*Small cell neuroendocrine bladder carcinoma; our experience*

*E Tartaglia, G Delicato, S Signore,*

UOC Urologia Ospedale S Eugenio Roma Italy

**Introduction.** Neuroendocrine bladder cancer is extremely rare, with an estimated incidence of 0.35-0.70% of all bladder tumors. The small-cell carcinoma represents the most frequent histologic variant described. Small-cell carcinoma is an epithelial tumor associated with a more aggressive behavior and poorer prognosis than transitional cell bladder carcinoma. The overall survival rate at 5 years does not exceed 8%. At the time of presentation 59% of patients have clinical stage >T2 and 56% show meta- static disease. In 50% of the patients, fatal progression occurrs within 6 months. Local recurrence after radical surgery occurred in 50-70% of cases.

Patients and Methods. We report two cases of pure neuroendocrine small-cell bladder cancer. Hematuria was the most common presenting symptom. Local advanced disease was present in all the cases with stage >T2, metastatic disease in 1 case. The patients were treated by radical cystectomy, bilateral pelvic limph node resections and urinary derivation. They received a platinum-based neoadjuvant chemotherapy .

Results. In 1 patient residual or relapsed cancer reappered within 2 months after surgery and he died of metastatic disease at 7 months. Median overall survival was 7 months. The most common site of relapse and spread of disease was the peritoneum and intestinal tract, and the reason of death was uncontrolled acute hemorrhage from gastro-intestinal district.

Conclusions. In the absence of a prospective study, and because of the rarity of the disease, the best treatment for small-cell bladder cancer remains uncertain. Neoadjuvant chemoterapy with platinum regimen plus aggressive surgical approach will be the treatment of choice. The association of chemo- therapy and radiotherapy should also be considered.

Key words: Small-Cell bladder carcinoma, Neuroendocrine differentiation, Therapeutic challange, Poor prognosis, Multimodal treatment

**Introduction**

Small cell neuroendocrine carcinoma (SCC) is a common histological variant that represents about 14% of all lung cancer primitive forms (1, 2). This histological form has been described in numerous extrapulmonary sites (3) and also at genitourinari tract, in the prostate and bladder (4). The neuroendocrine small cell bladder carcinoma (SCBC) is extremely rare, with an incidence of between 0.3 and 1.35% of all bladder cancers (5-7). This histological variant was originally described in 1981 by Cramer (8). Until 2001 had been described in the literature about an hundred cases (9-11). In subsequent years, the growing interest in this particular neoplastic form has led to a considerable increase in 12% of diagnoses. in 2006 it had reached about 550 r cases brought in the literature (12-18) and at present we have over 12% of diagnose(19) (Fig. 1). Among neuroendocrine tumors the small cell bladder carcinoma is ,however, the most frequent form. Carcinoids are extremely rare and large cell neuroendocrine carcinomas have been described in less than ten cases (20, 21) (Fig. 2). Small bladder carcinoma cells is a form of cancer with an extremely aggressive behavior and a much worse prognosis of transitional cell carcinoma (22, 23). The median survival rate for all stages is 19.6 months and the serviva at five years is only the 8.1% (24).

A standard treatment has not yet been defined because of the rarity of the disease that does not allow prospective studies(24). Surgery alone has not proved able to dominate the illness (10). In the most advanced centers it proposes a multimodal approach based on an aggressive chemo- therapy with regimens containing platinum and then surgery and / or radiotherapy (17). We present our experience of two cases of neuroendocrine small cell tumors of the bladder recently recovered at our center one of which went rapidly progressing resulting in death within months of diagnosis.

**Fig. 1 - Neuroendocrine carcinoma of the bladder (SCCB)**

**Major World Case Studies**

**Principali Casistiche Mondiali**

Mills Am.J.Surg Path. 1987 12

Blomjous Cancer 1989 18

Holmgang J.Urol 1995 25

Grignon Cancer 1992 22

Abbas Urology 1995 106

Lohrisch J.Urol 1999 16

Algaba Eur.Urol 2001 23

Siefker-Radtke J.Urol 2004 26

Cheng Cancer 2004 64

Choong Modern Pathol 2005 55

Bex Eur.Urol 2005 25

Asmis B.J.Urol 2005 12 (Canadian Ex)

Ismaili In.J.Urol 2008 17 (Leon-Berard)

Bex (mayo clinic) Eur.Urol 2005 25

**Mondiali**

**FIG 2 neuroendocrine bladder cancer**

**carcinomas subdivision**

43% CA small cell pure

37% Ca-small cell plus urothelial

8% large cells Ca

12% Ca-small cells genitourinary

**CASES**

From December 2013 AND January 2016 we observed two cases of bladder cancer with neuroendocrine small cell component in 1785 bladder cancer reached to our attention 0,012%.

Ca + Ca-small cell urothelial

Ca a small cell

case 1

D.C. 73 years old, suffering from chronic lymphatic leukemia with severe respiratory failure. In December 2013 after terminal hematuria is performed abdomen ultrasound that showed a lesion of 3.5 cm in the retrotrigonal area and also numerous liver metastases. At TURB neuroendocrine small cell carcinoma and urothelial ca massively infiltrating the muscle layer. The ultrasound-guided liver biopsy confirms the nature of neuroendocrine metastases. The patient for poor general condition is subjected to chemotherapy with gemcitabine and carboplatin suspended at the second cycle for intolerance. Since then, only supportive care. The patient arrives at exitus 13 months from turv twith disease progression in the liver, peritoneal and local recurrence after turv.

case 2

B.G.F. 60 years old. January 2015 after the appearance of hematuria underwent to TURB for neoplasia 3 cm on the dome. Histological examination revealed a neuroendocrine small cells carcinoma infiltrating T2B

Absence of metastases on bone scan and the tac

**FIG 3 TC scan of case 1**



**Fig. 4** - from radical cystectomy Preprato histological staining with hematoxylin-eosin. Massive infiltration of the muscular tunic thereof and pericyst by small neuroendocrine cells with very obvious nucleus.

**Fig. 5** - evaluation with immunohistochemistry preparation prior year. Intense positivity of neuroendocrine cells to chromogranin A.





**DISCUSSION**

The incidence of neuroendocrine carcinoma of the bladder is extremely rare. At the moment, in the literature are reported only 13 studies that reports at least ten cases. in the case study from the Mayo Clinic in 2004 (18), on a 28-year observation period of 8345 patients evaluated for early bladder cancer, were detected 44 cases of SCCB equal to 0.53%. The predominance of males was 3: 1 similar to transitional cell carcinoma, and the average age at diagnosis of 66.9 years with a range 47.5-87.7. In other cases the male prevalence reaches the ratio of 5: 1 (15). In reviewing Asmis (14) is referred a particularly high incidence of 1.4% (12 cases out of 858 bladder carcinomas), while for the prostate neuroendocrine cancers are reported only 10 cases out of 5066 carcinomi (0.2% ). The male: female ratio was 3: 1. in the series reported by ismaili (19) the percentage increases to 1.8% due to the high number of neoplastic forms metastatic pertaining to Leon-Berard center. The neuroendocrine carcinoma diagnosis with immunophenotype small bladder cells is based on detection of typical round cells and positivity to the chromogranin A and sinaptofina (14). The etiology of the neuro-endocrine carcinoma primitive bladder is unknown although have been postulated several theories about its origin. The presence of cellular elements neuroendocrine in bladder was still well documented and some authors (11) believe that it is possible a transformation in malignant transformation of these cells. Others believe that the malignant neuroendocrine neutral cells can originate from clones of totipotent cells bladder (6) or from a metaplasia arising in the urothelio (8, 25). Hailemariam (26), according with our study, reports a case of SCC occurred in patients already treathed with radiotherapy for prostate cancer. Similarly, other authors report neuroendocrine differentiation of prostate cancer after hormone therapy. In about 80% of cases there is prolonged exposure to cigarette smoke. The diagnostic criteria of small cellular carcinoma of the bladder are similar to those of small cell lung carcinoma according to the parameters set by the WHO (27). Histologically the tumor occurs in clusters of small round or oval cells with scant cytoplasm separated from each other by a delicate fibrovascular stroma, with very obvious chromatin, cell membrane and ill-defined reduction or absence of nucleoli. Mitoses are frequent. In some cases the diagnosis is exclusively based on the morphological study, although the neuroendocrine differentiation may not be obvious to the immunohistochemical studies or electron microscopy.

Frequently the small cell carcinoma is associated with another carcinoma (15) almost always poorly differentiated urothelial carcinoma (55%) and adenocarcinoma or carcinosarcoma often.

The differential diagnosis includes high-grade urothelial carcinoma, carcinoma of the bladder small cell lymphoma and metastatic lesion especially pulmonary neuroendocrine carcinoma. The lymphoma is the closest to neuroendocrine carcinoma. The cells are small with oval or round nuclei, with increase to the nuclear / cytoplasmic ratio, while the core is central and not as eccentric as in the neuroendocrine carcinoma, and the nucleolus is almost always prominent.

Immunohistochemistry demonstrates the expression of markers of neuroendocrine differentiation including comogranina A, the neuron-specific enolase (NSE) and the synaptic tofisina. Bladder small cell carcinoma can produce hormones or neuropeptides (23). Excretion of ACTH is reported by Choong (18) in a patient

A paraneoplastic syndrome is very rare in contrast to SCC of the lung and prostate. More than half of the forms of SCCB are associated with other histological types, normally the transitional cellular carcinoma. In the series by ismaili (19) 64% of cases were mixed tumors. And in the multicentric the percentage of mixed forms came to 69% of the Indian Cheng 2004 (15). Conversely in the series by Choong 2005 at the Mayo Clinic (18) of 44 cases of SCCB 27 (61.4%) tumors were associated with transitional cell carcinoma and 4 with adenocarcinoma or squamous cell carcinoma.

The disease typically begins with persistent hematuria and demonstrates an extremely aggressive pattern with rapid infiltration of the bladder wall and spread yo the retroperitoneum. Frequently liver and intestinal metastases.

At diagnosis, the small cell carcinoma is almost always (75-99% of cases) muscle-invasive and locally advancement to (4, 6, 11, 15, 19). Hematuria is the most frequent symptom occurring nell'80-95% of cases (18, 24), other frequent disorders are dysuria and irritative symptoms (6, 24). Symptoms all present in our 2 patients. Early infiltration ureter with rapid progression to urinary obstruction, hydronephrosis and i.r.C. found by us is reported also by other authors (14, 16, 24). The tumor tends to penetrate rapidly in the bladder wall and to express itself outside with infiltration of the rectum and the bowel Choong (18) reports that on 44 SCCB in 20% of cases the diagnosis was made incidentally to a returv or cystectomy performed for tCC.

In other cases neuroendocrine outbreak was below a transitional neoplasia (9). Many authors (14, 15, 18, 19) think very important to carry out numerous deep detrusor biopsies to avoid the risk of misunderstanding the disease. Extremely rare occurrence of the tumor in the bladder diverticula and in the uraco. Only two cases reported in the literature (28). The disease tends to metastasize through the blood, lymphatic tsistem and contiguity following the traditional way of spreading the transitional cell carcinoma. Also frequent bone disk location. Are rare lung and the brain metastasis, so that prophylactic cranial irradiation recommended in lung SCC is not recommended for bladder forms. Also the liver metastases appear frequently in the course of neoplastic progression (17). the ileum involvement is reported frequently. Bui (29) reported a first patient treated with TUR and subsequently with cystectomy with histologic outcome of T3N2 and numerous neoplastic emboli in perivesical fat that took the patient to die less than three months from diagnosis to massive infiltration of the duodenum, rectum , the peritoneum, the aorta and the mesentery and the peripancreatic fat. The autopsy showed a mass of 18 cm extended to the whole abdomen and death had been caused by severe bleeding gastrointestinal testinale complicated by DIC. Also 1 of our cases had died as a result of bleeding from the digestive tract. The lymph node diffusion is 68% in cases of Cheng (15), the most numerous reported in the literature. The median survival for all stages is 19.6 months with an overall 5-year survival 8.1% (24) .Because is an extremely rare and very aggressive and malignant form in the absence of controlled studies, there is still no agreed guidelines for an effective therapy dell'SCCB. A multi-institutional report has confirmed that the muscle-invasive disease surgery, radiotherapy and chemotherapy alone are not able to re influenced the progression of the disease (15). A recent study by the Mayo Clinic reported a better prognosis in patients treated with neoadjuvant chemotherapy and surgery compared with surgery alone. Sved (16) confirms the poor prognosis in the Treatment cases exclusively with radical cystectomy. Abbas (24) rseeing some of the published series concludes that chemotherapy must always be the first treatment approach preferably followed by surgery. Mackey (4) believes that the SCC of the prostate has a worse prognosis than the bladder and that chemotherapy regimens based on platinum prolongs survival especially in the bladder forms. Lohrish (30), refers to a 2-year survival of 70% and 5-year by 44% in 10 cases who had SCCB limited to the pelvis and treated with chemotherapy and radiotherapy and integrated Siefer-Ratke (17) shows the very positive experience of M. d. Anderson Cancer Center with a 78% 5 years survival after cystectomy and neoadjuvant chemotherapy. Bastus (31) described a high disease-free survival in 4 of 5 patients with small cell bladder cancer treated with sequential chemoradiotherapy. In the cases of the cancer center Leon Berard, ismaili in 14 cases of nonmetastatic SCCB reports a median survival of 38.6 months in patients treated with radical cystectomy and adjuvant chemotherapy (19). The experience of the Mayo-Clinic on 44 patients in 2004 reported 6 survivals free disease in patients in stage II sec. TNM 2002 of 8 treated with cystectomy and other 4 treated with partial cystectomy or TUR, there was a 50% recurrence with progression and metastasis. in the III stadium there were only two cases out of 12 patients alive and free from disease with cystectomy of total 13 with a 3-year survival of 76.9% and at 5 years of 15.4%. in the IV stadium on 19 evaluable patients only 2 equal to 14.3% were alive at three years. 5 patients with distant metastases present at diagnosis, they were all dead within 2 years of diagnosis. Survival was not significantly different for patients with endocrine neoplasia pure or mixed. Canadian experience of Toronto (14) of 12 cases treated with TUR and extensive chemotherapy combination with cisplatin and etoposide and then radiotherapy and even chemotherapy, 5 patients were still alive, four disease-free, at 19.8 months diagnosis. In the two cases reported by the school of Verona (32) the endoscopic treatment combined with chemotherapy was more effective than cystectomy. Fiorito (33) reported 3 cases went rapidly progressing in a few weeks with a picture of obstructive renal failure from incarceration ureteral, disease spread to the lymph nodes, and peritoneal and in which the exitus had occurred within a month to hemolytic paraneoplastic syndrome cachexia .

Bui (29) emphasizes the importance of the diagnosis of SCC already cytological examination to establish as soon as possible an aggressive combination chemotherapy based on schemes with platinum.

The experience of Mistrangelo (34) Molinette of Turin, in which a patient with neuroendocrine carcinoma infiltrating bladder had been treated with 5 cycles of RT on the bladder and after the appearance of liver metastases underwent further line coach always with carboplatin and etoposide with rC in the liver and recovery of bladder disease finally treated with cystectomy and still free from the disease 2 years, must be regarded as the systemic approach should be preferred when neuroendocrine carcinoma diagnosis small bladder cells.

**Conclusions**

The increased attention paid by phisicians with regard to neuroendocrine small cells bladder carcinoma allowed to expand in recent years the studies in literature and improve the knowledge of this cancer form. The prognosis remains extremely poor SCCB mind than other forms of bladder cancer for the marked tendency to local infiltration and metastasis. The multimodal therapy is the only therapeutic option.

**Summary**

The neuroendocrine carcinoma with small cells of the bladder (SCCB) is extremely rare, with an incidence of between 0.3 and 1.35% of all bladder cancers. In the literature are reported several hundred cases. It is a form of cancer with an extremely aggressive behavior and with a very poor prognosis of transitional cell carcinoma. The median survival rate for all stages is oscillating from 4 to 8 months and the five-year survival reaches only 3-8%. At presentation, 59% of patients have a clinical stage greater than t2 and 56% distant metastasis. 50% of patients go into fatal progression within 6 months of diagnosis. Local recurrence after surgery reaching 70% identity with a mortality rate within 2 years. A standard treatment has not yet been defined because of the rarity of the disease that does not allow prospective studies. A multimodal approach based on an aggressive chemotherapy regimens containing platinum and then surgery and / or radiotherapy is the only feasible treatment (17). We present our experience of 2 cases of neuroendocrine tumors of the bladder-small cell recently recover at our center one of which went rapidly progressing resulting in death within months of diagnosis.

Disclaimers

The authors have no proprietary interest in regards to this article.

Author s Address : Edoardo Tartaglia

Via Fiume Giallo 218

00144 roma italy

edoardo.tartaglia@gmail.com

BiBLIOGRAPHY

1. national Cancer institute, dCCPS SrP, Branch CS. Surveillance,

Epidemiology and End results (SEEr) Program, Public-

Use data (1973-2000). Available from: http: www.seer.

cancer.gov. (cited on 2003 Apr) (submitted on 2002 nov.)

2. Lenhard rE, ostreen rt, Gansler t, Clinical oncology. Atlanta:

American Cancer Society, 2001: 271-2.

3. ibrahim nB, Briggs JC, Corbishley CM. Extrapulmonary oat

cell carcinoma. Cancer 1984; 54: 1645-61.

4. Mackey Jr, Au HJ, Hugh J, Venner P. Genitourinary small

cell carcinoma: determination of clinical and therapeutic factors

associated with survival. J Urol 1998; 159: 1624-9.

5. Holmang S, Borghede G, Yohansson SL. Primary small cell

carcinoma of the bladder: a report of 25 cases. J Urol 1995;

153; 1820-1822. 6. Blomjous CE, Vos W, de Voogt HJ, Van del Valk P, Meijer

CJ. Small cell carcinoma and the urinary bladder. A clinicopathologic,

morphometric, immunoistochemical, and ultrastructural

study of 18 cases. Cancer 1989; 64: 1347-1357.

7. tria i, Algaba F, Condom E, et al. Small cell carcinoma of the

urinary bladder. Presentation of 23 cases and review of 134

published cases. Eur Urol 2001; 39: 85-90.

8. Cramer SF, Aikawa M, Cebelin M. neurosecretory granules

in small cell invasive carcinoma of the urinary bladder. Cancer

1981; 47: 724-730.

9. Mills SE, Wolfe Jt, Weiss MA, et al. Small cell undifferentiated

carcinoma of the urinary bladder. A light-microscopic,

immunocytochemical, and ultrastructural study of 12 cases.

Am J Surg Pathol. 1987; 11: 606-617.

10. Grignon dJ, ro JY, Ayala AG, et al. Small cell carcinoma of

the urinary bladder. A clinicopathologic analysis of 22 cases.

Cancer 1992; 69: 527-536.

11. Ali S, reuter V, zakowski M. Small cell neuroendocrine carcinoma

of the urinary bladder: a clinicopathologic study with

emphasis on cytologic features. Cancer 1997, 79: 356-361.

12. Mangar SA, Logue JP, Shanks JH, Cooper rA, Cowan rA,

Wylie JP. Small cell carcinoma of the urinary bladder: 10

years experience. Clin oncol 2004; 16: 523-7

13. Bex A, nieuwenhuijzen JA, Kerst M, Pos F, van Boven H,

Meinhardt W, et al. Small cell carcinoma of bladder: A singlecenter

prospective study of 25 cases treated in analogy to

small cell lung cancer. Urology 2005; 65: 295-9.

14. Amis tr, reaume Mn, dahrouge S, Malone S. Genitourinary

small cell carcinoma: A prospective review of treatment and

survival patterns at the ottawa Hospital regional Cancer

Center. BJU int 2006; 97: 711-5.

15. Cheng L, Pan CX, Yang WJ, Lopez-Beltran A, MacLennan

Gt, Haiqun L, et al. Small cell carcinoma of the urinary bladder:

Aclinicopathologic analysis of 64 patients. Cancer 2004;

101: 957-62.

16. Sved P, Gomez P, Manoharan M, Civantos F, Soloway MS.

Small cell carcinoma of the bladder. BJU int 2004; 94: 12-7.

17. Siefker-radtke Ao, dinney CP, Abrahams nA, Moran C,

Shen Y, Pisters LL. Evidence supporting preoperative chemotherapy

for small cell carcinoma of the bladder: A retrospective

review of the Md Anderson cancer experience. J

Urol 2004; 172: 481-4.

18. Choong nW, Fernando Quevedo J, Kaur JS. Small cell carcinoma

of the urinary bladder. Cancer 2005; 103: 1172-8.

19. ismaili n, Elkarak F, Heudel PE, Flechon A, droz JP. Small

cell carcinoma of the bladder: the Leon-Berard cancer centre

experience. indian J Urol 2008; 24: 494-497.

20. Evans AJ, Al-Maghrabi J, tsihlias J, Lajoie G, Sweet JM,

Chapman Wi. Primary lymphoma of the bladder. Arch J

Pathol Lab Med 2002, 126 (10): 1229-1232.

21. tanello M., Bettini E., Griggi S., Moretti A.i., et al. Primary

large-cell neuroendocrine carcinoma of the urinary bladder.

Urologia 2005; 72 (2): 280-281.

22. Madersbache S, Hochreiter W, Burkhard F, et al. radical

cystectomy for bladder cancer today: a homogeneous series

without neoadjuvant therapy. J Clin oncol. 2003; 21:

690-696

23. Stein JP, Lieskovsky G, Cote r, et al. radical cistectomy in

the treatment of invasive bladder cancer: long-term results

in 1054 patients. J Clin oncol. 2001; 19: 666-675.

24. Abbas F, Civantos F, Benedetto P, Soloway MS. Small cell

carcinoma of the bladder and prostate. Urology. 1995; 46:

617-630.

25. oesterling JE, Brendler CB, Burgers JK, Marshall 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 1990; 65: 1928-1936.

26. Hailemariam S., Gaspert A., Komminoth P., tamboli P., Amin

M. Primary, pure large-cell neuroendocrine carcinoma of the

urinary bladder. Mod Pathol. 1998; 11: 1016-20.

27. Mostofi FK, davis CJ, Sesterhenn iA. WHo histologic typing

of urinary bladder tumors. Berlin: Springer, 1999.

28. Henly dr, Farrow GM, zincke H. Urachal cancer: role of

conservative surgery. Urology 1993; 42: 635-639.

29. Bui M, and Walid E Khalbuss. Primary small cell neuroendocrine

carcinoma of the urinary bladder with coexisting highgrade

urothelial carcinoma: a case report and review of the

literature. Cyto J 2005; 2:18: 1186-90.

30. Lohrisch C, Murray n, Pickles t, Sullivan L. Small cell carcinoma

of the bladder: long term outcome with integrated

chemoradiation. Cancer 1999; 86: 2346-2352.

31. Bastus r, Caballero JM, Gonzalez G, Borrat P, Casalots J,

Gomez de Sequra G. Small cell carcinoma of the urinary

bladder treated with chemotherapy and radiotherapy: results

in five cases. Eur Urol 1999; 35: 323-6.

32. Caleffi G, d’Amico A, Porcaro A.B, Ficarra V, Malossini G. il

carcinoma neuroendocrino “a piccole cellule” della vescica:

descrizione di due casi. Cattedra e divisione Clinicizzata

di Urologia. Universita degli Studi di Verona. Abstracts 48°

convegno della SUni pag 89. 1999.

33. Fiorito C., Lucca L., oderda M., Mondino P., berta G., Cattaneo

E.A., Valentino F., zitella A., Pacchioni d., tizzani A.

neuroendocrine bladder cance. oncological emergency ?.

Urologia 2008; 75 (1): 57-61.

34. Mistrangelo M., Ardina M., donadio M. Carcinoma neuroendocrino

a piccole cellule della vescica. rapida evolutivita e

spiccata sensibilita alla terapia. Urologia 2005; 72 (2): 280-

281.