A RARE CASE OF COEXISTING BLADDER SMALL CELL NEUROENDOCRINE CARCINOMA AND PROSTATE ADENOCARCINOMA: CASE REPORT AND LITERATURE REVIEW

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ABSTRACT

Objective: *We present a case of synchronous malignancies of rare bladder small cell neuroendocrine carcinoma (SCNC) and prostate adenocarcinoma and provide literature review of bladder SCNC.* ***Case(s) presentation:*** *A 72-year-old male smoker presented with 3 months history of gross hematuria. Ultrasonography showed a large hypoechoic mass in the right bladder. TURBT was performed and histopathology of the TURBT specimen showed a high-grade papillary urothelial carcinoma. Abdominal contrast-enhanced computed tomography (CECT) demonstrated an isodenseheterogenous undefined mass, with irregular border at right anterolateral side of bladder wall. Radical cystoprostatectomy, bilateral radical lymph node dissection and bilateral ureterocutaneostomy was performed. Histopathology and immunohistochemical examination after radical cystoprostatectomy revealed bladder small cell neuroendocrine carcinoma coexisting with prostate adenocarcinoma (Gleason score 3+3=6, group 1). The patient eventually succumbed to disease after having symptomatic disease progression and metastatic disease five months after the surgery.* ***Discussion:*** *Bladder SCNC is a rare malignancy with an incidence of 1–9/1,000,000 reported. This tumor has an aggressive clinical course with high incidence of metastasis, and it tends to confer dismal prognosis. No specific clinical symptom exists. Histopathological recognition and immunohistochemistry is required to differentiate this rare entity.* ***Conclusion:*** *Clinicians and pathologists should be alert to the possibility of bladder SCNC despite extremely scarce incidence.*

Keywords: *Bladder cancer, small cell neuroendocrine carcinoma, synchronous malignancy, case report.*

ABSTRAK

Tujuan:*Kami menyajikan kasus langka dari karsinoma neuroendokrin sel kecil kandung kemih bersamaan dengan adenokarsinoma prostat serta memberikan tinjauan literatur mengenai karsinoma neuroendokrin sel kecil kandung kemih.* ***Presentasi kasus:****Seorang pria perokok berusia 72 tahun datang dengan riwayat hematuria selama 3 bulan. Ultrasonografi menunjukkan massa hipoekoik berukuran besar pada sisi kanan kandung kemih. TURBT dilakukan dan histopatologi dari spesimen TURBT menunjukkan karsinoma urothelial papiler high-grade. Computed tomography dengan kontras pada abdomen menunjukkan massa heterogenisodens, dengan batas ireguler pada sisi anterolateral kanan dinding kandung kemih. Sistoprostatektomi radikal, diseksi kelenjar getah bening radikal bilateral dan ureterokutaneostomi bilateral dilakukan pada pasien ini. Pemeriksaan histopatologi dan imunohistokimia pada spesimen sistoprostatektomi meunjukan karsinoma neuroendokrin sel kecil kandung kemih bersamaan dengan adenokarsinoma prostat (skor Gleason 3+3=6, kelompok 1). Pasien akhirnya meninggal setelah terjadi metastatis pada lima bulan post operasi.* ***Diskusi:****Karsinoma neuroendokrin sel kecil kandung kemih adalah keganasan yang langka dengan insidensi sebanyak 1–9/1.000.000 yang telah dilaporkan. Tumor ini memiliki perjalanan klinis yang agresif, memiliki insidensi metastasis yang tinggi, dan cenderung memberi prognosis yang buruk. Pada tumor ini, tidak terdapat gejala klinis yang spesifik. Pemeriksaan histopatologis dan imunohistokimia diperlukan untuk membedakan entitas langka ini.* ***Simpulan:*** *Klinisi dan ahli patologi harus waspada terhadap kemungkinan karsinoma neuroendokrin sel kecil kandung kemih meskipun insidensinya sangat jarang.*

Kata kunci: *Kanker kandung kemih, karsinoma neuroendokrin sel kecil, keganasan sinkron, laporan kasus.*

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INTRODUCTION

Synchronous primary malignancies of the bladder and prostate have been frequently mentioned in literature. Incidental synchronous prostate cancer is diagnosed in 23% to 54% patients after radical cystoprostatectomy and most were found coexisting with urothelial cell carcinoma as urothelial type constitutes more than 90% of all bladder cancer.[1] Bladder small cell neuroendocrine carcinoma (SCNC), a subtype of non-urothelial carcinoma is exceptionally rare, accounting for <0.7% of bladder cancer, with an incidence of 1–9/1,000,000 reported.[2-3]

Approximately 60% of patients with bladder SCNC present with metastatic disease at the time of diagnosis and this tumor has dismal prognosis with only <15% five-year survival.[2,4] There is no specific clinical symptoms, radiologic or morphologic feature exist and diagnosis are made by histopathological recognition and immunohistochemistry examination. Standard management guideline has not yet been defined due to low incidence of cases.[5] Herein, we provide a case of extremely rare case of synchronous coexistence of bladder SCNC and prostate adenocarcinoma and literature review of bladder SCNC.

CASE(S) PRESENTATION

A 72-year-old male smoker presented with 3 months history of gross hematuria. There was no history of fever, nausea, vomiting, unexplained weight loss, or loss of appetite. The patient did not have significant medical history or history of familial cancer. Physical examination showed no remarkable abnormalities. Laboratory parameter were within normal range except for anemia. Bladder ultrasonography showed a ± 10 x 3 x 8 cm hypoechoic mass in right side of bladder wall.

Cystoscopy and transurethral resection of bladder tumor (TURBT) was then performed. As the mass was large, complete resection could not be achieved. The histopathology of TURBT specimen showed a high-grade papillary urothelial carcinoma.

Further assessment by abdominal contrast-enhanced computed tomography (CECT) demonstrated an isodenseheterogenous undefined mass, with irregular border at right anterolateral side of bladder wall of ±11 x 2.2 x 8.5 cm in size, without perivesical fat stranding, bilateral grade II hydronephrosis and bilateral hydroureter (Figure 1). Chest computed tomography showed no abnormality in heart and lungs.

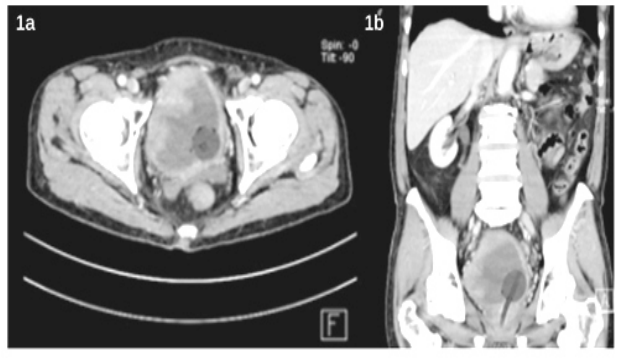

Figure 1. Abdominal CECT demonstrated tumor mass at right anterolateral wall of urinary bladder on (a.) transverse plane, (b.) coronal plane.

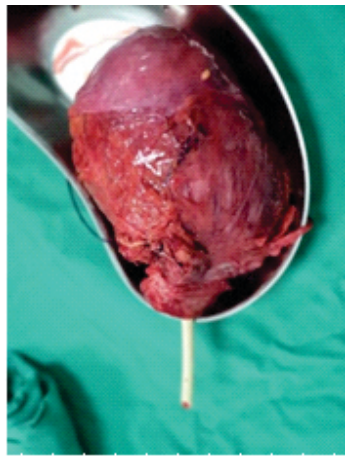

Figure 2. Gross photograph of radical cystectoprostatectomy specimen.

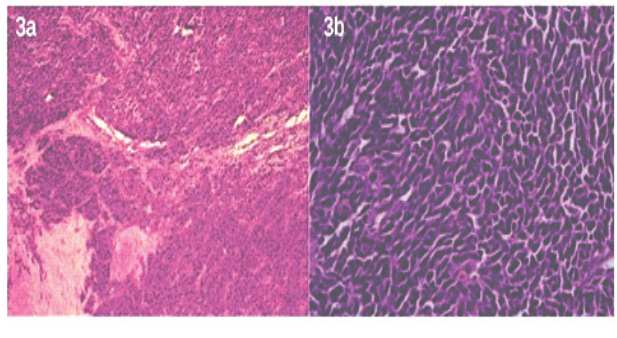

Figure 3. Histopathological findings of bladder small cell neuroendocrine carcinoma in (A.)HE, × 10 magnification (B.)HE, × 40 magnification.

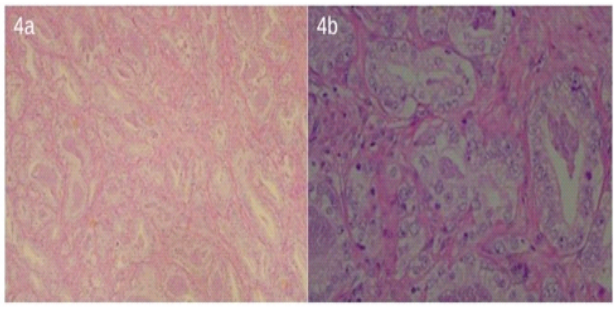

Figure 4. Histopathological findings of prostate adenocarcinoma (Gleason score 3+3=6, group 1) (A.)HE, × 10 magnification (B.)HE, × 40 magnification.

During the disease course, the patient experienced recurrent urinary retention caused by blood clots. Subsequently, the patient underwent radicalcystoprostatectomy, bilateral radical lymph node dissection and bilateral ureterocutaneostomy (Figure 2) Histopathologicalexamination suggested neuroendocrine carcinoma of bladder, right iliac lymph node containing tumor, reactive hyperplasia on left iliac lymph node [pT3aN2] coexisting with prostate adenocarcinoma (Gleason score 3+3=6, group 1) (Figure 3, 4). By immunohistochemistry smear, bladder tumor cells weak CD56+, synaptophisin+, diffuse NSE +, weak Cam 5.2 + and prostate tumor were AMACR+, HMWCK-, p63-. A final diagnosis of small cell neuroendocrine carcinoma coexisting with prostate adenocarcinoma was then confirmed.

Following the surgery, the patient recovered well. However, on the second month after surgery, the patient experienced worsening performance score on (ECOG PS 3). Follow up of abdominal CECT demonstrated no residual lesion in lower abdominal region, bilateral hydronephrosis and hydroureter, and right para-iliac lymphadenopathy of 1.5 cm in diameter. Meanwhile, chest x-ray showed left lung nodule, indicating a distant metastasis. The patient could not receive adjuvant chemotherapy since the presence of non-nodal metastasis and ECOG performance score ≥2 strongly predict poor outcome with chemotherapy. The patient eventually succumbed to disease after having symptomatic disease progression five months after the surgery.

DISCUSSION

Bladder SCNC is a rare and aggressive malignant neoplasm that is thought to derive from totipotent stem cells in bladder submucosa, submucosa neuroendocrine cells or urothelialmetaplastic differentiation.[5] This type has strong male predilection and usually arises between aged 50-80 years.[5] Previous studies mention smoking, long-standing cystitis and bladder stone as the putative risk factors.[6] Clinical symptoms are non-specific, hence early diagnosis is difficult to be made.[6] Patients could present with hematuria, irritative voiding syndrome, weight loss, abdominal pain, urethral obstruction.[6] Approximately 70% of patients present with locally advanced disease or 28-50% with lung, bone, liver or brain involvement when the tumors are diagnosed.[6] The median survival was 11.8 months and overall survival rates after 1, 3, 5 years were 46.6%, 26.2% and 14%.[4] Our patient in the present case has similar presentation in terms of age predilection, risk factor and painless hematuria. However, no evidence of metastatic disease at the time of diagnosis.

Suitable radiological examination is essential to help the clinical diagnosis and revealed the extend or size of the tumor. Cystoscopy could be done to assess tumor burden however its subtype cannot be differentiated by morphologic appearance alone and histopathological recognition is needed. Macroscopically, bladder SCNC usually appears as a single and sizeable polypoid mass. It also can be sessile, ulcerated and occasionally infiltrative, at a minimum level of muscularis propria.[7] Upon microscopic examination, bladder SCNC is composed of nests of small or intermediate cells with molding, scant cytoplasm, inconspicuous nucleoli, and salt-and-pepper chromatin.[8-10] Brisk mitotic activity, frequent crush artifact, necrosis and lymphovascular invasion are commonly found.10 Poorly differentiated urothelial carcinoma may become a differential for SCNC as it could also show solid sheets of immature cells with large nuclei and scant cytoplasm.[8] Furthermore, the diagnosis of bladder carcinoma variant other than pure urothelial carcinoma or bladder histological variant (BHV), may be challenging for pathologist due to extension and proportion of the BHV of the whole tumor, the pathologist's experience and possible artefacts caused by resection technique, sampling or staining.[11] One retrospective analysis concluded that TURBT alone could not provide an accurate and definitive histological diagnosis as 12.4% patients with pure urothelial carcinoma at TURBT showed BHV at subsequent radical cystectomy.[11] This may explain the difference between histopathological results in our case.

It is therefore important that immunohistochemistry stain is done to differentiate SCNC.[8-9] Immunohistochemical stains of SCNC could show positivity for chromogranin A, synapthophysin, neuron-specific enolase, CD56, keratin, Cam 5.2, synaptophysin, TTF-1; while negativity for CK20.[9,12] Metastasis from the lung or extension from adjacent viscera needs to be excluded by clinicopathologic correlation because of limited immunohistochemistry marker.[9] In our patient, immunohistochemical examinations showed reaction when bladder tumor were stained by CD56+, synaptophisin+, NSE +, Cam 5.2 +, indicating a neuroendocrine differentiation. Metastasis to bladder originating from lung and adjacent viscera was excluded by clear initial chest and abdominal computed tomography.

Although no standard guideline has yet been defined, a number of retrospective series and a phase 2 prospective study may provide some insight.[4,13] Therapeutic modalities range from cystectomy, chemotherapy, and radiotherapy.[14] In disease localized to bladder, perioperative chemotherapy may be added to cystectomy for improving overall survival to localized SCNC.[15] Chemotherapy regimens have been extrapolated from the pulmonary counterpart.[16] According to the 2022 National Comprehensive Cancer Network guidelines in bladder cancer, concurrent chemoradiotherapy or neoadjuvant chemotherapy using ifosfamide and doxorubicin alternating with etoposide and cisplatin, followed by local treatment (cystectomy or radiotherapy) is recommended for any patient with small cell component histology with localized disease regardless of stage.[16] Some patient benefit from neoadjuvant chemotherapy with radical cystectomy.[14] For patients with local disease who undergo surgery without chemotherapy which then identifies SCNC, postoperative chemotherapy with platinum and etoposide may be added.[15] Patients receiving adjuvant chemotherapy had improved 5-year overall survival compared with patients who did not receive adjuvant chemotherapy and a trend toward superior cancer-specific survival.[17] Radiotherapy has also been used as an alternative to cystectomy at many centers although no clinical trial comparing radiotherapy and cystectomy as local treatments has been done.[4] With bladder preservation, radiotherapy has an important role with regard to the patient's quality of life and is likely to become an option for local treatment, especially for patients who are not candidates for or refuse cystectomy.[18] In the case of metastatic disease, chemotherapy regimens similar to those used in SCNC of the lung or alternating ifosfamide and doxorubicin with etoposide and cisplatin could be used.[16] However, these responses are generally transient, and most patients eventually relapse. Lastly there are emerging data regarding the use of immunotherapy in relapsed/refractory SCNC of the bladder responding well to pembrolizumab, a PD-1 inhibitor.[19] In our case, neoadjuvant chemotherapy could not be administered since the patient had experienced recurrent urinary retention due to blood clot during the disease course. Adjuvant chemotherapy was also not initiated because of poor performance status of the patient, ECOG PS 3 and the patient began to develop metastatic disease to the lung. The presence of non-nodal metastasis and ECOG performance score ≥2 strongly predict poor outcome with chemotherapy.[16]

CONCLUSION

This case was an example exploring the presentation of a rare subtype of bladder cancer, and even becomes rarer as it coexisted synchronously with prostate adenocarcinoma. Clinicians and pathologists should be alert to the possibility of bladder SCNC despite of an extremely scarce incidence. Multiple therapeutic modalities could be considered to treat local and metastatic disease. However, further studies are still needed to determine the most effective treatment for SCNC.

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