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Small cell neuroendocrine carcinoma of the urinary bladder

An immunohistochemical and ultrastructural evaluation of 3 cases with a review of the literature

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Summary. Small cell carcinoma with the histological appearance of pulmonary small cell carcinoma is a rare tumour in the urinary bladder. In previous case reports the neuroendocrine nature of small cell bladder carcinoma has been accepted, but on review the evidence for true neuroendocrine differentiation appears unsatisfactory. In this study the histological, immunohistochemical and ultrastructural characteristics of three cases of small cell carcinoma of the urinary bladder are described. Ultrastructurally, the cytoplasm of all three tumours contained neurosecretory-type granules and each of the tumours demonstrated positive immunoreaction for two or more neuroendocrine markers, from a panel including neuron-specific enolase, chromogranin A, Leu-7, bombesin and synaptophysin. Although the combination of ultrastructural and immunohistochemical examination obviously offers the strongest evidence in establishing neuroendocrine differentiation, it is argued that immunohistochemistry alone may also yield important information in demonstrating a neuroendocrine nature, provided that at least neuron-specific enolase and synaptophysin are included as markers. The clinical relevance of identifying neuroendocrine differentiation in small cell bladder carcinoma is suggested by the favourable response to combination chemotherapy in two of our cases.

Key words: Neuroendocrine differentiation – Immunohistochemistry – Electron microscopy – Small cell undifferentiated bladder carcinoma

Introduction

Extrapulmonary small cell carcinoma with the light microscopical appearance of its pulmonary counterpart comprises approximately 4% of all small cell carcinomas (Levenson et al. 1981). Apart from the urinary tract, many other primary sites have been reported, including the nasopharynx, salivary glands, larynx, oesophagus, gastrointestinal tract, pancreas, uterus, prostate, skin and mammary gland (Richardson and Weiland 1982; Ibrahim et al. 1984). A primary origin in the urinary bladder has been recorded in 28 cases only, but the increasing number of reports during recent years suggests a more frequent occurrence than so far recognised (Cramer et al. 1981; Davis et al. 1983; Ibrahim et al. 1984; Kim et al. 1984; Partanen and Asikainen 1985; Reyes and Soneru 1985; Ordonez et al. 1986; Lee et al. 1986; Williams et al. 1986; Mills et al. 1987).

The neuroendocrine nature of this type of bladder carcinoma has been accepted in previous studies, although not conclusively documented in each case. However, other extrapulmonary small cell carcinomas, originating from the oesophagus, salivary glands and prostate, have shown a heterogeneous nature, some of them representing poorly differentiated squamous cell or adenocarcinoma (Briggs and Ibrahim 1983; Gnepp et al. 1986; Mendelsohn and Maksem 1986; Ro et al. 1987). Thus in the primary bladder lesion, careful evaluation of neuroendocrine features is desirable in order to exclude a poorly differentiated variant of transitional cell carcinoma.

Proper determination of neuroendocrine characteristics may carry clinical relevance. In some pulmonary small cell carcinomas that manifested ultrastructural features of squamous cell carcinoma instead of neuroendocrine characteristics, a different and more indolent tumour behaviour has been recorded (Churg et al. 1980; Mooi et al. 1986). Correspondingly, the absence of neuroendocrine differentiation in small cell bladder carcinoma might also be associated with a different tumour behaviour.

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In this study the clinical and light microscopical findings in three cases of small cell bladder carcinoma are presented. Their neuroendocrine nature is ascertained by electron microscopy and a panel of monoclonal antibodies, more or less specific for neuroendocrine differentiation. In addition, prior reports are reviewed with special regard to the documentation of neuroendocrine features. The clinical importance of recognizing these features is demonstrated.

Case reports

Case 1. A 70-year-old woman with a 30 year history of abuse of analgetics (acetosal and phenacetin) entered the hospital because of 4 months of macroscopic haematuria. Intravenous urography showed a tumour of the urinary bladder and at cystoscopy a large solid tumour was seen at the dome and left lateral wall which was staged T3 (TMN-classification). The tumour was partially removed by transurethral resection. No metastases were found by abdominal CT scan. Three months after admission and following radiotherapy (4750 rad) patient was readmitted for radiation enteritis with peritonitis and died within a week. At autopsy no residual tumour was found in the urinary bladder, but widespread metastases were present in the liver, bilary bladder wall, pancreas and left adrenal gland. Pulmonary lesions were absent.

Case 2. A 58-year-old man had been treated by Adriamycin instillation 4 years previously for carcinoma in situ of the urinary bladder. The clinical and cytological follow up had been negative. He complained of painful haematuria and at cystoscopy a 6 cm solid and partially necrotic tumour was found at the neck and posterior wall (TNM-classification: stage T3). Biopsy revealed undifferentiated small cell carcinoma. No metastases were found by roentgengraphy and skeletal scan. Three months afterwards a considerable reduction of tumour size was obtained by 4 cycles of combination chemothearapy with Cisplatin and methothrexate. Subsequent cystectomy showed a 2 cm diameter residual tumour mass, invading the muscular wall and with local perimuscular infiltration. Prostate and regional lymph nodes were not involved. Postoperatively, no recurrence or metastases were manifest during 9 months of follow up.

Case 3. A 62-year-old woman with a prior history of hysterectomy and radiotherapy for a stage 1 B moderately differentiated squamous cell carcinoma of the uterine cervix 23 years ago, was admitted because of two weeks gross haematuria. Cystoscopy revealed a solid and ulcerated tumour of 3 cm diameter at the right lateral wall, at least invading the muscular layer. Histology yielded undifferentiated small cell carcinoma. Exploratory laparotomy showed transvesical infiltration (stage T4) and iliac lymph node metastases. Bone scan suggested metastases in multiple lumbar vertebrae, first right thoracic rib and clavicle. A good response was obtained initially by combination chemotherapy with cyclophosphamide (Endoxan) and doxyrubicin hydrochloride (Adriamycin). Nine months afterwards local recurrence developed, but by a second cycle of chemotherapy, with in addition cisplatin, complete remission was acquired. At present, 18 months after primary diagnosis, the patient is alive and without clinical evidence of disease.

Materials and methods

In all three cases tissue specimens of the primary bladder tumour had been fixed in 4% neutral buffered formalin and embedded in paraffin wax (melting point 52 to 54° C). For conventional histology 5 μm sections were cut and stained with haematoxylin and eosin, Grimelius (argyrophil) and Fontana-Masson (argentaffin) silver impregnation.

A panel of commercially available polyclonal and monoclonal antibodies was used for immunohistochemical stainings (see Table 1). The antigens assessed included the epithelial determinants cytokeratin (broad spectrum) and CAM 5.2 (cytokeratin components 8, 18 and 19), the neuroendocrine markers neuron-specific enolase (NSE), bombesin, chromogranin A, synaptophysin and Leu-7 and some hormonal peptides, including ACTH, somatostatin, calcitonin, insulin and glucagon.

To block endogeneous peroxidase an incubation with 0.3% H_2O_2 in methanol was applied. All immunohistochemical stains were performed in a phosphate-buffered saline system at pH 7.4. Digestion of the paraffin tissue sections was employed, with exception of stains for bombesin, chromogranin A, synaptophysin and Leu-7. The methods of staining used were the indirect immunoperoxidase method (IP), the unconjugated peroxidase antiperoxidase method (PAP) or an avidine biotine complex technique (ABC), as described elsewhere (Hsu et al. 1981; Van der Valk et al. 1983), see Table 1.

Peroxidase activity was visualised using 3, 3′-diaminobenzidine. Optimal dilutions and incubation times were determined

Table 1. Immunohistochemical features of 3 cases of small cell neuroendocrine carcinoma of the urinary bladder

Antigen	CAM 5.2	Cytokeratin	NSE	Chromogranin A	Leu-7	Bombesin	Synaptophysin	ACTH
Source	BD	Dako	Dako	HT	BD	INC	BM	Dako
M/P[a]	M	P	P	M	M	P	M	P
Method[b]	ABC	PAP	PAP	IP	IP	PAP	IP	IP
Case 1	++	−	++	+	+	−	++	−
Case 2	++	+	++	++	−	+	+	−
Case 3	−	−	++	−	−	−	+	+

(−) negative, (+) focally positive; (++) positive

[a] M: monoclonal and P: polyclonal antibody

[b] Method of staining: ABC: avidine biotine complex technique, PAP: unconjugated peroxidase antiperoxidase method, IP: indirect immunoperoxidase method; Sources: BD: Becton & Dickinson, Dako: Dakopatts, HT: Hybritech, INC: INCorporation, BM: Boehringer Mannheim

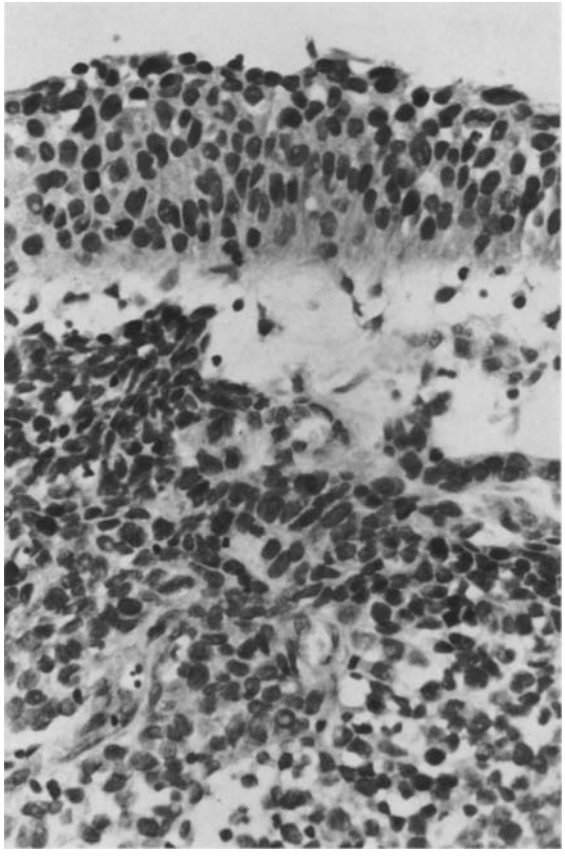

Fig. 1. *Case 1.* Small cell carcinoma of the urinary bladder. The tumour consists entirely of small tumour cells with round to oval nuclei and sparse cytoplasm with indistinct margins. The adjacent bladder mucosa (at the top) shows slight urothelial dysplasia, without continuity with the tumour. H&E, ×412

by standard techniques. In each staining series a positive control section was included. Phosphate buffered saline, non-immune ascites fluid or normal rabbit immunoglobulin instead of primary antibodies were used as negative controls.

Tissue for electron microscopy was obtained by deparaffinizing formalin fixed paraffin embedded material. The recovered material was washed in 0.1 M cacodylate buffer and postfixed in 1% osmium tetraoxide in the same buffer. Semithin toluidine blue stained sections were studied to ensure representative sampling. Ultrathin sections were stained with uranyl acetate and lead citrate and then were examined in a Zeiss 119 electron microscope.

Pathological findings

Histology of the primary bladder tumour in all 3 cases showed undifferentiated small cell carcinoma, in agreement with the criteria developed by the World Health Organization for pulmonary small cell carcinoma (Mostofi et al. 1973). The tumours were composed of large nests and sheets of small tumour cells with round to oval hyperchromatic nuclei, containing diffuse chromatin and inconspicious nucleoli (Fig. 1). The cells had sparse cytoplasm with indistinct margins. Mitoses were common. In case 3 some scattered multinucleated tumour giant cells were present. Focally, crushing artifacts were considerable. The intervening stroma contained few lymphoid infiltration. In case 1 the adjacent bladder mucosa showed slight urothelial dysplasia, but no continuity with the tumour was demonstrated (Fig. 1). Generally, there was a monotonous pattern of small cell carcinoma, but in one case (case 2) admixture with some foci of

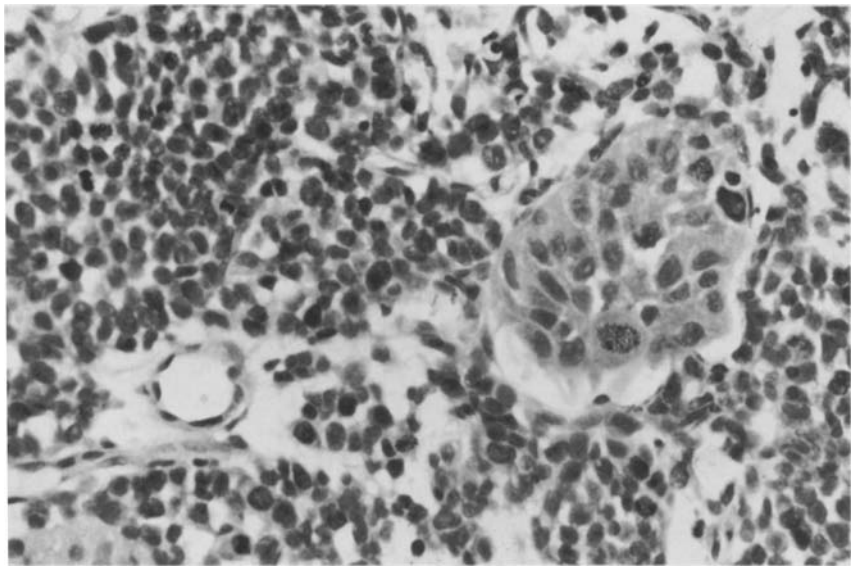

Fig. 2. *Case 2.* A monotonous pattern of small cell bladder carcinoma with an island of poorly differentiated transitional cell carcinoma (right). H&E. ×412

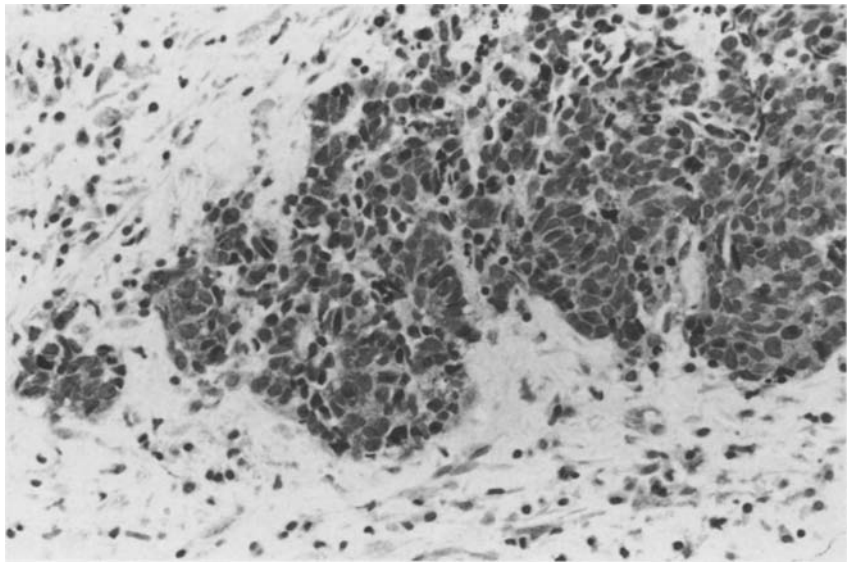

Fig. 3. *Case 3.* Immunoperoxidase preparation showing reactivity for synaptophysin. Most of the tumour cells display diffuse and moderate cytoplasmic staining. × 330

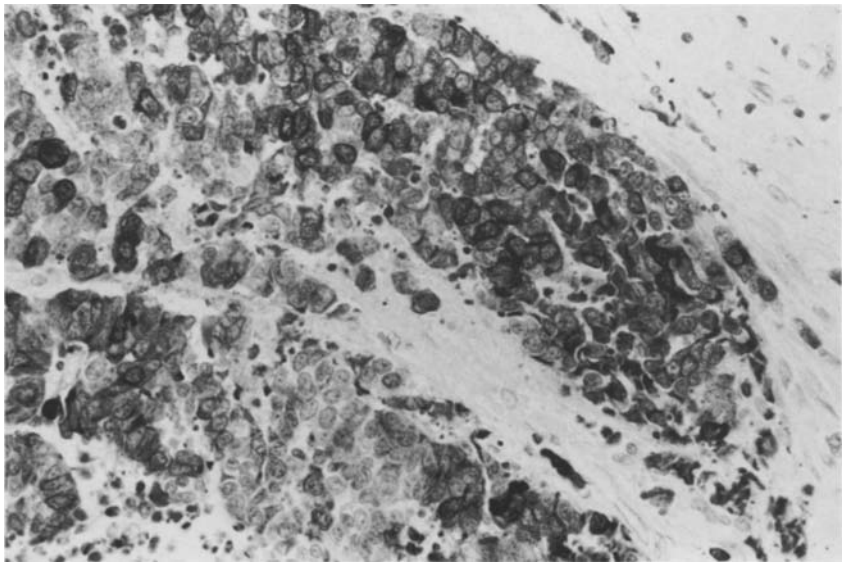

Fig. 4. *Case 2.* Immunostaining for chromogranin A. Focally the tumour shows distinct cytoplasmic positivity with granular appearance. × 528

poorly differentiated transitional cell carcinoma was present (Fig. 2). Additional argentaffin and argyrophylic stainings were negative in all 3 cases.

The immunohistochemical findings are presented in Table 1. Of the neuroendocrine markers, neuron-specific enolase and synaptophysin were identified in all 3 tumours. Immunoreactivity for chromogranin A was demonstrated in 2 cases and for bombesin and Leu-7 in only 1 tumour. The immunostainings for synaptophysin showed moderate and diffuse reactivity of the cytoplasm (Fig. 3) and a similar pattern was noticed for neuron-specific enolase and bombesin. Immunoreaction for chromogranin A revealed focally cytoplasmic positivity of varying intensity with a granular appearance (Fig. 4); the same pattern was shown for Leu-7. The transitional cell carcinoma component in case 2 stained positive for the epithelial determinants only.

Ultrastructural examination was impaired by suboptimal fixation, which resulted in cytoplasmic clumping and degenerative vacuoles. Nevertheless, varying amounts of free ribosomal rosettes, rough endoplasmic reticulum and degenerating mitochondria were seen in the cytoplasm, in addition to poorly developed desmosomes on the cytoplasmic membrane. Most important was the finding of some rounded dense core membrane bound

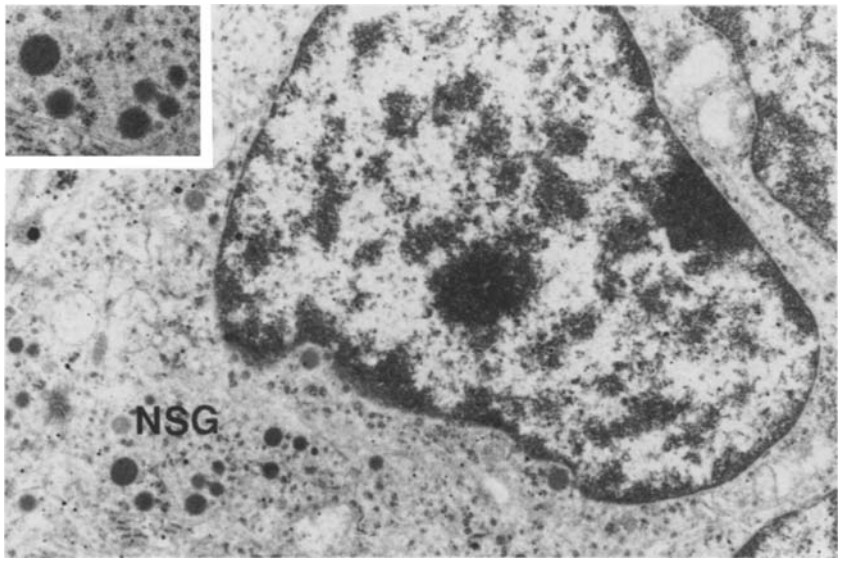

Fig. 5. *Case 3.* Ultrastructural appearance of small cell bladder carcinoma. The cytoplasm contains a cluster of electron dense, membrane bound neurosecretory-type granules (*NSG*). Inset: detail of granules. Formalin fixed material. ×13,800

granules (diameter 150 to 250 nm) in all 3 cases (Fig. 5), which occurred in just a few tumour cells and were only found after prolonged examination.

Discussion

The 3 carcinomas presented in this study fulfilled the light microscopical criteria established for pulmonary small cell carcinoma by WHO (Mostofi et al. 1973). In addition, their neuroendocrine nature was demonstrated by the recognition of dense core membrane bound granules (diameter 150 to 250 μm) on electron microscopy and the staining pattern of neuroendocrine markers on immunohistochemistry. Silver staining did not contribute to the diagnosis, as it was negative in all 3 carcinomas as previously reported (Table 2). This might be due to the paucity of neurosecretory granules.

In electron microscopy of pulmonary small cell carcinoma, neurosecretory granules may be sparse or even absent. Consequently, their prevalence reported in the literature varies widely (Mooi et al. 1986), in some studies consituting a 20% minority of positive cases (Yesner 1981; Sidhu 1982). Nevertheless, their identification is regarded by many authors as a prerequisite to establish the diagnosis of small cell carcinoma in cases of extrapulmonary origin (Cramer et al. 1981). In our three cases granules were scanty and, hampered by the suboptimal preservation of the reprocessed material, they were only found after prolonged examination in a few tumour cells. Additional immunohistochemistry can overcome these difficulties, since the use of antibodies to associated antigens provides a convenient technique to ascertain neuroendocrine differentiation. Although a sensitive marker, neuron-specific enolase is not truly specific for neuroendocrine nature, as it has been documented in various non-neuroendocrine tumours (Vinores et al. 1984; Leader et al. 1986). Therefore, in this study an additional panel of antibodies was used, directed to chromogranin A, Leu-7, bombesin and the novel marker synaptophysin, all of them being more or less specific for neuroendocrine differentiation (Bunn et al. 1985; Said et al. 1985; Gould et al. 1986; Angeletti 1986). In addition to neuronspecific enolase, only synaptophysin was identified in all three tumours. The remaining markers were demonstrated in two (chromogranin A) or one (Leu-7, bombesin) tumours only. Whereas the risk of a false positive result is diminished by the determination of more than one marker, the findings suggest that neuron-specific enolase and synaptophysin comprise a suitable combination to evidence neuroendocrine differentiation.

A non-neuroendocrine nature has been shown in some of the small cell carcinomas occurring in the oesophagus, salivary glands and prostate (Briggs et Ibrahim 1983; Gnepp et al. 1985; Ro et al. 1987). Correspondingly, the true neuroendocrine differentiation of the primary bladder lesion may be questioned. In 9 of the 28 previously reported cases electron microscopy was not documented or was negative (Table 2: case 6, 17, 22, 23, 24 and 28; and case 7, 8 and 15). In the remaining cases neuroendocrine differentiation was suggested by the sparse occurrence of neurosecretory-like granules, but in 6 of them additional immunohistochemistry was not performed and in another 6 cases a positive reaction to NSE only was found.

Table 2. Reported cases of small cell carcinoma of the urinary bladder

Case no.	Reference	Age/Sex	Immunohistochemical findings						Neuro-secretory granules	Therapy	Follow-up	Months
			NSE	CGR	Leu-7	ACTH	Ser	VIP				
1.	Cramer et al.	69 M	.	.	.	.	.	.	+	Resection	ANED	14
2.	Davis et al.	69 M	.	.	.	.	.	.	+	Cystectomy, radiation, chemotherapy	DWD	11
3.	Davis et al.	60 M	.	.	.	.	.	.	+	Cystectomy, radiation, chemotherapy	AWD	23
4.	Davis et al.	79 M	.	.	.	.	.	.	+	Resection, radiation	ANED	28
5.	Ibrahim et al.	75 M	.	.	.	.	.	.	+	Radiation	DWD	5
6.	Partanen & Asikainen	55 F	.	.	.	++	.	.	.	Partial resection	DWD	2
7.	Kim et al.	77 M	.	.	.	.	.	.	−	None	DWD	2
8.	Kim et al.	83 M	.	.	.	.	.	.	−	Resection, radiation	DNED	2
9.	Reyes & Soneru	64 M	++	.	.	.	.	.	+	Resection	DWD	5
10.	Reyes & Soneru	40 M	++	.	.	.	.	.	+	None	DWD	0
11.	Reyes & Soneru	66 M	++	.	.	.	.	.	+	Radiation, cystectomy	ANED	36
12.	Ordonez et al.	62 M	++	.	.	.	++	.	+	Cystectomy, nephrectomy, chemotherapy	AMED	10
13.	Ordonez et al.	60 M	++	.	.	.	−	.	+	Radiation	AWD	3
14.	Ordonez et al.	73 M	++	.	.	.	++	.	+	Partial resection	Not available	
15.	Lee et al.	59 M	−	.	.	.	.	.	−	Partial resection, chemotherapy	DWD	12
16.	Williams et al.	69 M	.	.	.	.	.	.	+	Cystectomy	ANED	24
17.	Mills et al.	79 M	++	++	−	.	+	−	.	Cystectomy, radiation	DWD	6
18.	Mills et al.	67 M	++	−	++	.	−	+	+	Cystectomy	AWD	10
19.	Mills et al.	74 F	++	−	−	.	−	−	+	Cystectomy, radiation, chemotherapy	AWD	6
20.	Mills et al.	77 M	++	−	++	.	−	−	+	Resection, radiation, chemotherapy	DWD	4
21.	Mills et al.	55 M	+	−	+	.	−	−	+	Chemotherapy, radiation	DWD	3
22.	Mills et al.	50 M	++	−	−	.	−	+	.	Cystectomy, chemotherapy	AWD	12
23.	Mills et al.	75 F	++	−	++	.	−	−	.	Cystectomy	Recent case	
24.	Mills et al.	82 M	−	−	−	.	−	−	.	None	DWD	0
25.	Mills et al.	80 M	−	−	++	.	−	−	+	Cystectomy	Recent case	
26.	Mills et al.	59 M	+	−	−	.	−	−	+	Cystectomy, chemotherapy	DWD	12
27.	Mills et al.	80 M	++	+	+	.	−	−	+	Cystectomy, chemotherapy	Recent case	
28.	Mills et al.	79 M	++	+	+	.	−	−	.	Cystectomy, chemotherapy	Recent case	

(−) negative; (+) focally positive; (++) positive; (.) not performed or not reported

NSE: neuron-specific enolase, CGR: chromogranin A, Ser: serotonine, VIP: vasoactive intestinal peptide, ANED: alive without evidence of disease, DWD: dead with disease, AWD: alive with disease, DNED: dead without evidence of disease

Overall, in 10 cases a positive staining to more than one marker was recorded (Table 2).

In our opinion, the neuroendocrine nature of small cell bladder carcinoma should be identified by electron microscopy or a panel of immunohistochemical markers. When unmistakable granules are not found or electron microscopy is not available, we advocate the use of a panel of antibodies, including at least neuronspecific enolase and synaptophysin. In the absence of ultrastructural and immunohistochemical evidence for neuroendocrine differentiation, one might be dealing with a rare variant of a poorly differentiated transitional cell carcinoma. In fact, this is the current classification of small cell bladder carcinoma in the AFIP-fascicle on urinary bladder tumours (Koss 1975).

The histogenesis of small cell neuroendocrine bladder carcinoma has yet to be established. An origin from preexistent neuroendocrine cells has been suggested (Cramer et al. 1981). However, it is more likely that there is an indifferent mucosal stem cell, which may lead to divergent differentiation (Richardson and Weiland 1982; Ibrahim et al. 1984). This multipotent stem cell concept is in keeping with that conceived for pulmonary neoplasms (Gould et al. 1983) and may explain the frequent coexistence of small cell bladder carcinoma with other components, such as transitional

cell, squamous cell or adenocarcinoma (Mills et al. 1987) (see case 2).

Small cell carcinoma may be associated with endocrine symptoms, resulting from ectopic hormone production. So far, this event has been reported in one bladder tumour, which presented with hypertension from ACTH secretion (Partanen and Asikainen 1986). In one of our cases ACTH was shown focally in a few tumour cells, without clinical symptoms. The apparently rare ectopic hormone production additionally argues against a true neuroendocrine nature of all these cases.

Just as in the pulmonary lesion, small cell bladder carcinoma behaves as an aggressive tumour, with early metastases and rapidly progressive disease (Mills et al. 1987). A favourable response to combination chemotherapy is indicated: in two of our patients presenting with advanced disease, complete remission was obtained by different regimens of chemotherapy, combined with cystectomy in one case. Both patients are alive and free of disease at 9 and 18 months after the beginning of the treatment. The follow up of 4 patients from the literature (Table 2: case 3, 12, 19 and 22) also suggests that chemotherapy is a promising approach. However, aberrant tumour behaviour and the chemotherapeutic response of pulmonary small cell carcinoma noted in the absence of neuroendocrine differentiation (Mooi et al. 1986), necessitates careful evaluation of this feature.

It is concluded that small cell bladder carcinoma is an aggressive disease, where the prognosis may be improved by chemotherapy. To identify the neuroendocrine nature, the use of a panel of antibodies, including at least neuron-specific enolase and synaptophysin, is advocated, especially when electron microscopy is inconclusive or impossible. In the absence of true neuroendocrine differentiation, the tumour may be considered to represent a poorly differentiated transitional cell carcinoma, that shares light microscopical features of the neuroendocrine type of small cell carcinoma. This possibility should be considered when clinical course and therapy are evaluated.

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