Coexistence of renal cell carcinoma of clear cell type with sarcomatoid cell type component and adrenal mature ganglioneuroma with myelolipoma – a case of 69-year-old female patient

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Abstract
This report presents a case of 69-year-old woman, who was operated due to renal tumor. Apart from renal neoplasm, the adjacent adrenal gland contained another one tumor in medulla of the organ. The renal lesion was diagnosed renal cell carcinoma, clear cell type with undifferentiated cell sarcomatoid component. The adrenal neoplasm was composed of wavy S100-positive, Schwann-like cells and dispersed chromogranin A-reactive ganglion cells to be consistent with mature ganglioneuroma. It was accompanied by coexistent myelolipoma that contained hematopoietic cells including clearly visible megakaryocytes and foci of fat. To our knowledge, our paper is the first to report sporadic clear cell renal cell carcinoma with sarcomatoid cell type component and mature adrenal ganglioneuroma with myelolipoma in the same patient.

Keywords: renal cell carcinoma, clear cell type, sarcomatoid component, mature adrenal ganglioneuroma, myelolipoma.

Introduction
Renal cell cancers do not constitute a uniform group of tumors. Depending on histopathological type, they differ in patients’ survival [1]. Namely, collecting duct and sarcomatoid renal cell carcinomas are more advanced and easily disseminating neoplasms in comparison to clear cell type cancers, while papillary and chromophobe tumors grow much slower and usually present as limited disease to kidney organ. Their biology is variably reflected in expected average survival with the worst prognosis for collecting duct and sarcomatoid ones and excellent survival for patients with chromophobe cancer [1]. It is worth to mention that, in the last few years, prognosis of clear cell carcinoma has improved thanks to targeted therapies, especially engaging vascular endothelial growth factor and mammalian target of rapamycin in the so-called post-cytokine era [2, 3]. Concerning genetic background, von Hippel–Lindau (VHL) gene is established as a crucial factor in pathogenesis of renal clear cell carcinoma [4]. Namely, inactivation of VHL was found in 86.6% of sporadic clear cell carcinomas of kidney in one study to reveal that germline VHL SNPs (single nucleotide polymorphisms) and a haplotype were accompanied by promoter hypermethylation in tumor tissue. Interestingly, there was an inverse relationship between VHL inactivation and smoking in a result of a prevalence of wild-type clear cell cancers in smokers’ population with no significant difference in the genetic profile concerning occupational exposure to trichloroethylene [4]. Besides smoking, a work in metal-related industries seems to be an important risk factor for occurrence of clear cell carcinoma and consequently perchloroethylene and tetrachlorocarbonate are responsible for higher incidence of this neoplasm [5].

Definitely, the most common of renal cancers, clear cell carcinoma usually occurs sporadically with no coexistence with other tumors. However, clear cell renal cancer is a classical component of von Hippel–Lindau syndrome (currently included in category of MEN [Multiple Endocrine Neoplasia] besides MEN1, MEN2A and MEN2B) that is characterized by development of following multiple tumors and tumor-like conditions: pheochromocytoma, retinal and central nervous system hemangioblastomas, renal cysts and clear cell carcinoma, pancreatic cysts or islet cell tumors, endolymphatic sac tumors, papillary cystadenomas of the epididymis and broad ligament as well [6].

Sporadically, clear cell carcinomas of kidney were reported to coexist with other tumors of distant location to kidney, e.g., gastrointestinal stromal tumor, sigmoid adenocarcinoma without tuberous sclerosis or malignant melanoma [7–9]. It is worth mentioning that, there can be much combined sets of different tumors, e.g., colonic carcinoma, renal cell carcinoma and gastrointestinal stromal tumor that were found in one patient [10].
Here, we present a case of 69-year-old woman with clear cell renal cell carcinoma with sarcomatoid cell-type component that was accompanied by combined adrenal ganglioneuroma and myelolipoma.

**Patient, Methods and Results**

A 69-year-old woman without any characteristic clinical data of hereditary abnormalities, presented with complaints of slight, flank, abdominal pain with onset about four months before surgery. There was no hypertension, no renal cancer in family history, lack of diarrhea, flushing of the skin or dyspnea and so on. There was no family history of adrenal and renal neoplasms or clinical signs of von Hippel–Lindau syndrome or other genetic syndromes in the patient, either. Thus, a case was not submitted for any molecular genetic testing for mutations, e.g., in the VHL gene. General condition clinical inspection was well and laboratory tests did not reveal any essential anomalies. Thus, she was examined routinely with an ultrasoundography (USG) imaging that visualized a pathological tumor mass in medium of left kidney.

In computed tomography (CT) scanning, there was a solid hypodense tumor of diameter of 6 cm that was accompanied with another one 3 cm in diameter tumor in left adrenal area. A transabdominal nephrectomy of left kidney collectively with adrenal gland, Gerota’s fascia and paranephric fat was performed. A postoperative period was without complications and the patient was discharged home after seven days. Then, the patient was referred to a regional Center of Oncology where is, to date on observation.

### Pathological findings

#### Macroscopic evaluation

The left kidney measured 13×7×6 cm with a 6 cm long part of ureter. In the middle part of the kidney, there was the solid white, partly yellowish tumor of diameter 6.5 cm (staged pT1bN0M0 according to 7th edition of pTNM Classification) [11] that contained foci of necrosis and was limited by fibrous renal capsule with no extension into renal pelvis, hilar and perirenal fat or hilar vessels and ureter. In the left adrenal gland there was a solid, whitish 3.5 cm in diameter tumor, of a little bit fascicular consistency in medulla of the organ that adhered to preserved rim of adrenal cortex (Figures 1 and 2).

![CT scan: (A) An irregularly demarcated tumor of left kidney (arrows); (B) Left adrenal tumor (arrows).](image)

### Microscopic diagnosis

The renal tumor was diagnosed a renal cell carcinoma, clear cell type Furhman grade 4 with undifferentiated cell sarcomatoid component. Approximately 30% of main tumor texture was occupied by well-differentiated areas of Furhman grade 2 renal clear cell cancer (Figure 3A), but rest of tumor areas were less differentiated with mixture of fields presenting various grades of differentiation including Furhman grade 4 foci and undifferentiated sarcomatoid component, that was composed of atypical spindle cells (Figure 3, B–D). Following the recommendations by de Peralta-Venturina et al. to report a rate of sarcomatoid-type component, we assessed that the area of this histopathological type comprised 15% that occupied four low power fields (4×) of the examined tumor [12].

The cancer growth was limited to kidney parenchyma with no microscopically proved invasion of either perirenal fat or a renal vein. Outside the tumor, there was chronic interstitial nephritis.
Adrenal tumor was composed of spindle cell fascicles without cellular atypia that presented a prominent wavy appearance (Figure 4A). In such a texture, there were dispersed large polygonal ganglion cells with plump violet to amphiphilic cytoplasm with traces of brown pigment and eccentrically centered nuclei with prominent nuclei and smooth delicate chromatin pattern. This feature was diagnosed as mature ganglioneuroma.

Another one counterpart of adrenal tumor was mature adipose tissue. This adipose tissue limited an area of hematopoietic tissue with megakaryocytes, that measured 1.5 cm in diameter and was consisted with diagnosis myelolipoma (Figure 4D).

Spindle cell, fascicular part of tumor was positive for S100 immunostain (Figure 5A) and negative for alpha-SMA and desmin.

Ganglion cells coexpressed diffusely S100 (Figure 5B) and in the same cells chromogranin A with lacked immunoreactivity for cytokeratins AE1/AE3.

Postoperative serum levels of adrenalin, dopamine and vanillylmandelic acid were not increased. Imaging and hormonal tests did not reveal any disorders, which would suggest existence of multiple endocrine neoplasia (MEN) syndromes or other endocrine abnormalities.

We found residual nests of normal adrenal medulla composed of pheochromocytes that were entrapped within ganglioneuroma and myelolipoma (Figure 4B). Nests of pheochromocytes were located at the margin of the appropriate adrenal tumor and near residual part of the adrenal cortex. They showed only a slight atypia and cytoplasmic degenerative changes (Figure 4C).

Therefore, these very small foci we have recognized as residual parts of the adrenal medulla. Not prominent mitoses neither necrosis or invasive manner of growth was associated with rests of adrenal medulla. Expression of chromogranin A was distributed in peripherally located ganglion cells in the tumor (Figure 5C).

An intensity of chromogranin A staining was not influenced by cellular polymorphism, size of nuclei and nucleoli or degenerative cytoplasmic changes (Figure 5, C and D).

Not only adrenal medulla rests were found within tumor (Figure 6, A and B) but also cells of adrenal cortex were intermingled within the tumor (Figure 6, C and D), what could oppose non-infiltrative mode of growth which is attributed to this tumor type.
Figure 4 – Adrenal composite tumor: (A) Adrenal ganglioneuroma – spindle cell texture with wavy appearance of cells and interspersed adipocytes and ganglion cells (HE staining, 100×); (B) Ganglion cell with pigmented cytoplasm in background of spindle cell texture and adipose tissue islands (HE staining, 200×); (C) Cellular pleomorphism and degenerative changes of ganglion cells (HE staining, 400×); (D) Mature foci of hematopoietic cells including one clearly visible megakaryocytes and scattered adipocytes (HE staining, 200×).

Figure 5 – Mature ganglioneuroma of adrenal gland. Immunohistochemical evaluation: (A) Wavy appearance of Schwann cell with prominent expression of S100 stain (100×); (B) Expression of S100 in ganglion cells in ganglioneuroma (200×).
Figure 5 (continued) – *Mature ganglioneuroma of adrenal gland. Immunohistochemical evaluation:* (C) Strong expression of chromogranin A in nests of pheochromocytes and mild expression in cortical cell (200×); (D) Expression of chromogranin A in ganglion cells (200×).

Figure 6 – *Adrenal neoplasm and its surroundings:* (A) Rests of adrenal medulla presenting as nests of chromaffin cells entrapped within tumor (HE staining, 100×); (B) Distinct nested architecture of growth displaying spheroid, alveolar pattern with prominent sustentacular cells (HE staining, 200×); (C) Small nests of adrenal cortex within the tumor (HE staining, 200×); (D) Distinct border between tumor and adrenal cortex with presence of pigmented cells (HE staining, 200×).
Discussion

Removal of adrenal gland belongs to surgical protocol in case of kidney resection within renal cancer because there is a need to determine if adrenal gland is involved by malignant spread. Myelolipoma and ganglioneuroma are incidental findings in our case report presentation of patient who underwent operation due to kidney malignancy. In opposition to clear cell carcinomas, which are the most common primary malignancies of kidneys, adrenal ganglioneuromas are rare tumors. Thus, our report of clear cell carcinoma and ganglioneuroma is not usual. Ganglioneuroma can occur together with pheochromocytoma both in adrenal and extradural location. Gong et al. reported non-functioning such a composite tumors with typical texture of paraganglioma/pheochromocytoma intimately intermingled with ganglioneuroma foci [13]. Indeed, there is quite essential prevalence of coexistence of both pheochromocytoma and ganglioneuroma in adrenal glands. For instance, Rondeau et al. reported pheochromocytoma counterpart in three of all seven investigated ganglioneuromas [14]. In addition, a close linkage between ganglioneuromatous growth and pheochromocytoma is classically illustrated in MEN2B syndrome [15]. It is believed that pheochromocytoma and ganglioneuroma converts into a common lineage in adrenal gland. However, the idea of existing residual pheochromocytoma was excluded.

Interestingly, ganglioneuromas occur to be accompanied by adrenal hyperfunctioning neuroendocrine cells exceptionally secreting of ACTH and one of such cases presented even with Cushin’s syndrome (CS) [16]. Thus, in case of every diagnosis of adrenal ganglioneuroma hormonal disorders and any hormonal active tumors as pheochromocytoma should be ruled out. In our case, there was no classical component of pheochromocytoma and nests of adrenal cortex and medulla were excluded from diagnosis of residual pheochromocytoma.

Ganglioneuromas can also be found in retroperitoneal space in extradural location and are believed to derive from the neural crest [17].

Although pure ganglioneuromas are very well differentiated and benign as rule, they can reach quite possible large size exceeding 5 cm in diameter [18]. Moreover, concerning possible regression of neuroblastoma to benign ganglioneuroma, each ganglioneuroma should be carefully evaluated in order to exclude existence of neuroblastoma foci within ganglioneuroma counterpart no matter what the location of the tumor is [19]. Nevertheless, composite adrenal tumors that consist of pheochromocytoma, ganglioneuroma and ganglioneuroblastoma, can occur and such neoplastic growth reflect a histogenesis of adrenal medulla that is believed to be closely related to highly modified and specialized sympathetic ganglia in developmental perspective [20, 21]. One case of retroperitoneal ganglioneuroma was discovered within malignant pheochromocytoma of both adrenals with catecholamine overproduction in the background of medullary thyroid carcinoma and primary hyperparathyroidism in course of MEN2B syndrome [22].

A close and intimate admixture of adrenal cortical and medullar cells was noted in our case of myelolipoma-ganglioneuroma. Such an entrapment of these adrenal cell types was also reported by Merchant et al. [23]. He postulated that presence of adrenal cortical cells in the stroma of ganglioneuroma could contribute to the onset of the myelolipoma in a peculiar hormonal microenvironment [23].

In experimental mouse model of MEN2B, Smith-Hicks et al. reported C-cell hyperplasia and chromaffin cell hyperplasia developing into pheochromocytoma [24]. However, gastrointestinal ganglioneuromas did not develop but instead ganglioneuromas of adrenal medulla and enlargement of the accompanying sympathetic ganglia were revealed in homozygotes with substitution of threonine for Met918 in the RET receptor tyrosine kinase [24]. Similarly to Smith-Hicks et al., Sweetser et al. induced ganglioneuromas in sympathetic ganglia and adrenal glands of DbetaH-RET[MEN2B] transgenic mice [25]. These mice were generated with involvement of the dopamine beta-hydroxylase promoter to evoke RET expression and constitute experimental model of MEN2B [25]. Such a finding could suggest that adrenal location could be a possible variant for ganglioneuroma growth in course of MEN2B syndrome [24, 25].

Molecular background is indeed quite intriguing in particular in our set of three coexistent tumors that are presented in this rather unusual case report.

The adrenal myelolipoma is viewed as sporadic tumor is rather not associated with genetic abnormalities that underline multiple endocrine neoplasia type 1 (MEN-1) as any loss of heterozygosity on chromosome 11q13 was not found but there was intragenic heterozygosity within codon 418 of the menin gene [26]. Tumorgenesis of myelolipoma is obscure but this lesion is regarded as true neoplasm due to its clonal nature, which is confirmed by finding of nonrandom X-chromosome inactivation in hematopoietic cells and adipocytes in eight of 11 female cases investigated by Bishop et al. [27]. Interestingly, so far, eight ganglioneuromas have been reported in well-known monosomy of chromosome X-chromosome inactivation in X-chromosome Y-Turner syndrome and adrenal screening is recommended in this kind of genetic disorder [28]. Moreover, a balanced translocation [3;21]q(25;p11) was also found in 26-year-old man [29]. Abnormality in chromosome 3 is also found in renal cell carcinoma sarcomatoid type. This neoplasm displays a great array of genetic abnormalities and among them there is also loss of 3p [30]. Both sarcomatoid and clear cell carcinomas share similar molecular profile, leading to opinion that a sarcomatoid component is closely related and probably derivates from clear cell carcinoma [30].

Particularly, loss of heterozygosity (LOH) was observed at the D3S1300, D7S522, D8S261, D9S171, and TP53 loci in 15% to 50% studied cases of clear cell carcinoma, while in the sarcomatoid type LOH was detected in the D3S1300, D7S522, D8S261, D9S171, and TP53 loci in 18% to 70% of cases [31]. Furthermore, the pattern of X-chromosome was non-randomly inactivated in the same pattern in both clear cell and sarcomatoid type to ground a hypothesis that these both histopathological types derive from the one progenitor cell [31].
A mutation in the succinate dehydrogenase subunit B [SDHB] gene is another molecular link for coexistence of ganglioneuroma and clear cell carcinoma with sarcomatoid component. This mutation was revealed in a patient with two small mature ganglioneuromas between the superior mesenteric artery and the left adrenal gland [32]. It is worth to mention that germline succinate dehydrogenase B [SDHB] mutation is responsible with pheochromocytoma/paraganglioma syndrome type 4 [PGL4] that is associated with increased incidence of pheochromocytoma, paraganglioma, type 2 [SDHB negative] gastrointestinal stromal tumors as well as renal cancers. SDHB mutation is so important because it probably affects morphology of in renal cell carcinomas. Namely, such a mutation was found in sarcomatoid component of renal cancer [33].

In our case, we did not attempt to detect any above described mutations that seem to link these quite different tumors at first sight. Although being quite promising, molecular profiling was not expected to bring any essential clinical benefit for our patient. Obviously, the prognosis was dependent only on one tumor: clear cell carcinoma with sarcomatoid component.

**Conclusions**

We would like to emphasize that adrenal mature ganglioneuroma is an uncommon entity. Its coexistence with myelolipoma seems to be truly exceptional in the same organ. To our knowledge, our present case description has been the first report of such neoplasms in combination with renal cancer cell type clear cell type with sarcomatoid component so far.

**References**


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