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"Pure" Primary Large Cell Neuroendocrine Carcinoma of the Urinary Bladder

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Dear Editors,

Large Cell Neuroendocrine Carcinoma (LCNC) is defined in the urinary bladder, as in other sites, as a high-grade neoplasm exhibiting neuroendocrine features at the hematoxylin and eosin level, and high mitotic activity and evidence of neuroendocrine differentiation at the immunohistochemical level. Recently we observed a case of LCNC of the bladder in a 68-year-old man. The patient presented with gross hematuria of two weeks duration in October 2011. No significant clinical history was found. Urinary cytology identified malignant cells (Figure 1). Chest radiography and computerized tomography of the abdomen and pelvis showed no evidence of other primary tumours. A contrast total body CT revealed a 3x4 cm mass in the dome of the urinary bladder. Transurethral resection (TR) and subsequently radical cystoprostatectomy (CP) with bilateral lymphadenectomy (L) were performed in December 2012. The macroscopic examination of the CP revealed a 2.8x2.2 cm mass situated on the dome with infiltration of muscularis propria (Figure 2). Histologically the tumour showed organoid nesting, trabecular growth, rosettes and perilobular palisading patterns, suggesting a neuroendocrine differentiation. The tumour cells were large, with moderate cytoplasm. Nucleoli were frequent and prominent. Mitotic count was 12 per mm^2. Large zones of necrosis were found (Figure 3). The tumour invaded the deep muscularis propria. The 56 lymph nodes were free of disease (pT2bN0). Immunohistochemical staining showed that the tumour neuroendocrine components were positive for cytokeratin 7 and for neuroendocrine markers such as neurone specific enolase (NSE) and CD 56. The PET TC total body revealed diffuse liver and bone metastases in April 2013. Radiotherapy (R), chemotherapy (Ch) and adjuvant Ch were administered.

We read with great interest Sarı et al.'s paper (1) "*Large cell neuroendocrine carcinoma of urinary bladder; case presentation*". The literature review of this authors is incomplete. The legend of Table I should be modified and replaced with **"*Published cases of pure (6 cases) or mixed (8 cases) bladder large cell neuroendocrine carcinoma*"**. In fact Sarı et al. included mixed tumours with the LCNC component. We examined all published pure bladder LCNC cases with exclusion of mixed neoplasms in order to establish the clinical-pathological, immunohistochemical,

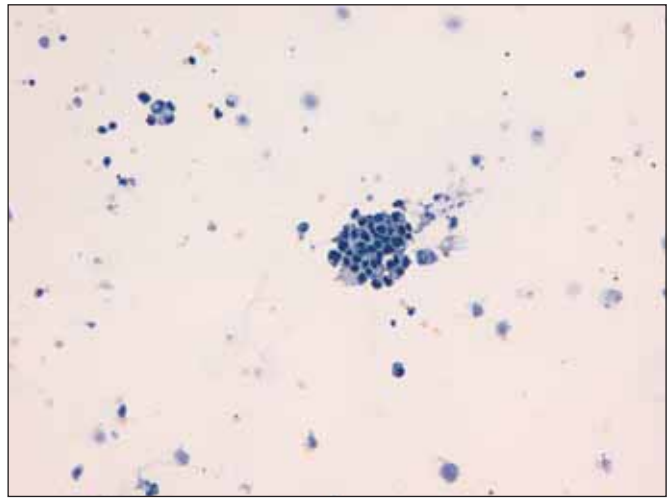

Figure 1: Urinary cytology identified malignant cells (x20 PAP).

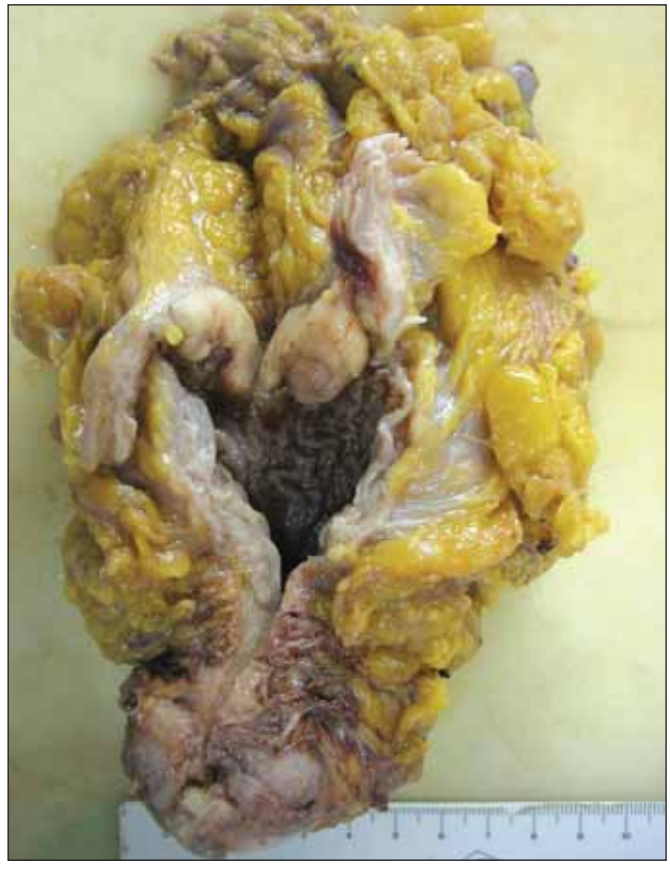

Figure 2: The macroscopic examination of the cystoprostatectomy revealed a 2.8x2.2 cm mass situated on the dome with infiltration of muscularis propria.

Table I: Pure large-cell neuroendocrine bladder carcinoma: review of the literature

Source	Age/ Sex	Symptoms	Clinical history	Location	Tumor size (cm) / TNM	Immunostaining	Treatment	Follow up
Hailemarian et al. 1998 (2)	73 / M	H	R for prostatic cancer (clinical stage T2N0M0), diagnosed on needle biopsy. Insulin-dependent diabetes mellitus. Kidney transplant 27 years previously.	Dorsal wall	4 / T3N0M0	NSE+, CK+, Cg+, Syp+, LCA-, PSA-, VIP-, PP-, In-, Glu-, So-, SP-, Se-	Radical CP and bilateral pelvic L	DOD 2 months after disseminated M
Lee KH et al.2006 (3)	32 / M	H	Unremarkable	Dome and anterior wall	3 / T3N0M0	NSE+, CK+, Cg+, Syp+, EMA+, CD56+,S100, LCA-, PSA-,Vim-	Partial C	Multiple metastases in the lung and liver.
Alijo SF et al. 2007 (4)	40 / M	NR	NR	NR	NR / NR	NSE+,TTF1+,Leu7+, PSA-,**Cg+ 1 de 2, **Syp+ 1 de 2	TR, radical CP, Ch	AWD 13 months after treatment
	43 / F	NR	NR	NR	NR / NR	NSE+,TTF1+,Leu7+, PSA-	TR, radical CP, Ch	DOD 12 months after treatment
Bertaccini A et al. 2008 (5)	37 / NR	H	History of cigarette use.	Posterior wall	2.5 / T3N2M0	NSE+, CK+, Cg+, Syp+	CP, Ch.	AWD 22 moths after surgery.
Lee W et al. 2009 (6)	20 / M	Metastatic cutaneous nodule on the scalp	Partial C and Ch 1 year before of cutaneous M.	NR	NR / NR	NSE+, CK+, Syp+, TTF1+, CD56+	Partial C and Ch.	Lung , retroperitoneal nodal metastases , 12 months after surgery
Martin IJ et al. 2011 (7)	69 / M	Absent	Uterine adhesions and amigdalectomy	Anterior wall	3 / T2N0M0	NSE+, CK-, Cg+, Syp+, S100-, HMB45-	TR , radical C and L	AWD 12 months after surgery

Table I: Continuation

Tsugu A et al. 2011 (8)	74 / M	Brain metastasis	No clinical evidence of bladder cancer before brain metastasis diagnosis.	Left lateral wall	NR / NR	CD56+, Cg+, Syp+, TTF1+.	Ch, R	DOD 5 months after brain metastasis rejection for pulmonary embolism.
Colarossi C et al. 2013 (9)	53 / F	H	NR	Posterior wall	4 / PT3BN2M1	NSE+, CD56+, Syp+, Cg focally+, TTF1-, CK-.	C, histero-annessectomy, L and Ch.	DOD 7 months after initial diagnosis .
Oshiro H et al. 2008 (10)	74 / F	H	Initial history of TR for BUC situated on the left posterior side and 8 courses of intravesical bacillus Calmette-Guerin immunotherapy.	Left lateral wall.	1 / T2aN0M0	CK+,Syp+,Cg+, CD56+, CD57+, TTF1-.	TR , radical C, bilateral pelvic L.	Healthy and free from recurrence of cancer for 48 mo after C.
Macak J et al. 2013 (11)	66 / M	H	NR	NR	NR / NR	CK-, CD56+, Syp+ Cg-, NSE+, G-, C-, PP-, VIP-, So-, Glu-, Se-, TTF1-.	Ch	Liver, adrenal, nodal, spleen metastasis.
Sari A et al. 2013 (1)	67 / M	H	Chronic obstructive lung disease and congestive heart failure for 15 years	Right half	6 / PT3BN1M0	Syp+, Cg+, CD56+, TTF1-PSA-, CK7+, high molecular weight CK-, P63+, PSA-, PSAP-.	TR,	DOD 15 days later.
Our case	68 / M	H	Unremarkable	Dome	2.8 / pT2BN0	CD56+, NSE+, TTF1+, CK7+, Syp-,Cg-.	TR,CP,R and Ch	Liver and bone metastases, 16 months after surgery.

H – Hematuria, **Ca** – Carcinoma, **R** – radiotherapy, **CP** – Cystoprostatectomy, **L** – lymphadenectomy, **DOD** - died of disease, **M** – metastases, **C** – cystectomy, **Ch** – chemotherapy, **NR** – not reported, **TR** – transurethral resection, **BUC** – Bladder urothelial carcinoma, **AWD** – alive without disease, **NSE** – Neuron-specific enolase, **CK** – cytokeratin, **Cg** – chromogranin A, **Syp** – synaptophysin, **LCA** – leucocyte common antigen, **PSA** - Prostate-Specific Antigen, **VIP** – vasoactive intestinal polypeptide, **PP** – pancreatic polypeptide, **In** – insulin, **Glu** – glucagon, **So** – somatostatin, **SP** - substance P, **Se** – Serotonin, **EMA** – epithelial membrane antigen, **LCA** – leukocyte common antigen, **Vim** – vimentin, **TTF1** - thyroid transcription factor 1, **G** – gastrin, **C** – calcitonin, **PSAP** - Prostatic Acid Phosphatase.

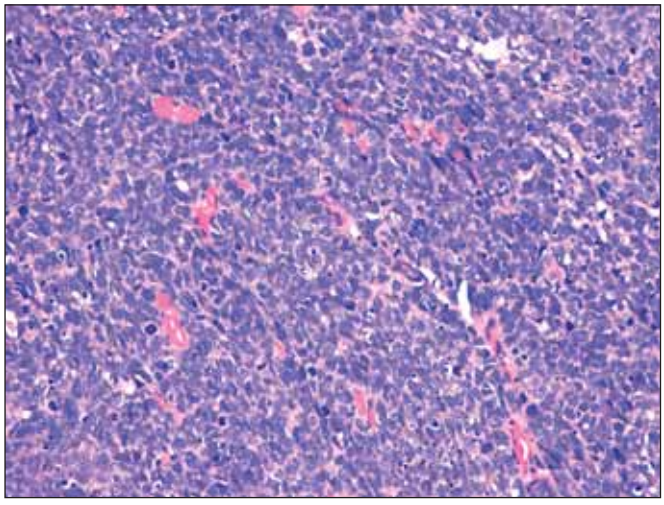

Figure 3: Histologically the tumour showed organoid nesting, trabecular growth, rosettes and perilobular palisading patterns, suggesting neuroendocrine differentiation. The tumour cells were large, with moderate cytoplasm. Nucleoli were frequent and prominent. Mitotic count was 12 per mm^2 (x40 H&E).

prognostic features of the disease (1-11). In our review we excluded the case reported by Abenoza et al. (12). These authors described a primary mixed adenocarcinoma-neuroendocrine carcinoma of the urinary bladder of probable urachal origin. Neuroendocrine differentiation was confirmed by ultrastructural (neurosecretory granules) and immunohistochemical studies (chromogranin and neuron-specific enolase). Two local recurrences and multiple metastases consisted exclusively of the neuroendocrine component. The patient died 30 months after diagnosis with widely metastatic neuroendocrine carcinoma.

Evans et al. case (13) case was not considered because only less than 5% of the total tumour volume was adenocarcinoma. Dundr et al.'s case (14) was excluded because the tumour showed neuroendocrine markers (chromogranin A, NSE, and synaptophysin), but lymphoepithelioma-like features were found and a high-grade papillary transitional cell carcinoma was present in the overlying mucosa. The neoplasm reported by Li et al. (15) is a mixed malignancy composed of large cell neuroendocrine and mesenchymal components. Quek et al. (16) reported 25 neuroendocrine tumours of the bladder including 5 cases of LCNC of which 3 had a secondary urothelial cell carcinoma component. However, this authors did not describe the clinical-pathological, and prognostic features and these cases have therefore been excluded in present literature review. Trimeche et al. (17) described a mixed tumour composed 95% by LCNC and a high-grade urothelial invasive part (5%). Consequently the present case has not been considered in our review of "pure" LCNC. Akamatsu et al. (18) reported a case of LCNC with the presence of squamous cell carcinoma and urothelial carcinoma. This case is a bladder mixed malignant tumour. Engles et al. (19) reported one case of bladder malignancy composed of high-grade urothelial carcinoma, small cell carcinoma and LCNBC. Hata and Tasaki (20) described LCNBC localised on the anterior wall associated with urothelial carcinoma and primary lung cancer.

In conclusion pure LCNC of the bladder is a very aggressive malignancy, unresponsive to therapy.

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Author's Reply:

We thank the author for his interest and valuable comments on our recent publication (1). In our article, we investigated all the English literature to the best of our knowledge, and summarized all the reported cases of large cell neuroendocrine carcinoma of the urinary bladder in one table.

Our paper has been accepted for publication in the Turkish Journal of Pathology on April 20, 2011 and published in the 2nd issue (May) of 2013, which is approximately 2 years after the acceptance date. Therefore newly published cases of large cell neuroendocrine carcinoma (LCNEC) of the bladder in this time period of two years did not appear on the review table of our article. However after careful investigation of the English literature, we noticed that articles published by Bertaccini A et al. (2) in 2008 and Lee W et al. (3) in 2009 were not presented in our table.

We preferred to include and specify both pure and mixed forms of this tumor in our table in order to better understand the behaviour of this very rare tumor as many of these cases were reported to have mixed histology.

Yours sincerely

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