

Carcinosarcoma/sarcomatoid carcinoma of the urinary bladder with features of malignant fibrous histiocytoma: the role of p53 in growth of the tumor

Malign fibröz histiyositom özellikleri taşıyan mesane karsinosarkoması/sarkomatoid karsinoması: Tümör gelişiminde p53'ün rolü

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Abstract

This is a report of a case of carcinosarcoma/sarcomatoid carcinoma (CS/SC) of the urinary bladder. The patient underwent multiple excisional biopsies of the urinary bladder. Following development of multiple lung metastases, the patient died at 21 months after diagnosis. This case represents a very rare example of CS/SC of the urinary bladder with a malignant fibrous histiocytoma component that was characterized by morphologic and immunohistochemical findings, and proves that CS/SC of the urinary bladder is a very aggressive neoplasm. Analysis of the tumor indicated that different factors other than p53 may be associated with the growth of this tumor.

Key words: Carcinosarcoma; malignant fibrous histiocytoma; p53; sarcomatoid carcinoma; urinary bladder; urothelial carcinoma.

Özet

Burada mesane karsinosarkoması/sarkomatoid karsinoması (KS/SK) olan bir vaka sunulmaktadır. Hastaya çoklu eksizyonel mesane biyopsisi uygulanmıştır. Çok sayıda akciğer metastazı gelişimi sonrası, hasta tanıyı takibeden 21. ayda ölmüştür. Bu vaka morfolojik ve immünohistokimyasal bulgular ile karakterize malign fibröz histiyositom bileşkesi olan çok ender bir mesane KS/SK örneğidir, ve mesane KS/SK'sının çok agresif bir tümör olduğunu ortaya koymaktadır. Tümör analizi, bu tümörün gelişiminin p53'den farklı faktörler ile ilişkili olduğunu göstermektedir.

Anahtar sözcükler: Karsinosarkom; malign fibröz histiyositom; mesane; p53; sarkomatoid karsinoma; üretelyal karsinoma.

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Carcinosarcomas (CS) are neoplasms characterized by the presence of both malignant epithelial and mesenchymal components. CS in the urinary bladder (UB) is rare, and only approximately 80 well-documented cases have been reported.^[1] Here, we present a rare neoplasm of the UB characterized by the presence of both malignant epithelial and mesenchymal components. This case represents a very rare example of carcinosarcoma/sarcomatoid carcinoma (CS/SC) of the urinary bladder with a malignant fibrous histiocytoma component that was characterized by morphologic and immunohistochemical (IHC) analysis.

Case report

A 70-year-old male admitted to the department of urology presented with pollakiuria. He had a his-

tory of surgical intervention in both the prostate and left testis for benign causes four years prior to his admission, and he had undergone two transurethral resections of a bladder tumor (TURB). The resections revealed CS and high-grade urothelial carcinoma (HGUC), respectively, in other institutions. Upon his admission, a computed tomography (CT) of the abdomen and pelvis revealed thickened posterior and lateral walls of the bladder and a 4.5×4.5 cm tumor protruding into the lumen and spreading into the perivesical fat; however, enlarged lymph nodes were not observed. Urinalysis showed hematuria, but other laboratory studies were normal. TURB revealed a tumor that occupied the left lateral surface of the bladder, extending into the trigone and bladder neck and obstructing the orifice of the left ureter. Histology

of the tumor revealed a CS/SC of the UB. There was no history of radiation, and no occupational risk factors were identified. The patient refused cystectomy. A chemotherapy regimen (gemcitabine, cisplatin) was given twice. Three months later, the patient was tumor free. Control biopsies of the UB one month later and a repeat biopsy ten days later revealed a HGUC. Nine months later, a CT scan of the abdomen and pelvis displayed an 8×7 cm mass in the right parailiac region (Fig. 1). CT of the thorax revealed multiple metastatic nodules in the lungs. Repeat TURB done at two-month intervals revealed tumor tissues corresponding with HGUC. Perfusion adriablastin and cisplatin chemotherapy was given. The patient died of the disease 21 months after the initial diagnosis.

Pathological findings

Five-micron thick sections of paraffin-embedded tissues were stained with hematoxylin and eosin (H-E), and IHC studies were performed using the streptavidin-biotin peroxidase procedure. The results of a large panel of immunostains are shown in Table 1.

Microscopic examination of the first three TURB specimens revealed a highly malignant neoplasm

with a biphasic growth pattern that invaded the lamina propria, muscularis propria and perivesical fat. One part of the tumor consisted of pleomorphic epithelial cells with hyperchromatic nuclei and scant cytoplasm, which is typical of HGUC (Fig. 1). The other sarcomatous-like part of the tumor (i.e., sarcomatoid tumor component with features of malignant fibrous histiocytoma) was separated from the epithelial component (Fig. 2).

Histologically, the last three biopsy specimens had only monophasic proliferation of the malignant epithelial cells and were characterized by the IHC features of the epithelial component of previous specimens. No nuclear immunoreactivity for p53 was observed in the tumor, and both components of the tumor demonstrated very high proliferative activity, as assessed by nuclear reactivity for Ki-67 (Fig. 3).

Discussion

Pure mesenchymal tumors and biphasic neoplasms rarely occur in the UB. CS is defined by the WHO as tumor composed of mixed malignant epithelial and mesenchymal elements and have been reported in many systems. SC is a malignant spindle cell neo-

Table 1. The results of the antibody panel. Histostain-plus kit was used (Zymed).

Antigen	Clone	Source	Titer	Pretreatment	CC	SRC
PanCK	AE1/AE3	Novocastra	1:50	Trypsin	+++	-
CEA	Polyclonal	Novocastra	1:50	Trypsin	-	-
VIM	V9	Neomarkers	1:200	PC-C	-	+++
SMA	1A4	Neomarkers	1:300	None	-	-
Desmin	DE-R-11	Novocastra	1:50	Trypsin	-	-
A1AT	Polyclonal	Immunon	1:200	Trypsin	+	+++
A1ACT	Polyclonal	Biogenex	1:50	None	+	+++
CD68	KP1	Dako	1:75	Trypsin	-	+++
LYS	Polyclonal	Neomarkers	1:100	PC-C	-	+
NSE	E27	Neomarkers	1:25	PC-C	+	+++
S-100	4C4.9	Neomarkers	1:200	None	-	+
SYNF	Polyclonal	Neomarkers	1:40	PC-C	-	-
ChrA	LK2H10	Novocastra	1:50	PC-C	-	-
p53	DO7/BP53-12	Neomarkers	1:100	PC-C	-	-
Ki67	7B11	Zymed	1:50	PC-C	↑	↑

CK: Cytokeratin, CEA: Carcinoembryonic antigen, VIM: Vimentin, SMA: Smooth muscle antigen, A1AT: α1-antitrypsin, A1ACT: α1-antichymotrypsin, LYS: Lysozyme, NSE: Neuron specific enolase, SYNF: Synaptophysin, ChrA: Chromogranin A, CC: Carcinomatous component, SRC: Sarcomatoid component.

+: Weak, +++: Strong, -: Negative, ↑: High proliferative activity.

Trypsin: Sections preheated with 0.1% trypsin (sigma) for 3 min at 37°C.

PC-C: Sections preheated in a conventional pressure cooker for 90 sec in a citrate buffer solution.

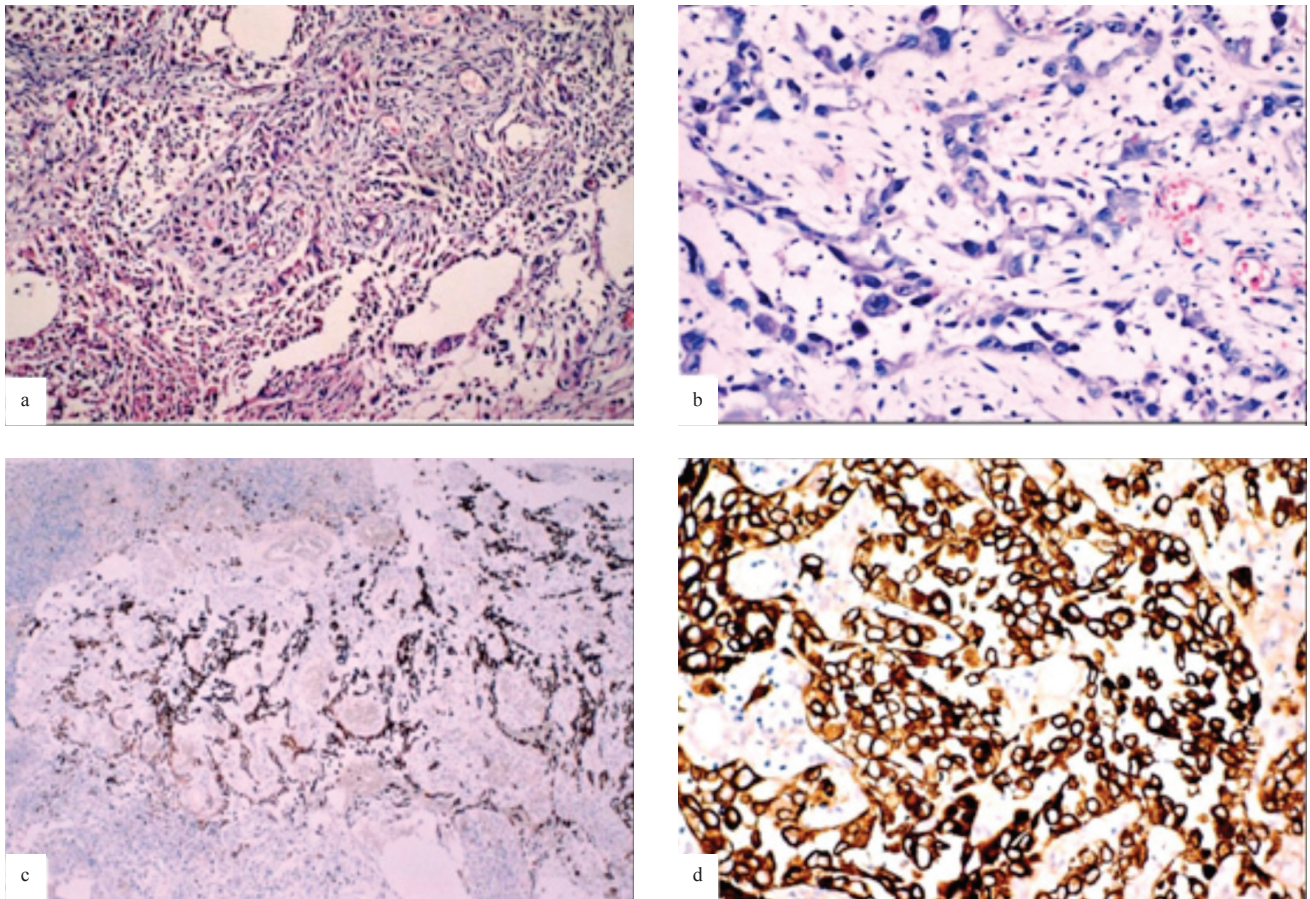


Figure 1 Microscopic view of the epithelial component of the tumor. (a, b) Sheets of malignant urothelial epithelium with technical artifacts reveal focal pseudoglandular architecture (H-E, $\times 25$, $\times 50$). (c, d) panCK positivity of the epithelial component of the tumor (Peroxidase, $\times 10$, $\times 50$).

plasm with epithelial cell differentiation.^[2] Research indicates that CSs and SCs are closely related, if not identical, and are urothelial in their origin. At present, there is no overall agreement on the definition of CS and SC. In some instances, SC is used synonymously with CS, whereas others consider them separate entities.^[3,4] Both tumors are highly aggressive malignancies and show comparable tumor biology.^[5] Some investigators have found an association between previous radiation exposure and previous long-term systemic chemotherapy and the development of CS/SC in the UB.^[2] No predisposing factor was identified in the present case. To date, the exact histogenesis of these neoplasms remains a controversial issue in tumor pathology.^[6] Sarcomas are usually not stained by epithelial markers, although there are rare exceptions.^[2] Multiclonal and monoclonal hypotheses have been proposed to explain the histogenesis of SC and CS,^[6] although there have been conflicting

results.^[7] Halachmi et al.^[8] demonstrated in CS that both CC and SRC are derived from a common stem cell. Additionally, analysis by comparative genomic hybridization strongly suggests a monoclonal origin for CS and SC.^[7]

The diagnosis of CS and SC can be made using HE alone in most cases, but it is difficult to distinguish them from sarcomas. The reverse is also a possibility. In the present case, SRC of the tumor was present in the first three TURB specimens. However, in the recurrent tumor biopsies, which all consisted of small specimens, SRC was missing. This is most likely due to a sampling error. The CC can be sharply demarcated from SRC, similar to the present case, or they can gradually merge with each other. The malignant epithelial component in CS is usually a high grade papillary UC. The commonly observed CS include chondrosarcoma, leiomyosarcoma, osteosarcoma,

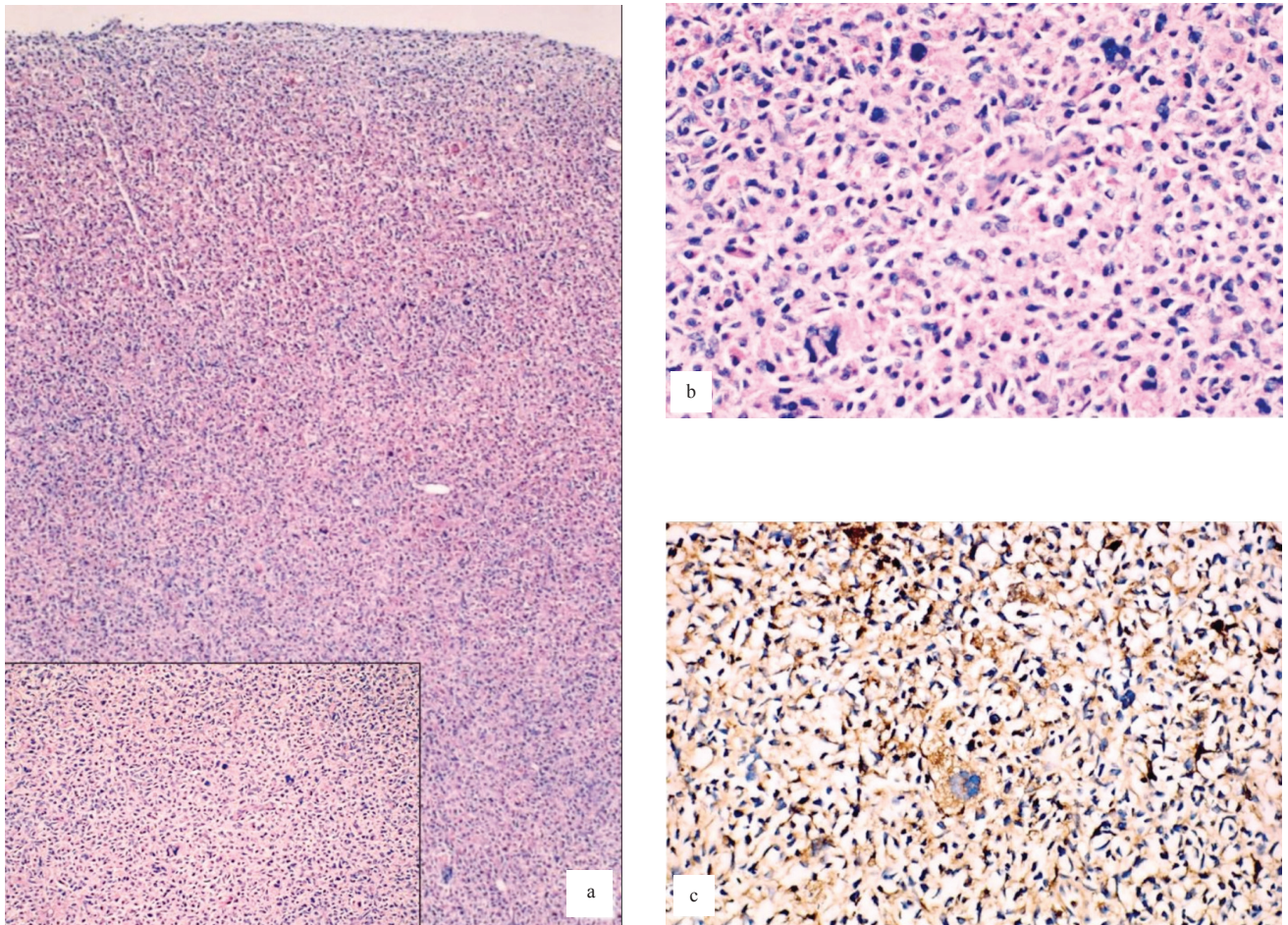


Figure 2 (a, b) Microscopic overview of the sarcomatoid tumor component with features of malignant fibrous histiocytoma (H-E, $\times 10, \times 50$, inset $\times 25$). (c) Tumor cells including giant cells are CD68 positive (Peroxidase $\times 50$).

fibrosarcoma, rhabdomyosarcoma, and very rarely malignant fibrous histiocytoma. Fibrohistiocytic tumors are a heterogeneous tumor group, and malignant fibrous histiocytomas (MFH) are encountered more frequently than their benign counterpart in the UB. Pancytokeratin, alpha1 antichymotrypsin and alpha 1 antitrypsin are immunomarkers for the diagnosis of CS and MFH.^[9] Although p53 immunoreactivity has been reported in both components of a CS of the UB,^[10] the negative immunostaining for p53 of both components of the present case may indicate that different factors other than p53 are associated with the pathogenesis of CSs in the UB.

CS/SC of the UB is very aggressive neoplasms and there is no universal agreement on their therapy. The only curative management of this kind of neoplasm is early detection and aggressive surgery. Because most

patients present with a high stage malignancy, the preferred modalities of treatment include cystectomy or TURB with or without radiation therapy and chemotherapy. Radical cystectomy, which was refused by the patient in the present report, does not yield long-term survival rates. Additionally, chemotherapy and radiotherapy do not provide apparent survival advantages.^[11] The prognosis for this disease is dismal, and most patients die within a few months of diagnosis because the tumor is usually at an advanced stage at the time of detection.^[11] Further studies with more cases may provide histological findings with more clinical and therapeutic significance.

As a conclusion, the present case represents a CS/SC with MFH component of the UB. Elevated MIB-1 labeling index and the IHC profile of the tumor characterize it as an MFH.

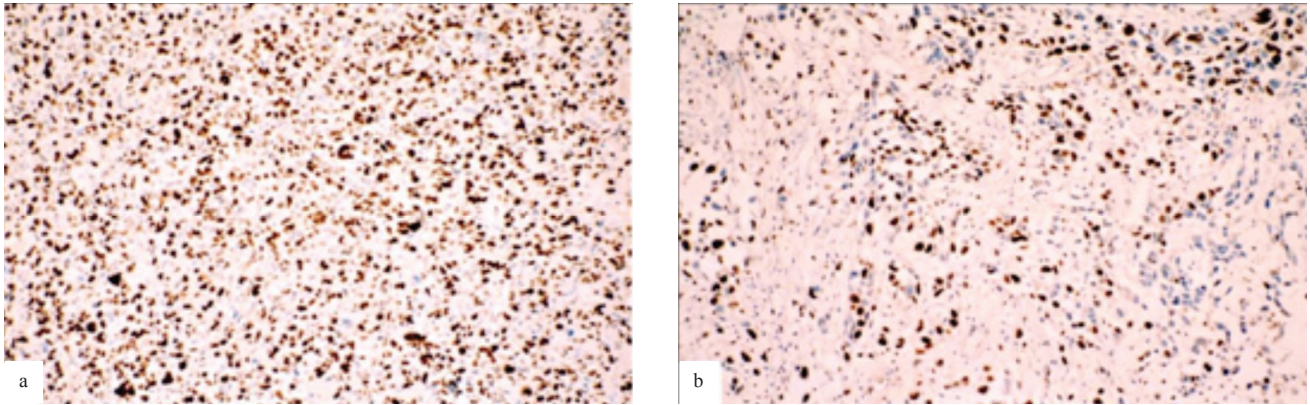


Figure 3 Proliferative activity of the tumor components. Both (a) sarcomatous and (b) epithelial components have a high proliferation index as shown by Ki-67 reactivity (Peroxidase, $\times 25$, $\times 25$).

Conflict of interest

No conflict of interest was declared by the authors.

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