gland origin requires different therapeutic decisions. Metastatic disease should always be kept in mind when evaluating a major salivary gland lesion. Metastasis may develop after a long time interval, occasionally even more than 10 years after nephrectomy.

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Address for correspondence

Hanna Majewska MD, PhD
Department of Pathology
Medical University of Gdansk,
Dębinki 7
80-211 Gdansk, Poland
tel. +48 601 762 460
fax +48 58 349 37 45
e-mail: hania.majewska@gumed.edu.pl