Tumori, 89: 328-330, 2003

SMALL CELL CARCINOMA OF THE URINARY BLADDER. A CLINICOPATHOLOGIC STUDY OF FIVE CASES

Ozkan Kanat[1], Turkkan Evrensel[1], Saduman Balaban Adım[2], Ismet Yavascaoglu[3], Ender Kurt[1], Mutlu Demiray[1], Guzin Gonullu[1], and Osman Manavoglu[1]

[1]Department of Medical Oncology, [2]Department of Pathology, [3]Department of Urology, Faculty of Medicine, Uludag University, Bursa, Turkey

Aims and background: **Small cell carcinoma of the bladder (SCCB) is a rare entity characterized clinically by an aggressive behavior with a high incidence of systemic metastases. We report the clinicopathologic findings of five cases.**
Methods: **We reviewed five consecutive patients with SCCB treated at our institute. In each case the following clinical data were recorded: age, sex, presenting symptoms, endoscopically determined location of the tumor, clinical staging, node involvement (if any), site of metastases (if any), treatment, follow-up and outcome.**
Results: **There were four male and one female patients, age range 42 to 68 years, mean 57.6 years. The clinical presentation was not different from conventional transitional cell carcinoma, with hematuria being the most frequent complaint (four cases). Microscopic examination revealed oat cells in three cases and an intermediate variant in one. At the time of diagnosis the tumors were staged as T3bN2M0, T2N2M0, T4N0M0, T3aN0M0, and T2N0M0. Primary therapy consisted of radical cystectomy alone (one case), transurethral resection (TUR) alone (one case), TUR with chemotherapy (two cases), or TUR with chemotherapy and radiotherapy (one case). Four patients died of progressive disease, with survival from the time of diagnosis ranging from 7 to 16 months (mean, 12.2 months). One patient died of myocardial infarction (unrelated to the primary disease) one month after diagnosis.**
Conclusion: **Our study indicates that primary small cell carcinoma of the urinary bladder is as aggressive as its pulmonary counterpart and the overall prognosis of this tumor is very poor.**

Key words: bladder, small cell carcinoma, treatment.

Introduction

Small cell carcinoma (SCC), which characteristically occurs in the lungs, has been described in a number of extrapulmonary sites[1-5]. Although it has been rarely reported, urinary bladder is the most common site of extrapulmonary SCC in the genitourinary tract[6]. The first case of SCCB was reported by Cramer in 1981[7]. Since then, approximately 160 cases have been reported worldwide[8].

The biological behavior and microscopic, ultrastructural, and immunohistochemical features of SCCB are similar to those of small cell lung carcinoma (SCLC). Based on published reports, SCCB usually has an aggressive clinical course characterized by early systemic dissemination and high mortality from metastatic disease. The overall five-year survival rate for all reported cases has been estimated at 8.3%[8]. This article describes the clinical and pathologic features of five cases among a total of 550 patients diagnosed with bladder carcinoma and treated at our institute during an eight-year period (1994-2001).

Patients and methods

The following clinical data were recorded in each case of SCCB: age, sex, presenting symptoms, endoscopic tumor location, clinical stage, node involvement (if any), site of metastases (if any), treatment, follow-up and outcome. Clinical staging was done according to the 1997 TNM staging system[9].

Light microscopic examination

Cystectomy and transurethral resection specimens were processed in a routine manner and embedded in paraffin blocks. Tissue sections stained with hematoxylin and eosin were examined in all cases. A diagnosis of small cell carcinoma was made only when the morphologic criteria established by the World Health Organization (WHO) for SCLC were met[10]. Histologically the tumors were subdivided into three groups according to the WHO definitions: 1) oat cell carcinoma, 2) intermediate cell type carcinoma, and 3) combined carcinoma type.

Immunohistochemical studies

Immunohistochemical studies were performed using the avidin-biotin complex method of Hsu *et al.*[11] in all patients. Antibodies against the following antigens were used: neuron-specific enolase (NSE) (DAKO, monoclonal mouse antihuman neuron-specific enolase), chromogranin (Neomarkers, monoclonal mouse antihuman chromogranin A Ab-3), cytokeratin (DAKO, monoclonal mouse, antihuman cytokeratin), leukocyte common antigen (LCA) (DAKO, monoclonal mouse antihuman leukocyte common antigen, CD45), and synaptophysin (Neomarkers, polyclonal rabbit antihuman synapto-

Correspondence to: Ozkan Kanat, Department of Medical Oncology, Faculty of Medicine, Uludag University, Gorukle, 16059 Bursa, Turkey. Tel +90-224-4428400/1341; fax +90-224-4428049; e-mail ozkanat@uludag.edu.tr

Received August 19, 2002; accepted January 13, 2003.

physin Ab-1). Appropriate positive and negative controls were used.

Results

Clinical findings

Clinical details are summarized in Table 1. There were four male and one female patients, age range 42 to 68 years, mean 57.6 years. The most common presenting symptom was gross hematuria, observed in four patients. One patient presented with dysuria and obstructive uropathy. No patient showed evidence of paraneoplastic syndromes. Cystoscopy revealed the lateral walls to be the site of origin in all cases.

At the time of diagnosis the tumors were staged as T3bN2M0 (case 4), T2N2M0 (case 1), T4N0M0 (case 5), T3aN0M0 (case 3), and T2N0M0 (case 2). One patient (case 2) was treated only with cystectomy. Three months later this patient developed distant metastases in the liver and parailiac and paraaortic lymph nodes. Six cycles of cisplatin (80 mg/m^2 day 1) and etoposide (100 mg/m^2 days 1 to 3) were given but no remission was achieved. The patient died of progressive disease 14 months after the diagnosis of SCCB.

Four patients (cases 1, 3, 4 and 5) were treated with tumor debulking by cystoscopy- guided transurethral resection (TUR). One patient (case 4) could not receive radiotherapy or chemotherapy after TUR because of the development of congestive heart failure and cardiac rhythm disturbance. The patient died of myocardial infarction one month after the diagnosis of SCCB.

The remaining three patients received systemic chemotherapy consisting of cisplatin and etoposide (case 5) or cyclophosphamide 1000 mg/m^2, doxorubicin 45 mg/m^2 and vincristine 1.4 mg/m^2 (cases 1 and 3). These patients completed the six scheduled cycles. At the end of chemotherapy, one patient (case 5) achieved a complete remission and received adjuvant radiotherapy to bladder and pelvis (6660 cGy). However, the patient developed recurrences in the brain and died 16 months after the diagnosis of SCCB. The other two patients (cases 1 and 3) died of progressive disease 7 and 12 months, respectively, after the diagnosis of SCCB.

Microscopic type and immunophenotype

Three patients had oat cell type SCC, two had the intermediate type. Small cell carcinomas were composed of relatively uniform small cells consisting mainly of a nucleus. These nuclei were densely chromatic. NSE was the most consistently positive neuroendocrine marker, with reactivity being observed in all five cases studied. Staining was cytoplasmic and strongly reactive. Chromogranin reactivity was seen in three cases, synaptophysin reactivity in two. Cytokeratin positivity was found in two of five cases. Negative results were obtained with LCA in all cases.

Discussion

SCCB accounts for 0.5% to 1.0% of bladder malignancies[12-14]. The histogenesis of SCCB has not been clearly defined. There are three possible explanations for its origin[12,15,16]. One possibility is that the tumor arises from a neuroendocrine stem cell (Kultschitzky-type) that exists in the urothelium of the bladder. Another hypothesis is that these tumors arise from cells in the submucosa or muscularis that are of neural crest origin. A third explanation for the origin of SCCB is that these tumors arise, through a process of metaplasia, from conventional high grade transitional cell carcinoma (TCC).

The clinical presentation of SCCB does not differ from that of other malignant tumors of the bladder. There is male predominance and patients are usually in their seventh or eighth decade[8]. Hematuria is the most common presenting symptom. Less common symptoms are bladder irritability, suprapubic or flank pain, and obstructive uropathy[17].

The optimal management of SCCB has not been established. Long-term survivors after surgery alone were reported among patients with SCCB[17,18]. In our series, one patient (case 2) was managed with radical cystectomy alone for a T2N0 tumor but subsequently developed early distant metastases and died at 14 months from diagnosis. Thus, radical cystectomy alone might not be sufficient for invasive disease.

Table 1 - Clinical features of patients with SCCB

Case no.	Age/Sex	Symptoms	Cell type	Stage	Primary therapy*	Metastases	Additional therapy**	Follow-up (months)
1	54/M	Hematuria	Intermediate	T2N2M0	TUR, CH (Cy, Vinc, Dox)	Lymph nodes, brain	RT to brain	DOD/ 7
2	42/M	Hematuria	Intermediate	T2N0M0	Total cystectomy	Liver, lymph nodes	CH (Cis-P, VP-16)	DOD/ 14
3	57/M	Hematuria	Oat cell	T3aN0M0	TUR, CH (Cy, Vinc, Dox)	Adrenal gland, liver	No	DOD/ 12
4	67/F	Hematuria	Oat cell	T3bN2M0	TUR	Lymph nodes	No	DUC/ 1
5	68/M	Dysuria, obstructive uropathy	Oat cell	T4N0M0	TUR, CH (Cis-P, VP-16), RT (6660 cGy)	Brain	RT to brain	DOD/ 16

TUR: transurethral resection; CH: chemotherapy; RT: radiotherapy; Cis-P: cisplatin; Vinc: vincristine; Dox: doxorubicin; VP-16: etoposide; Cy: cyclophosphamide; DOD: dead of disease; DUC: dead of unrelated cause; *Primary therapy refers to all treatments given after the diagnosis of SCCB; **additional therapy refers to any subsequent therapy for local recurrence or metastatic disease.

Cystectomy may not be required in some patients with SCCB confined to the pelvis. Some authors demonstrated that systemic chemotherapy and local radiation therapy for SCCB may produce long-term complete remission[19,20]. This approach allows preservation of the bladder and improves the quality of life. Some authors suggested that surgery (cystectomy or TUR) plus adjuvant systemic chemotherapy is the treatment of choice[15,21]. Like for SCLC, cisplatin-based chemotherapy regimens are most commonly used for the management of SCCB. Newer chemotherapeutic agents such as gemcitabine and paclitaxel could increase the chemotherapeutic options for SCCB and may improve the survival rate[22].

Relapse of SCLC in the brain is frequently reported and prophylactic brain irradiation is the standard of care in these cases. Considering the clinical course in one of our patients (case 5), there may be a role for prophylactic brain irradiation for SCCB cases in complete remission after the completion of chemotherapy and pelvic radiotherapy. We assume that the risk of metastases to the brain may be high in patients with bulky primary tumors.

Our experience reemphasizes the poor prognosis of SCCB compared to other bladder tumors, even at the same stage. It is difficult to draw conclusions about the best therapeutic strategy based on our small series. Although we think that systemic chemotherapy is the cornerstone of therapy for SCCB, the poor outcome we observed in our study might be associated with inadequate local treatment. Whether local treatments improve the survival of these patients has not been established yet and should be investigated in further studies.

References

1. Richardson RL, Weiland LH: Undifferentiated small cell carcinomas in extrapulmonary sites. Semin Oncol, 9: 484-496, 1982.
2. Ibrahim NBN, Briggs JC, Corbishley CM: Extrapulmonary oat cell carcinoma. Cancer, 54: 1645-1661, 1984.
3. Lo Re G, Canzonieri V, Veronesi A, Dal Bo V, Barzan L, Zancanaro C, Trovo M: Extrapulmonary small cell carcinoma. A single-institution experience and review of the literature. Ann Oncol, 5: 909-913, 1994.
4. Vrouvos J, Ash DV: Extrapulmonary small-cell cancer. Clin Oncol, 7: 377-381, 1995.
5. Galanis E, Frytak S, Lloyd RV: Extrapulmonary small-cell carcinoma. Cancer, 79: 1729-1736, 1997.
6. Petersen RO: Urologic pathology, 2nd ed, pp 260-394, JB Lippincott, Philadelphia, 1992.
7. Cramer SF, Aikawa M, Cebelin M: Neurosecretory granules in small cell invasive carcinoma of the urinary bladder. Cancer, 47: 724-730, 1981.
8. Trias I, Algaba F, Condom E, Espanol I, Segui J, Orsola I, Villavicencio H, Garcia del Muro X: Small cell carcinoma of the urinary bladder: presentation of 23 cases and review of 134 published cases. Eur Urol, 39: 85-90, 2001.
9. TNM classification of malignant tumors, 5th ed, pp 187-190, Wiley-Liss, New York, 1996.
10. World Health Organization: The World Health Organization histogical typing of lung tumors. Am J Clin Pathol, 77: 123-136, 1982.
11. Hsu SM, Raine L, Fanger H: Use of avidin-biotin peroxidase complex (ABC) in immunoperoxidase technique: a comparison between ABC and unlabelled antibody (PAP) procedures. J Histochem Cytochem, 29: 577-580, 1981.
12. Blomjous CE, Vos W, De Vooght HJ, Van Der Valk P, Meijer CJ: Small cell carcinoma of the urinary bladder: a clinicopathologic, morphometric, immunohistochemical, and ultrastructural study of 18 cases. Cancer, 64: 1347-1357, 1989.
13. Holmang S, Borghede G, Johansson SL: Small cell carcinoma of the bladder: a report of 25 cases. J Urol, 153: 1820-1822, 1995.
14. Lohrisch C, Murray N, Pickles T, Sullivan L: Small cell carcinoma of the bladder. Long term outcome with integrated chemoradiation. Cancer, 86: 2346-2352, 1999.
15. Oesterling JE, Brendler CB, Burgers JK, Marschall FF, Epstein JI: Advanced small cell carcinoma of the bladder. Successful treatment with combined radical cystoprostatectomy and adjuvant methotrexate, vinblastine, doxorubicin and cisplatin chemotherapy. Cancer, 65: 1928-1936, 1990.
16. Ali SZ, Reuter VE, Zakowski MF: Small cell neuroendocrine carcinoma of the urinary bladder. A clinicopathologic study with emphasis on cytologic features. Cancer, 79: 356-361, 1997.
17. Abbas F, Civantos F, Benedetto P, Soloway MS: Small cell carcinoma of the bladder and prostate. Urology, 46: 617-630, 1995.
18. Podesta AH, True LD: Small cell carcinoma of the bladder: report of five cases with immunohistochemistry and review of the literature with evaluation of prognosis according to stage. Cancer, 64: 710-714, 1989.
19. Oblon DJ, Parsons JT, Zander DS, Wajsman Z: Bladder preservation and durable complete remission of small cell carcinoma of the bladder with systemic chemotherapy and adjuvant radiation therapy. Cancer, 71: 2581-2584, 1993.
20. Bastus R, Caballero JM, Gonzalez G, Borrat P, Casolots J, Gomez de Segura G, Marti LI, Ristol J, Cirera L: Small cell carcinoma of the urinary bladder treated with chemotherapy and radiotherapy: results in five cases. Eur Urol, 35: 323-326, 1999.
21. Grignon DJ, Ro JY, Ayalo AG, Shum DT, Ordenez NG, Logothesis CJ, Johnson DE, Mackoy B: Small cell carcinoma of the urinary bladder: a clinicopathologic analysis of 22 cases. Cancer, 69: 527-536, 1996.
22. Matsui Y, Fujikawa K, Iwamura H, Oka H, Fukuzawa S, Takeuchi H: Durable control of small cell carcinoma of the urinary bladder by gemcitabine and paclitaxel. Int J Urol, 9: 122-124, 2002.