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NEUROENDOCRINE BREAST CARCINOMA METASTATIC TO RENAL CELL CARCINOMA AND IPSILATERAL ADRENAL GLAND

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Summary

We report a 60-year-old woman with neuroendocrine carcinoma of left breast metastasizing to renal cell carcinoma (RCC) of the left kidney and to adrenal gland. A yellow, well circumscribed tumor, 11 cm in largest diameter limited to the kidney was found. Histopathology revealed RCC with foci of neuroendocrine differentiation. Solid sheets of hyperchromatic epitheloid cells with high mitotic activity were found between typical clear cells of RCC. These cells were CAM5,2 and E-cadherin focally positive, synaptophysin, and NSE weakly positive, CK19 moderately positive, and AE1-AE3 and EMA strongly positive. Chromogranin A, CD10, CK 14, CK 20, HER2 (score 1+), vimentin and HMB45 were negative. The left adrenal gland contained multiple, separate foci of a tumor composed of neuroendocrine component. Because of the biphasic tumor in the kidney, extensive clinical examination and further analyses were recommended. Tumor in the left breast was revealed. Two months later the patient underwent mastectomy with axillary lymph node dissection. The tumor was histologically and imunohistochemically similar to neuroendocrine component within RCC. All axillary nodes were positive.

To our knowledge this is the first case of neuroendocrine breast carcinoma with metastasis to renal cell carcinoma and ipsilateral adrenal gland.

Introduction

Breast cancer is the most common malignant tumor and the main cause of tumor-related death in women. Its occurrence with other primary malignances, especially renal cell carcinoma, is not a rare event. However, tumor metastatic to another neoplasm is rarely seen. There are four cases of breast cancer metastasis to renal cell carcinoma described in the literature [7,15,17,18]. We report the first case of breast carcinoma showing neuroendocrine differentiation with metastasis to the renal cell carcinoma and ipsilateral adrenal gland.

Clinical history

A 60-year-old woman presented with painless macrohematuria persisting for several months. Clinical examination including ultrasound, intravenous pyelography and CT scan showed a well circumscribed tumor on the upper pole of the left kidney. The tumor of the left breast was also found. Nephrectomy with ureterectomy was performed. During the same operation, the left adrenal gland and spleen were removed. The patient underwent mastectomy with axillary lymph node dissection two months later.

The patient received postoperative radiation therapy followed by hormonal treatment. The patient is 18 months after second surgery well and without recurrence.

Material and methods

Specimens were fixed in 10% buffered formalin, embedded in paraffin, cut at 5 μm thickness, and routinely stained with hematoxylin and eosin. Immunohistochemical staining was performed following Microwave Streptavidin ImmunoPeroxidase (MSIP) protocol on DAKO TechMate Horizon automated immunostainer using following primary antibodies CK7, CK19, CK20, AE1-AE3, EMA, synaptophysin, S-100, chromogranin A, vimentin,

HMB45, Ki-67, ER, PR and HER2 (DAKO), CK14 (Novocastra) and CAM5.2 (Becton Dickinson).

Results

Grossly, the kidney showed a yellow, well circumscribed tumor, 11 cm in largest diameter, with elevated capsule but limited to the kidney (Fig. 1A). Histopathologic diagnosis revealed typical renal cell carcinoma (RCC) with foci of solid sheets of hyperchromatic epitheloid cells with high mitotic activity and apoptosis (Fig. 1B and C). Small foci of necrosis were observed within the hyperchromatic epitheloid component. RCC component was composed of atypical epithelial cells with clear cytoplasm and nuclei with nucleoli that were seen under higher magnification. Tumor cells were arranged in alveolar structures and solid nests. Hyperchromatic epitheloid cells were CAM5,2 and E-cadherin focally positive, synaptophysin (Fig. 1D) and NSE weakly positive, CK19 moderately positive, and AE1-AE3 and EMA strongly positive. Estrogen (ER) was positive in approximately 60% of tumor cells and progesterone (PgR) in almost all tumor cells. Chromogranin A, CD10, CK 14, CK 20, HER2 (score 1+), vimentin and HMB45 were negative (Table 1). RCC cells were focally positive for CAM5,2, weakly positive for EMA, strongly positive for vimentin, NSE and CD10, and negative for CK14, CK19, CK 20, AE1-3, E-Cadherin, ER, PgR, HER2 (score 1+) as well as for HMB45, chromogranin A and synaptophysin. Ki-67 showed very low activity in RCC (≤5%) but up to 15% of positive cells in the epitheloid component were found (Table 1). Tumor microscopically infiltrated the kidney calyceal system but did not involve renal blood vessels and ureter. Adjacent renal tissue was not affected by the tumor. Diagnosis of RCC with foci of neuroendocrine component was established, and the tumor was staged as T3N0M1 with nuclear grade 2 according to Fuhrman. Macroscopically and microscopically adrenal gland contained multiple separate foci of a tumor composed of neuroendcrine

component similar to that described above. Spleen showed no significant changes. Two months later the patient underwent mastectomy with axillary lymph node removal. Tissue of the left breast and left axilla was obtained for histopathologic analysis. The tumor measured up to 4.5 cm in largest diameter, with nipple and dermal infiltration. The tumor was composed of solid areas of atypical epithelial cells with pronounced nuclear polymorphism and high mitotic activity (more than 20 mitoses in 10 high power fields) (Fig. 1E). In a minor part the tumor was composed of tubular formations. Histologically it appeared similar to the one found within RCC. Immunohistochemically, tumor cells showed focally positive staining for E-cadherin, vimentin and synapthophisin (Fig. 1F), weakly positive for NSE and CK19 and strongly positive staining for AE1-AE3, EMA, CAM5,2. ER was positive in approximately 70% and PgR in approximately 85% of tumor cells. Other antibodies (CK14, CK20, CD10, HER2 /score 1+/, and chromogranin A) were negative. Immunohistochemistry showed reactions very similar to the neuroendocrine component of RCC (Table 1). Diagnosis of invasive ductal carcinoma with neuroendocrine differentiation was made and classified as poorly differentiated neuroendocrine carcinoma according to the WHO classification [16]. From axillary fat 2 conglomerates of lymphatic tissue measuring 3 and 4 cm in the largest diameter and 9 lymph nodes were isolated and tumorous tissue identical to that described in the breast was found in all nodes. The tumor of the breast was staged as T4N2M1 and G3.

On the basis of similar histology and imunohistochemical profile of neuroendocrine cells in RCC and neuroendocrine cells in the breast carcinoma we concluded that breast carcinoma metastasized to RCC; therefore, the initial diagnosis was changed in accordance to new findings.

Discussion

The occurrence of multiple primary malignances is a rare but well-known phenomenon. It has been reported in 2.3% of clinical and 8.1% of autopsy series [10]. RCC is the most common tumor found to coexist with other malignancies [1,10,12,13,14]. In different studies the incidence of second primary malignancy associated with RCC is reported to be 12%-27.4% [1,10,11,14]. About 19% of these tumors appeared synchronously [1]. Other primary malignant tumors most often associated with RCC are bladder, prostate, colorectal and lung cancer [1,10,12,20]. Breast cancer is also one of the tumors known to coexist with RCC [1,11].

Tumor to tumor metastasis is a very rare event. Campbell et al. [3] established criteria for metastatic carcinoma to a second primary carcinoma: evidence for the existence of more than one primary tumor; the recipient tumor shown to be a true neoplasm; and evidence that the second malignant neoplasm is a true metastasis with established growth or invasion in the host tumor and not due to contiguous growth or embolism of tumor cells. By these criteria less than 60 cases of tumor to tumor metastasis can be found in PubMed.

The first case of tumor to tumor metastasis was described by Berent in 1902 [2]; it was a squamous epithelial cancer to an RCC. RCC is the most common recipient tumor (71.7%) and the second is sarcoma (6.5%) [15]. The most common donor cancers are lung, prostate and thyroid [15]. In co-existing malignancies with RCC, Sella and Ro [15] report on 15% incidence of tumor to tumor metastasis. Three of these were female patients with asymptomatic renal cell carcinoma that contained metastasis from the breast, colon and lung cancer that was detected at autopsy [15].

Two mechanisms have been postulated to explain the phenomenon of metastasis to RCC [13]

1) Mechanical theory [15] is based on the fact that 25% of the minute volume flow goes through the kidney and RCC, which is highly vascular. Because of this RCC is receiving a large proportion of donor tumor emboli.
2) The "seed and soil" theory **[9]** is based on the provision of a fertile environment in which compatible tumor cells could proliferate. **The theory was introduced by Stephen Paget [9] in 1889 year in his seminal paper in Lancet. He proposed that the processes of metastasis did not occur by chance but, rather, that certain favored tumor cells with metastasis activity (the "seed") had a special affinity for the growth-enhancing milieu within specific organ (the "soil") [9]. Extensive research into chemokines and their receptors has elucidated and confirmed this theory [4,8]. Muller et al. [8] showed that the chemokine receptors CXCR4 and CCR7 are highly expressed in human breast cancer cells, malignant breast tumors and metastases. Their respective ligands CXCL12 and CCL21 exhibit peak levels of expression in organ representing the first destination of breast cancer metastasis. Similar model was discovered for other tumors where adhesion molecules and chemokines also represent the navigation system for circulating tumor cells to metastasize in an organ-specific manner [4].**

Breast carcinoma is known to coexist and metastasize more often to intracranial meningeoma [19]. In the literature there are only 4 cases of breast carcinoma metastasizing to RCC [6,15,17,18]. Two cases are described in living patients with known metastatic breast cancer including metastasis to RCC [7,18]. In the report by Sella and Ro, it was discovered at autopsy [15]. It can be expected that cases like this may be more often discovered in living patients because of the widespread use of ultrasonography and computer tomography in imaging of the kidneys as part of abdominal evaluation of other diseases [7].

To our knowledge, the case presented is the first case of breast carcinoma with neuroendocrine differentiation metastatic to RCC reported in the literature. In our case, RCC was found first and then other malignancy was suspected and actually diagnosed almost synchronously. Neuroendocrine breast carcinoma is quite uncommon, accounting for 2%-5% of breast carcinomas [16]. In the differential diagnosis, a primary neuroendocrine tumor of the kidney, especially carcinoma should be considered. Neuroendocrine carcinoma of the kidney accounts for much less than 1% of all epithelial renal malignant tumors [5]. Gross and microscopic features are similar to the same tumor type occurring at other, more typical locations. A concomitant urothelial carcinoma is common [5]. **We revealed an overlap in the immunohistochemical expression of neuroendocrine markers (NSE) and cytokeratins in primary breast cancer and neuroendocrine component that was observed within clear cell RCC. Similar pattern of immunoreactivity was found in the adrenal gland metastasis. However it is well known that NSE is quite nonspecific and unreliable marker. Described foci within RCC and adrenal gland metastasis also showed similar morphologic features to primary neuroendocrine carcinoma of the breast.**

In summary, multiple synchronous primary malignances are rare but may be occasionally seen. One should be especially careful in patients with RCC where the incidence is even higher. A newly diagnosed renal tumor next to an existing cancer is challenging since a primary or a secondary renal neoplasm has to be considered in the differential diagnosis.

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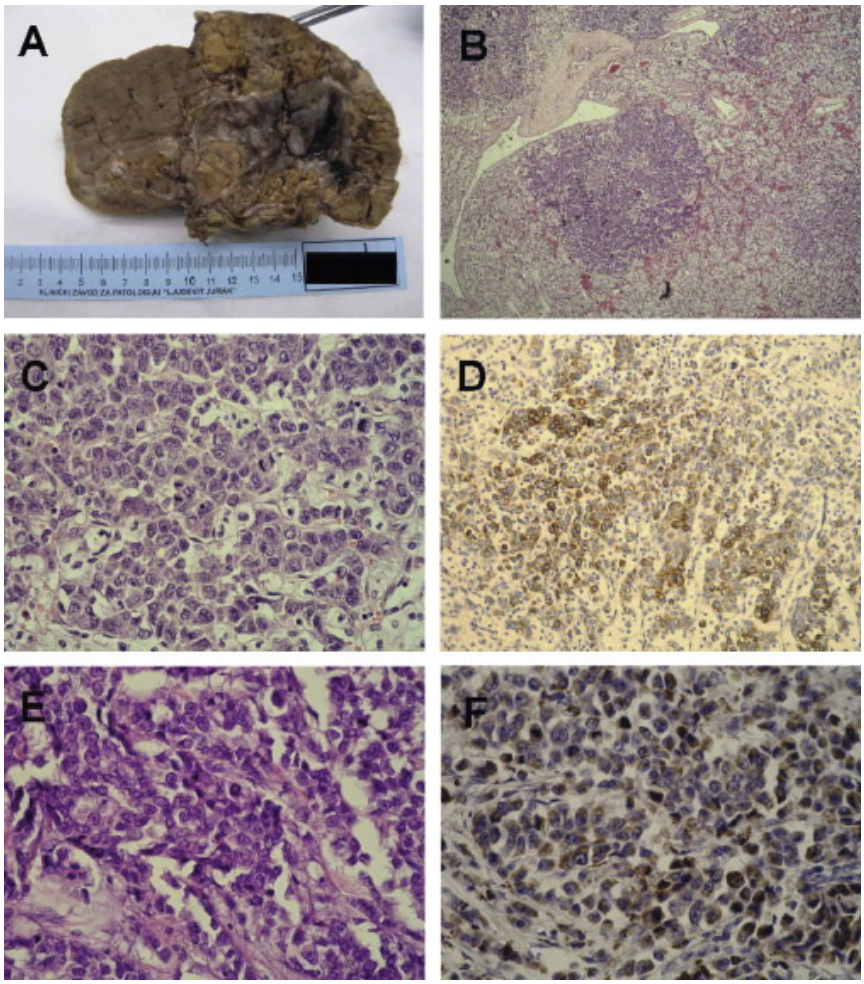
Table 1. Immunohistochemistry of primary and metastatic breast cancer to renal cell carcinoma, renal cell carcinoma (RCC) and adrenal gland metastasis of breast cancer

	RCC	Metastasis to RCC	Primary breast cancer	Adrenal gland metastasis
AE1-AE3	-	+++	+++	+++
CAM 5.2	+/-	+/-	+++	+/-
CK14	-	-	-	-
CK19	-	++	+	+
CK20	-	-	-	-
EMA	+	+++	+++	+++
PgR	-	100%	85%	80%
ER	-	60%	70%	60%
HER2	- (score 1+)	- (score 1+)-	- (score 1+)	- (score 1+)
CD10	+++	-	-	-
E-cadherin	-	+/-	+/-	+/-
NSE	+++	+	+	+
Chromogranin A	-	-	-	-
Synaptophysin	-	+	+/-	+
Vimentin	+++	-	+/-	-
HMB45	-	-	not analyzed	not analyzed
Ki-67	≤5%	≤15%	≤22%	≤15%

Legend: - negative; +/- focally positive; + weakly positive; ++ moderately positive; +++ strongly positive

Figure 1. a) Gross photograph of kidney with well circumscribed tumor measuring up to 11 cm at the upper pole, b) histology revealed renal cell carcinoma with foci of neuroendocrine component (HEx40), c) neuroendocrine component was composed of solid sheets of hyperchromatic epitheloid cells with high mitotic activity (HEx400) d) positive immunostaining for synaptophysin in neuroendocrine component of renal cell carcinoma (RCC), (x200), e) breast carcinoma was composed of solid areas and pseudotubular formation of atypical epithelial cells histologically similar to neuroendocrine cells in RCC (HEx400) f) immunohistochemistry showed similar reactions for synaptophysin in breast carcinoma like neuroendocrine component within RCC, (x400)



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