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Achieving a one-year-tumor-free survival in a female with primary large cell neuroendocrine carcinoma of the urinary bladder and liver metastasis; a case report

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ABSTRACT

Primary neuroendocrine tumor (NET) of bladder is rare. It has four subtypes, and large cell neuroendocrine carcinoma (LCNEC) is the rarest. LCNEC affects mostly men over 60. Most common symptom is gross hematuria. It has no specific treatment. Metastasis is common and once occurred, average survival would be less than three months. Herein we present diagnostic and therapeutic management of a 65-year-old female with LCNEC of bladder and concurrent high-grade urothelial carcinoma. Despite developing early liver metastasis, she achieved a one-year tumor-free survival.

1. Introduction

Primary NET of bladder is rare; accounting for less than 1% of bladder cancers.[1] Least common type is LCNEC which is aggressive and associated with poor outcome.[2] Most common symptom is gross hematuria, others include dysuria, frequency, and can even be asymptomatic.[1] Metastasis is common and mostly involves lymph nodes, and liver.[2] Due to its rarity, there is no guideline for treatment. Diagnosis is made by imaging and immunochemistry (IHC) studies. Further research is needed to standardize diagnostic and therapeutic approaches.

2. Case presentation

A 65-year-old woman presented with painless intermittent gross hematuria for at least a week. There was no history of urothelial cancer or previous hematuria. Urine cytology was suspicious for malignancy. Ultrasonography of abdomen showed a 14.5 × 16.2 mm right sided bladder wall mass highly suspicious for cancer [Fig. 1]. Contrast enhanced computed tomography scan (CECT scan) showed a 14.6 × 15 mm mildly enhancing right bladder wall sessile lesion, without lymphadenopathy. There was no evidence of metastasis. TURBT was performed. Pathology revealed mixed high-grade LCNEC (90%) and high-grade papillary urothelial carcinoma (10%). Evaluation of H&E-stained slides showed neoplasm with highly atypical urothelial cells arranged in confluent branching papillae with extensive invasion into lamina propria. Neoplastic cells had moderate amphophilic to eosinophilic cytoplasm and large, hyperchromatic, irregular nuclei [Fig. 2a–b] and exhibited positive immunoreactivity for HMWCK 34-beta-E12. At some parts intermediate-sized cells with nuclear molding, scant cytoplasm, inconspicuous nucleoli and evenly dispersed finely stippled chromatin were evident which were positive for NSE, Chromogranin A and synaptophysin in IHC staining.[Fig. 2a and b]. One month later, she underwent re-TURBT with pathology report suggestive of inflammation without malignancy. Induction BCG therapy was started and continued for six weeks. After two months, ultrasound exam revealed an 11 mm liver metastasis confirmed by CT [Fig. 3a]. Fine needle biopsy was performed, and pathology came as NET suggestive of bladder tumor as origin. Following oncology consult, she received systemic chemotherapy (four courses of etoposide-cisplatin) followed by radiofrequency (RF) ablation of liver metastasis.

Due to impaired renal function and raised serum creatinine, chemotherapy regimen was changed, and she received two additional

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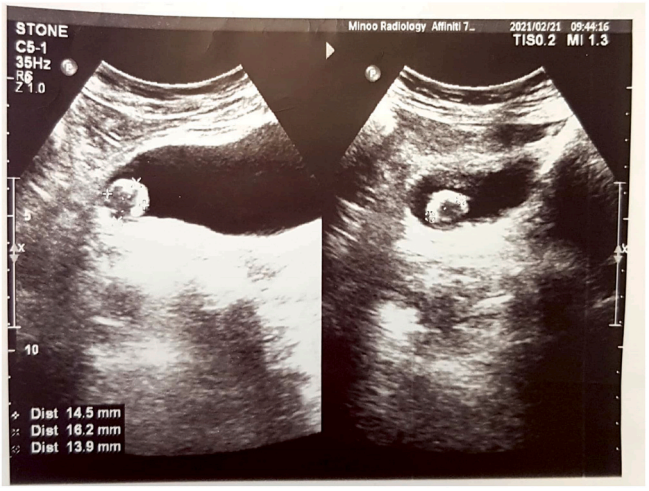

Fig. 1. Ultrasonography view of the bladder mass.

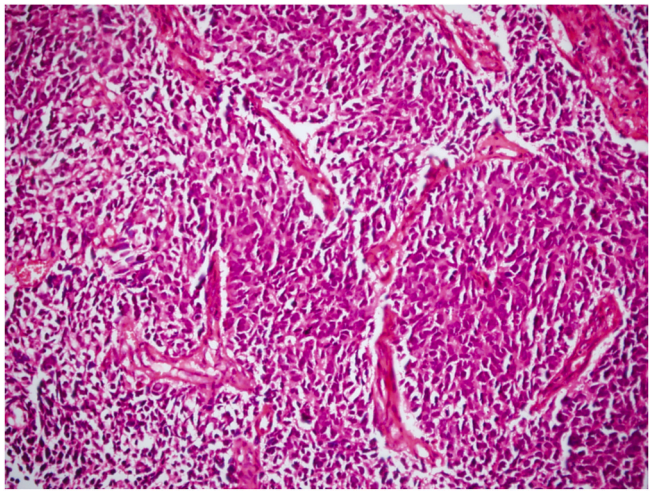

Fig. 2a. Photomicrograph showing a tumor arranged in nests and trabeculae separated by thin fibrovascular septae (H&E staining, 100X).

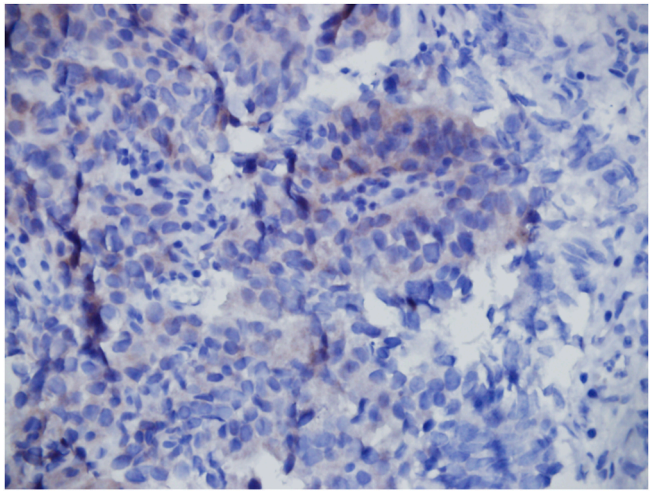

Fig. 2c. On IHC, the tumor cells were positive for chromogranin A (100X).

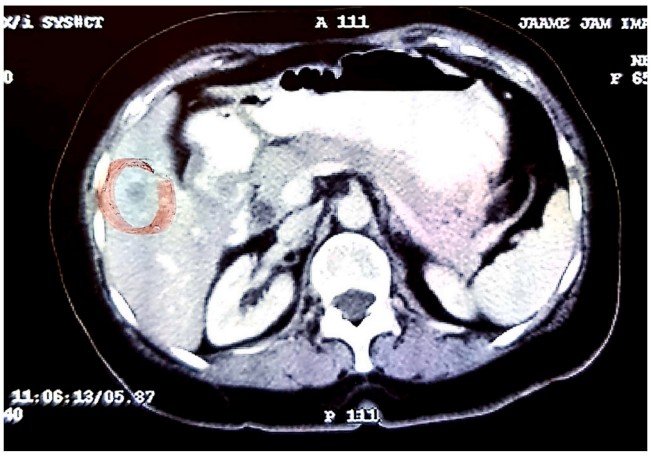

Fig. 3a. Liver metastasis in CT scan.

courses of etoposide-carboplatin.

Cystoscopy and urine cytology were performed for follow-up, every three months.

After one year of follow-up, PET/CT and MRI were negative for metastasis [Fig. 3b], urine cytology and cystoscopy were normal, and serum creatinine was 1.5 ng/dl.

3. Discussion

Primary neuroendocrine carcinoma accounts for less than 1% of bladder cancers.[1] It has four subtypes, small cell neuroendocrine carcinoma (SCNEC), LCNEC, paraganglioma, and well-differentiated.[2] LCNEC affects mostly men.[1] Average age of patients is 61.5 years.[1] Most common symptom is asymptomatic hematuria, others include dysuria, frequency, and flank pain.[2] It can also be asymptomatic, discovered incidentally on imaging studies.[2] Risk factors include smoking, family history, brachytherapy, and radiation for pelvic organ tumors like prostate cancer radiotherapy.[2,3] LCNEC is least common accounting for less than 0.5% of bladder neoplasms, but since it's misdiagnosed as undifferentiated UC, it could be underdiagnosed.[2] It's highly aggressive and likely poorly differentiated.[1] One-year, and three-year survival rates are 54% and 21.4%, respectively.[1] Metastasis happens in 40% of cases.[2] Most common sites include lymph nodes, lungs, and liver.[1] Skin and brain metastasis have also been reported.[2] Survival rate in metastatic form is less than 3 months.[1] Recurrence happens in more than half the

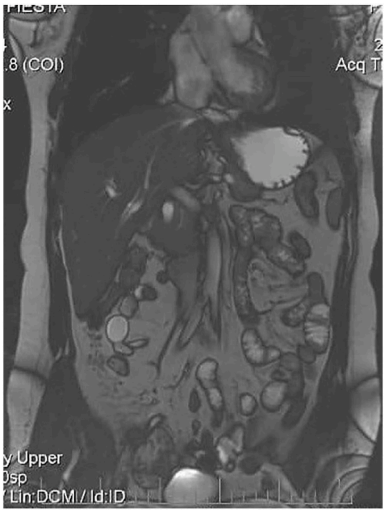

Fig. 3b. Follow-up MRI after one year (no metastasis).

cases.[1] Coexistence of LCNEC with other carcinomas is common. In one study, 25% had coexisting UC and 10% had SCNEC combined with LCNEC.[2] Coexistence with lymphoma, carcinosarcoma, and adenocarcinoma has also been reported.[2] Concurrence is associated with primary LCNEC and not metastatic form.[2] Further research is needed to determine the difference between survival rate of pure and mixed LCNEC.[1,2]

Contrast-enhanced ultrasound (CEUS) may help detect LCNEC of bladder. Staging of NET is done using CT, PET/CT, or MRI. PET seems to be more sensitive than CT or MRI.[4] Octreotide is used for localization of primary and metastatic NETs.[2]

IHC studies provide additional information like specific cell markers to distinguish NET subtypes.[2] These include synaptophysin, chromogranin A, CD56, CAM5.2, EMA, and pan-cytokeratins.[2] Ki67 has a 40% sensitivity and an 80% specificity distinguishing LCNEC and UC.[2] Urine cytology isn't reliable for early diagnosis.[4]

Factors associated with poor outcome include advanced T staging, distant metastasis at time of diagnosis, treatment without adjuvant chemotherapy, and single modal therapy.[1] Carboplatin-based chemotherapy is associated with worse survival.[5] Number of involved lymph nodes, or sites of metastasis didn't affect overall survival.[5]

LCNEC has an unpredictable behavior. Treatment options include radical cystectomy, bladder sparing methods, chemotherapy, and radiotherapy. Chemotherapy regimens are same as those for pulmonary LCNEC, so etoposide and platinum drugs are treatment of choice, whether adjuvant or neoadjuvant.[2] Those ineligible for chemotherapy are recommended to undergo cystectomy or TURBT with radiotherapy.[3] Neoadjuvant therapy can result in a 5-year-survival rate of 80%.[3] Immunotherapy like intravesical BCG therapy isn't proposed as a treatment for LCNECs. But since tumor may have urothelial carcinoma components, BCG therapy should be considered in cases of non-muscle invasive pure urothelial carcinoma, since it's the standard treatment for high-grade NMIBC.

4. Conclusion

Primary NET of bladder is a rare condition. Among its four subtypes, LCNEC is least common, highly aggressive and unpredictable.[2] Diagnosis is based on pathology. Due to its rare incidence, treatment is extrapolated from its pulmonary counterparts.[2]

Average survival time for metastatic disease is less than 3 months. Our patient achieved a one-year tumor-free survival, this could be explained by early detection of primary and metastatic disease plus multimodal therapy using TURBT, BCG therapy, RF ablation of liver metastasis, and systemic chemotherapy. This means early diagnosis and treatment helps to increase the survival rate.

Consent

Informed consent was taken from the patient to write this report.

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Declaration of competing interest

The authors have no conflict of interest to declare.

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