

Small Cell Carcinoma of the Bladder: A Rare Entity

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BACKGROUND

Primary small cell carcinoma of the urinary bladder is a rare tumor, accounting for less than 1% of the annual 70,000 cases of urinary bladder cancer.¹ Accordingly, little data is available beyond case series to guide diagnosis or treatment. Overall prognosis remains poor with five year survival often markedly below 50%. Current staging and treatment remains largely based on extrapolation from small cell carcinoma of the lung. We review two recent cases of bladder small cell carcinoma with a focus on comparing and contrasting with lung small carcinoma.

CASE REPORTS

CASE 1 - 73 y.o. Male presents with gross hematuria

73-year-old man presented for second opinion following trans-urothelial biopsy of tumor (TURBT) at an outside institution, initially diagnosed after developing gross hematuria. TURBT specimen shows urothelial carcinoma and small cell carcinoma with typical scant cytoplasm, "salt and pepper" stippled chromatin, molding and many mitoses. Treatment was declined due to poor performance status.

CASE 2 - 84 y.o. Male presents with outflow obstruction

Patient presented for biopsy of existing urothelial carcinoma. Surveillance of low grade papillary carcinoma began in 2003 following nephrectomy for papillary renal cell carcinoma the year prior. Bladder carcinoma had been managed with BCG until BCG sepsis in 2006. Despite mitomycin treatment, carcinoma in situ was detected in 2009. Now he presented with urinary symptoms consistent with outflow obstruction. TURBT showed sarcomatoid carcinoma and small cell carcinoma. Further treatment was declined due to age and performance status.

CASE 3 - 60 y.o. Female presents with left lung lower lobe nodule

Patient was under surveillance following history of laryngeal squamous cell carcinoma resected in 2013 and her 20 pack-year smoker. Patient underwent left lower lobectomy and mediastinal node dissection.

Histology is presented here for comparison between small cell carcinoma of the lung versus bladder.

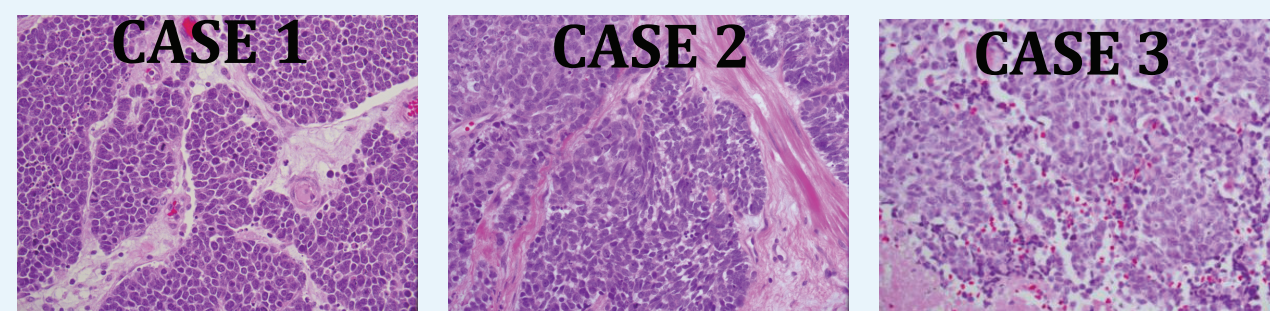


Figure 1: Differential diagnosis for small round blue tumor cells in the bladder includes lymphoma, Ewing Sarcoma, poorly differentiated urothelial carcinoma, small cell carcinoma of prostate, primary small cell carcinoma of bladder and metastatic small cell carcinoma. Immunohistochemistry can rule out lymphoma, Ewing Sarcoma and poorly differentiated urothelial carcinoma (see figures 2, 3). Clinicopathological correlation is ultimately needed to rule out prostatic or metastatic small cell carcinoma when PSA, PSMA and P501S are negative (40% of cases)² or when thyroid transcription factor-1 is positive (40% of cases)³ respectively. H&E stains 400x.

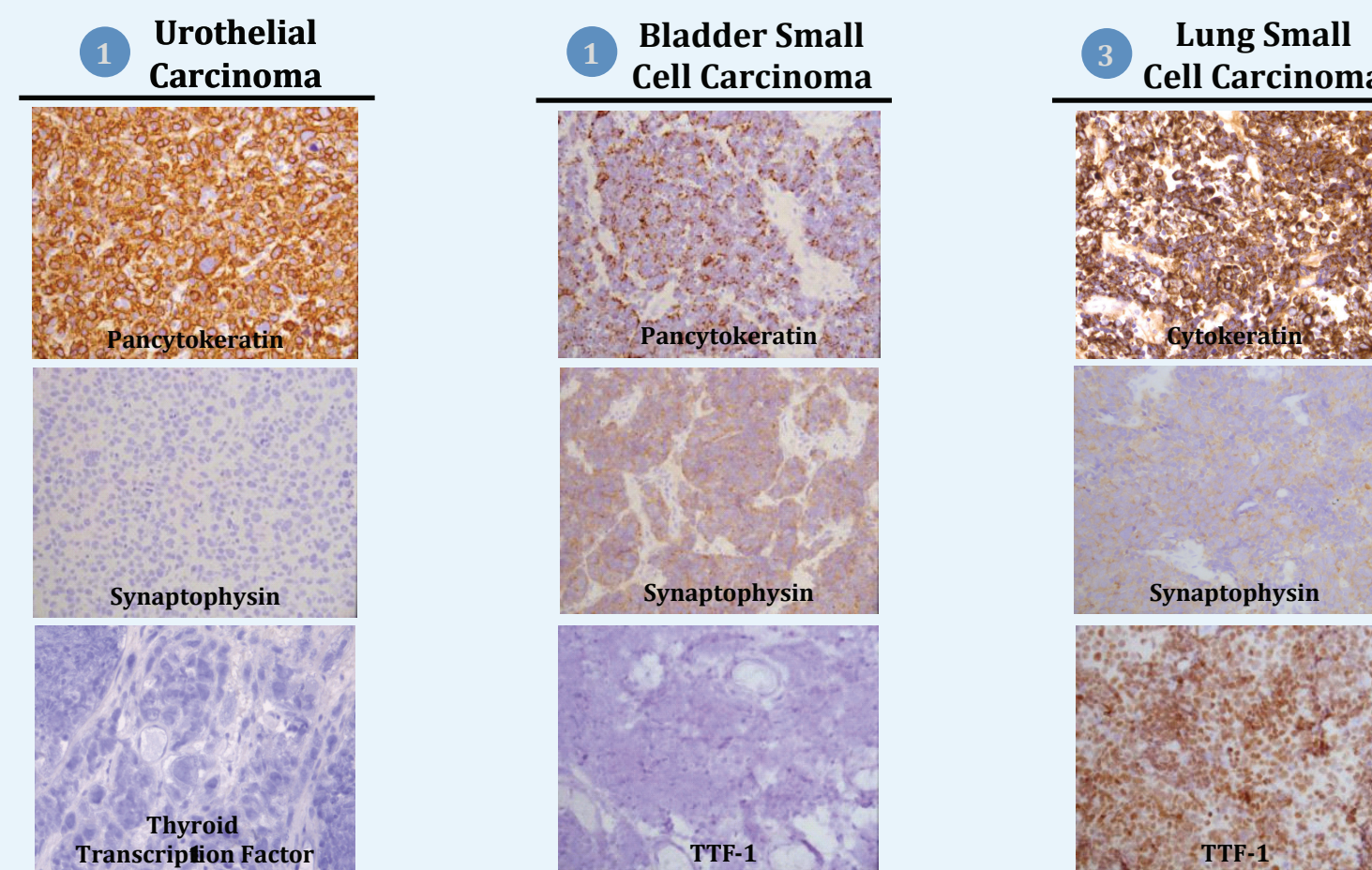


Figure 2: Immunohistochemistry (IHC) shows dot-like positivity for cytokeratins, indicating tumor cells do not represent an Ewing Sarcoma or leukemia. Synaptophysin positivity confirms neuroendocrine nature of cells. TTF-1 has historically been used to confirm a primary lung tumor but may be positive in bladder small cell carcinoma. Diagnosis of bladder small cell carcinoma and high grade urothelial carcinoma was made in case 1.

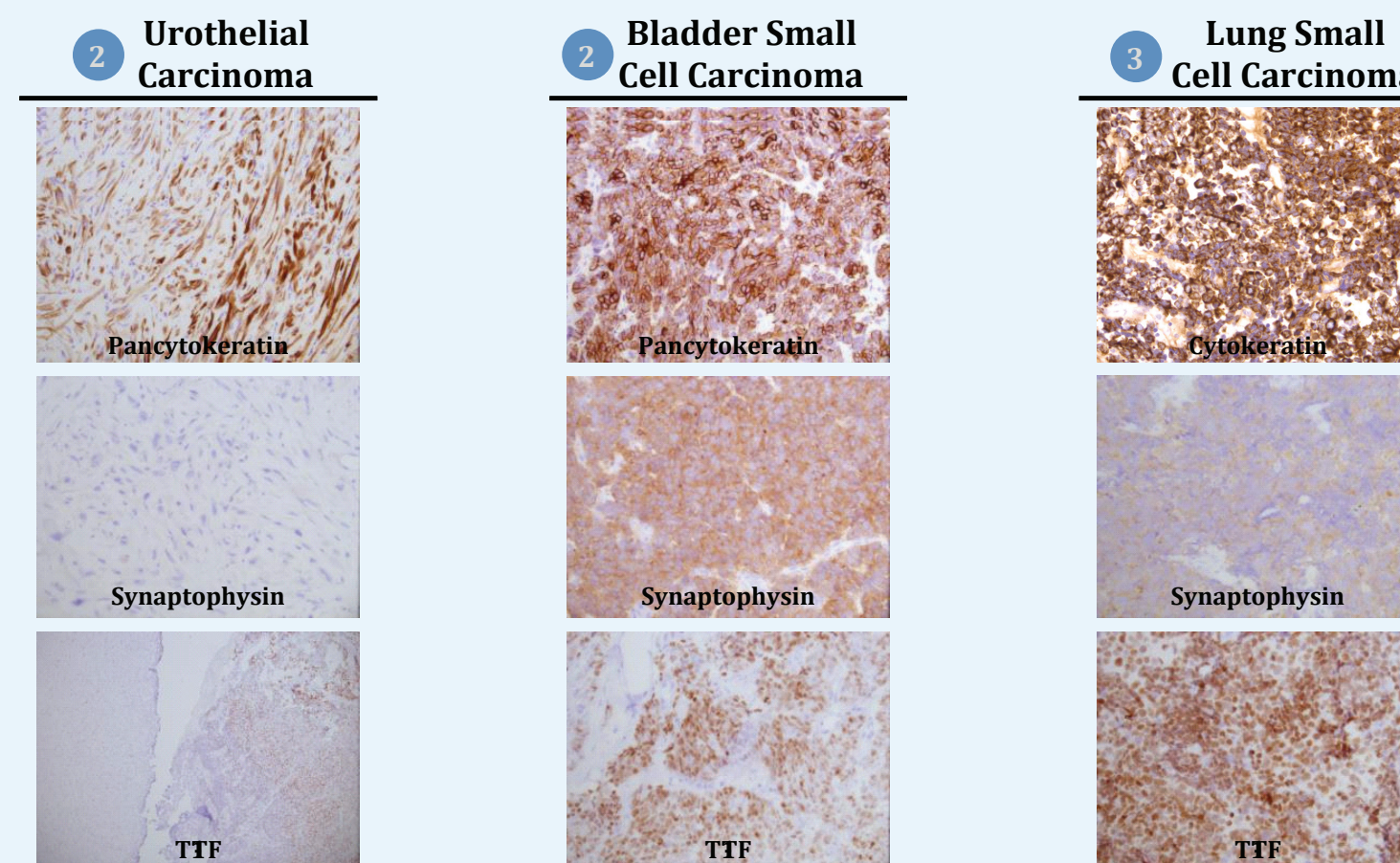


Figure 3: Immunohistochemistry shows similar patterns to patient 1. However, in this case TTF-1 stains positively. As above, an admixture of concomitant urothelial carcinoma in the presence of small cell like histology is virtually pathognomonic for primary bladder small cell carcinoma. Diagnosis of bladder small cell carcinoma and sarcomatoid urothelial carcinoma was made in case 2.

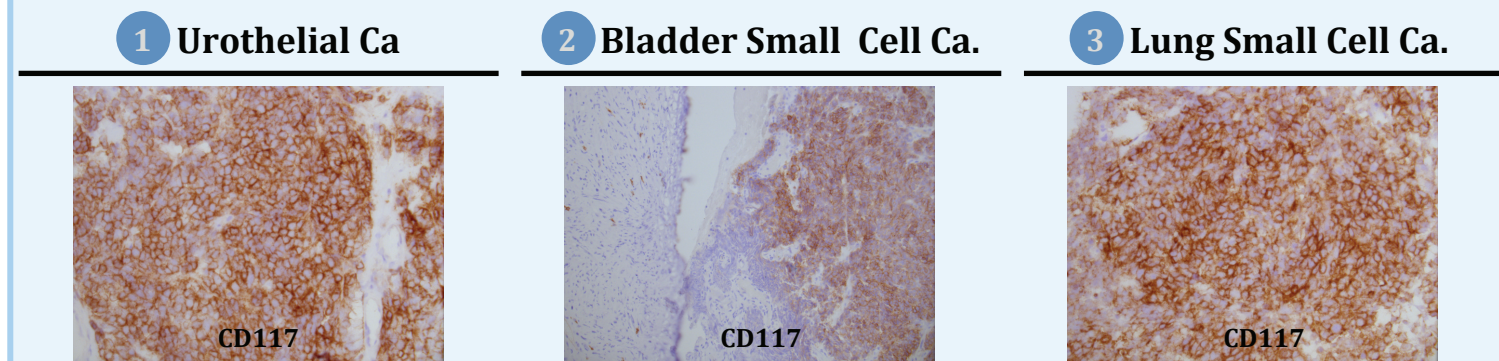


Figure 4: Intriguingly, IHC of small cell carcinoma in all three patients stained positively for CD-117 (c-Kit). Targeting CD117, with the tyrosine kinase inhibitor Imatinib, has proven successful in gastrointestinal stromal tumors but that success has not yet translated to small cell carcinomas.

DISCUSSION

Prognosis for bladder small cell carcinoma remains poor. Reported overall median survival from major case series is typically less than 12 months, with a median overall survival of 10 months reported for 663 cases identified within the SEER database.⁴ Among the larger case series reported to date, overall 5 year survival was reported to be 16%, 14% and 40%.^{5,6,7} Few prognostic factors exist beyond a survival benefit among patients with mixed histology.

Clinically, staging for bladder small cell carcinoma is usually done based on burden of disease, limited or extensive, rather than applying the tumor staging from urothelial carcinoma of the bladder. As in lung small cell carcinoma, limited and extensive staging of bladder small cell carcinoma provides clearer guidance for prognosis and therapy. Palliative chemotherapy remains standard of care for extensive disease.

Although treatment of localized disease has traditionally paralleled lung small cell carcinoma, management has been rapidly evolving. However, surgical resection remains common. Unfortunately, there is near universal recurrence of disease despite high initial response rate to surgery and chemotherapy. Chemotherapy regimens mirror lung with cisplatin-etoposide rather than urothelial carcinoma (cisplatin-gemcitabine).

Given the limited benefit of cystectomy alone, neoadjuvant chemotherapy prior to resection in the setting of localized disease is generally recommended and has shown a 78% 5-year cancer specific survival versus 36% in those receiving surgery initially in a major case series.⁵ Additionally, another large study has recently shown the potential of bladder-sparing chemoradiation.⁹

Lastly, we propose that evaluation of bladder small cell carcinoma for overexpression or mutation of c-Kit may help validate a potential new therapeutic target in small cell carcinoma of the bladder.

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