Mixed Small Cell Neuroendocrine Carcinoma and High-grade Urothelial Carcinoma with Sarcomatoid Differentiation Coexisting with (Primary/Metastatic) Melanoma of the Urinary Bladder: A Case Report

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Abstract

Both mixed neuroendocrine non-neuroendocrine neoplasms and melanomas of the urinary bladder are rare, and the coexistence of these neoplasms is extremely rare. This case report highlights a 77-year-old male who presented with gross hematuria for the past 1 week. Transurethral resection of bladder tumor was performed and the resected tissue was sent for histopathology, which revealed mixed (1) small cell neuroendocrine carcinoma with a minor component of high-grade urothelial carcinoma with focal sarcomatoid differentiation and (2) melanoma (primary bladder melanoma is considered after exclusion of metastasis). This case highlights the critical role of meticulous histopathological evaluation in bladder tumors, as rare and aggressive neoplasms may coexist and require accurate diagnosis for appropriate management.

Keywords: mixed neuroendocrine non-neuroendocrine neoplasm (MiNEN), small cell neuroendocrine carcinoma, high-grade urothelial carcinoma, bladder melanoma, collision tumor, bladder neoplasms, case report.

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Introduction

Mixed neuroendocrine non-neuroendocrine neoplasms (MiNENs) are tumors composed of an admixture of a neuroendocrine component and a non-neuroendocrine component, whether it is urothelial carcinoma, squamous cell carcinoma, or adenocarcinoma.[1] Neuroendocrine tumors (NETs) in the urinary bladder are admixed with non-neuroendocrine components in as many as 50% of cases and generally have a poor prognosis.[1,2] Mixed small cell neuroendocrine carcinoma (SCNEC) and urothelial carcinoma of the bladder is a rare occurrence, with small cell neuroendocrine carcinoma itself comprising only 0.48%-1% of all bladder carcinomas, but it usually coexists with urothelial carcinoma.[3] The urothelial carcinoma component may exhibit sarcomatoid differentiation. The most common heterologous element is osteosarcoma, followed by chondrosarcoma.[1,4,5]

Mucosal melanoma of the urinary system is a malignant melanocytic neoplasm arising in a non-cutaneous urogenital site.[1] Primary melanoma of the bladder is very rarely seen and accounts for 0.2% of all melanomas. Rather than being a primary lesion, melanomas of the bladder are more commonly metastatic lesions.[6] The prognosis for patients with primary melanoma of the urinary tract is poor.[1,6,7]

This is a case report of a mixed small cell neuroendocrine carcinoma and high-grade urothelial carcinoma with sarcomatoid differentiation coexisting with a melanoma of the urinary bladder.

Timeline

Date / Period	Clinical Event
~30 years prior	Brain tumor status post surgery (with no recorded histologic type) Epilepsy, well controlled
Ongoing	Medications: Phenytoin 100 mg, 3 tablets orally at bedtime; Vitamin B complex, 1 tablet orally three times daily
26 September 2025	Hospital presentation for gross hematuria Investigations: urinalysis, PSA, plain film KUB Foley catheter insertion Discharged with ciprofloxacin 500 mg orally twice daily for 5 days
6 October 2025	Cystoscopy with transurethral resection of bladder tumor (TURBT) Resected tissue sent for histopathological diagnosis
24 October 2025	Final pathological diagnosis: mixed (1) small cell neuroendocrine carcinoma with a minor component of high-grade urothelial carcinoma with focal sarcomatoid differentiation (approximately 50%) and (2) melanoma (approximately 50%) (primary bladder melanoma is considered after exclusion of metastasis from cutaneous or mucosal/visceral melanoma from other sites)
10 November 2025	Initiation of intravesical therapy with mitomycin C 20 mg once weekly Continuation of intravesical mitomycin C therapy for a total of eight weeks (from 10 November to 29 December 2025)
31 January 2026	The patient developed progressive right upper abdominal pain, and liver metastasis was suspected based on CT findings. The clinical stage was subsequently upstaged to T4. The patient declined systemic chemotherapy and opted for best supportive care.

Case Presentation

A 77-year-old Thai man, weighing 51 kg and measuring 165 cm in height, with a 30-year history of a brain tumor status post surgery (with no recorded histologic type), and well-controlled epilepsy treated with phenytoin 100 mg (three tablets orally at bedtime) and vitamin B complex (one tablet orally three times daily), was unemployed and had a history of smoking and alcohol consumption. He presented with gross hematuria for one week. On physical examination, including skin and eye examinations, no significant abnormalities were identified. Neither computed tomography (CT) nor magnetic resonance imaging (MRI) was performed.

Transurethral resection of bladder tumor (TURBT) was performed. The cystoscopic findings were not recorded, and urine cytology was not performed. The resected tissue was sent for histopathological examination. Gross examination revealed multiple pieces of soft gray brown tissue, measuring 6.0 x 5.7 x 1.5 cm in aggregate. The entire specimen was submitted for histologic evaluation. Upon microscopic examination, the tumor was composed of nests of small round cells in a background of epithelioid cells (Fig. 1A). The small round cells showed hyperchromatic nuclei, high nuclear to cytoplasm ratio, fine stippled chromatin, inconspicuous nucleoli, mild nuclear pleomorphism, nuclear molding, scant cytoplasm, high mitotic activity and necrosis; morphologically consistent with small cell neuroendocrine carcinoma (Fig. 1B) admixed with urothelium with high-grade nuclear features invading the lamina propria with retraction artifact (Fig. 1C), with focal chondrosarcomatous differentiation (Fig. 1D). The small cell neuroendocrine carcinoma and high-grade urothelial carcinoma were positive for AE1/AE3 (Fig. 1E), CD56 (Fig. 1F), focal positive for synaptophysin (Fig. 1G), CK7 (Fig. 1H), CK20 (Fig. 1I), GATA3 (Fig. 1J) and p63 (Fig. 1K), but were negative for chromogranin A, S100, HMB45, melan-A, actin, desmin, h-caldesmon and CD45.

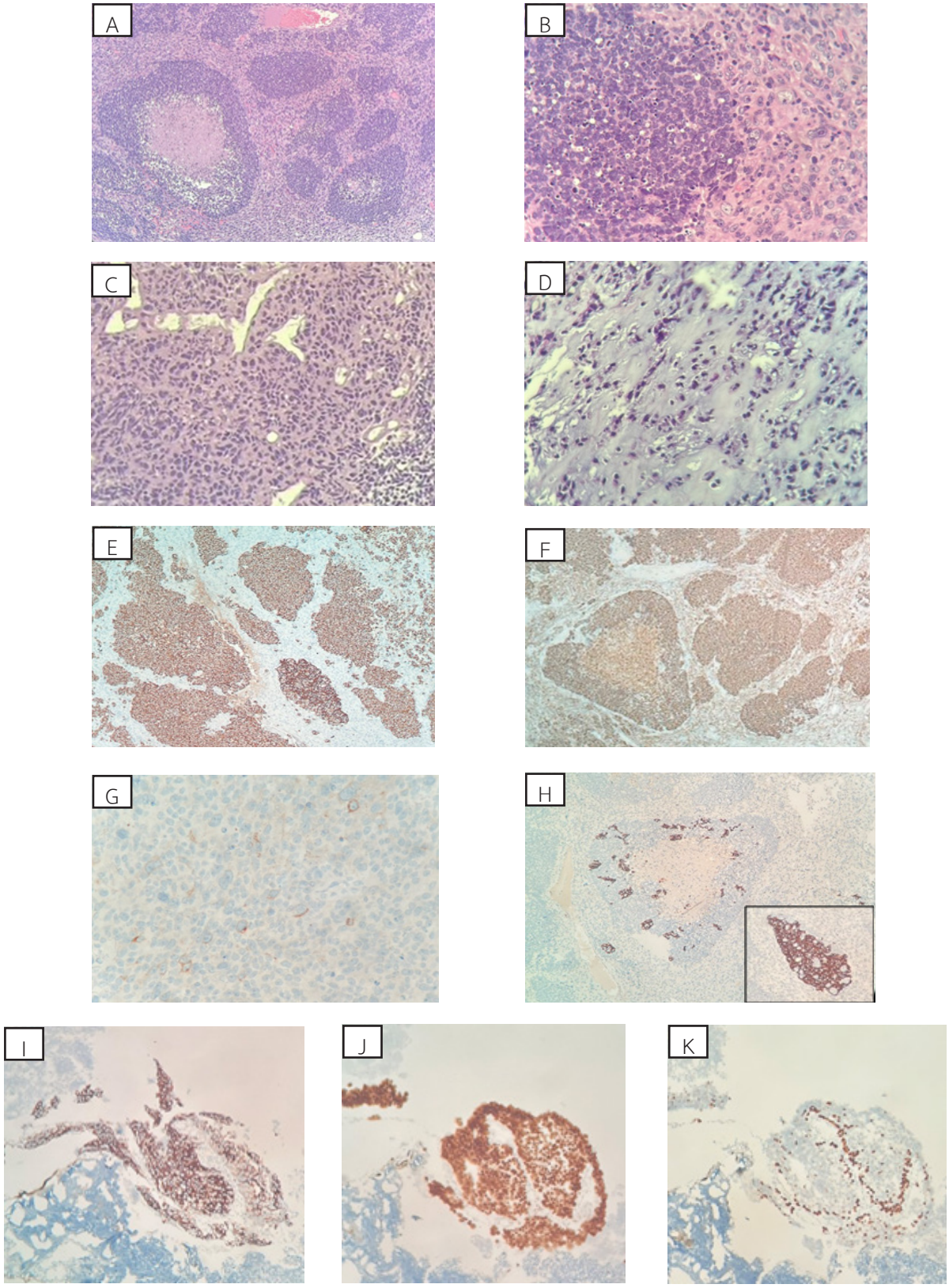

Fig 1. Mixed neuroendocrine non-neuroendocrine neoplasms. (A) Nests of small round cells in a background of epithelioid cells (these epithelioid cells will be mentioned in the figure 2) (H&E, 100x). (B) Small round cell tumor (left side of the picture) (H&E, 400x). (C) Urothelial carcinoma (H&E, 400x). (D) Chondrosarcomatous differentiation (400x). (E) AE1/AE3 showed cytoplasmic and membranous positivity in the small round cell and urothelial components (100x). (F) CD56 showed membranous positivity in the small round cell component (100x). (G) Synaptophysin showed focal cytoplasmic positivity in the small round cell component (400x). (H) CK7 showed focal membranous **positivity**

in the small round cell and urothelial components (100x). (I) CK20 showed focal membranous positivity in the urothelial component (100x). (J) GATA3 showed focal nuclear positivity in the urothelial component (100x). (K) p63 showed focal nuclear positivity in the urothelial component (100x).

As mentioned above, in the same tumor, epithelioid cells were present in the background (Fig. 2A). The epithelioid cells showed focal melanin pigment, large pleomorphic nuclei, vesicular chromatin and prominent nucleoli (Fig. 2B) that were positive for S100 (Fig. 2C), HMB45 (Fig. 2D) and melan-A (Fig. 2E), but were negative for AE1/AE3, CK7, CK20, GATA3, p63, CD56, synaptophysin, chromogranin A, actin, desmin, h-caldesmon and CD45. The findings were morphologically and immunohistochemically consistent with melanoma. Muscularis propria is not present for evaluation of invasion.

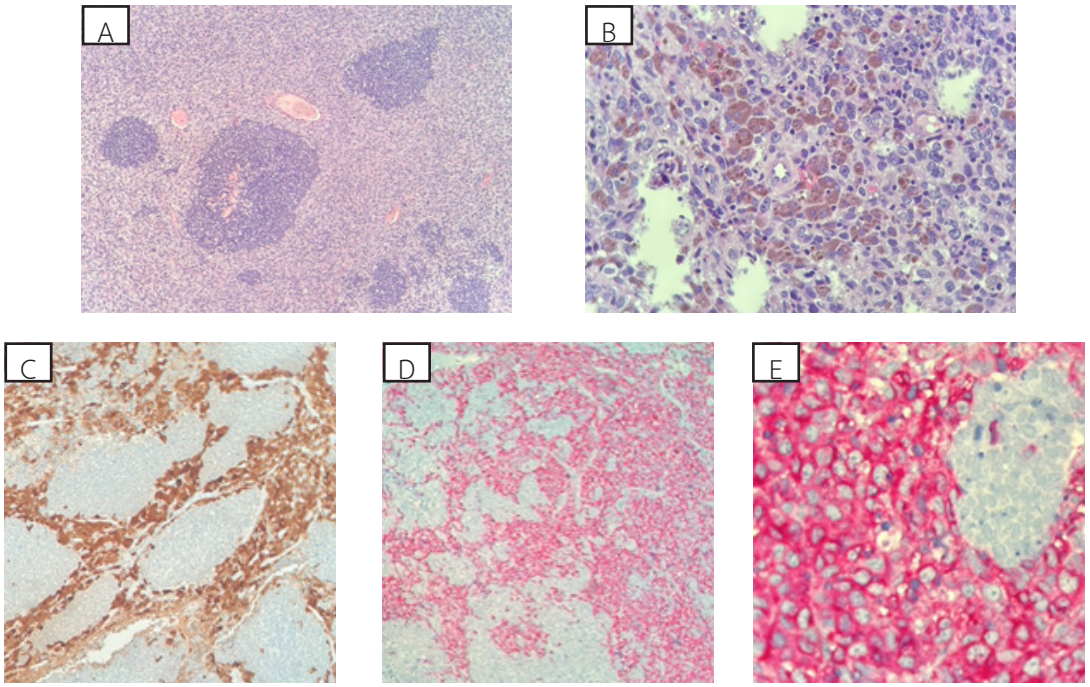

Fig 2. Melanoma. (A) Epithelioid cells in the background (H&E, 100x). (B) Epithelioid cells showed melanin pigment, nuclear pleomorphism and prominent nucleoli (H&E, 400x). (C) S100 showed cytoplasmic and nuclear positivity in the melanoma component (100x). (D) HMB45 showed cytoplasmic positivity in the melanoma component (100x). (E) Melan-A showed cytoplasmic positivity in the melanoma component (400x), whereas it showed negativity in the small cell neuroendocrine carcinoma component (right side of the picture).

The final pathological diagnosis was mixed (1) small cell neuroendocrine carcinoma with a minor component of high-grade urothelial carcinoma with focal sarcomatoid differentiation (approximately 50%) and (2) melanoma (approximately 50%) (primary bladder melanoma is considered after exclusion of metastasis from cutaneous or mucosal/visceral melanoma from other sites). For staging, there was evidence of lamina propria invasion; thus, it could be considered at least pT1 according to the pTNM classification (AJCC, 8th edition).

After diagnosis, the patient received intravesical therapy with mitomycin C 20 mg once weekly for a total of eight weeks. Following the final dose, he presented to the emergency department with progressive right upper abdominal pain. A CT scan of the abdomen revealed multiple hypoenhancing lesions in both hepatic lobes, measuring up to 4.5 cm, possibly liver metastases, with cirrhosis. The clinical stage was subsequently upstaged to T4. However, a liver biopsy for histologic confirmation was not

performed. The patient declined systemic chemotherapy and opted for best supportive care.

Discussion

The coexistence of small cell neuroendocrine carcinoma and urothelial carcinoma in the bladder is a recognized entity, referred to as a mixed neuroendocrine non-neuroendocrine epithelial neoplasm (MiNEN).[1] Most common carcinoma that found to be mixed with small cell neuroendocrine carcinoma is urothelial carcinoma, but also adenocarcinoma or squamous cell carcinoma. The prevailing theory for this coexistence is that both components originate from a multipotential, undifferentiated stem cell present in the urothelium. This theory is supported by molecular findings demonstrating that both small neuroendocrine carcinoma and urothelial carcinoma components of the same urinary bladder tumor showed similar molecular profiles, using Loss of Heterozygosity (LOH) and X chromosome inactivation analysis, demonstrated that both components showed concordant X chromosome inactivation and genetic alterations.[2,3,8,9] Methylation analysis of tumor-suppressor genes demonstrated that the both components of the same neoplasms showed an overlapping methylation profile including frequent methylation of RASSF1 and MGMT genes and infrequent methylation of MLH1 and DAPK1.[9,10] These mixed tumors are considered to have a more aggressive behavior and a worse prognosis than pure urothelial carcinoma or cases without small cell elements.[2,3] Any amount of small-cell carcinoma should be reported, as this is relevant in guiding therapy.[4]

Sarcomatoid differentiation can present in urothelial carcinoma and the term 'sarcomatoid carcinoma' can be applied.[1,4] Sarcomatoid carcinoma may progress through multistep carcinogenesis with the accumulation of genetic alterations, genetic instability, and generation of multiple subclones, or may represent transdifferentiation from an epithelial to a mesenchymal phenotype, secondary to molecular programs, induced by the stromal microenvironment.[5] Another possibility of sarcomatoid transformation in carcinomas may be epithelial-to-mesenchymal transition (EMT).[12] Some genetic studies suggest that the epithelial and sarcomatoid elements share a common monoclonal cell origin.[14] The presence of one or more heterologous components has been suggested to impart a more adverse behaviors and relatively poor prognosis.[1,5,11,12,14]

Primary melanoma of the urinary bladder is an extremely rare, with few cases reported in medical literature. Most melanomas found in the bladder are metastases from a primary site elsewhere in the body. For a melanoma to be considered primary to the bladder, the absence of melanoma at other sites (e.g., skin, eyes, etc.) must be confirmed through thorough examination and staging. The prognostic factors include size and depth of invasion as well as metastatic lesions; however, prognosis is generally poor.[13] Molecular data on mucosal melanoma of the male genital tract and urinary system are limited.[1] The most common presenting symptom is gross hematuria and may involve pigmented masses seen during cystoscopy.

Adequate grossing of TURBT specimens requires extensive sampling and meticulous attention to heterogeneous areas. Proper tissue submission is essential to prevent underdiagnosis of variant histology. Specimens should be weighed in aggregate and entirely processed, particularly when weighing up to 10 g. At least one cassette per centimeter of tumor (up to 10 cassettes) should be submitted initially.[15]

Histopathologically, even though the tumor cells are admixed, their morphology can still be distinguished. The small cell neuroendocrine carcinoma demonstrates round to oval nuclei, high nuclear to cytoplasm ratio, stippled (salt-and-pepper) chromatin, inconspicuous nucleoli, nuclear molding, scant cytoplasm, high mitotic activity, necrosis, arranged in sheet-like, nested and trabecular architectures, positive staining for synaptophysin, chromogranin A, cytokeratins, and CD56.[1] The high-grade urothelial carcinoma is characterized by striking nuclear pleomorphism and hyperchromasia, irregular nuclear contours, high mitotic activity, pale to eosinophilic cytoplasm in moderate to abundant quantities, arranged in variably sized nests, sheets, trabeculae, cords and individual cells, positive staining for p63, GATA3, high-molecular-weight cytokeratins, and frequently coexpresses CK7 and CK20.[1,16] The differential diagnosis

of mixed small cell neuroendocrine carcinoma and high-grade urothelial carcinoma of the urinary bladder includes entities that can mimic either component or the mixed pattern histologically and immunophenotypically, such as pure small cell neuroendocrine carcinoma, high-grade urothelial carcinoma with neuroendocrine differentiation, large cell neuroendocrine carcinoma with urothelial carcinoma, poorly differentiated urothelial carcinoma, metastatic small cell carcinoma, lymphoma, and primitive neuroectodermal tumor/ewing sarcoma (rare). Recognition of true biphasic morphology and appropriate immunohistochemistry is critical.

The melanoma is usually formed by sheets or expansive nodules of large pleomorphic epithelioid or (less commonly) spindle-shaped cells, vesicular chromatin and prominent nucleoli, variable melanin production, positive staining for S100, SOX10, HMB45 and melan-A.[1,17] The differential diagnosis of primary melanoma of the urinary bladder includes metastatic melanoma (most common), high-grade urothelial carcinoma, small cell neuroendocrine carcinoma, lymphoma, clear cell sarcoma–like tumor of the bladder (rare), PEComa, and rhabdomyosarcoma. Immunohistochemistry is essential for diagnosis.[18]

Possible scenarios of coexistence, explanations are considered: (1) collision tumor; two independent neoplasms occurring in the same organ, such as bladder MiNEN coexisting with metastatic melanoma; this is the most plausible explanation in reported cases, or (2) synchronous primary tumors; separate primary MiNEN and primary bladder melanoma; theoretically possible, but extremely rare. The role of molecular genetic analysis in differentiating collision tumors from synchronous primary tumors has not yet been clearly established. A melanoma of the urinary bladder does not originate from urothelial carcinoma or neuroendocrine carcinoma. They are biologically and histogenetically distinct tumors and not lineage transformation. [18,19,20,21]

Clinical significance of a mixed small cell neuroendocrine carcinoma and high-grade urothelial carcinoma coexisting with a (primary or metastatic) melanoma of the urinary bladder lies in its generally poor prognosis, which is driven by the high-grade neuroendocrine component and the melanoma. Primary melanomas of the male genital tract and urinary system are associated with a relatively poor overall survival (median survival time: 28 months; 5-year survival: 28%).[1]

Conclusion

Mixed small cell neuroendocrine carcinoma and high-grade urothelial carcinoma with melanoma of the urinary bladder is extremely rare. Diagnosis depends on clinical and pathological evaluation. A complete workup to distinguish primary from metastatic melanoma is essential. In general, the prognosis is poor. Due to the limited number of cases reported to date, the clinical and pathological features, treatment strategies, and prognosis require further investigation.

Conflict of interest statement

The author declares no conflict of interest regarding the publication of this paper.

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