REVIEW

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The Clinical and Uropathological Aspects of Neuroendocrine Tumours of the Bladder: A Review

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What's known on the subject? and What does the study add?

Primary neuroendocrine tumors of the bladder are extremely rare tumors. Since metastatic tumors are seen more often, it is necessary to distinguish between primary and secondary tumors. Histopathological and immunohistochemical examination gains importance at this stage. With this review, it is aimed to improve the uropathological perspective and to guide the treatment to be given. At the same time, this review is emphasized that most neuroendocrine-like tumors do not have histological features compatible with neuroendocrine bladder tumors, but phenotypically resemble traditional urothelial carcinoma.

Abstract

Neuroendocrine tumours of the bladder are less common than other histologic types (e.g., urothelial carcinoma, squamous cell carcinoma, adenocarcinoma), constituting 1% of malignant bladder cancers. Based on the "2016 World Health Organization Classification of Tumours of the Urinary System and Male Genital Organs", neuroendocrine tumours are classified into four subtypes: small cell neuroendocrine carcinoma (SCNC), large cell neuroendocrine carcinoma (LCNC), well-differentiated neuroendocrine tumour (carcinoid tumour) and paraganglioma. SCNC is more common than other subtypes, and LCNC is exceedingly rare in the bladder. Although neuroendocrine tumours are not as common as neuroendocrine neoplasms of the lungs, the differential diagnosis of these tumours remains crucial and should be considered in uropathology. Neuroendocrine tumours of the bladder can present with distinctive morphology and grades, similar to their pulmonary counterparts. The knowledge of this diagnosis is critical to advance the uropathological field and accelerate drug development with inclusion, rather than exclusion, of patients with SCNC and other variants of neuroendocrine tumours of the bladder. Therefore, in this review, the bladder's clinical and uropathological aspects of neuroendocrine tumours are reviewed. This classification provides a useful platform to discuss the aetiology, pathogenesis, clinical and pathological characteristics and treatment of the neuroendocrine tumours of the urinary bladder. The overall prognosis of urinary bladder neuroendocrine tumours is worse than urothelial carcinoma. Various advances are expected in the clinical characterisation, prognostication and treatment of neuroendocrine tumours of the bladder with the technologies developed in genetic and cellular investigations.
Keywords: Bladder cancer, neuroendocrine tumours, small cell carcinoma, large cell neuroendocrine carcinoma

Introduction

Neuroendocrine tumours of the bladder are less common than the other histologic variants (e.g., urothelial carcinoma, squamous cell carcinoma, adenocarcinoma) in the genitourinary system, constituting 1% of malign bladder cancers (1). Based on "2016 World Health Organization (WHO) Classification of Tumours of the Urinary System and Male Genital Organs", neuroendocrine tumours are classified into four subtypes: small cell neuroendocrine carcinoma (SCNC), large cell neuroendocrine carcinoma (LCNC), well-differentiated neuroendocrine tumour (carcinoid tumour) and paraganglioma. LCNC is exceedingly rare in the bladder (2). Although the types of neuroendocrine tumours of the bladder are not as common as neuroendocrine neoplasms of the lungs, the differential diagnosis of these tumours is still crucial and should be considered in uropathology. The knowledge of this diagnosis is critical to advance the uropathological field and accelerate drug development with inclusion, rather than exclusion, of patients with SCNC and other variants of neuroendocrine tumours of the bladder. Therefore, in this review, the bladder's clinical and uropathological aspects of neuroendocrine tumours are reviewed.

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A. SCNC

SCNC, more commonly known as small cell carcinoma, is the most common malignant neuroendocrine neoplasia of the urothelium. It constitutes 0.5%-0.7% of all bladder carcinomas (3). Derived from the urothelium, SCNC has histologically similar features to those seen in the lung (4). However, it is a high-grade invasive disease. The overall 5-year survival rate is low, with reports ranging from 25% to as low as 8% (2,5-7). Patients are usually in the seventh or eighth decade of life. It is three times more common in men than in women (8).

1. Aetiology and Pathogenesis

SCNC has no known specific aetiology. Studies have shown that the neuroendocrine cells scattered in the normal bladder or metaplasia of the urothelium are derived from malignant transformation or multipotential urothelial stem cells (2,9,10).

Now, SCNC is believed to have a urothelial origin, determined by current molecular data. It has been demonstrated that it is frequently associated with other histological types of conventional urothelial carcinoma of the bladder. Since one of the same risk factors involved in urothelial carcinoma, mainly smoking, is also seen in SCNC, they are proposed to share the same origin (11,12).

Recently, routine standard-of-care DNA sequencing confirms and identifies SCNC as a distinct entity with a predictable mutation profile, similar to SCLC. RNA expression profiling differentiates pure SCNC from urothelial carcinoma (13). At the molecular level, bladder SCNC displays some chromosomal variations, such as inactivation of the tumour suppressor's p53 (encoded by the *TP53* gene) and retinoblastoma protein, pRb (encoded by the *RB1* gene), similar to that defined in lung SCNC (11,12). Besides this similarity, all SCNC of the bladder harbour promoter mutations of telomerase reverse transcriptase (TERT), which is frequently upregulated in many human cancers, but not identified in SCLC. Multiple studies have demonstrated that up to 70-80% of urothelial cancers carry the TERT promoter mutations regardless of grade, stage or location (14,15). Publications suggest that these promoters may be clinically measurable potential markers for the differential diagnosis of SCNC (11,14,16-18).

2. Clinical Characteristics

Macroscopic haematuria, dysuria and obstructive symptoms are the most common symptoms of SCNC. Metastases are frequently observed in the regional lymph nodes, and the bones, liver and lung (2,5,7). Brain metastases of SCNC are less common than those of the lung (6).

SCNC of the bladder generally arises in the lateral walls, the dome of the bladder (19-21).

3. Macroscopic and Microscopic Characteristics

SCNC usually appears as a single and sizeable polypoid mass. However, it can also be sessile, ulcerated and occasionally infiltrative. Most are invasive at least to the level of the muscularis propria. Histologically, SCNC tumours are arranged as sheets or islands of small to medium-sized cells with narrow cytoplasm, separated by the limited stroma. These cells have small, round to oval, overlapping nuclei with finely distributed chromatin, without prominent nucleoli (2) (Figure 1).

The Azzopardi effect, a histomorphologic phenomenon of incrustation of the blood vessel wall with basophilic nuclear material, indicates the tumour's high proliferative activity. Vascular invasion, mitosis and coagulative necrosis are common in SCNC (2,3).

For a tumour to be classified as SCNC histopathologically, small cell histology must be found in most of the tumour. Approximately 40-50% of cases have non-small cell carcinomas, such as carcinoma *in situ*, classical urothelial carcinoma, squamous cell carcinoma, adenocarcinoma and sarcomatoid carcinoma. The appearance of these morphologies does not exclude the diagnosis of SCNC (2,5,9,22).

Tumour cells immunohistochemically show both epithelial and neuroendocrine differentiation. Tumour cells are stained with synaptophysin, chromogranin and cytokeratin. Extensive staining is seen with Ki-67. Thyroid transcription factor-1 (TTF-1) staining occurs in half of the cases (23,24).

Metastases from other organs should be excluded to accept SCNC as a primary urinary bladder tumour. Differential diagnosis

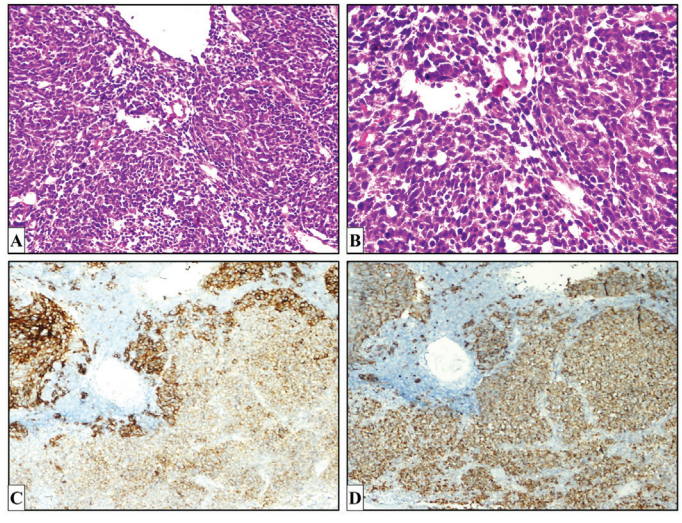

Figure 1. Small cells with ill-defined borders, scant cytoplasm, finely granular nuclear chromatin and absent nucleoli, H&E, (A) x100; malignant epithelial tumour- consisting with prominent nuclear moulding- are round and oval-shaped, H&E, (B) x200; micrographs of CD56 immunostainings, original magnification: (C) x100; micrographs of synaptophysin immunostainings, original magnification: (D) x100

should include lymphoma, lymphoepithelioma-like carcinoma, plasmacytoid carcinoma and poorly differentiated urothelial carcinoma. In these cases, immunostaining with TTF-1, GATA-3 and p63 would support the diagnosis of SCNC.

4. Treatment

Since SCNC is rare, the surgical or medical standard treatment strategies are not well established. Systemic chemotherapy, surgery and radiotherapy are the available treatment modalities. Some clinics perform radical cystectomy in non-metastatic cases. The chemotherapy applied is the same as that used in lung SCNC. In many clinics, adjuvant chemotherapy and radiotherapy or neoadjuvant chemotherapy and partial/radical cystectomy combinations are recommended. Due to its poor prognosis regardless of the treatment applied and low overall survival, research should be continued for new therapeutic agents specific for bladder SCNC (8).

B. LCNC

As a high-grade neuroendocrine tumour, the incidence of LCNC of the bladder is rare, with only a few case reports in the literature. Most cases have reported an aggressive clinical course, often with metastasis (25,26). The prognosis resembles that of SCNC.

1. Aetiology and Pathogenesis

The etiological factors for LCNC includes the personal or family history of cancer, possibly because of genetic predisposition, iatrogenic causes (chemotherapy- or radiotherapy-related factors e.g., postprostate-cancer external beam radiation therapy), or common environmental exposure (e.g., smoking) (27,28). As in SCNC pathogenesis, the most common hypothesis for LCNC include the origin of the multipotent urothelial stem cells that can differentiate into various cell types (29,30).

2. Clinical Characteristics

The clinical presentation of LCNC resembles conventional urothelial bladder carcinoma, with gross haematuria, which is a frequently observed symptom, and less frequently, dysuria and mucosuria, or no symptoms at presentation (29,31). Distant metastases have been reported mostly to the liver and lung (32-34). Both brain and skin metastases of the bladder LCNC have also been reported (29,33,35).

3. Macroscopic and Microscopic Characteristics

Macroscopically, LCNC presents in 4 cm diameter lesions, including nodular/polypoid, single, solid tumours, mostly located in the lateral bladder wall (2,8,29,36,37).

The tumour is a high-grade and poorly differentiated neoplasm exhibiting neuroendocrine features on H&E staining, high mitotic activity and necrosis, and immunohistochemical evidence of neuroendocrine differentiation.

Neoplastic cells are organised in sheet-like, trabecular palisading, or organoid nested growth patterns. Single cells are large, polygonal, with abundant cytoplasm and low nuclear to cytoplasmic ratio. Their nuclei are often large, polymorphic, oval, featuring coarse, granular or vesicular chromatin, often with prominent nucleoli (Figure 2). Occasional giant cells may be observed (38). Compared with SCNC, rosettes are often observed (2,26,29,39-41).

Some reported cases were associated with a component of conventional urothelial carcinoma. LCNCs may exist as either pure tumours or mixed forms with varying amounts of conventional urothelial and/or variant histology carcinomatous components (29).

4. Treatment

Although surgery alone is not recommended in LCNC cases, it plays an essential role in the accurate management of these cases. For radiotherapy, a bladder-sparing protocol seems to be less effective than radical surgery, but data remain contradictory (42). Since LCNC has potentially aggressive behaviour, early diagnosis and treatment with radical cystectomy and neoadjuvant or adjuvant chemotherapy may offer long-term control of a localised tumour. They may extend the overall survival of patients (34).

C. Well-differentiated Neuroendocrine Tumour (Carcinoid Tumour)

Well-differentiated neuroendocrine tumour, formerly named as carcinoid tumour, is a neuroendocrine neoplasm resulting from

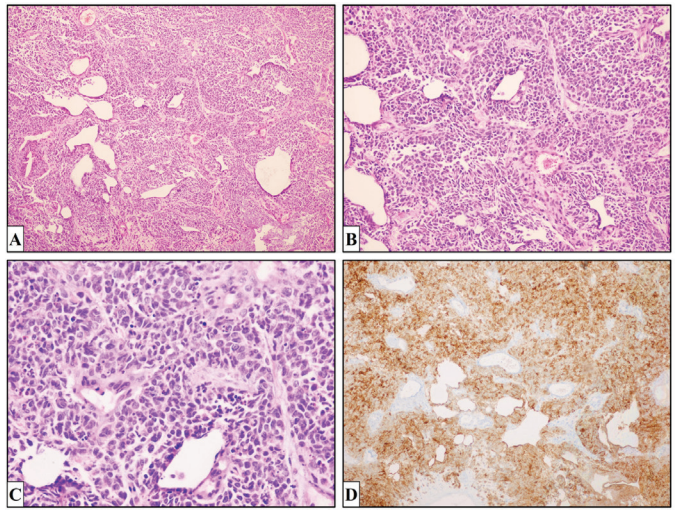

Figure 2. Histopathological section showing tumour tissue located inside the bladder, with neoplastic cells which are arranged in sheet-like, palisading, trabecular growth patterns, H&E, (A) x40; malignant cells with abundant cytoplasm are polygonal, large, and low nuclear to cytoplasmic ratio, H&E, (B) x100; nuclei with prominent nucleoli are polymorphic, oval, featuring coarse, vesicular chromatin, H&E, (C) x200; micrographs of chromogranin immunostainings, original magnification: (D) x100

isolated neuroendocrine cells located in the basal layer of the urothelium. These cells may become more abundant in reactive conditions. Well-differentiated neuroendocrine tumours have been rarely described in the true primary bladder (2,43). The patients were in the same age range associated with usual urothelial carcinoma.

The distinctive small well-differentiated neuroendocrine tumour is associated with a good prognosis. However, well-differentiated neuroendocrine tumours of the bladder may rarely present as muscle-invasive tumours, which must be distinguished from metastasis from other sites, such as the gastrointestinal tract (44).

1. Aetiology and Pathogenesis

Derived from the urothelium, well-differentiated neuroendocrine tumours are potentially malignant neuroendocrine tumours (45). These tumours' pathogenesis is believed to resemble SCNC of the bladder closely.

2. Clinical Characteristics

Haematuria is the most classical clinical presentation of well-differentiated neuroendocrine tumours, followed by irritative voiding symptoms. These tumours are generally observed in the bladder neck and trigone. Their relationship with Carcinoid syndrome has not been reported (2).

3. Macroscopic and Microscopic Characteristics

Well-differentiated neuroendocrine tumours characteristically present as small (mean diameter of 5 mm) polypoid masses restricted to the lamina propria. Histopathologically, these tumours exhibit the same typical features described at other sites, including uniform cells with round nuclei containing stippled chromatin, often with intracytoplasmic eosinophilic granules resembling Paneth cells. Hence, these lesions occasionally resemble adenocarcinoma. A distinctive feature of small well-differentiated neuroendocrine tumours is that the cells are arranged in a pseudoglandular pattern associated with cystitis cystica and cystitis glandularis, resulting in their misdiagnosis as a non-neoplastic condition. In rare cases, anastomosing trabeculae, nests and cords of cells without the prominent pseudoglandular morphology have been demonstrated in smaller superficial lesions. These well-differentiated neuroendocrine tumours are aggressive, express neuroendocrine markers immunohistochemically, and express prostate-specific acid phosphatase, but do not express other prostate markers (2,45).

4. Treatment

At present, there are no standard treatment guidelines for the management of well-differentiated neuroendocrine tumours. Metaiodobenzylguanidine therapy may offer some benefit in the adjuvant settings in specific cases, especially those considered not suitable for chemotherapy (2,45).

D. Paraganglioma

The primary paraganglioma is very rare among neuroendocrine tumours of the bladder, accounting for 0.05% of all bladder tumours. In contrast to SCNC and LCNC, paraganglioma is more common among females and whites (2,46).

1. Aetiology and Pathogenesis

Paraganglioma of the bladder derives from the paraganglion cells in the bladder wall. Although the exact aetiology is unknown, paraganglioma develops from the chromaffin tissue of the sympathetic nervous system (47).

2. Clinical Characteristics

Paraganglioma can locate in any part of the bladder and at any level of the bladder wall, preferring the detrusor muscle more. The most common sites of paraganglioma are the dome and trigone of the bladder (2). Paraganglioma patients may present with hypertension and hypertensive crisis during micturition and with headache, palpitation, blurred vision, and intermittent gross haematuria, based on the functional (i.e., secrete catecholamine) or non-functional features (48).

3. Macroscopic and Microscopic Characteristics

Cystoscopically, paragangliomas are well-circumscribed, dome-shaped/exophytic nodules smaller than 3.9-cm in size, covered with an intact mucosa but ulcerations can also exist. Unlike the extraadrenal ones found in other localisations, they exhibit malignant behaviour in a ratio of 20%. There is no definitive histopathological finding showing the distinction between malignant and benign disease. The presence of nuclear pleomorphism, mitosis and necrosis are unreliable findings in determining its clinical behaviour. The definitive malignancy criterion for these tumours is the presence of regional or distant metastases (2,49).

Histopathologically, paraganglioma consists of eosinophilic or granular cytoplasm and polygonal epithelioid or round cells. Nuclei are localised centrally, including vesicular and finely granular chromatin. Cells are present in an organoid/nest pattern called a Zellballen. These nests comprise the surrounding blood sinus and fibrous stroma (Figure 3). Immunohistochemically, cells are stained positive with chromogranin, synaptophysin and neuron-specific enolase. Sustentacular cells are stained with S100 (46,47).

4. Treatment

Complete resection is the most pivotal treatment of paraganglioma. However, there are other available strategies

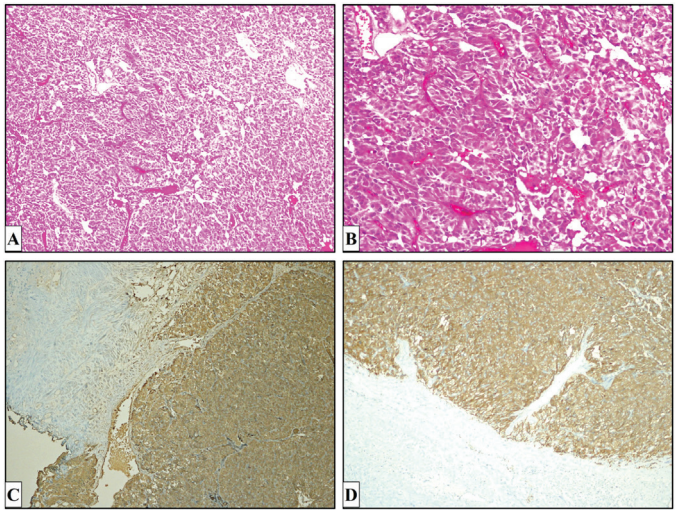

Figure 3. The trabecular pattern of neoplastic cells within a prominent vascular network, H&E, (A) x100; round cells with abundant eosinophilic finely granular cytoplasm, H&E, (B) x200; micrographs of chromogranin immunostainings, original magnification: (C) x100; micrographs of CD56 immunostainings, original magnification: (D) x100

depending on the disease stage, such as endourethral surgeries, including electrocision and laser resection, partial or radical cystectomy. Recently, minimally invasive surgery is increasingly replacing open surgery, which was generally performed in the past (47).

Conclusion

Neuroendocrine bladder tumours are rare variants, such as small cell or LCNC, well-differentiated neuroendocrine tumours, and paraganglioma varieties, based on 2016 WHO Classification of Tumours of the Urinary System and Male Genital Organ classification system. This classification provides a useful platform to discuss the aetiology, pathogenesis, clinical and pathological characteristics of neuroendocrine tumours of the urinary bladder. The overall prognosis for urinary bladder neuroendocrine carcinomas is worse than the prognosis of urothelial carcinoma. In some cases, a small cell neuroendocrine-like subtype has been defined, having high expression of the neuronal marker and poor outcomes (50). Particularly, most neuroendocrine-like tumours did not have histological features consistent with neuroendocrine bladder tumours but were phenotypically similar to conventional urothelial carcinoma. Early and accurate differential diagnosis of neuroendocrine-like tumours may be possible by genomic analysis, which improves patient outcomes for the management of treatment, regardless of histological presentation (51).

Developing technologies in the genetic and cellular investigations, various advances are expected in the clinical characterisation, prognosis, and treatment of neuroendocrine tumours of the bladder. Based on the information reviewed on urology practice, diagnosis, treatment or follow-up, there is currently no recommended scientific guideline to use routinely. In summary, TUR-biopsy is the gold standard method in the differential diagnosis of neuroendocrine bladder tumours and immunohistochemical investigations.

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