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A Rare Case of Primary Neuroendocrine Tumor of the Bladder

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Case Study

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ABSTRACT

We present the case of a 45-year-old gentleman who presented with gross hematuria and underwent radical cystectomy, leading to an unexpected post-operative diagnosis of primary neuroendocrine tumor of the urinary bladder. This case underscores the diagnostic challenges associated with this rare malignancy and emphasizes the importance of considering neuroendocrine tumors in the differential diagnosis of bladder neoplasms. We discuss the clinical presentation, diagnostic workup, surgical intervention, and post-operative management of this unique case.

Keywords: Neuroendocrine tumor; bladder neoplasms; urothelial carcinomas; radical cystectomy.

1. INTRODUCTION

Neuroendocrine tumors (NETs) of the bladder are exceptionally rare, accounting for less than 1% of all bladder malignancies. Their clinical presentation often mimics more common urothelial carcinomas, making accurate diagnosis a formidable challenge. Herein, we describe the case of a 45-year-old male who presented with gross hematuria and was

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ultimately diagnosed with a primary neuroendocrine tumor of the bladder following radical cystectomy.

2. CASE PRESENTATION

A 45-year-old male presented with a chief complaint of gross hematuria, with passage of clots for two weeks. There was no previous history of hematuria, renal stones, dysuria or features suggestive of bleeding disorders. On bimanual palpation no lump was palpable. On investigations coagulation profile was normal and ultrasound showed heterogeneously echogenic mass at right Vesico-ureteric junction projecting into lumen measuring 4.1 x 2.6cm with internal vascularity (low resistance arterial flow) s/o neoplastic etiology; prompting a thorough diagnostic workup after initial resuscitation. Initial imaging studies, including computed tomography (CT) scans and magnetic resonance imaging (MRI), revealed a bladder mass involving bladder muscle wall.Urine for malignant cytology showed high grade urothelial carcinoma [1,2]. Cystoscopy confirmed the presence of a tumor, and transurethral biopsy was performed which came out to be inconclusive.

3. DIAGNOSTIC CHALLENGES

The patient's journey began with the presentation of painless gross hematuria, a concerning symptom strongly suggestive of a malignancy within the bladder. In light of this clinical presentation and the immediate suspicion of malignancy a surgical approach was swiftly chosen. An attempt to confirm diagnosis was done in form of various radiological modalities like ultrasonography, CECT Urography, MR Urography and pathological investigations like Urine for malignant cytology and cystoscopic guided tissue biopsy were performed which showed results as follows:

I. USG-KUB(07/05/2023) - heterogeneously echogenic mass at right Vesico-ureteric junction projecting into lumen measuring 4.1x2.6cm with internal vascularity (low resistance arterial flow) s/o neoplastic etiology
II. CECT-KUB(08/05/2023) - heterogeneously enhancing irregular bladder wall thickening with a polypoidal mass lesion (virtual non contrast-37HU , post contrast-70HU) noted to arise from right postero-superior wall of urinary bladder, the mass is of approx. size 5.0x3.9x3.0 cm (APxTRxCC) with no calcification or peri-vesicle extension ; s/o neoplastic etiology (T2N0M0). B/l VUJ, kidneys, ureters appear normal with no involvement of prostate or seminal vesicles, with few subcentimetric iliac lymph nodes.
III. MR UROGRAPHY(16/05/2023) - heterogeneous lesion of altered signal intensity measuring approx 6 x 4.7x4.5cm(APxTRxCC) arising from anterosuperior and right lateral wall of the bladder, appearing heterogeneously iso to hyperintense on T2W1, diffusion restriction on DW1 and heterogenous post contrast enhancement with focal bladder wall thinning involving bladder wall, however no obvious perivesical spread s/o neoplastic etiology; B/l ureters, kidneys,VUJ, seminal vesicles and prostate remains uninvolved; with multiple suspicious subcentimetric as well as enlarged lymph nodes are seen in b/l inguinal region and b/l iliac vessels showing areas of diffusion restriction.
IV. Urine for malignant cytology - s/o possibility of high grade urothelial carcinoma.
V. Cystoscopy - diffuse polypoidal mass seen protruding into lumen; biopsy report showed inconclusive report.

Based on clinical, radiological and pathological diagnosis of high grade urothelial carcinoma with muscle involvement but no perivesical spread, decision of surgical resection was made for complete resection and management.

As a result, radical cystectomy was promptly undertaken, aiming to address both the diagnostic and therapeutic aspects of the patient's condition. This approach allowed for the expeditious removal of the tumor and provided an opportunity for detailed histopathological examination to confirm the nature of the malignancy.

4. SURGICAL INTERVENTION

Given the diagnosis of high grade urothelial carcinoma of the bladder, radical cystectomy with ileal conduit was deemed necessary. The surgery involved the removal of the entire bladder, nearby lymph nodes, and a urinary diversion procedure (ileostomy urinary diversion). Intraoperative frozen section

assessment of surgical margins (b/l ureteric and urethral) and lymph node involvement revealed no evidence of tumor spread beyond the bladder.

5. POST-OPERATIVE MANAGEMENT

Following radical cystectomy, the patient underwent close postoperative surveillance. Post-operative period seems to be essentially uneventful. Patient was allowed orally on POD3 and drain was removed on POD5.

Histopathology report post radical cystectomy procedure came out to be Small cell neuroendocrine tumor of high grade with negative margins and no lymphovascular involvement; all 32 dissected lymph nodes came out to be negative. pT2b N0 M0

IHC : CK7 - negative; CK20 - negative; P63 - negative; GATA3 - negative; P53 - null phenotype; Ki67 –

>95%; AR - negative; Chromogranin - Positive; LCA - negative; Vimentin - negative; CEA-negative; CDX2 - negative.

6. OUTCOME

The patient's postoperative course was uneventful, and follow-up imaging studies showed no signs of tumor recurrence or distant metastases at 3 month follow up interval. His urinary diversion procedure provided adequate quality of life. Continued surveillance was planned to monitor for any potential disease recurrence or long-term complications.

7. DISCUSSION

Urothelial carcinoma, also referred to as transitional cell carcinoma, constitutes the most common form of bladder cancer, accounting for the majority of cases. Conversely, non-urothelial malignancies represent a mere 10% of bladder carcinomas, with small cell carcinoma of the bladder, a neuroendocrine tumor, being an exceptionally rare occurrence. Pure neuroendocrine variants of bladder cancer, although infrequent, exhibit a notably aggressive nature, often presenting at advanced pathological stages or with metastatic disease [3].

The established standard treatment for non-urothelial carcinomas, regardless of histologic subtype, is radical cystectomy. However, the timing of neoadjuvant chemotherapy and/or radiation therapy can vary depending on the specific histologic subtype [4]. In the case of neuroendocrine bladder tumors, the standard approach involves neoadjuvant chemotherapy followed by radical cystectomy [5].

While the data supporting perioperative chemotherapy for non-urothelial carcinomas is limited, neoadjuvant chemotherapy has shown promise for patients with small cell carcinoma of the bladder. It is recommended for any patient with small-cell component histology and localized disease, regardless of the stage. Patients diagnosed with small cell carcinoma of the bladder are best initially managed with systemic therapy, following the NCCN Guidelines for Small Cell Lung Cancer, followed by either radiation therapy or cystectomy as consolidation if metastatic disease is absent. Furthermore, a regimen involving alternating ifosfamide plus doxorubicin with etoposide plus cisplatin has demonstrated efficacy in treating small cell bladder cancer, both in the neoadjuvant and metastatic settings [6].

A noteworthy development is the evaluation of the combination of nivolumab plus ipilimumab in a phase II trial for advanced rare genitourinary malignancies, including the BUTCVH cohort of 19 patients with bladder or upper tract tumors of variant histology, including 3 patients with small cell bladder cancer. The overall response rate for the BUTCVH cohort reached 37%, with two complete responses observed [7]. Concurrent chemoradiotherapy is also considered as an option for these patients.

This case underscores the vital importance of considering neuroendocrine tumors in the differential diagnosis of bladder neoplasms, especially when confronted with typical clinical presentations. An accurate diagnosis relies on a combination of histopathological examination and immunohistochemical staining. In situations where obtaining a sufficient histological diagnosis proves challenging, as cystoscopic biopsy samples may sometimes be inadequate despite suggestive radiological features of operable muscle-invasive bladder tumors, surgery remains the primary treatment modality.

Due to the rarity of neuroendocrine tumors of the urinary bladder, there is a scarcity of data to support the use of adjuvant chemoradiotherapy in these cases. Therefore, they are primarily

managed in accordance with the protocols established for small cell carcinoma of the lung.

Clinical symptoms are non-specific, with the most common manifestations being gross hematuria, pelvic pain, and irritative voiding symptoms. The diagnosis depends on histopathological recognition and reactivity to neuroendocrine markers such as Synaptophysin, chromogranin A, and neuron-specific enolase. These tumors are often diagnosed at a locally advanced stage, with lymph node involvement in 57% of cases and lung, bone, liver, or brain involvement in 28%-50% of cases [8,9]. In our case, the radiological evaluation did not detect evidence of metastatic disease at the time of diagnosis.

For localized tumors, it has been observed that despite local treatment of the primary tumor, most patients eventually develop metastasis. Sved et al. reported discouraging outcomes for patients treated solely with radical cystoprostatectomy, with a 3-year overall survival rate of 16% and a 5-year progression-free survival of 0%. However, a retrospective study from Mayo Clinic in 2004 suggested that all patients with small-cell bladder carcinoma should undergo radical cystectomy unless metastatic disease is present, with adjuvant chemotherapy based on cisplatin considered as an option [10].

8. CONCLUSION

Primary neuroendocrine tumors of the bladder are exceedingly rare but should be considered in the diagnostic workup of bladder masses. This case report highlights the challenges in diagnosing and managing this unique malignancy, emphasizing the need for a multidisciplinary approach to ensure optimal patient outcomes. In view of the aggressive nature of this variety, early detection and prompt aggressive management may improve outcome and prognosis of these patients and require long-term follow up of these patients.

ETHICAL APPROVAL

As per international standard or university standards written ethical approval has been collected and preserved by the author(s).

CONSENT

As per international standards or university standards, patient(s) written consent has been collected and preserved by the author(s).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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