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Carcinosarcoma of the urinary bladder: a distinct variant characterized by small cell undifferentiated carcinoma with neuroendocrine features

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Summary. The clinicopathological features of two carcinosarcomas of the urinary bladder are reported. The tumours occurred in a 64- and a 66-year-old patient presenting with haematuria and both were polypoid. The epithelial component was consistent with small cell undifferentiated carcinoma with neuroendocrine differentiation, whereas the sarcomatous component did not display specific features. The carcinomatous component showed immunohistochemical reactivity for different epithelial markers as well as for chromogranin and neuron specific enolase. Conversely, the sarcomatous cells stained strongly for vimentin and in one case for muscle actin and smooth muscle actin. The differential diagnosis of biphasic tumours of the bladder is discussed and the literature reviewed.

Key words: Urinary bladder – Carcinosarcoma – Small cell undifferentiated carcinoma – Neuroendocrine differentiation – Immunohistochemistry

Introduction

In adults, 98% of urinary bladder tumours are of epithelial lineage (Peterson 1986). They are usually transitional cell carcinomas, but histological variants represent up to 15% of the cases (Young and Eble 1991). Among these variants, carcinoma histologically identical to pulmonary small cell undifferentiated carcinoma (SCUC) is a rare finding. The frequency has been estimated to be less than 0.5% (Blomjous et al. 1989). Tumours with a biphasic pattern are another rare occurrence, consisting of atypical spindle cells admixed with cells having obvious epithelial characteristics and designated "sarcomatoid carcinoma", "carcinoma with pseudosarcomatous stroma" and "carcinosarcoma". The histological criteria and the immunophenotype of these rare neoplasms have been described (Young 1987; Ro et al. 1988; Wick et al. 1988; Young and Wick 1988; Young et al. 1988). However, the occurrence of SCUC admixed with sarcomatoid stroma has been briefly mentioned under different labels in only a few reports (Mills et al. 1987; Wrba et al. 1990; Young and Eble 1991). To understand better the histological and cytological characteristics of this unique bladder tumour, we present the clinical and histopathological features of two cases in more detail.

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Materials and methods

Tissue from patient 1 consisted of transurethral resection material of a polypoid tumour. From patient 2 a radical cystoprostatectomy specimen was obtained. The tissues were fixed in buffered 4% formalin, embedded in paraffin and sections routinely stained with haematoxylin and eosin, alkaline alcian blue, periodic acid-Schiff, Masson trichrome and iron stains. Formalin-fixed tissue was available for electron microscopy in one case. Immunohistochemical studies were performed on paraffin sections using commercially available primary antibodies directed against a set of epithelial, mesenchymal and neuroendocrine antigens as well as different polypeptides (Table 1). The avidin-biotin-peroxidase complex (ABC) technique (Hsu et al. 1981), using diaminobenzidine (Sigma, St. Louis, Mo., USA) as a chromogen, was applied and the sections were counterstained with haematoxylin. Biotinylated secondary antibodies and ABC reagents were obtained from Dakopatts, Denmark. Clinical histories and follow-up information were obtained by review of the patients charts and by consultation with the physicians.

Results

A 64-year-old woman (patient 1) and a 66-year-old man (patient 2) presented with complaints of haematuria for some weeks. They had no prior history of neoplastic disease of the bladder. A polypoid tumour was discovered by cystoscopy in both cases.

Patient 1 underwent transurethral tumour resection. Five grey-white fragments not larger than 1 cm were used for microscopic examination. As samples from the internal layers of the bladder at the tumour resection

Table 1. Primary antibodies and their reaction with epithelial and sarcomatous components of the tumours

Antibody (clone)	Source	Dilution	Epithelial patient 1/ patient 2	Sarcomatous patient 1/ patient 2
Epithelial:				
Pancytokeratin (AE1/AE-3)	Ortho (CRL)	1:1[a]	+/+	−/−
Anticytokeratin (CAM 5.2)	Becton Dickinson	1:1	+/+	−/−
Cytokeratin 19 (Ks 19.1)	Progen	1:100[a]	−/+	−/−
Epithelial membrane antigen (E29)	Dakopatts	1:100[a]	+/+	−/−
Epithelial antigen (Ber-EP4)	Dakopatts	1:100[a]	+/+	−/−
Carcinoembryonic antigen (rabbit)	Dr. Carrel, Lausanne	1:500[a]	+/−	−/−
Mesenchymal:				
Vimentin (V9)	Dakopatts	1:10	−/−	+/+
Desmin (D33)	Dakopatts	1:50	−/−	−/−
Muscle actin (HHF35)	Enzo	1:1000[a]	−/−	weak +/+
Smooth muscle actin (1A4)	Sigma	1:300	−/−	−/+
Neuroendocrine:				
Chromogranin (LK2H10)	Hybritech	1:100	+/+	−/−
Neuron-specific enolase (MIG-N3)	Sanbio	1:50	+/+	−/−
Synaptophysin (SY 38)	Progen	1:50	−/+	−/−
Protein S-100 (rabbit)	Dakopatts	1:200[a]	−/−	−/−
Neurofilaments (2F11)	Sanbio	1:10[a]	−/−	−/−
Polypeptide hormones[b]	Dakopatts, Amersham	various	−/−	−/−

[a] Sections subjected to digestion in 0.02% trypsin (Difco, "Trypsin 1:250") at 37° C for 10 min prior to incubation with antibody reagents

[b] Adrenocorticotropin, calcitonin, thyreotropin, somatotropin, prolactin, insulin, glucagon, somatostatin, gastrin and vasoactive intestinal polypeptide

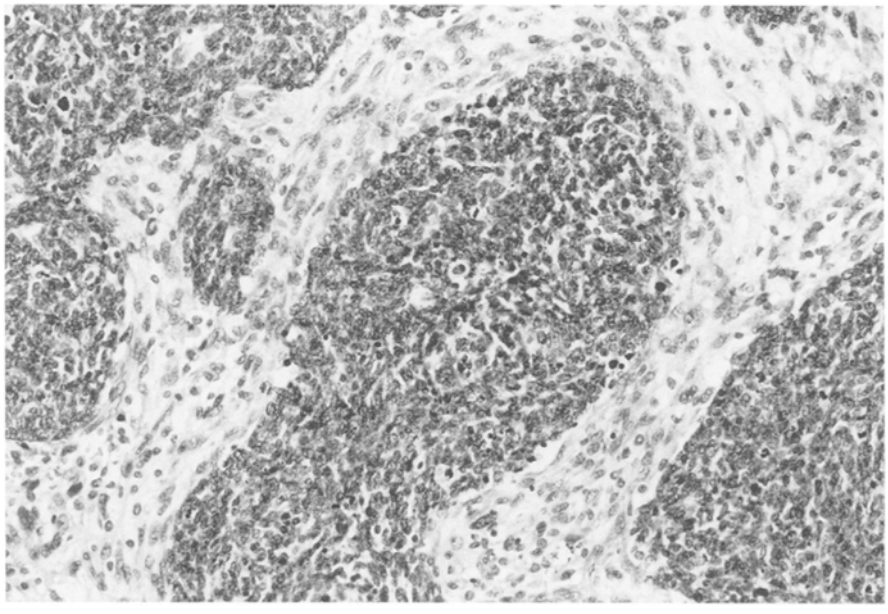

Fig. 1. Irregular nests and trabeculae of small cell undifferentiated carcinoma (SCUC) surrounded by sarcomatous stroma. H&E, ×200

site consisted of normal smooth muscle and as second transurethral resection after 15 days did not show any further malignant tissue, radical cystectomy was not deemed necessary. Because of the presence of transitional cell carcinoma in situ, local therapy with instillation of bacille Calmette Guérin was initiated. The patient was alive without evidence of disease at 15 months of follow-up.

In patient 2 a SCUC with infiltration of the tunica muscularis was found in the transurethral biopsy specimens. A radical cystoprostatectomy with urinary diversion was performed. On macroscopic examination the

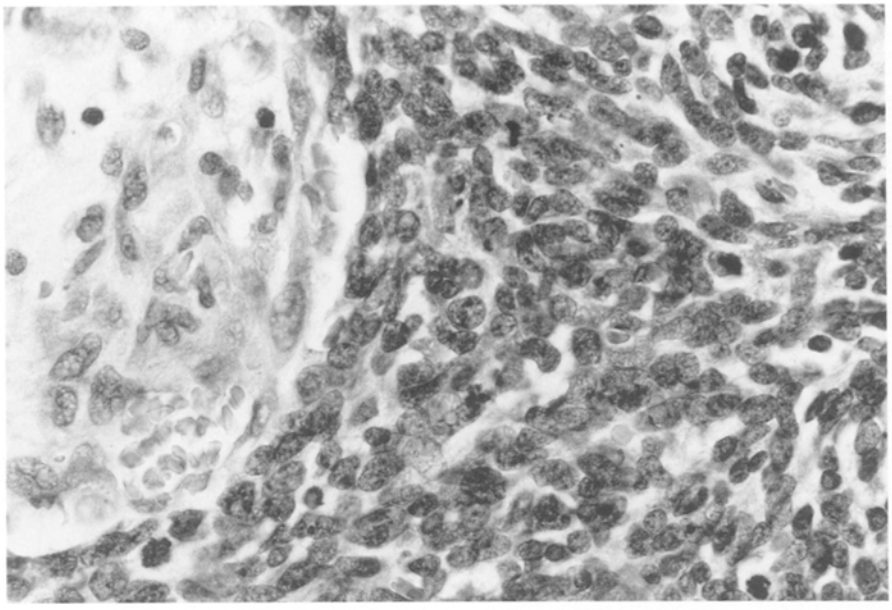

Fig. 2. Intermediate cell type of small cell carcinoma. Notice the abrupt junction between the two distinct tumour components. H&E, ×400

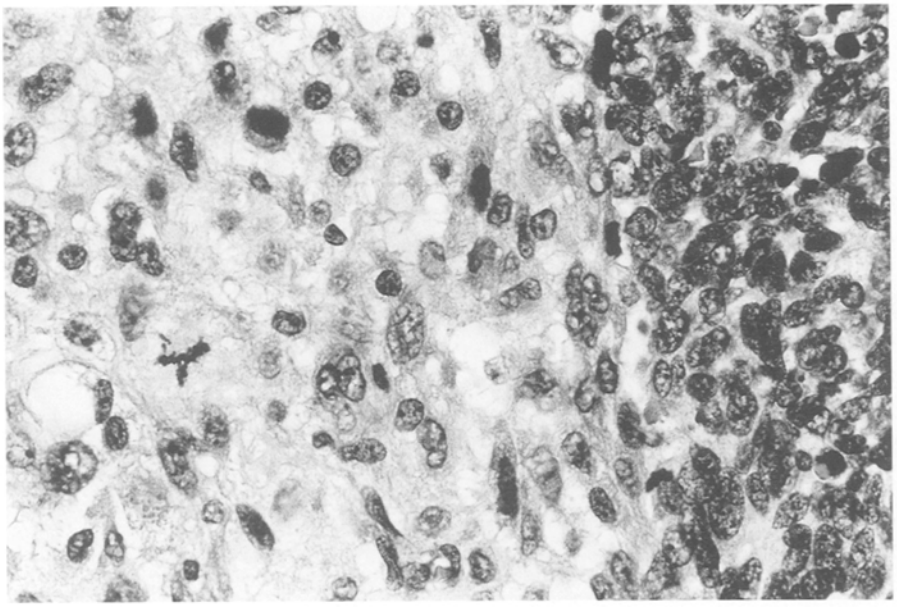

Fig. 3. Sarcomatous stroma consisting of polymorphous and spindle-shaped cells with one atypical mitotic figure. H&E, ×400

lumen of the bladder was partially filled by a 6×4 cm polypoid and pedunculated tumour with a soft consistency, originating from the right lateral wall. The cut section was grey with haemorrhagic areas. At the base of the polyp the tumour gradually merged into a firm grey tissue that invaded the whole of the bladder wall. The histological study of the cystectomy specimen disclosed a malignant neoplasm similar to that seen in the former case, and transitional cell carcinoma in situ. After radical cystoprostatectomy patient 2 underwent adjuvant chemotherapy because of the advanced tumour stage with invasion in the perivesical fat. He was still alive 15 months after diagnosis in spite of metastatic disease in the lung and the liver. A histological examination of the metastatic lesions was not performed.

On light microscopy the tumour in patient 1 consisted of an intimate admixture of epithelial cells, arranged in large irregular nests and sheets, scattered among atypical spindle-shaped cells (Fig. 1). The epithelial component was composed entirely of medium-sized cells with round or irregular configuration of the nuclei and equally distributed chromatin without prominent nucleoli (Fig. 2). Cytoplasm was sparse, cell margins were not distinct and mitotic figures were numerous. Necrosis was not observed. The mesenchymal component was well vascularized and consisted of spindle cells with severe nuclear atypia, eosinophilic cytoplasm and numerous mitotic figures (Fig. 3). Erythrophagia and prominent haemosiderosis were observed. The tumour did not exhibit cartilaginous or osseous metaplasia. The junction

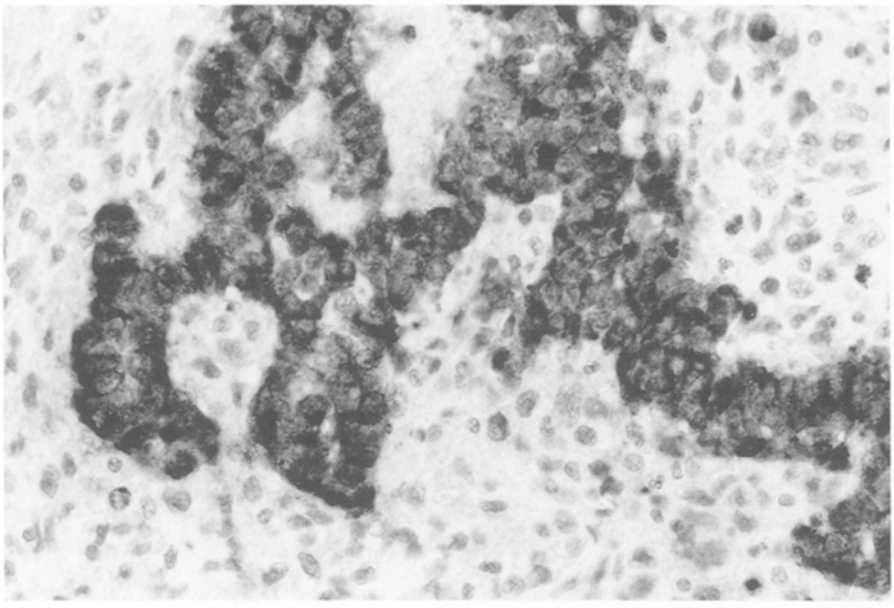

Fig. 4. Intense immunoreactivity for epithelial membrane antigen in SCUC. ×400

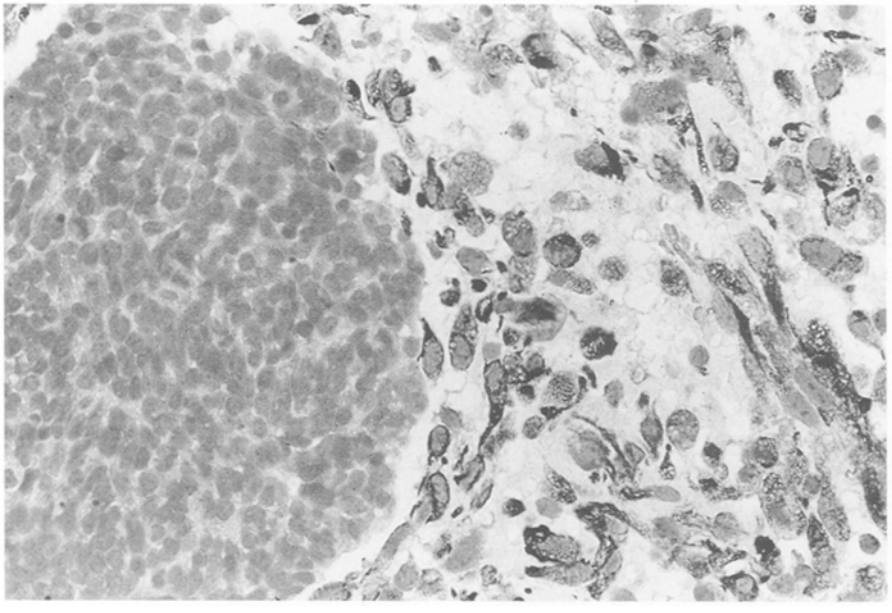

Fig. 5. Vimentin expression in the sarcomatoid component. By the same patient a similar reaction was obtained with staining for muscle actin and smooth muscle actin. ×400

between the two components was abrupt, and the neoplastic tissue showed an equal proportion of carcinomatous and sarcomatoid elements. Mapping of the bladder revealed foci of transitional cell carcinoma in situ in other locations.

In patient 2, a biphasic pattern was detectable only in the polypoid portion of the tumour. The epithelial component was practically identical to that described in patient 1. The sarcomatous component was less vascularized than that seen in patient 1 and consisted of spindle-shaped cells amongst which bizarre giant cells were frequently observed. Broad trabeculae and nests of carcinomatous small cells invaded the bladder wall and infiltrated the perivesical fat without visible stromal reaction. Invasion of blood vessels was observed. Transitional cell carcinoma in situ was demonstrable in the bladder in other locations remote from or adjacent to the tumour.

In patient 1 the epithelial cell nests stained strongly with antibodies against epithelial markers including pancytokeratin, anticytokeratin (CAM 5.2), epithelial membrane antigen (EMA; Fig. 4), epithelial antigen (Ber-EP4) and carcinoembryonic antigen. They also reacted with antibodies against neuroendocrine markers: chromogranin and neuron specific enolase. The sarcomatous spindle-shaped cells showed a reaction with antibody specific for vimentin (Fig. 5) and weak focal expression of muscle actin, but no staining with antibodies against epithelial markers.

The results in patient 2 were similar. The carcinomatous component expressed the majority of the epithelial and all neuroendocrine markers tested (Fig. 6). The sar-

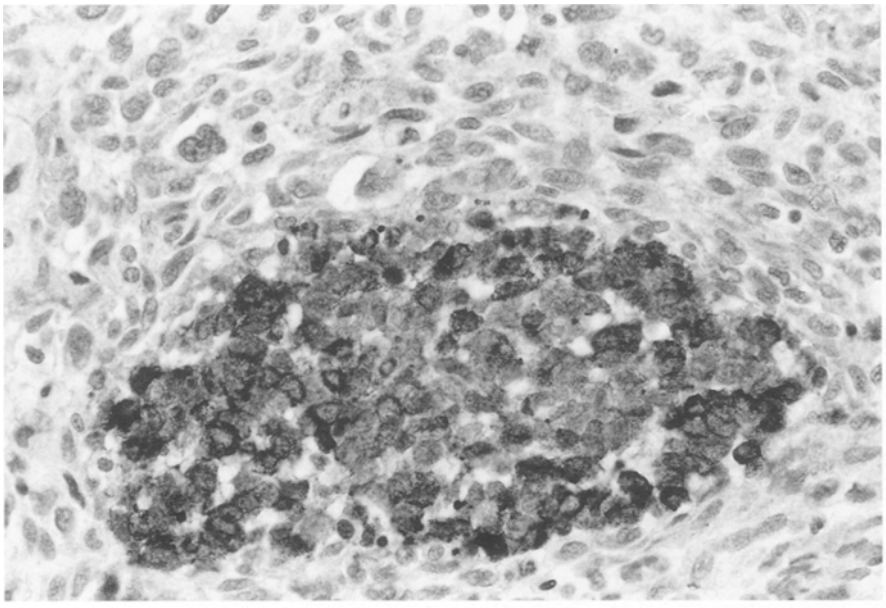

Fig. 6. SCUC shows prominent cytoplasmatic staining for chromogranin. ×400

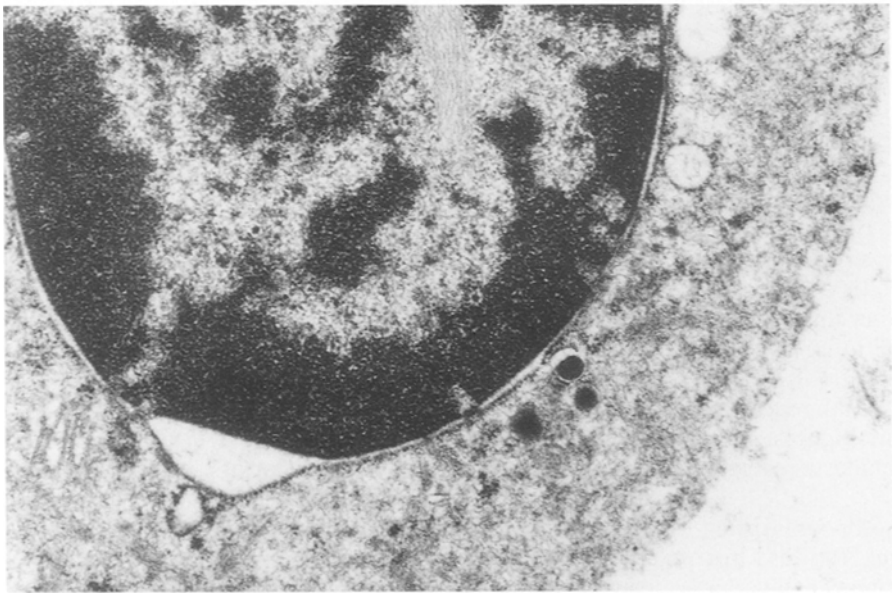

Fig. 7. Electron microscopical detail of SCUC. Notice the neurosecretory type granules in the cytoplasma. The nucleus shows clumped chromatin. ×27,210

comatous component stained strongly with antibodies to muscle actin and smooth muscle actin. In both tumour components no labelling occurred with antibodies to a set of polypeptide hormones (Table 1).

Only the carcinomatous component of patient 2 could be studied ultrastructurally. Nuclei were relatively uniform with clumped chromatin. The cytoplasma contained membrane-limited neurosecretory-type granules ranging from 150 to 250 nm in diameter (Fig. 7).

Discussion

The two mixed malignant bladder tumours described in this report exhibit a unique morphology. For the epithelial component the findings are consistent with those of SCUC of the bladder with neuroendocrine differentiation. The neoplasm resembles the intermediate cell variant of pulmonary SCUC (Mills et al. 1987; Blomjous et al. 1988, 1989; Podesta and True 1989; Oesterling et al. 1990; Grignon et al. 1992). The mesenchymal component consists of spindle cells with malignant cytological characteristics without any expression of epithelial markers. The two tumours are therefore bimorphic and the differential diagnosis includes: (1) spindle-shaped cell carcinoma (sarcomatoid carcinoma; Ro et al. 1988; Young et al. 1988), (2) transitional cell carcinoma with pseudosarcomatous stromal reaction (Young and Wick 1988; Mahadevia et al. 1989) and (3) carcinosarcoma (Holtz et al. 1972; Patterson and Dale 1976; Babian et al. 1980; Schoborg et al. 1980; Uyama and Moriwaki 1981; Grossman et al. 1984; Young 1987; Bloxham et

al. 1990). The essential features of these three bimorphic tumour types of the bladder include the following characteristics.

In sarcomatoid carcinomas, spindle cells are compactly arranged and exhibit a variety of growth patterns and appearances. Malignant cytological characteristics are generally demonstrable with ease. Mitotic figures are usually numerous, but may be inconspicuous. Foci of identifiable urothelial carcinoma or urothelial carcinoma in situ are often encountered; they typically merge and show transition with sarcomatoid foci, at least focally. The latter is an important histological feature that supports the diagnosis of sarcomatoid carcinoma and was not observed in our two cases. Further, staining for cytokeratin and EMA was apparent in all 12 cases of sarcomatoid carcinomas reported by Young and coworkers (1988). The same authors also observed a coexpression of vimentin in the spindle cells. Conversely, spindle-shaped tumour cells that express only vimentin, or both vimentin and muscle cell-related proteins, should be classified as sarcoma (Wick et al. 1988). In this study we did not observe any reaction of the spindle cell component with six different epithelial antibodies, whereas vimentin was strongly expressed.

It may be very difficult to distinguish pseudosarcomatous stromal reactions from bladder tumour with a neoplastic spindle cell component. This kind of reactive lesion exhibits foci of carcinoma cells sharply demarcated from stromal cells which are widely separated from each other. Although the stromal cells are atypical with elongated cytoplasm and tapering ends, they do not strictly fulfil the cytological criteria for a diagnosis of malignancy, but appear to be reactive in nature. In contrast to carcinosarcoma and spindle cell carcinoma this exuberant stromal reaction usually shows an inflammatory background. Moreover, the dearth of mitotic figures is characteristic of pseudosarcomatous stromal reaction; in contrast, the presence of atypical mitotic figures, such as was seen in the two reported cases, excludes a reactive origin of the spindle cells.

Carcinosarcoma is a well-documentated neoplasm in other organs, particularly in the uterine fundus, but amounts to only 0.5% of human bladder cancer (Uyama and Moriwaki 1981). Several theories exist concerning its histogenesis. A simultaneous malignant change of epithelial and mesenchymal cells, as well as the hypothesis of a tumour originating from a totipotent cell have been discussed (Bloxham et al. 1990). Collision tumours consisting of two separate neoplasms invading each other have also been suggested (Holtz et al. 1972). The basic criterion for the diagnosis of carcinosarcoma is an intimate admixture of malignant epithelial and frankly sarcomatous components throughout most of the tumour (Young 1987). The epithelial component in carcinosarcoma usually stands out prominently from the sarcomatous component and most often consists of high-grade transitional cell carcinoma; glandular as well as squamous differentiation may occur, however. Occasionally, undifferentiated carcinoma may be observed (Young 1987). The sarcomatous component may be similar to high-grade leiomyosarcoma, fibrosarcoma, or undifferentiated sarcomas. It may be heterologous, with areas of osteogenic sarcoma, chondrosarcoma and, less frequently, rhabdomyosarcoma (Holtz et al. 1972). The presence of sarcomatous tissue in metastatic lesions can obviously confirm the diagnosis of a carcinosarcoma; however, metastatic lesions exhibit histological variation and pure sarcoma or carcinoma may be observed (Smith et al. 1983).

In this study the lack of immunostaining for epithelial markers and the presence of atypical mitotic figures in the spindle cell component are strong arguments against sarcomatoid carcinoma and pseudosarcomatous stromal reaction respectively. Thus, pending further definitive evidence, we believe the tumours described in this report represent carcinosarcomas. However, this diagnosis may be subject to the following criticisms: in patient 2 the spindle cell component was not observed throughout most of the tumour, but was confined to its superfical part; the deep layers of the bladder and the perivesical fatty tissue were invaded by SCUC without stromal reaction. Further, although several histological samples from both tumours have been taken, the lack of a transition zone between epithelial and mesenchymal components and the absence of staining for epithelial markers in the spindle cells may be due to a sampling error. These findings are known to occur in small foci (Ro et al. 1988). Finally, we did not observe heterologous differentiation of the mesenchymal component, a characteristic but not obligatory feature of carcinosarcoma.

A peculiar observation is the finding of a neuroendocrine differentiation of the epithelial component. There appear to be few neoplasms described in the literature that are identical with or similar to the present cases. Mills and co-workers (1987) reported on a series of 12 small cell carcinomas of the urinary bladder. One neoplasm exhibited a prominent sarcomatoid spindle cell component composed of large elongated cells with prominent cytoplasm. Wrba and co-workers (1990) observed one case of carcinosarcoma of the bladder which showed an epithelial component consistent with small cell carcinoma and a mesenchymal component of undifferentiated sarcoma with foci of chondrosarcoma and osteosarcoma. Young and Eble (1991), in a review of unusual forms of carcinoma of the urinary bladder, reported on some cases where small cell carcinoma was admixed with a prominent component of sarcomatoid carcinoma. However, this type of tumour has been poorly characterized immunohistochemically; we know of only one other study presenting immunophenotypic data (Wrba et al. 1990); the findings were similar to those in the two present cases.

These rare lesions of the urinary bladder thus may in fact represent a single tumour group, characterized by a tendency to polypoid growth, the presence of SCUC with neuroendocrine features, and a mesenchymal component exhibiting some variations in morphology and immunophenotype. The question of whether this entity represents a carcinosarcoma that is totally distinct from sarcomatoid carcinoma cannot be answered clearly. The classification in a single group may be appropriate since these tumours seem to behave in the same way whether

they are truly carcinosarcoma or sarcomatoid carcinoma (Ro et al. 1988). In contrast, we recommend extreme caution in excluding a pseudosarcomatous stromal reaction because of its different prognosis.

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