

REVIEW OF SMALL CELL CARCINOMA OF THE KIDNEY WITH FOCUS ON CLINICAL AND PATHOBIOLOGICAL ASPECTS

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Small cell carcinoma (SmCC) of the kidney is extremely rare. In this article, we present a review of SmCC of the kidney with the focus on clinical and pathobiological aspects. Macroscopically, this tumor often shows a bulky mass extensively replacing the renal parenchyma with vascular invasion and metastasis to lymph nodes. Histologically, the tumor is composed of small cells with scant cytoplasm, round to oval nuclei, finely granular chromatin and inconspicuous nucleoli. Rosette or tubular formation may be present. Immunohistochemically, neoplastic cells show variable positivity for neuron-specific enolase, chromogranin A, synaptophysin, CD57 (Leu7) and CD56. A dot-like staining pattern for cytokeratin may also be observed. An electron microscopic examination may identify electron-dense neurosecretory granules in the cytoplasm. As a therapeutic option, nephrectomy and systemic chemotherapy should be considered. However, despite multimodal therapy, most patients have a dismal outcome and die of widely metastatic disease within one to two years. As there are limited genetic data on SmCC of the kidney, a large series studying this will be needed in the future.

Key words: small cell carcinoma, kidney, dismal prognosis.

Introduction

Small cell carcinoma (SmCC) predominantly occurs in the lung, but may arise in a wide variety of organs. Primary renal SmCC is an extremely rare neoplasm. According to the present World Health Organization (WHO) classification of the lung, neuroendocrine tumors are subdivided into four categories: (1) typical carcinoid, (2) atypical carcinoid, (3) small cell and (4)

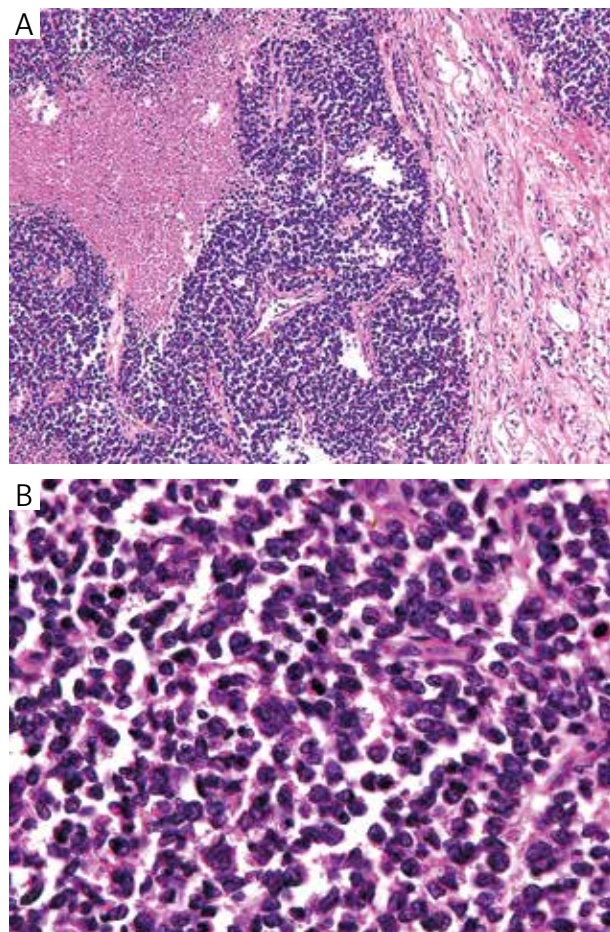
large cell neuroendocrine carcinoma (LCNEC) [1]. All these tumors have also been reported in the kidney [2-5]. In this article, we present an overview of SmCC of the kidney with clinical and pathobiological aspects.

Clinical characteristics

Clinical data of 31 previously reported cases of SmCC of the kidney are summarized in Table I. Some

Table I. Clinicopathological data of 31 previously reported cases of small cell carcinoma of the kidney

Sex	Male : female = 14 : 17
Age	22-87 years (mean 57 years)
Follow-up	27 cases available
	18 died of disease
	2 alive with disease
	7 alive without disease
Immunohistochemistry (positive/examined)	Neuron specific enolase 7/9
	Chromogranin A 11/14
	Synaptophysin 12/13
	Cytokeratin CAM5.2 12/13
	TTF-1 1/1
	CD56 1/1

**Fig. 1.** Microscopic findings. A) Sheet-like growth pattern with extensive necrosis is seen. B) The size of tumor cells is not larger than three times that of resting lymphocytes. Nuclear chromatin is finely granular and nucleoli are inconspicuous

investigators have reported a female preponderance whereas other studies suggest that there is no gender predominance [3, 6-8]. Patients frequently present with abdominal pain, gross hematuria, flank mass and weight loss [3, 6-10]. A smoking history is present in some cases [2]. Imaging analysis may disclose a large heterogeneous renal mass frequently with extension into the renal vein or inferior vena cava and/or metastasis to lymph nodes [7, 11]. An association with papillary RCC and chromophobe RCC has been reported [2, 12]. Small cell carcinoma with foci of glandular or squamous differentiation seems to be restricted to tumors that arise from the renal pelvis, but not from renal parenchyma [8, 13]. Primary renal SmCC arising after renal transplantation has been reported [14].

Pathological findings

Macroscopic findings

The tumor usually presents as a huge mass when discovered, and extends into the perinephric adipose tissue [3, 6-11, 15]. The cut surface of the tumor shows white, gray-white or gray-yellow color [10, 16, 17]. Multilobulation is frequently seen [18]. Invasion into the inferior vena cava or renal vein and metastasis to lymph nodes are frequent [3, 6, 7, 10, 11, 15]. Direct invasion into adjacent anatomical structures such as liver, diaphragm or abdominal wall may be observed [2, 6, 17].

Microscopic findings

The tumor consists of small neoplastic cells with a size of up to three times as large as a small, non-stimulated/resting lymphocyte [6, 10, 17]. Several growth patterns such as solid-sheet, nesting, trabecular, rosette or tubular formation may be seen [17]. Extensive necrosis is often present (Fig. 1A) [2, 3, 8]. Nuclear molding and/or smudging of the chromatin, as seen in the pulmonary SmCC, are common features [8]. Tumor cells possess scant cytoplasm, oval to round nuclei, finely granular nuclear chromatin, and absent to inconspicuous nucleoli (Fig. 1B) [3, 6, 8, 9, 15-17, 19]. Mitotic activity is brisk and atypical mitotic figures are frequent [6, 15, 17].

Histochemical findings

The cytoplasm of tumorous cells demonstrates positivity for the argyrophilic Grimelius stain [15, 17, 19]. Argentaffin Fontana-Masson silver impregnation stain is generally negative [9, 16].

Immunohistochemical findings

Neoplastic cells show variable positivity for neuron-specific enolase, chromogranin A, synaptophysin,

CD57 (Leu 7) and CD56 [2, 3, 6, 8-11, 16, 18-20]. In addition, tumor cells frequently demonstrate dot-like staining for cytokeratin (Fig. 2) [3, 20]. In some cases, immunoreactivity to hormonal polypeptides including calcitonin, serotonin and adrenocorticotrophic hormone has been documented [3, 6, 15]. The main immunohistochemical data are summarized in Table I.

Ultrastructural findings

Tumor cells contain electron-dense neurosecretory granules, mitochondria, endoplasmic reticulum, Golgi apparatus, polyribosomes and intermediate filaments in the cytoplasm [6, 16, 19, 20]. Intercellular junctions with features suggesting desmosomes may be observed [3, 9, 20].

DNA flow cytometry

DNA analysis of the tumor cells shows an aneuploidy peak [9, 17].

Molecular genetic study

In a case with combined renal SmCC and papillary RCC, fluorescence *in situ* hybridization analysis showed the amplification of the *Myc* gene [21].

Differential diagnosis

Renal SmCC should be discriminated from typical carcinoid, atypical carcinoma, LCNEC, high grade urothelial carcinoma, small cell oncocytoma with pseudorosettes (SCOP), thyroid-like follicular carcinoma of the kidney, blastemal-dominant Wilms' tumor, Ewing's sarcoma/primitive neuroectodermal tumor (ES/PNET), neuroblastoma, malignant lymphoma, rhabdomyosarcoma (RMS), desmoplastic small round cell tumor (DSRCT), synovial sarcoma (SS) and metastatic SmCC. Tumor cells of typical carcinoid are arranged in trabecular, ribbon-like, gyriform, insular, glandular and solid patterns, but mitotic figures are sparse [5]. In atypical carcinoid, increased mitotic activity is observed [22]. The size of tumor cells in LCNEC is larger than that of SmCC. Abundant cytoplasm, vesicular chromatin, prominent nucleoli and perilobular palisading are seen [2-4, 18]. High grade urothelial carcinoma including the plasmacytoid variant or lymphoepithelioma-like variant should be distinguished from SmCC [23]. Neoplastic cells of SCOP consist of oncocytes and oncoblasts surrounding hyaline-basement membrane-like material [24]. Thyroid-like follicular carcinoma has follicular architecture composed of microfollicles and macrofollicles filled with colloid-like material [25]. Wilms' tumor predominantly occurs in children and the blastemal component is positive for WT1 [26]. Ewing's sarcoma/primitive neuroectodermal tumor is

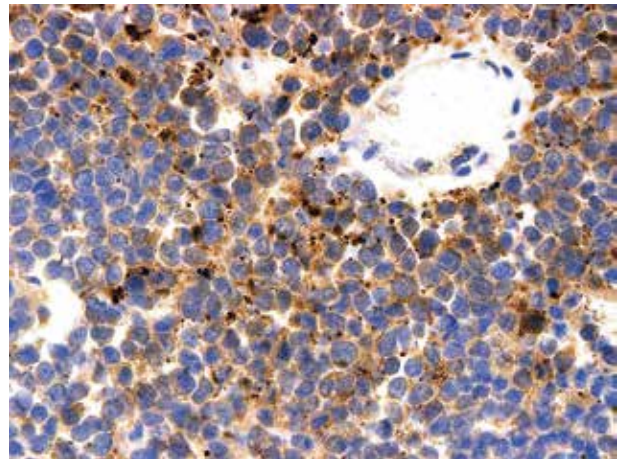


Fig. 2. Immunohistochemical findings. The cytoplasm of neoplastic cells shows a dot-like staining pattern for cytokeratin CAM5.2

immunohistochemically positive for CD99 and Fli-1. The identification of a chimeric transcript specific for ES/PNET is diagnostically useful [26]. Malignant lymphoma has cleaved, convoluted or lobulated nuclei and is generally immunoreactive for CD45 (leukocyte common antigen). Neuroblastoma generally occurs in the adrenal gland and histologically has a delicate cytoplasmic process. Rhabdomyosarcoma generally affects infants or children and tumor cells display eosinophilic or clear cytoplasm and may show striation. Rhabdomyosarcoma is positive for desmin, myogenin or Myo D1. Desmoplastic small round cell tumor generally occurs in children and adolescents and is immunohistochemically positive for WT1 and desmin. The detection of *EWS-WT1* chimeric transcript is very helpful in establishing the accurate diagnosis [27]. Synovial sarcoma is immunohistochemically positive for CD99 and *bcl-2*. The identification of a chimeric transcript such as *SYT-SXX1* or *SYT-SXX2* is diagnostic for this tumor [28]. Finally, it is for clinicians to exclude the possibility of metastatic cancer, particular SmCC derived from the lung [9, 17]. In this situation, TTF-1 immunohistochemistry is not helpful in determining the primary site, because TTF-1 is generally expressed in SmCC of various anatomic sites. Accordingly, the clinical information is most important in establishing the differential diagnosis whether the tumor is primary or metastatic.

Therapy

Surgical resection by nephrectomy and systemic chemotherapy is the currently available therapeutic modality [7, 9, 16, 29, 30]. Nephrectomy helps to establish the correct diagnosis, i.e. to rule out other more common renal neoplasms within the spectrum of malignant small round blue cell tumors [10]. However, as renal SmCC often shows extra-renal extension, the tumor may be amendable to com-

plete resection [18]. Regarding chemotherapy, platinum-based chemotherapy improves overall survival [7]. Tumor thrombectomy may be effective [10]. Radiation therapy can be used for postoperative residual local disease or metastatic lesions [18, 20].

Prognosis

Patients usually have a poor clinical outcome despite multimodal therapy [2, 6-8, 18, 20, 30]. Most patients die of the disease within a few years [7, 8]. Distant metastasis occurs in the brain, bone, lung, liver and adrenal gland [2, 3, 6, 8, 16, 17, 20, 30]. It is possible that patients with organ-confined tumor may have a long-term survival with early discovery and treatment [8].

Future perspectives

Owing to the rarity of this tumor, there is a limited amount of genetic data on renal SmCC to date. Accordingly, a large scale genetic study is necessary to elucidate the pathogenesis of this tumor. According to the WHO classification of tumors of the digestive tract, the grading of neuroendocrine neoplasm is based on mitotic counts and the Ki-67 index. According to this scheme, neuroendocrine epithelial neoplasms have been subdivided into neuroendocrine tumor (NET) G1, NET G2 and neuroendocrine carcinoma (large cell and small cell types) [31]. It is possible that neuroendocrine neoplasm arising from the kidney may follow the classification of other organs such as the digestive or respiratory tract in the near future [1, 31].

Authors declare no conflict of interest.

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