Small Cell Neuroendocrine Tumour of Bladder: A Rare Entity and Review of the Literature

Mesanenin Küçük Hücreli Nöroendokrin Tümörü: Nadir Bir Varlık ve Literatürün Gözden Geçirilmesi

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ABSTRACT

Small cell neuroendocrine cancer of the bladder (SCNCB) is a rare tumor with highly aggressive characteristics and poor differentiation. It comprises less than 1% of bladder malignancy and usually diagnosed at an advanced stage. It is challenging to differentiate between SCNCB with other bladder tumors as they had a similar presentation. We presented a case of a 60-year-old gentleman who presented with painless hematuria and ultrasound and cystoscopy examination show mass on the right urinary bladder wall. Computed tomography revealed urinary bladder mass with invasion to the prostate. Histopathological examination after transurethral resection of bladder tumor display features consistent with small cell neuroendocrine carcinoma with muscularis propria invasion, positive for synaptophysin, chromogranin A and p53 in immunohistochemistry. The patient currently underwent neoadjuvant chemotherapy with Etoposide and cisplatin for 4-cycles. We, with this, presented a rare case of SCNCB, along with a discussion on the clinical presentation, histological characteristics, management, and prognosis.

Keywords: Neuroendocrine tumor, bladder neoplasm, small cell carcinoma, histological variant

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ÖZET

Mesanenin küçük hücreli nöroendokrin kanseri (SNCCB), oldukça agresif özelliklere ve zayıf farklılaşmaya sahip nadir bir tümördür. Mesane malignitesinin %1'den azını oluşturur ve genellikle ileri evrede teşhis edilir. Benzer bir sunuma sahip oldukları için SCNCB ve diğer mesane tümörleri arasında ayrım yapmak zordur. Ağrısız hematüri ile başvuran, ultrason ve sistoskopi incelemesi ile sağ mesane duvarında kitle saptanan 60 yaşında bir erkek olguyu sunduk. Bilgisayarlı tomografide prostatı invaze eden mesane kitlesi saptandı. Mesane tümörünün transüretral rezeksiyonu sonrası histopatolojik inceleme, immünohistokimyada muskularis propria invazyonu olan küçük hücreli nöroendokrin karsinom ile uyumlu, sinaptofizin, kromogranin A ve p53 için pozitif özellikler gösterdi. Hastaya 4 kür boyunca Etoposide ve sisplatin ile neoadjuvan kemoterapi uygulandı. Bununla birlikte, klinik prezentasyon, histolojik özellikler, yönetim ve prognoz hakkında bir tartışma ile birlikte nadir bir SCNCB vakası sunulmuştur.

Anahtar Sözcükler: Nöroendokrin tümör, mesane neoplazmı, küçük hücreli karsinom, histolojik varyant

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INTRODUCTION

Bladder cancer is the eleven most common cancer in the world, and the seventh most commonly diagnosed cancer in the male population (1). It has male predominance with a ratio of 9:3 in women (1). Bladder cancer-associated mortality is 3.2 for men vs. 0.9 for women worldwide in 2012 (1). Bladder cancer incidence in Malaysia ranked 9th among males with sex ratio approximately 3:1 in favor of males (2). Neuroendocrine cancer, which includes large- cell neuroendocrine, small- cell and carcinoid tumor that commonly occurs in the respiratory and gastrointestinal (3) Small cell neuroendocrine cancer is an extremely rare bladder malignancy with a frequency of 0.7%. Incidence reported is less than 1-9/1,000,000 population (4). In Malaysia, no incidence of small cell neuroendocrine cancer of the bladder had been reported(2). SCNCB characterized by poor differentiation and highly aggressive behaviors and mostly presented during advanced stages that result in poor prognosis (3). We present a case of SCNCB managed by neoadjuvant chemotherapy and a brief review of the relevant literature and discussion on the regard of the epidemiology, clinical features, biological behavior, management and prognosis of SCNCB.

CASE REPORT

Mr. AZ, a 60-year-old gentleman with underlying Hypertension, Dyslipidemia, and Ischemic Heart disease with history of CABG done one year ago, initially presented with painless hematuria that required bladder irrigation for 24 hours then was allow home.

Subsequently, ultrasound kidney, urinary, and bladder (KUB) examination reveal echogenic lesion at the right urinary bladder wall measuring about 3.0× 3.8× 3.2cm with no significant vascularity within via color Doppler that could represent blood clot or mass. He then undergoes cystoscopy examination as outpatients procedures that show cauliflower mass arises from the right anterior wall of the bladder near the bladder opening. An elective date for transurethral resection of bladder tumor (TURBT) set for him; however, he has admitted again for another episode of painless hematuria requiring bladder irrigation. He underwent TURBT during the same admission for bleeding control show tumor at the right lateral wall 3-4cm, extending just proximal to the bladder neck.

Computed tomography Thorax, Abdominal, and Pelvis (TAP) lobulated mass with heterogeneous enhancement seen at right urinary bladder wall with thickened and enhancing bladder wall. It measures 3.8 × 2.2 ×4.5cm and involves the vesicoureteric junction (VUJ), causing mild right hydroureter and hydronephrosis. It crosses the midline posterior-inferiorly with a poor fat plane with the prostate: Sub centimeter para-aortic or pelvic lymph nodes.

Histopathology report displayed features of small cell neuroendocrine tumors, which is tumor tissue formed by sheets of small malignant cells separated by scanty stroma. It exhibits medium, round to oval, overlapping nuclei without prominent nuclear detailed or prominent nucleoli. The cytoplasm is sparse. Numerous mitoses and apoptotic bodies are present. Invasion of underlying muscularis propria observed in multiple places. The tumor cells show diffuse and robust reactivity for synaptophysin, and some of them show weak to moderate positivity for p63 marker, and the Chromogranin A show very focal positivity. The tumor cells do not express LCA, CK 5/6, CK7, and CK20. Ki-67 proliferation index is about 80%.

He subsequently referred to oncology and underwent neoadjuvant chemotherapy with Etoposide/ Cisplatin for four cycles and followed by radiotherapy. He had ongoing neo-adjuvant chemotherapy completed 3 cycles with complication. He was plan for 4th cycle chemotherapy and repeat computed tomography to look for tumor respond. Subsequent CT show no tumor recurrence.

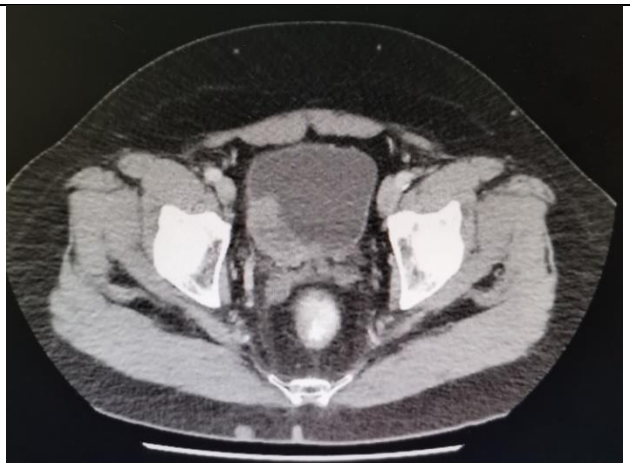

Figure 1: Computed Tomography scan (axial view) demonstrated a about 3.0× 3.8× 3.2cm mass involving the right lateral wall of the urinary bladder.

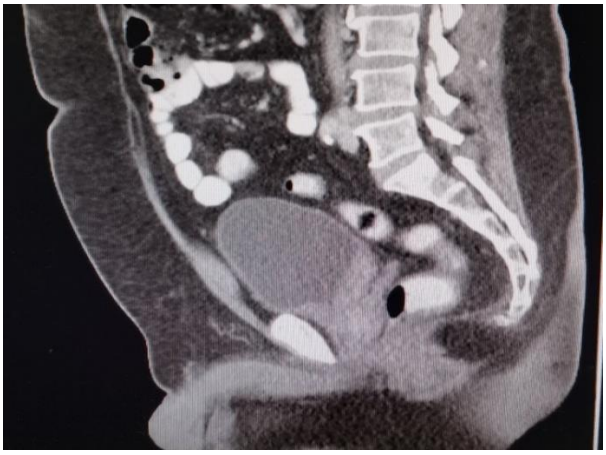

Figure 2: Computed Tomography scan showing tumor in sagittal plane that demonstrated poor fat plane between tumor and the prostate

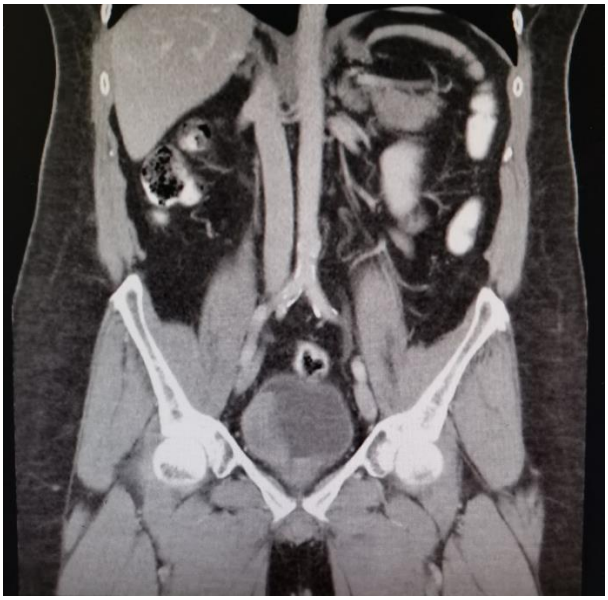

Figure 3: Computed Tomography scan showing tumor in coronal plane.

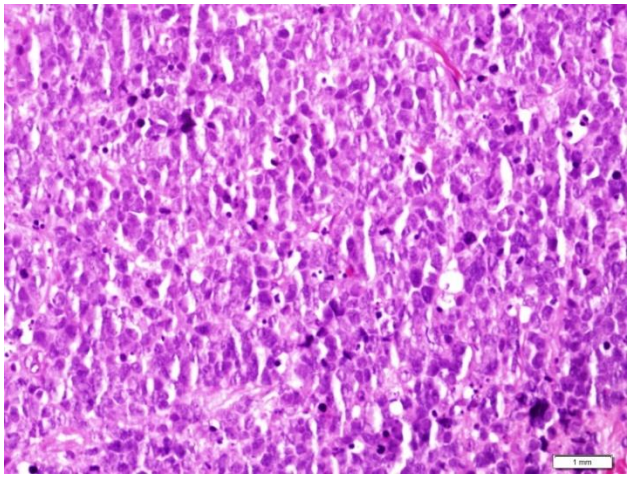

Figure 4: A Hemtoxylin and eosin (H and E) staining of biopsy staining showing typical scant cytoplasm, increase mitotic index, spindling, and prominent nuclear molding

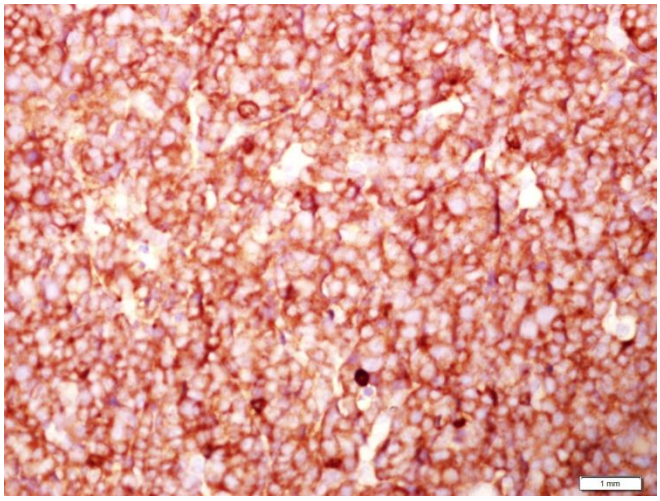

Figure 5: A immunohistochemical stains show that the tumor is diffuse and highly reactivity to synaptophysin

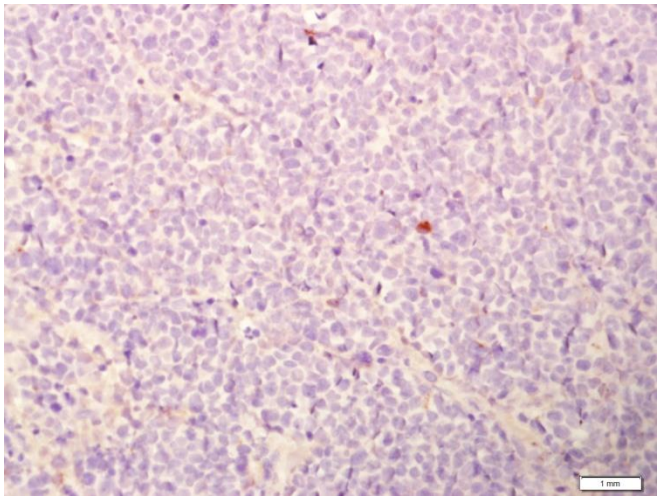

Figure 6: A immunohistochemical stains show very focal positivity to the chromogranin A.

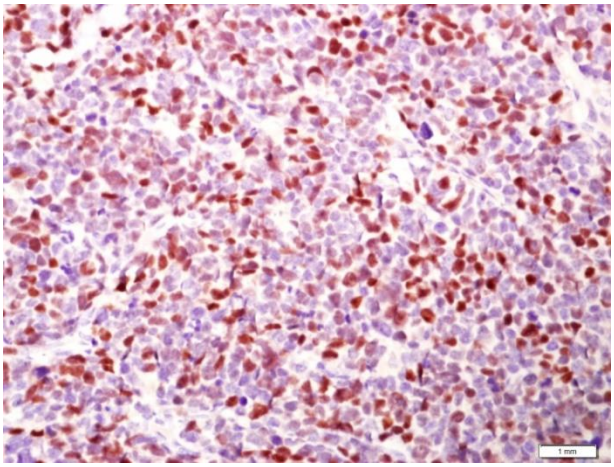

Figure 7: A immunohistochemical stains show moderate positivity to p63

DISCUSSION

Cramer first reports small cell neuroendocrine cancer of the urinary bladder in 1981 (SCNCB) (5). It is a rare, aggressive cancer with a high rate of local recurrence and metastasis (6, 7). It has male predominant with aged of occurrences between 50-80 year old (8). Smoking, long-standing cystitis, and bladder lithiasis are among risk factors to develop small cell neuroendocrine cancer (9). The clinical features of SCNCB are similar to other type bladder cancer. The most common presentation is painless hematuria, which is occurring in 63-68% of cases followed by dysuria as a second most common symptom (4, 10). Other symptoms that reported occasionally included abdominal pain, urinary tract infection, urinary obstruction, and weight loss (4, 10). Rarely, SCNBC can present with a paraneoplastic syndrome such as ACTH secretion and hypercalcemia (4).

Pathogenesis of SCNCB is not well understood, but several hypotheses been proposed. The most popular theory suggests that small cell neuroendocrine cancer originate from multipotential normal stem cell in submucosa that can differentiate into any cell depending on specific stimulus or progression –related gene (11). The second hypothesis suggested that metaplastic changes in urothelial cells give rise to small cell neuroendocrine cancer (5, 12). The other hypothesis involves a malignant transformation of neuroendocrine cells that give rise to bladder small cell cancer, which supported by the fact that neuroendocrine cells were found previously in the urinary bladder (12).

SCNCB diagnosis can be accomplished via histopathology, immunohistochemistry, and cytomorphological characteristic identification. The presence of tumor necrosis, either punctate (78%) and >10 mitotic figures/10 HPF (x400 magnification), should give a hint to the pathologist to focus on small cell neuroendocrine tumor of the bladder. Other cytomorphological findings are high mitotic rate (57%), present of tumor rosette (23.5%), crush artifact (Azzopardi effect) (78.4%) and vascular invasion (16.7%) (10). The immunohistochemical aspect also plays an important role in diagnosing small cell neuroendocrine cancer. In Abraham study, the most expressed markers that demonstrated by SCNCB are chromogranin (30%), synaptophysin (70%) and neuron-specific enolase(NSE) (25%) (10). It is comparable to the previous study done by Trias el al that demonstrated that SCNCB was positive for NSE (88%), chromogranin (38%) and p53 (88%), which is consistent with the immunohistochemical findings in the present case (13).

There are no guidelines or standard treatment for the management of this disease due to its rarity. The National Comprehensive Cancer Network's (NCCN), 2015 guideline-recommended multimodal approach (based on small cell lung cancer) for non-locally advanced tumor, underwent resection and chemotherapy with or without radiotherapy, an advanced locoregional disease for radiotherapy and chemotherapy, and metastatic disease for chemotherapy alone (14). Siefker-Radtke et al. show that neoadjuvant chemotherapy followed by cystectomy can achieve a disease-specific survival rate in 78% in 21 patients compared with patients treated with radical cystectomy alone 36% in 25 patients (15).

This finding similar to the study done prior by Lynch et al. the median overall survival was 159.5 months in patients who underwent neoadjuvant chemotherapy + cystectomy versus 18.3 months in cystectomy + adjuvant chemotherapy patients (16).

Small cell neuroendocrine tumor of the bladder has a poor prognosis. A study by Abraham et al. shows a median overall survival of 23month and 40% five-year survival rate (10). Another study by Choong et al. also reported that a five-year survival rate for patients with Stage II, III, and IV disease were 63.6%, 15.4%, and 10.5%, respectively, with overall median survival was 1.7 years(4). The overall survival is associated with multiple factors such as patient age, size, and shape of the tumor, perineuronal invasion, vascular invasion, and distant organ metastasis and pathological type (17).

CONCLUSION

In conclusion, small cell neuroendocrine cancer of the bladder is a rare but aggressive cancer with known of a high incidence of local recurrence and metastasis. Diagnosis involves histopathology, immunohistochemistry, and cytomorphological characteristic study. Management of this cancer involves a combination of chemotherapy, radiotherapy, and surgical resection depend on the stage of the disease. Long term follow up is a must due to risk of local recurrence and distant metastasis.

Conflict of interest

No conflict of interest was declared by the authors.

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