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An Uncommon Poorly Differentiated Small Cell Neuro-endocrine Carcinoma of Urinary Bladder: A Review with Case Report

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Abstract:- Primary small cell neuro-endocrine carcinoma is rare malignancy in urinary bladder. We report a case of 57-years-old male presenting with history of haematuria and dysuria for 2 months. Transurethral resection of bladder tumor (TURBT) was performed. Histopathologic examination showed poorly differentiated small cell carcinoma (SmCC) with neuro-endocrine differentiation, infiltrating the muscle tissue. Due to presence of gross hematuria and deterioration in general condition, patient received haemostatic palliative external beam radiation therapy (EBRT) followed by adjuvant chemotherapy with cisplatin/ etoposide after resolution of hematuria. Patient died after 4 months of diagnosis of malignancy despite treatment due to aggressive nature of malignancy.

Keywords:- *Neuro-endocrine, Oat Cell Carcinoma, Radiotherapy, Urinary Bladder.*

I. INTRODUCTION

Small cell neuroendocrine tumor of the bladder, also known as oat cell carcinoma, is a very rare and aggressive malignancy. It represents only 0.5- 1% of all bladder tumors.[1] Incidence is reported higher in males than females and is frequently reported between the fifth and ninth decade of life.[2] Smoking, long standing cystitis and bladder stones are known risk factors for bladder tumor. Lack of established guidelines for treatment in the clinical practice may be attributed to its low incidence which compels to accumulate retrospective evidence and experience to determine best treatment plan. Here, we report a case of small-cell neuroendocrine tumor of urinary bladder treated with multimodality approach with an effort to summarise previous work about this disease.

II. CASE SUMMARY

A 57-year-old male presented with history of gross haematuria and dysuria for 2 months. Patient was chronic smoker and alcoholic with no other comorbidity. Family history was not suggestive of a relevant malignancy. General physical and systemic examination revealed no significant findings. Routine investigations like complete blood count and biochemical parameters were found to be within normal limits. Urine culture was negative. Chest radiograph did not indicate any evidence of metastatic lesion. Ultrasound abdomen and pelvis revealed urinary bladder with hypoechoic mass lesion measuring 5.7×2.9 cm at right lateral wall with flow on colour doppler. Contrast enhanced magnetic resonance (CEMR) imaging revealed urinary bladder with altered signal intensity intraluminal soft tissue mass lesion 6.5×3.0× 5.0 cm at dome and right lateral wall showing restriction on diffusion weighted image with post contrast enhancement. Lesion was bulging out at dome of bladder and appeared to be extending into muscular plane. No significant lymphadenopathy in para-aortic area was seen and no other visceral metastases were observed (Figure-1). Transurethral resection of bladder tumor (TURBT) was done and tissue was sent for histopathology. Histopathologic examination showed poorly differentiated carcinoma with small cell neuroendocrine differentiation, infilterating the muscle tissue involved in the biopsy (Figure-2A and B). Immuno-histochemical staining was positive for synaptophysin (Figure-2C) where-as cytokeratin-7 (CK-7) and CK 20, p16, p63, CD56, leucocyte common antigen (LCA), epithelial membrane antigen (EMA) were negative. A multi-disciplinary discussion was made in the case, for treatment plan. Patient was planned for neo-adjuvant chemotherapy with cisplatin/etoposide followed by radical radiotherapy with the intent to preserve urinary bladder. The patient was given information regarding the risks and complications associated with various treatment options. Due to presence of gross hematuria and deterioration in general condition of patient, treatment plan was modified. Patient received haemostatic palliative external beam radiation therapy (EBRT) 20 gray (Gy) in 5 fractions, by anterior- posterior fields to pelvis in supine position. Patient further received adjuvant chemotherapy with cisplatin/ etoposide after resolution of hematuria. Patient general condition deteriorated post two cycles of adjuvant chemotherapy. He developed severe bone marrow suppression and neutropenia. Patient died after 4 months of diagnosis of malignancy despite of treatment due to aggressive nature of malignancy.

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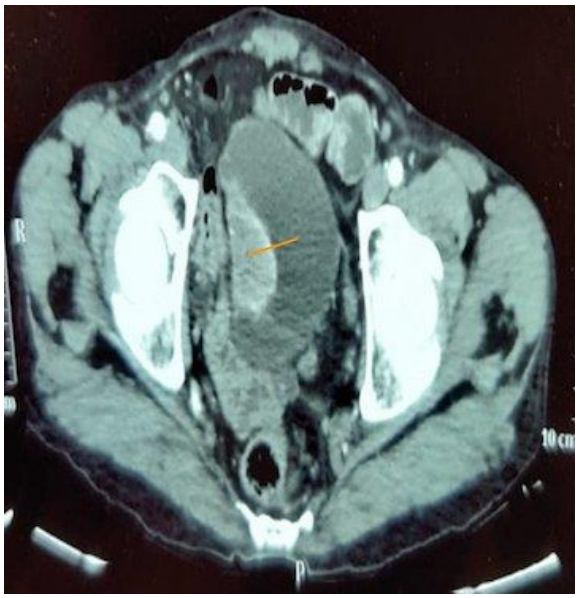

Fig. 1: Pre-operative CEMRI imaging of abdomen and pelvis showing urinary bladder showing altered signal intensity intraluminal soft tissue intensity mass 6.5×3.0× 5.0 cm at dome and right lateral wall showing restriction on diffusion weighted image with post contrast enhancement (orange arrow).

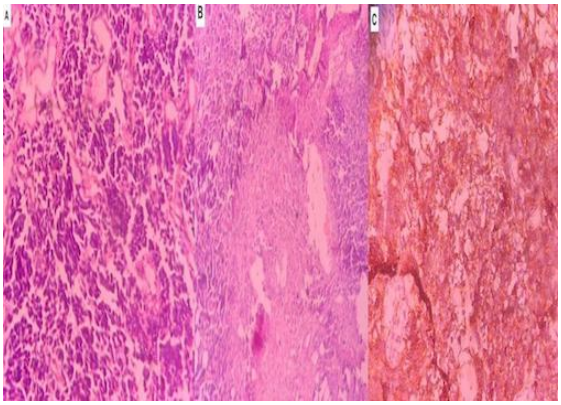

Fig. 2: A) Hematoxylin and eosin (H and E) staining: High-power view (×40) of a transurethral resection of bladder mass showing tumor cells which are small in size, pleomorphic having salt and pepper chromatin with scant amount of cytoplasm. B) Hematoxylin and eosin (H and E) staining: High-power view (×40) showing muscle invasion (muscularispropria) by the small round cells tumor. C. Immunostaining: Synaptophysin positivity in tumor cells (granular cytoplasmic).

I. DISCUSSION

Bladder cancer constitutes about 3% of new cancer cases annually in the world. Neuroendocrine tumors of urinary bladder are uncommon and include subtypes like-small cell neuroendocrine carcinoma, large cell neuroendocrine carcinoma and differentiated neuroendocrine tumors such as carcinoid tumor and paraganglioma. Most common subtype of neuro-endocrine tumor is small cell, but it represents only 0.5- 1% of all bladder tumors. Most commonly small cell neuroendocrine tumors are reported in lung and very rarely in urinary bladder.[1] Majority of patients presented with non-specific symptoms; most commonly gross hematuria, pelvic pain and burning micturation.[1,2] In order to confirm the diagnosis, histopathological examination and immuno-histochemical analysis for neuroendocrine markers such as Synaptophysin, Chromogranin A, and Neuron-specific enolase (NSE) etc is necessary.[3]

Majority of the cases i.e 70% are present at locally advanced stage with involvement of lymph nodes in 57% of cases. Distant metastasis to organs like lung, bone, liver or brain is seen in 28-50% of cases.[2,4] Even in early stage tumors, despite local treatment, most of patients develop metastasis suggesting aggressive nature of malignancy. In the present case, the metastatic work-up did not reveal any evidence of distant metastasis at the time of diagnosis, it was localized tumor confined to urinary bladder.

Analysis of Surveillance, Epidemiology, and End Results (SEER) database revealed median survival of the patients with small cell neuroendocrine tumors of the bladder to be 11 months. Survival rate was worse among patients with distant metastatic disease.[5]

The preferred local treatment for early stage tumors is surgery. In retrospective study at Mayo clinic, the 5-year survival rates for patients with Stage II, III, IV were 63.6%, 15.4% and 10.5% respectively.[6] Unexpectedly, duration of survival for localized and surgically resectable tumor were also found to be less than 1 year.[7] Discouraging results have been reported by Sved et al for patients treated by radical surgery cystoprostatectomy alone; with 3-year overall survival rate of just being 16% only.[7]

Radiotherapy represents a good alternative; with reported complete response rate up to 88% and median survival duration of 32.5 months.[8] For metastatic disease or relapse, chemotherapy with cisplatin-etoposide alone or in alternation with vincristine, doxorubicin, and cyclophosphamide is treatment of choice.[9]

Previous researchers have suggested the use of neoadjuvant chemotherapy, in view of early metastatic potential of the disease. In a clinical trial from M. D. Anderson Cancer Center, patients received four cycles of chemotherapy with cisplatin, ifosfamide, doxorubicin, and etoposide, median survival duration was observed to be 58 months.[10] Comparable results were reported in another study conducted among 95 patients with locally advanced, operable neuroendocrine carcinoma of the bladder and median overall survival duration was found to be 159.5 months.[11]

II. CONCLUSION

Small-cell neuroendocrine bladder tumor is unusual malignancy with potential of metastasize early and bears poor outcome. Treatment of this rare malignancy has been a challenging task for oncologists due to aggressive behaviour of the disease and lack of standard treatment strategy. Therefore, early diagnosis by histological and immune-histochemical examination and equally aggressive multimodality therapy may be the key to better outcome. Molecular marker analysis and targeted therapy may be the

future of management. Systematic data collection is required to have expertise by experience, till then.

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