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Mixed Urothelial and Large-Cell Neuroendocrine Carcinoma of the Bladder With Synchronous Prostatic Adenocarcinoma: A Case Report

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Fatima Zahra Bouayed [1], Mohamed Moukhlissi [2], Yousra El Hadi [1], Mohammed Meziane [3], Amal Bennani [3], Soumiya Samba [4], Ahmed BenSghier [4], Soufiane Berhili [1], Loubna Mezouar [4]

1. Radiation Oncology, Faculty of Medicine and Pharmacy, Mohammed First University, Oujda, MAR 2. Radiotherapy, Faculty of Medicine and Pharmacy, Mohammed VI University Hospital, Oujda, MAR 3. Pathology, Faculty of Medicine and Pharmacy, Mohammed VI University Hospital, Oujda, MAR 4. Radiation Oncology, Faculty of Medicine and Pharmacy, Mohammed VI University Hospital, Oujda, MAR

Corresponding author: Fatima Zahra Bouayed, fatimazahrabouayed@outlook.fr

Abstract

Among bladder malignancies, large-cell neuroendocrine carcinoma is an uncommon histological type with an aggressive clinical course. It is associated with rapid progression, early distant spread, and poor prognosis. Its rarity and the limited available clinical data make its diagnosis and management challenging. In this article, we present the case of an 82-year-old man with hematuria and dysuria diagnosed with mixed urothelial and large-cell neuroendocrine carcinoma of the urinary bladder alongside synchronous prostatic adenocarcinoma. Histopathological examination of the transurethral resection specimen revealed muscle-invasive carcinoma comprising approximately 70% high-grade urothelial carcinoma and 30% large-cell neuroendocrine carcinoma, with the neuroendocrine component staining positive for chromogranin A and synaptophysin. Prostate biopsies revealed adenocarcinoma with a Gleason score of 7 (3 + 4). Subsequent imaging showed pulmonary metastases. This case highlights the rare coexistence of these distinct malignancies and underscores the importance of thorough histopathological and immunohistochemical evaluation to establish an accurate diagnosis and guide management.

Categories: Pathology, Radiation Oncology, Oncology
Keywords: bladder tumour, large cell neuroendocrine bladder carcinoma, prostatic adenocarcinoma, synchronous occurrence, urothelial carcinoma

Introduction

Urothelial carcinoma is the most prevalent type of bladder cancer, making up over 90% of all cases [1]. On the other hand, neuroendocrine neoplasms (NENs) of the bladder are quite rare, representing less than 1% of all bladder malignancies [2] and include a variety of histological subtypes. Among these entities, small-cell neuroendocrine carcinoma (SCNEC) predominates, while large-cell neuroendocrine carcinoma (LCNEC) is extremely uncommon [3]. In 1986, Abenoza et al. documented the very first case of bladder LCNEC [4]. Since that time, there have been only a handful of reported cases, leaving much of its clinical behavior and optimal management poorly understood. Hematuria is the most commonly reported presenting symptom of LCNEC of the bladder [3].

Histologically, LCNEC of the bladder can be pure or mixed, the latter being most often combined with urothelial carcinoma. Also reported were adenocarcinoma, squamous cell carcinoma, and sarcomatoid urothelial carcinoma [5,6]. In this report, we present an unusual coexistence of mixed urothelial and LCNEC of the urinary bladder with synchronous prostatic adenocarcinoma.

Case Presentation

We report the case of an 82-year-old man with a history of diabetes, hypertension, and a 50-year smoking history, with no family history of cancer, who presented to our department with dysuria and hematuria. His serum prostate-specific antigen (PSA) level was 29.06 ng/mL. Abdominopelvic computed tomography (CT) was performed and showed regular circumferential thickening of the bladder wall with associated perivesical fat stranding (Figure *1*), as well as a heterogeneous prostatic enlargement with a suspicious median lobe extending into the bladder trigone and invading the right ureteric orifice, resulting in moderate right-sided hydroureteronephrosis.

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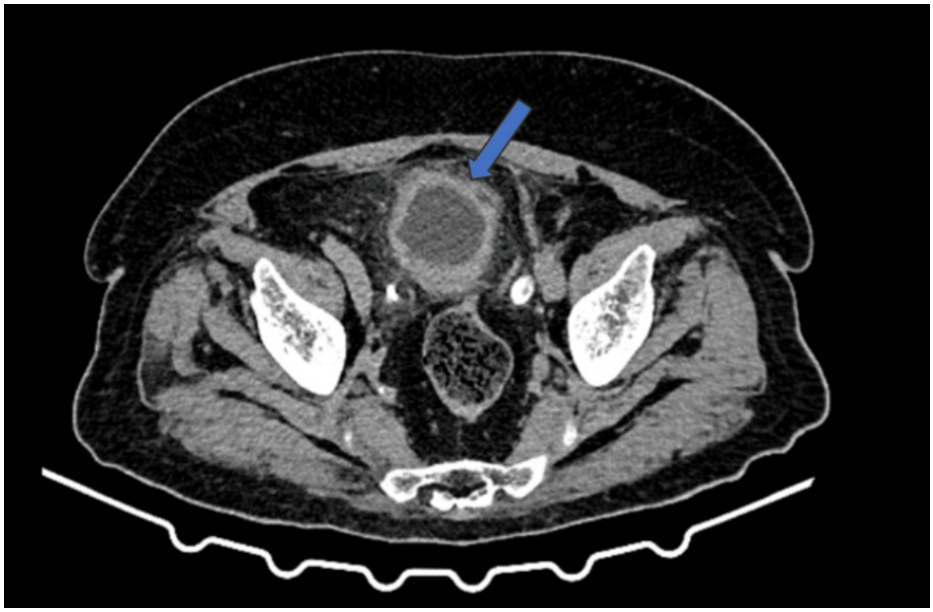


FIGURE 1: Computed tomography showing regular circumferential thickening of the bladder wall with associated perivesical fat stranding

A biopsy was subsequently performed, and histopathological examination showed invasive acinar adenocarcinoma, Gleason score of 7 (3 + 4), corresponding to International Society of Urological Pathology (ISUP) Grade Group 2, involving 80% of the examined prostatic parenchyma with perineural invasion and no vascular invasion identified (Figure *2*).

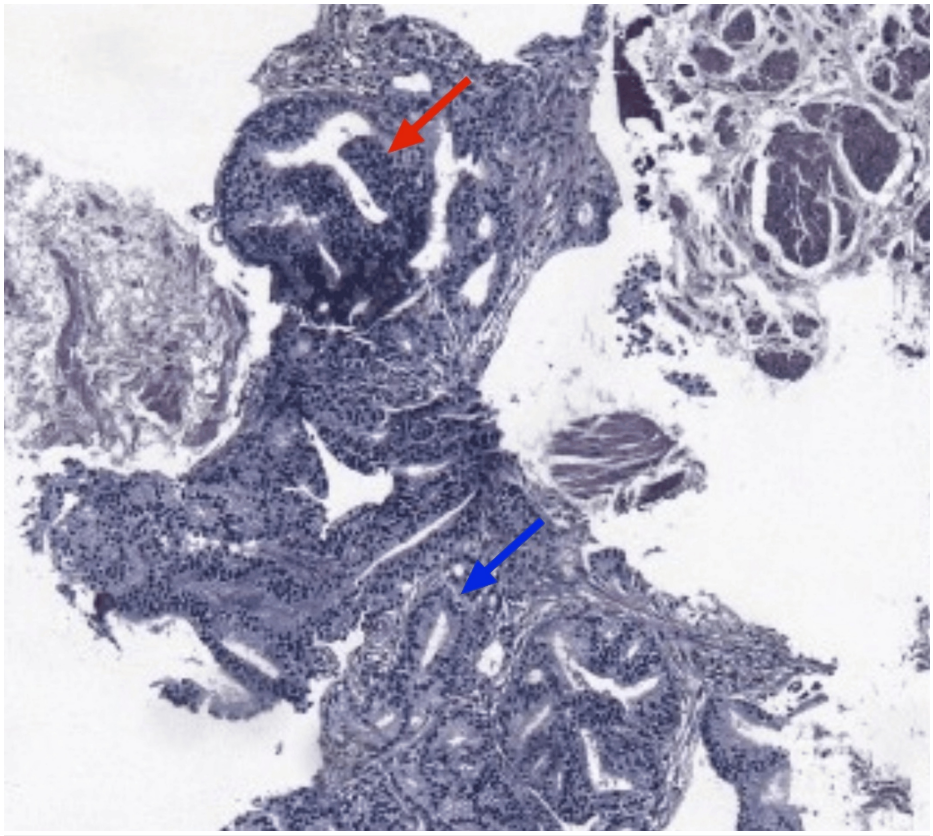


FIGURE 2: Histopathological examination

Histological image (hematoxylin and eosin (H&E) staining, ×4) showing prostatic adenocarcinoma, Gleason score 7 (3 + 4), composed predominantly of well-formed glands (blue arrow) with focal cribriform architecture (red arrow).

The patient subsequently underwent cystoscopic evaluation followed by transurethral resection of the bladder tumor. Histopathological examination (Figure *3*) revealed a malignant tumor composed of two distinct morphological components. The predominant component, accounting for approximately 70% of the tumor, consisted of high-grade urothelial carcinoma exhibiting a papillary architecture with fibrovascular cores lined by atypical epithelial cells displaying enlarged, irregular nuclei, vesicular chromatin, prominent nucleoli, and abundant eosinophilic cytoplasm. The remaining 30% consisted of a neuroendocrine carcinoma component arranged in solid nests and sheets of atypical cells characterized by round to oval nuclei with heterogeneous chromatin and moderate amphophilic cytoplasm. Immunohistochemical analysis demonstrated positive staining for chromogranin A and synaptophysin in the latter component, supporting neuroendocrine differentiation. These findings were consistent with a high-grade urothelial carcinoma associated with LCNEC. A follow-up CT scan of the neck, chest, abdomen, and pelvis revealed pulmonary metastases. Following discussion at a multidisciplinary team meeting, the disease was deemed unresectable. The patient subsequently received palliative chemotherapy with carboplatin and etoposide, along with androgen deprivation therapy with triptorelin for the synchronous prostatic adenocarcinoma. Unfortunately, his general condition deteriorated, and he was subsequently lost to follow-up.

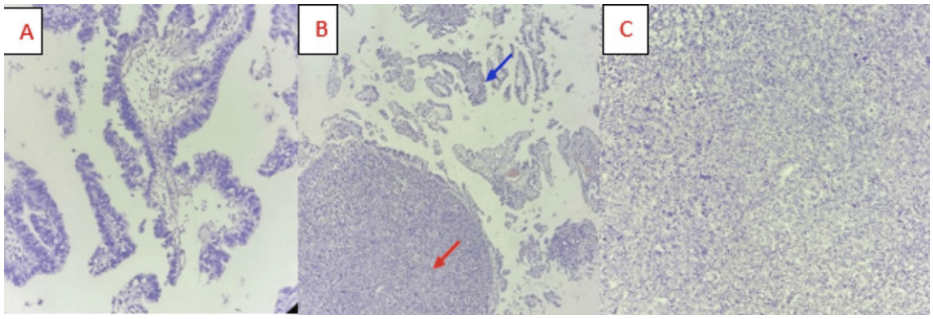


FIGURE 3: Histopathological examination

(A) High-power view of the urothelial carcinoma component, showing papillary structures lined by multilayered atypical urothelial cells. (B) Low-power view (x4) showing a urothelial carcinoma component displaying papillary architecture (blue arrow) adjacent to a neuroendocrine carcinoma component showing a predominantly solid growth pattern (red arrow). (C) High-power view of the neuroendocrine carcinoma component, showing solid sheets of large atypical cells.

Discussion

Neuroendocrine carcinomas are a rare type of urinary bladder cancer, making up less than 1% of all bladder carcinoma cases [5]. The 2016 World Health Organization (WHO) classification categorizes primary NENs of the urinary bladder into four types: SCNEC, LCNEC, well-differentiated neuroendocrine tumor (WDNET), and paraganglioma (PGL) [7]. In addition to these four entities, the 2022 WHO classification acknowledges an additional category that includes mixed NENs [6,8].

The first documented case, reported by Cramer et al. in 1981, was a SCNEC [9]. Despite the rarity of SCNEC, which accounts for less than 0.7% of all bladder cancers, LCNEC is encountered even less frequently and was first described in 1986 [9].

LCNEC typically exhibits neuroendocrine architecture such as organoid nests, peripheral palisading, rosettes and trabecular arrangements, and increased mitotic activity, while immunohistochemical expression of neuroendocrine markers, such as synaptophysin and chromogranin A, supports the diagnosis [2,10,11].

It mostly occurs in older men, with hematuria as the most common presentation. A smoking history is commonly present [3]. Studies have shown that prostate cancer radiotherapy, the use of cyclophosphamide, and a family history of bladder cancer are all associated with an increased risk of developing bladder cancer [12]. Its aggressive nature is reflected in rapid disease progression and early spread to distant sites [13].

Histologically, it can occur alongside other histological components, including urothelial carcinoma, as revealed by histological examination of our patient's bladder tumor, and less frequently with adenocarcinoma, squamous cell carcinoma, and sarcomatoid urothelial carcinoma [6].

To date, we have identified only three publications describing the coexistence of bladder LCNEC and prostatic adenocarcinoma, highlighting the rarity of this association [5,10,14]. Although mixed urothelial and LCNECs of the bladder have been described [6], our literature search did not identify a previous report of this mixed bladder tumor occurring with synchronous prostatic adenocarcinoma as observed in our patient; such an uncommon combination makes the present case even more interesting. Understanding the difference between pure and mixed histology could also influence patient prognosis; recent studies have indicated that patients with mixed tumors might actually have a better chance of survival [4]. However, another study found no statistically significant difference in overall survival between pure and mixed LCNEC ($P = 0.826$) [3].

The ideal approach to treat bladder LCNEC remains a mystery, largely due to its rarity. A treatment strategy that combines chemotherapy, radiotherapy, and partial or radical cystectomy is highly recommended. This strategy has been linked with improved patient survival in multiple studies [3]. Platinum-based chemotherapy is the go-to choice for treatment [13]. Given the limited evidence available to guide treatment, multidisciplinary discussion is vital to define a personalized treatment plan, taking into account the disease stage, the patient's overall condition, and the goals of care.

Conclusions

This case highlights the unusual combination of mixed urothelial and LCNEC in the urinary bladder, occurring alongside synchronous prostatic adenocarcinoma. It highlights the need for detailed histopathological and immunohistochemical examination to give an accurate diagnosis. This finding points

out the complexity of the differential diagnostic process and the importance of multidisciplinary management. In this case, the loss to follow-up limited our ability to evaluate treatment response and long-term outcomes. Further similar cases collected with detailed treatment and follow-up information are of great interest for understanding the natural history of the disease.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Concept and design: Fatima Zahra Bouayed, Mohamed Moukhlissi, Yousra El Hadi, Mohammed Meziane, Amal Bennani, Soumiya Samba, Ahmed BenSghier, Soufiane Berhili, Loubna Mezouar

Acquisition, analysis, or interpretation of data: Fatima Zahra Bouayed, Mohamed Moukhlissi, Yousra El Hadi, Mohammed Meziane, Amal Bennani, Soumiya Samba, Ahmed BenSghier, Soufiane Berhili, Loubna Mezouar

Drafting of the manuscript: Fatima Zahra Bouayed, Mohamed Moukhlissi, Yousra El Hadi, Mohammed Meziane, Amal Bennani, Soumiya Samba, Ahmed BenSghier, Soufiane Berhili, Loubna Mezouar

Critical review of the manuscript for important intellectual content: Fatima Zahra Bouayed, Mohamed Moukhlissi, Yousra El Hadi, Mohammed Meziane, Amal Bennani, Soumiya Samba, Ahmed BenSghier, Soufiane Berhili, Loubna Mezouar

Supervision: Mohamed Moukhlissi, Soumiya Samba, Ahmed BenSghier, Soufiane Berhili, Loubna Mezouar

Disclosures

Human subjects: Informed consent for treatment and open access publication was obtained or waived by all participants in this study. **AI use statement:** The authors used ChatGPT (GPT-6; OpenAI, San Francisco, CA, USA) as follows: structure or formatting, translation, language polishing, rephrasing in Abstract, Introduction, Case Presentation, Discussion, and Conclusions. AI was used exclusively for translation, language polishing, and rephrasing to improve the clarity and readability of the manuscript. The authors confirm that they have reviewed and verified all AI-assisted content and take full responsibility for the work. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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