CASE REPORT

Primary Small Cell Neuroendocrine Carcinoma: A Rare Entity of Bladder Neoplasm

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ABSTRACT

Primary small cell neuroendocrine carcinoma (SCNEC) is a rare high-grade malignant neoplasm with neuroendocrine differentiation derived from the urothelium. Herein, we report a case which presented with symptomatic anaemia secondary to haematuria, complicated with acute kidney injury following obstructive uropathy caused by the SCNEC, along with the discussion of the clinical presentation, radiological imaging and pathological findings of the disease.
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INTRODUCTION

Urinary bladder cancer is the seventh most common cancer worldwide, with the most common type being the urothelial carcinoma accounting for 80% to 90% of the cases (1). The occurrence of SCNEC in the urinary bladder is exceedingly rare, comprises for only less than 1% of all primary bladder malignancies (2). SCNEC commonly affects adults in their sixth or seventh decade of life, with mean affected age of 67 years and having a male-to-female ratio of 3:1 (3). Neuroendocrine carcinoma commonly occurs in the respiratory and gastrointestinal systems. However, <1% of all bladder cancer is primary SCNEC. To the best of our knowledge, only 150 cases of primary SCNEC of the urinary bladder have been reported to date (5). Tobacco smoking is one of the aetiological factors of SCNEC (2). It is an aggressive tumour, with high metastatic potential and carries poor prognosis.

Some researchers hypothesized an origin from totipotent stem cells in the submucosa of the urinary bladder or metaplastic differentiation from transitional cell carcinoma that is associated with tumorigenesis (5). A rare case of primary SCNEC of the urinary bladder is presented, together with the discussion of the clinical presentation, radiological imaging, pathological findings, and treatment options.

CASE REPORT

A 55-year-old Malay lady with no known medical illness presented with frank haematuria and sandy urine for 3 weeks. It was associated with lethargy and reduced in effort tolerance for 3 days. There were no constitutional symptoms, suprapubic pain, dysuria or frequency. On physical examination, she was pale and tachycardic. X-ray kidney, ureter and bladder (KUB) revealed no radio-opaque stone. Urinalysis findings were positive for blood and negative for leucocyte and nitrite. Laboratory investigations revealed of 6.3g/dL, indicating anemia, with otherwise normal range for other parameters; white cell count of 5.82 $x10^9$/L, platelet of 464 $x10^9$/L, sodium 140 mmol/L, potassium 3.4 mmol/L, urea 3.0 mmol/L and creatinine 134 µmol/L. Her anaemia improved after 2 pint/L of packed cells transfusion. She underwent bladder irrigation in the ward. Further ultrasound KUB showed moderate right hydronephrosis with right proximal hydroureter and mild left hydronephrosis likely due to obstructive effect of the tumour. A cystoscopy was performed, revealing a large surface area covered by

tumour, exhibiting papillary growth pattern with broad base. The tumour was confined to the right lateral wall of the bladder, spreading to the dome, and was heavily vascularized. Two soft stones were seen embedded within the growth. A biopsy was taken from the bladder tumour.

Microscopically, the tumour displayed classical features of SCNEC (Fig. 1). The tumour was composed of uniform small cells in sheets, separated by thin fibrocollagenous stroma. The cells exhibited small round to oval overlapping nuclei with nuclear moulding, 'salt and pepper' chromatin pattern, inconspicuous nucleoli and scanty cytoplasm. This is different when compared with urothelial carcinoma, whereby the nucleus exhibits hyperchromatic or vesicular nuclei with prominent nucleoli and abundant cytoplasm. Mitotic figures were frequently seen (12 per 10 high power fields). Foci of necrosis and numerous apoptotic bodies were present. There was no lymphovascular invasion seen. Synaptophysin immunohistochemistry revealed widespread tumour cells with cytoplasmic positivity but it will be negative in urothelial carcinoma. Pancytokeratin (CKAE1/AE3) showed perinuclear dot like positivity in this tumour cells but will be diffuse with cytoplasmic and membrane positivity in urothelial carcinoma. Thyroid transcription factor 1 (TTF-1) and leucocyte common antigen (LCA) were both negative.

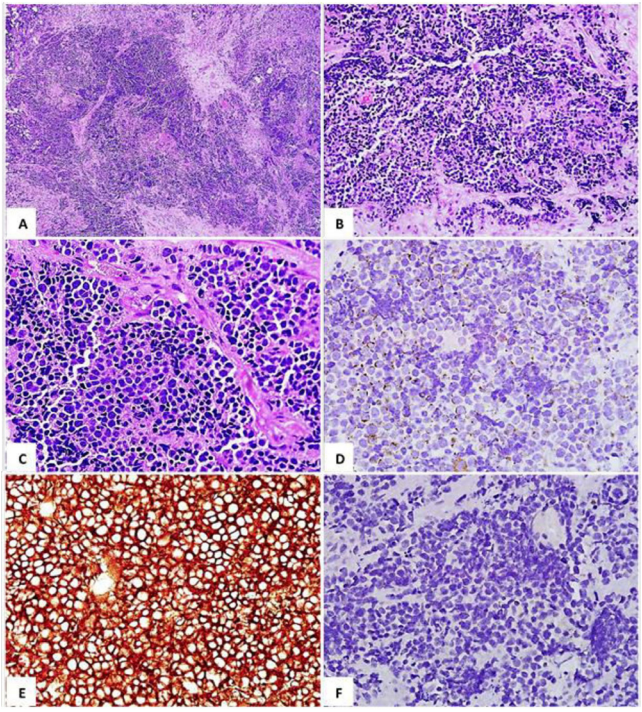

Figure 1: Histological findings of the bladder growth. The tumour tissue is composed of infiltrating small malignant cells within the lamina propria arranged in sheets, separated by minimal fibrous stroma (Haematoxylin and Eosin (H&E) staining; magnification x40 (A) magnification x200 (B)). The malignant cells exhibit small, round to oval, overlapping and moulding nuclei with evenly dispersed chromatin pattern (H&E staining; magnification x400 (C)). The cells show perinuclear dot like positivity with CKAE1/AE3 immunostain (magnification x400 (D)), diffuse cytoplasmic positivity with synaptophysin immunostain (magnification x400 (E)) and negative for TTF-1 immunostain (magnification x 400 (F)).

Following the diagnosis of SCNEC of bladder, she underwent CT thorax, abdomen and pelvis (TAP) which revealed a lobulated heterogenous enhancing soft tissue lesion seen at urinary bladder with relative sparing of the left lateral wall, measuring 7.0 cm x 8.3 cm x 6.3 cm (Fig. 2). There was loss of clear plane of demarcation between the urinary bladder, anterior aspect of uterus, cervix and right ovary likely representing direct invasion of the tumour to the adjacent organs. Laterally, the lesion extended to the right parametria space. There were multiple enlarged and matted lymph nodes metastases seen at the right external iliac region, right common iliac, para-caval, aorto-caval and para-aortic region. Right hydronephrosis, hydroureter were also seen. The clinical staging based on The American Joint Committee on Cancer (AJCC) TNM classification was at least T4a N2.

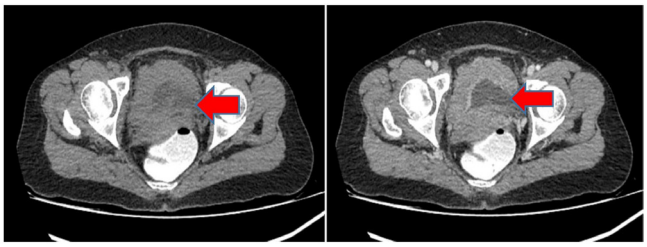

Figure 2: CT TAP findings. A lobulated heterogenous enhancing soft tissue lesion (red arrow) seen at urinary bladder with relative sparing of the left lateral wall of the urinary bladder, plain (A) and contrast (B).

A month after the initial diagnosis, patient developed acute kidney injury secondary to obstructive uropathy, in which she required temporary haemodialysis. Subsequently, she underwent bilateral retrograde pyelogram (RPG) and ureteral stenting to relieve the obstruction. She received six cycles of haemostatic radiotherapy and Non-Enhanced Computed Tomography (NECT) stimulation. She also underwent six cycles of carboplatin/ etoposide chemotherapy following the completion of the radiotherapy. Her renal function test improved after six months of follow-up. However, she defaulted treatment and no repeat CT scan was done to compare the tumour size post treatment.

DISCUSSION

The clinical presentations of SCNEC are similar to other types of invasive urothelial carcinoma with gross haematuria being the most common presenting complaint (4), followed by dysuria and obstructive symptoms.

The vesicle lateral walls and the dome of bladder are the most frequently affected sites, with 4.7% of cases arises in bladder diverticula. This is in line with the tumour's current position, which is confined to the bladder's

right lateral wall and extended to the dome. SCNEC may appear as a large, solid, isolated, polypoid and nodular mass and often invasive with advanced stage at presentation. There is also bilateral hydronephrosis found in the CT scan of this patient likely caused by obstructive growth of the tumour within the bladder, causing outlet occlusion leading to backward flow of the urine.

Most cases of SCNEC are diagnosed microscopically. The diagnosis of SCNEC can be made on histomorphologic ground alone or supported with neuroendocrine differentiation immunohistochemically. Histologically, they exhibit similar features as their counterpart at the lung. The tumour cells are frequently arranged in sheets or nests separated by scant fibrous stroma. High nuclear to cytoplasmic ratio, small round to oval nuclei with overlapping, nuclear moulding, inconspicuous nucleoli, and equally dispersed 'salt and pepper' chromatin are visible in the cells. Mitoses is numerously seen, with crush artefact (Azzopardi effect) present (2). Apoptotic bodies and necrosis are often seen. In contrast, there is lack of necrosis present in the urothelial carcinomas, which also show a lower mitotic count. SCNEC can be admixed with another histological components in 40% to 50% of cases (2), namely components of urothelial carcinoma, squamous cell carcinoma or adenocarcinoma, and rarely, sarcomatoid differentiation. For a tumour to be classified as SCNEC, it has to constitute the majority of the tumour.

Immunohistochemically, most cases of SCNEC expressed cytoplasmic neuron-specific enolase (NSE), cluster of differentiation 56 (CD56) and synaptophysin (4). Chromogranin A expression seen in only one third of cases. SCNEC may exhibit perinuclear dot-like positivity for CKAE1/AE3. Nuclear TTF-1 expression can also be seen in up to 39% of bladder SCNEC, indicating that this marker can be found in SCNEC other than those of pulmonary origin (2).

The differential diagnoses by histomorphology for SCNEC include lymphoma, poorly differentiated urothelial carcinoma, poorly differentiated squamous cell carcinoma, metastatic small cell carcinoma and lymphoepithelioma-like carcinoma. Even though the morphology features more or less similar, but we can exclude other differential diagnoses with the help of immunohistochemistry stains such as pan cytokeratin (positive for carcinoma), LCA (positive for lymphoma) and P40 (positive in squamous cell carcinoma).

There is no consensus for the management of bladder SCNEC. A multimodal approach is recommended by an Association of Genitourinary Medical Oncologists. Transurethral resection of bladder tumor and radical cystectomy are considered as surgical treatment options based on each individual patient. Adjuvant chemotherapy has been well-documented to increase long-term survival rates (5). Radiation therapy is also recommended for SCNEC of the bladder with skull or bone metastasis. Unfortunately, all these modalities unable to apply because the patient defaulted following surveillance and no further surgical management was carried out in this case.

The tumour has a bad prognosis due to its aggressive clinical course. At the time of diagnosis, over 60% of patients have advanced metastatic disease as seen in the present case. It follows the metastasis to the regional lymph nodes and visceral organs such as bone, liver and lung. Similarly in this patient, upon diagnosis, there is already multiple lymphadenopathy detected in CT scan likely representing lymph nodes metastases. CT scan of the patient also revealed extension of the tumour to the adjacent organs, fitting to the aggressive nature of this tumour. The overall 5-year survival rate with local disease has been reported as ranging from 8% to 25% (2). There are few negative prognostic factors as seen in this case include advanced age high clinical stage and positive for metastasis at presentation.

CONCLUSION

To summarise, primary SCNEC of the urinary bladder is an aggressive malignancy with a dismal prognosis. Early diagnosis is crucial for the early initiation of treatment due to rapid progression of the tumour. The diagnosis of this malignant neoplasm mainly depends on histological characteristic with the supported immunohistochemical markers. Although the prognosis is unfavourable, treatment with multimodal approach is recommended.

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