Clinical Case Report

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Primary small cell carcinoma of the ureter

Case report and review of the literature

Fabiola Farci, MD[a,*], Francesca Manassero, MD[b], Ramona Baldesi, MD[b], Annamaria Bartolucci, MD[a], Laura Boldrini, PhD[a], Cesare Selli, MD[b], Pinuccia Faviana, MD[a]

Abstract

Rationale: Primitive small cell carcinoma of the ureter is extremely rare, in this case report is meticulously described its aggressive clinical course and the pathological clues that help with the diagnosis. Also, a detailed table with the clinico-pathological features of analogous case reports in literature is provided.

Patient concerns: A 79-year-old female presented with gross hematuria and flank pain.

Diagnoses: Small cell carcinoma of the ureter. The surgical specimen showed a mixed histology of small cell carcinoma and transitional cell carcinoma; the common neuroendocrine markers (chromogranin A, synaptophysin, CD56) were positive, and vimentin and thyroid transcription factor 1 were negative. The patient had an advanced stage at presentation with regional nodes involvement (pT3N1).

Interventions: Segmental ureterectomy was performed but it was only possible to administer 1 cycle of platinum-based adjuvant chemotherapy due to the rapid decline of her clinical parameters.

Outcomes: The disease rapidly spread locally and metastasized.

Lesson: The clinicians must be aware of this aggressive tumor with silent clinical course and advanced stages at presentation.

Abbreviations: CT = computed tomography, CK = cytokeratin, SCC = small cell carcinoma, TTF-1 = thyroid transcription factor 1.

Keywords: carcinoma, case report, mixed histotype, neuroendocrine, pathology, small cell, urology

1. Introduction

Primary small cell carcinoma (SCC) of the urinary tract is a rare cancer, accounting for less than 0.5% of urinary tract tumors,[1] mostly localized in the bladder and prostate, while its localization in the renal pelvis or in the ureter is extremely rare. Smoking exposure causes reactive and genetic damage to the tissues, and is a main risk factor for urothelial carcinoma and small cell neuroendocrine carcinoma.[2] Being such a rare disease, the pathogenesis is still unclear, and 2 theories have been postulated. The first claims its origin from a neuroendocrine cell population derived from the neural crest (enterochromaffin cells) migrated in the genitourinary tract during embryogenesis; the second theorizes its genesis from the pluripotent epithelial cells of the genitourinary tract. The latter could explain the common finding of a mixed histologic profile (transitional cell carcinoma, squamous cell carcinoma, adenocarcinoma, sarcomatoid carcinoma, and sarcoma), often described as a gradual transition from 1 subtype to the other.

Small cell carcinoma of the ureter has been described in about 40 patients so far[3–35] with similarities in symptoms, management, and outcome, as outlined in Table 1.

2. Case report

A 79-year-old female presented with right-sided back pain and gross hematuria. Her clinical history was significant for atrial fibrillation treated with oral anticoagulant, which was suspended due to hematuria. She had a smoking history of more than 20 cigarettes per day for nearly 60 years. Physical examination revealed pain at the right costovertebral angle extended to the right groin over the location of the ureter. Creatinine levels at the admission were 1.37mg/dL. Abdominal ultrasound was immediately performed, revealing a grade 3 right hydronephrosis without lithiasis and hematic material in the bladder. A functional scintigraphy study with 99mTc-diethylene-triamine-penta-acetate revealed a decreased function of the right kidney, and the calculated glomerular filtration rate (GFR, Gates method) was 27 mL/min for the right kidney and 40 mL/min for the left kidney. At cystoscopic examination, the bladder wall was irregular in the right emitrigon, and the right ureteral orifice was swollen and bleeding. Urine cytology showed atypical morphological features, classified as suspicious for high-grade urothelial carcinoma (the Paris System for reporting urinary cytology). The following abdominal computed tomography

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[a] Department of Surgical, Medical, Molecular Pathology and Critical Area, University of Pisa, [b] Unit of Pathology, Department of Translational Research and New Technologies in Medicine and Surgery, University of Pisa, Via Roma, Pisa, Italy.

[*] Correspondence: Fabiola Farci, Department of Surgical, Medical, Molecular Pathology and Critical Area, University of Pisa, Via Roma 57, Pisa 56126, Italy (e-mail: fabiolafarci@gmail.com).

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Table 1

Small cell carcinoma literature review.

A: References	B: Age/sex	C: Smoking	D: Symptom	E: TNM, size	F: Surgical treatment	G: Adjuvant therapy	H: Immunohistochemistry	I: Associated histotypes	J: Follow-up (postsurgery)
Current report	79, F ca	Heavy smoker	FP, GH	pT3N1Mx (2 cm)	U + LA	Et (1 cycl)	chrA+, syn+, CD56+; TTF1−, vim−	SCC, UC	3 mos local recurrence, DOD
Zhong et al, 2017[3]	62, M as	No	None	T3N0M0 (10.5 cm)	NU	Yes	NSE+/−, chrA+/−, syn+/−	SCC, UC, S, Ly	4 mos DOD
	64, F as	No	GH	T3N1M0 (2 cm)	NU + LA	Yes	NSE+, chrA+/−, syn−	SCC	9 mos NOD
	62, F as	No	GH	T4N0M0 (3 cm)	NU + LA	None	NSE+, chrA−, syn−	SCC	6 mos NOD
	56, M as	No	GH	T3N0M0 (2.5 cm)	NU	None	NSE+/−, chrA−, syn+/−	SCC, UC, S	6 mos NOD
Hensley et al, 2017[4]	89, M ca	Yes	FP, GH	Not stated	Biopsy	None	CAM 5.2+	SCC	2 mos, local recurrence
	67, F ca	No	FP, GH	cT4N1M1	NU+L	cisPt + Et (4 cycl), RT	syn+, chrA+, panCK+	SCC	Metastatic (adrenal glands, pelvis). 7 mos DOD
Alevizopoulos et al, 2016[5]	78, M ca	Not stated	GH	cT3N1M1 (4.3 cm)	Refused	Refused	CD56+, CK7−, CK20−	SCC	13 mos DOD
Sood et al, 2016[6]	55, F	No	FP, GH	cT3N2M0	Planned	cisPt + Et (neoadj)	syn+	SCC	3 mos NED
Ueda et al, 2016[7]	63, M as	Not stated	GH	T3N0M1	NU	cisPt + Ge (3 cycl)	Not stated	SCC, UC	12 mos. Local recurrence (bladder) at 3 mos.
Wang et al, 2016[8]	69, M as	Not stated	FP, GH, HUN	cT3N0M1 (3.5 cm)	NU	Refused	CD56+, syn+, EMA+, CK7+; NSE−, chrA−, Ki67 20%	SCC	Metastatic; 12 mos DOD
Acosta et al, 2015[9]	71, F ca	Not stated	FP	pT3N1Mx (4.3 cm)	NU	cPt + Et (neoadj)	TTF1+, chrA+, syn+, CD56+	SCC	6 mos DOD
Osaka et al, 2015[10]	70, M as	Yes	FP	cT3N0M0 (before neoadj) pT2N0M0 (after neoadj)	Neoadj (cisPt + Iri 3 cycl) + NU	None	AE1/3+, CK7+, syn+, CD56+	SCC	38 mos NED
Ahsaini et al, 2013[11]	54, M, af	Yes	GH	T1N0M0	Neoadj (If, Do, Et, cisPt) NU	None	chrA+, syn+, CD56+, NSE+	SCC	24 mos NED
Yang et al, 2013[12]	59, M as	Heavy smoker	HUN	T3NxMx (3.5 cm)	NU	cisPt + Et (4 cycl), RT (180cGyx30)	chrA+, syn+, CD56+, NSE+	SCC, HGUC	10 mos NED
Ping et al, 2013[13]	65, F as	Not stated	FP	NA (5 cm)	NU	cisPT + Iri (4 cycl)	chrA+, syn+, CD56+, Ki67 67%	SCC	4 mos NED
Zhao et al, 2012[14]	70, F as	Not stated	FP, HUN	cT3N0M1 (1.6 cm)	NU	Not stated	CK7+, chrA+, syn+, NSE+	SCC	Metastatic (liver, lungs, lymph) at 9 mos. Died at 10 mos (MOF)
Miller et al, 2011[15]	80, F	Not stated	FP	T3NxM1	None	None	chrA+, syn+, CD56+	SCC	Died at 4 mos (MI)
	73, F	Not stated	GH	T3NxM0	NU	None	chrA+, syn+, CD56+, TTF1+	SCC	5 mos DOD
	73, F	Not stated	None	T3NxM0	NU	None	chrA+, syn+, CD56+, TTF1+	SCC	10 mos DOD
Patil et al, 2011[16]	75, M	Yes	FP	T3N1M0	NU	Refused	chrA+, NSE+	SCC	2 mos DOD
Kho and Chan, 2010[17]	77, M as	Heavy smoker	FP	T3N0M0 (2 cm)	NU	cPt + Et (3 cycl)	chrA+	SCC	Died at 4 mos (sepsis)
Kozyrakis et al, 2009[18]	78, M ca	Heavy smoker	GH	pT3NxMx (1.7 cm)	NU	None	chrA+, syn+, CD56+, Ki67 70%	SCC, UC, Sq	Metastatic lung. 6 mos DOD
Kuroda et al, 2009[19]	79, M as	Not stated	GH	T2NxMx (3.7 cm)	NU	None	chrA+; syn−, CK7−, grimelius−	SCC, UC	36 mos NED
Terada, 2009[20]	48, M as	Not stated	FP	pT2N0M0 (1.5 cm)	U	None	CK7+, CD56+, PDGFRA+, chrA−, syn−, NSE−	SCC	24 mos DOD
Ito et al, 2009[21]	84, F as	Not stated	NA	Not stated	NU	None	NA	SCC	Not stated
Banerji et al, 2008[23]	55, M	Not stated	FP	pT3N0M0	NU	cPt + Ge (6 cycl)	chrA+, syn+	SCC, UC	Not stated
Masui et al, 2008[22]	69, M	Not stated	NA	T4NxMx	NU	CT, RT	NA	SCC	14 mos NED
Ryu et al, 2008[24]	78, M as	Not stated	FP, GH, HUN	pT3N1M0 (5 cm)	U, LA	None	AE1/3+, EMA+, N-CAM+ chrA +; syn−, S100−	SCC, UC	3 mos

(*continued*)

Table 1

(continued).

A: References	B: Age/sex	C: Smoking	D: Symptom	E: TNM, size	F: Surgical treatment	G: Adjuvant therapy	H: Immunohistochemistry	I: Associated histotypes	J: Follow-up (postsurgery)
Sakuma et al, 2008[25]	73, F as	Not stated	GH, HUN	pT4NxMx	NU	Senile for chemio	chrA+, syn+, grimelius+	SCC, UC	9 mos DOD
Martin et al, 2007[26]	77, M	Not stated	GH, HUN	T3NxM0 (1 cm)	NU	cPt + Et (4 cycl), RT: (50.4 Gy)	CKpan+, NSE+; TTF1−, EMA−, CK7−, CK20 -	SCC	13 mos, NED
Busby et al, 2006[27]	NA	NA	NA	pT3N0M0	NU	adj	NA	SCC	11 mos DOD. Metastatic (liver)
Chang et al, 2005[28]	67, M as	NA	NA	NA	NA	NA	NA	NA	NA
Ishikawa et al, 2004[29]	53, M as	Not stated	HUN, SIADH	TN1	NU	Mtx + cisPt + Et	NA	SCC	5 mos DOD
Chuang and Liao, 2003[30]	57, M as	Not stated	GH, FP	T3N1Mx	NU	None	NSE+, vim+, EMA+, S100+	SCC, UC	17 mos DOD
	50, M as	Not stated	GH	T3N0Mx	NU	None	NSE+, vim−, EMA−	SCC, UC	>55 mos NED
Kim et al, 2001[31]	60, M as	Yes	FP	pT2NxM0 (3.8 cm)	NU	Refused	NSE+, chrA+, syn+	SCC, UC, Sq	36 mos NED
Gupta et al, 1999[32]	72, M	Not stated	GH	NA	NA	NA	NA	NA	NA
Tsutsumi et al, 1993[33]	60, M as	Not stated	GH	T2NxM0 (<8 cm)	NU + pC	cPt + Et (4 cycl), RT (50 Gy)	NSE+, N-cam+, chrA−	SCC, UC, Sq, S	16 mos, metastatic (bone)
Sakamoto et al, 1993[34]	64, F as	Not stated	FP	pT4N0M0	NU + tC	Cyc, Ad, cisPt	Not stated	SCC, UC	8 mos NED
Sakai et al, 1990[35]	62, M as	Not stated	GH	T2N1M0 (1.8 cm)	NU + pC + LA	cisPt + Et (2 cycl)	NSE+	SCC, UC	8 mos NED

Clinical–pathological features of all known cases of small cell carcinoma reported in literature since 1990. For each patient are briefly specified the significant clinical and pathological factors (columns A–J).

A: reference; B: age, sex, and ethnicity of the patient (when available); C: smoking history (classified as heavy smoker if the daily consumption is more than 20 cigarettes); D: symptoms at presentation; E: TNM staging at the time of resection with tumor size (when available); F: type of surgical resection; G: adjuvant (or neoadjuvant) chemo/radiotherapy; H: immunohistochemical phenotype; I: the associated histotypes; J: follow-up post-surgery, including the duration and the recurrence/metastatic data.

AC = adenocarcinoma, af = African, as = Asian, ca = Caucasian, CAM = cytocheratin CAM 5.2, chrA = chromogranin-A, CK = cytokeratin, CT = chemotherapy, DOD = died of disease, EMA = epithelial membrane antigen, F = female, FP = flank pain, GH = gross hematuria, HGUC = high-grade urothelial carcinoma in situ, HUN = hydro-ureteronephrosis, If = ifosfamide, Iri = Irinotecan, LA = lymphadenectomy, Ly = lymphoma, M = male, MI = myocardial infarction, MOF = multiorgan failure, mos = months, Mtx = methotrexate, NA = data not available, NED = nonevidence of disease, neoadj = neoadjuvant therapy, NSE = nonspecific enolase, NU = nephroureterectomy, pC = partial cystectomy, PDGFRA = platelet-derived growth factor receptor A, RT = radiotherapy, S = sarcoma, SCC = small cell carcinoma, SIADH = inappropriate ADH secretion syndrome, Sq = squamous carcinoma, syn = synaptophysin, tC = total cystectomy, TTF1 = thyroid transcription factor 1, U = ureterectomy, UC = urothelial carcinoma, vim = vimentin.

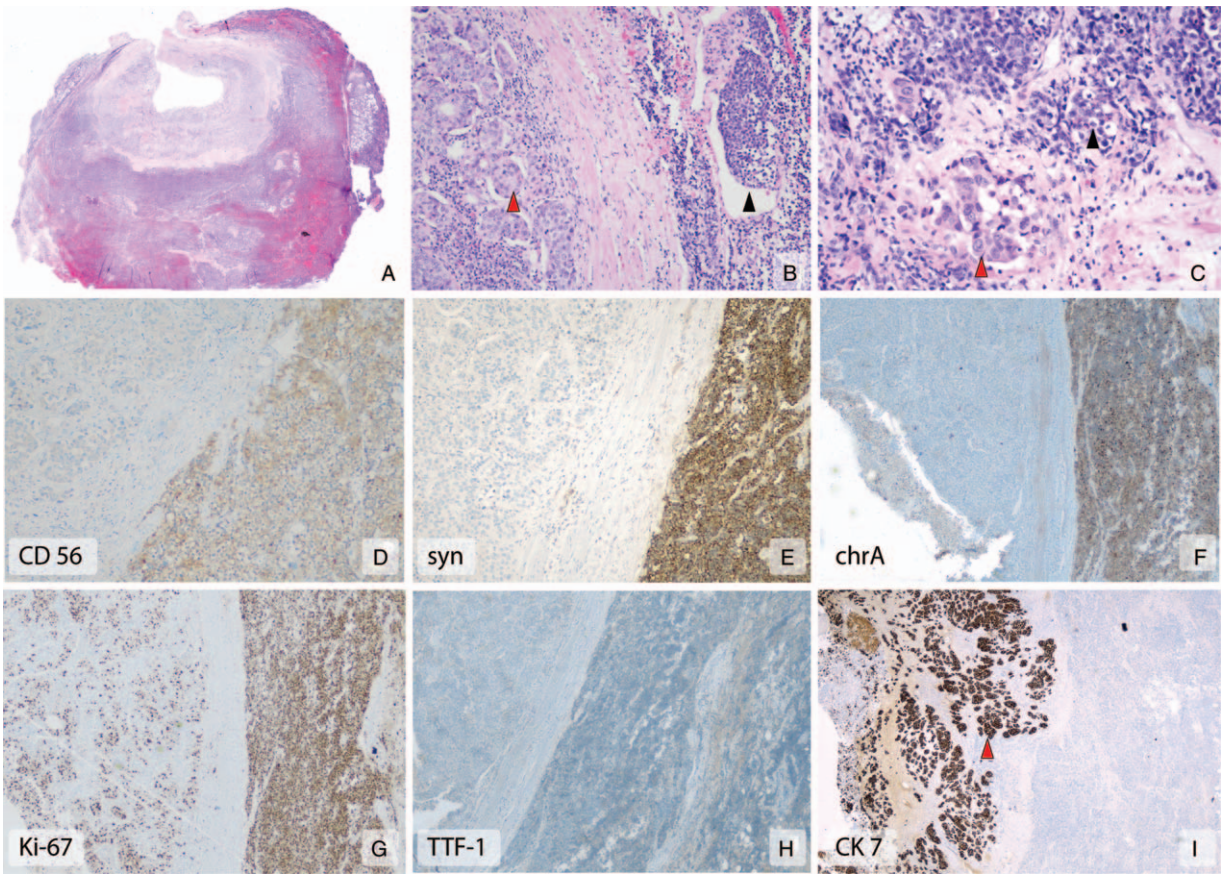

Figure 1. (A) Panoramic view of the ureteral tumor, hematoxylin–eosin stain (H&E). (B) The transitional cell carcinoma (red triangle) infiltrates the ureteral wall together with the small cell carcinoma (SCC) component with a clear lymphovascular invasion (black triangle) (H&E 10x). (C) The transitional cell carcinoma is intermixed with the SCC (H&E 20x). (D–F) The neuroendocrine markers are all positive in the SCC component (D: CD56, 10x; E: synaptophysin, 10x; F: chromogranin-A, 2x). (G) Ki-67 is remarkably high, especially in the SCC component of the tumor (2x). (H) TTF-1 immunohistochemistry is completely negative (2x). (I) The transitional cell carcinoma is CK7 positive (2x).

(CT) scan found thickened walls in the distal part of the right ureter in the absence of lithiasis. A nephroureterectomy was planned, but had to be suspended due to the patient's clinical condition, and a segmental ureterectomy was performed instead. The right distal ureter was resected together with some enlarged regional nodes; its macroscopic inspection showed a thickened and hemorrhagic wall, with a nodular neoplasm of 2×1.5 cm obstructing the lumen and infiltrating the surrounding adipose tissue. The tumor was composed of small cell carcinoma admixed with infiltrating transitional cell carcinoma (Fig. 1). The neuroendocrine markers (synaptophysin, chromogranin-A, CD56) were positive in the SCC part of the tumor, the mitotic count was high, and the proliferative index counted by Ki-67 was more than 90%; the tumor was negative for vimentin and TTF-1. The final diagnosis was small cell neuroendocrine carcinoma invading 80% of the surgical specimen associated with high-grade urothelial carcinoma, both infiltrating the ureteral wall, the perineural spaces, and the perivisceral adipose tissue. The ureteral resection margins were negative. The right external iliac and presacral nodes were both metastatic for small cell neuroendocrine carcinoma. The pathological stage at the diagnosis was pT3N1 and the patient underwent a 2-week cycle of etoposide chemotherapy that had to be suspended for renal failure. The disease rapidly progressed: at 2 and a half months after admission and less than a month after segmental ureterectomy, an abdominal CT scan showed a contrast-enhanced 19×10 cm mass surrounding and obstructing the ureter, extended without clear margins to the aortocaval space, displacing the iliac vessels and infiltrating the surrounding tissues with diffuse pelvic lymphadenopathy. Chest and cranial CT scan did not detect any other lesions. The patient died for the progression of disease 5 months after admission.

3. Discussion

The usual presentation is flank homolateral pain due to hydronephrosis (with or without irradiation to the groin) and gross hematuria due to the vascular invasion; less frequently the patient laments weight loss, dysuria, and urinary tract infection. When those symptoms appear, the disease might be already at late stages, also because the pain gradually increases over time, becoming chronic, allowing a differential diagnosis from lithiasis that presents as acute pain. Ultrasonography is the initial choice for imaging in a suspected obstruction of the urinary tract, helping the clinician to differentiate between lithiasis and other causes of obstruction; urography and CT scan are second-level procedures that allow to establish the presence of a mass, confirm an associated hydronephrosis due to the obstruction, and the extension of the tumor and the regional node status. Urine cytology can be a precious diagnostic tool, but it requires an

expert cytologist to get the right diagnosis, considering the paucity of the neoplastic cells in the smear, the mixed histotypes, and the infrequency of small cell carcinoma. A CT-guided biopsy or a nephro-ureteral resection are the usual choices for the urologist, allowing a pathological diagnosis.

At gross examination, SCC is usually described as a firm greyish tumor, often with hemorrhagic areas, protruding and occluding the ureteral lumen, with ill-defined borders and with peritumoral wall thickening. Small cell carcinoma has an architecture similar to the neuroendocrine tumors of other sites, composed by solid sheets or different pattern such as rosette or nests, often associated with a desmoplastic reaction. Crush artefact ("Azzopardi effect") is common. The cells are small to medium-sized with scant cytoplasm and prominent nucleus with granular (classically described as "salt and pepper") chromatin. Mitosis and necrosis are frequent, and also vascular invasion. As previously mentioned, there may coexist other histological types such as squamous carcinoma, transitional carcinoma, adenocarcinoma, and sarcomatoid carcinoma. The differential diagnoses include poorly differentiated urothelial carcinoma, primitive neuroectodermal tumor, malignant lymphoma, lymphoepithelioma-like carcinoma, and plasmacytoid carcinoma, from which this tumor can be differentiated by immunohistochemistry.[27] The neuroendocrine stains are usually positive (chromogranin A, synaptophysin, CD56, neuron-specific enolase) and it may show positivity for keratins such as cytokeratin (CK)7, epithelial membrane antigen, and pan-CK. Uroplakin III is usually negative, and this may help the differential diagnosis with transitional cell carcinoma. Vimentin expression has been previously related to a higher metastatic potential and a poor outcome in a clinical report.[30] The tumor is frequently diagnosed at late stages, when it has already invaded the periuretheral tissues and the surrounding structures. The overall median survival is 17 months, with a 51.9% of 1-year survival rate.[3] The primary treatment is surgical remotion of the tumor by ureterectomy or nephroureterectomy depending on the clinical status of the patient, stage, and localization of the tumor. Due to the aggressive course of SCC, the surgeon must address the radicality of the excision as early as possible, considering that in most cases the resection alone does not seem to stop the progression of the disease. If the clinical parameters of the patient are stable, the surgical treatment is usually followed by adjuvant chemotherapy and radiotherapy. It is important to note that the patient might be anemic for the long-term hematuria, and the obstruction caused by the tumor often causes hydronephrosis and impaired kidney function, so the clinical status of the patient might hinder a radical excision and/or an effective course of a systemic chemotherapy. There are promising reports about neoadjuvant chemotherapy, which has been used successfully to downstage the disease and lengthen the overall survival.[10,11,36]

4. Conclusions

Small cell carcinoma of the ureter is an aggressive disease, and the factors that seem correlate with its prognosis are smoking history, age, male sex, tumor size, nodes, metastasis grading and size at diagnosis, the expression of vimentin, and incomplete resection. Although this is a rare tumor, effective targeted therapies are expected to be applied to improve the overall survival.

Author contributions

Conceptualization: Fabiola Farci.
Data curation: Fabiola Farci, Annamaria Bartolucci, Laura Boldrini.
Formal analysis: Fabiola Farci.
Investigation: Francesca Manassero, Ramona Baldesi, Annamaria Bartolucci, Laura Boldrini.
Resources: Cesare Selli.
Supervision: Cesare Selli, Pinuccia Faviana.
Writing – original draft: Fabiola Farci.
Writing – review & editing: Pinuccia Faviana.

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