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Small Cell Carcinoma of the Urinary Bladder: a Rare and Aggressive Tumor

Carcinoma de Pequenas Células da Bexiga: um Tumor Raro e Agressivo

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Abstract

The authors describe a case of small cell neuroendocrine carcinoma (SmCC) of the urinary bladder in a 60-year-old woman who arrived at the Emergency Room with macroscopic hematuria and pelvic discomfort. Computed tomography revealed a broad-based polypoid tumor on the posterior wall of the bladder, infiltrating both ureters with bilateral hydronephrosis. After an attempt of transurethral resection, the pathology revealed a malignant, non-urothelial tumor, and the patient was referred to our center. Magnetic resonance imaging performed for better characterization and local staging, confirmed an aggressive tumor with perivesical fat invasion. SmCC is a rare type of bladder tumor with clinical and macroscopic presentation similar to urothelial carcinoma. Radiologically it is usually an aggressive tumor, with advanced disease at the initial diagnosis. The clinical and radiological features of bladder SmCC are revised, including a discussion on the usefulness of immunohistochemical markers.

Keywords

Carcinoma neuroendocrine; Carcinoma small cell; Urinary bladder; Magnetic resonance imaging.

Resumo

Os autores apresentam um caso de carcinoma neuroendócrino de pequenas células da bexiga (SmCC) numa mulher de 60 anos de idade que se apresentou no serviço de Urgência com hematúria macroscópica e desconforto pélvico. A tomografia computadorizada revelou um tumor polipóide de base larga na parede posterior da bexiga infiltrando ambos os ureteres e condicionando hidronefrose bilateral. Após tentativa de ressecção transuretral a anatomia patológica mostrou um tumor maligno, não urotelial, e a doente foi encaminhada para o nosso centro. A ressonância magnética realizada para melhor caracterização e estadiamento local, mostrou um tumor agressivo com invasão da gordura perivesical. O SmCC é um tipo raro de tumor da bexiga com apresentação clínica e macroscópica semelhantes ao carcinoma urotelial. Radiologicamente é geralmente um tumor agressivo, com doença avançada no diagnóstico inicial. As características clínicas e radiológicas do SmCC da bexiga são revistas, incluindo uma discussão sobre a utilidade dos marcadores imunohistoquímicos.

Palavras-chave

Carcinoma neuroendócrino; Carcinoma pequenas células; Bexiga; Ressonância magnética.

Case Presentation

A 60-year-old woman with gross hematuria and pelvic discomfort was admitted in the emergency department of a tertiary hospital. She was a sporadic smoker with no other relevant personal and familial histories. On physical examination, a painless mass was detected in hypogastric region. Routine laboratory data confirmed low hemoglobin level (8.6 g/dL). Pelvic ultrasonography (US) and abdominopelvic computed tomography (CT) revealed a polypoid tumor with irregular margins in the posterior urinary bladder wall measuring about 10cm and infiltrating both ureters with bilateral hydronephrosis. Cystoscopy was performed, and transurethral resection of the tumor was attempted without success. The artifacts of the sampled tumor tissue were initially misleading, and the first pathology analysis suggested the diagnosis of myxoid/round-cell liposarcoma.

Positron emission tomography–computed tomography (PET-CT) was therefore performed and no metastatic disease was identified. The patient was referred to our institute and pelvic magnetic resonance (MR) imaging was performed for further characterization and tumor staging. MRI revealed a large broad-based polypoid tumor with lobulated margins in the posterior bladder wall. The tumor invaded the bladder wall with extension to the perivesical fat without invasion of the vagina or uterus (Figure 1). On diffusion-weighted imaging (DWI), the tumor showed diffused restriction, with high signal intensity on b 1000 and low signal on ADC map (Figures 2 a-b). On dynamic contrast-enhanced T1-weighted MR imaging the tumor demonstrated early and intense enhancement (Figure 2c). No lymph node metastases or other pelvic metastases were identified.

Pelvic exenteration was performed. The urinary bladder measured 100 x 70 x 50mm and contained a white firm tumor involving the trigonus and the base. The tumor measured about 6cm in greatest dimension and was about 70% necrotic. The tumor invaded the perivesical fat but not the uterus or the adnexa. Microscopy revealed a small

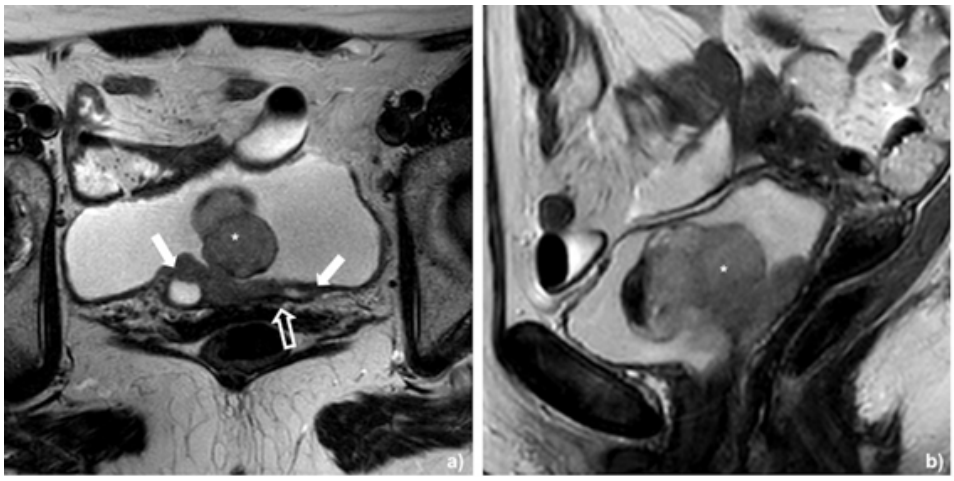

Fig. 1 – Pelvic MR imaging in a 60-year-old woman with Small Cell Carcinoma of the urinary bladder. Axial (**a**) and sagittal (**b**) high-resolution T2-weighted images showed a polypoid broad-based solitary tumor (*asterixis*) on the posterior wall of the bladder with bilateral ureter invasion (*arrows)* and mural invasion with perivesical fat infiltration (*open arrow*). No lymph node metastases nor other lesions were identified.

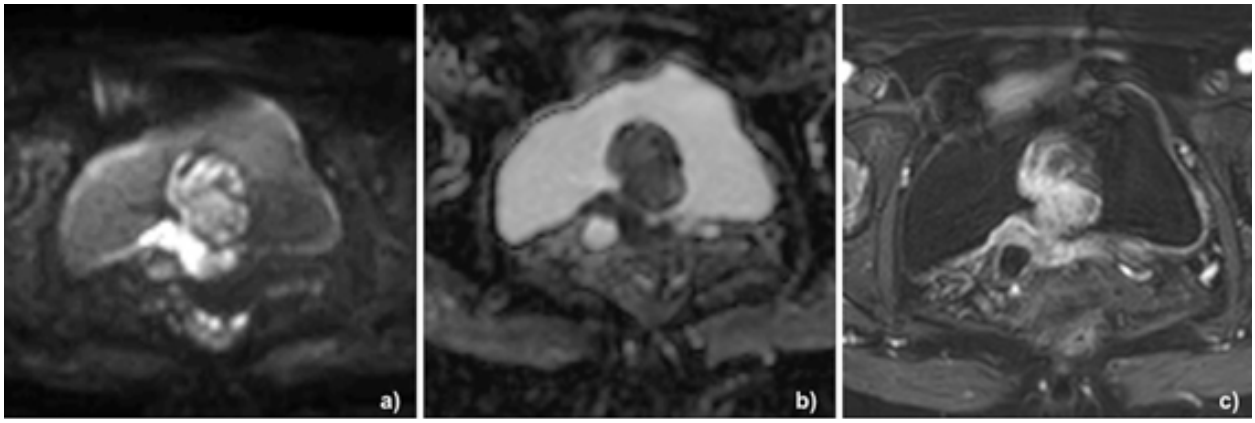

Fig. 2 – Pelvic MR imaging in a 60-year-old woman with Small Cell Carcinoma of the urinary bladder. Diffusion-weighted imaging confirmed a high cellular tumor with high signal intensity on b 1000sec/mm^2 (**a**) and corresponding low signal on ADC map (**b**). On dynamic contrast enhanced MR imaging (**c**), the tumor demonstrated rapid and intense enhancement.

cell neuroendocrine carcinoma with a minor component of invasive urothelial carcinoma (< 5%) (Figure 3a). The tumor cells expressed chromogranin A (Figure 3b), synaptophysin, thyroid transcription factor 1 (TTF-1), uroplakin, and focally S100. CD99 was negative.

Eight weeks after surgery, another PET-CT was performed and revealed multifocal liver metastases and supraclavicular, retroperitoneal and bilateral iliac lymph node metastases. Chemotherapy with carboplatin and etoposide was started.

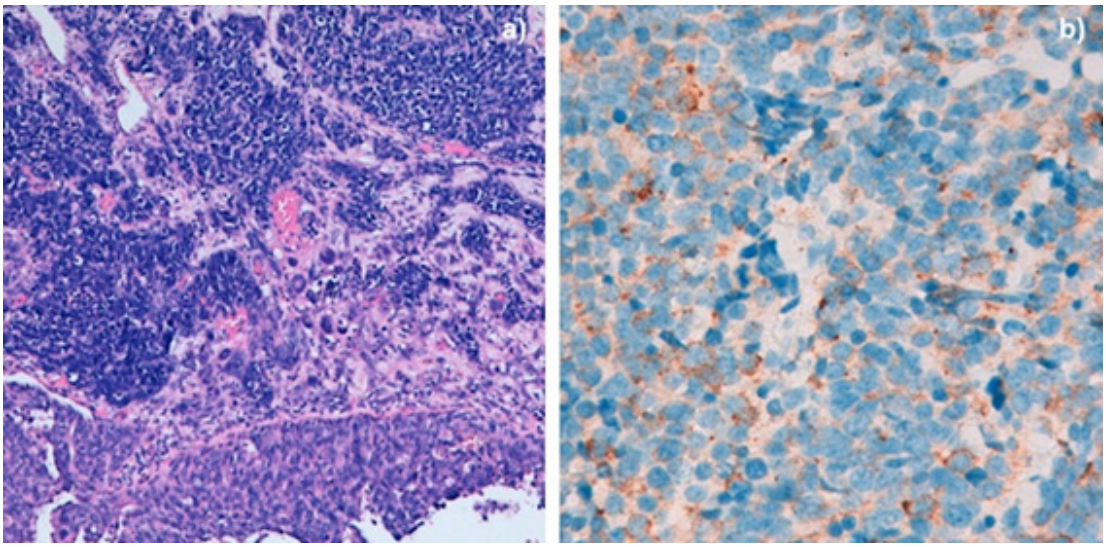

Fig. 3 – Photomicrograph (original magnification, ×100; hematoxylin-eosin stain) (**a**) showed sheets of hyperchromatic cells with scant cytoplasm, nuclear molding and inconspicuous nucleoli. Immunohistochemical stain showed positivity for chromogranin A (**b**).

Discussion

Neuroendocrine tumors (NETs) represent a diverse group of rare neoplasms arising from cells of the neuroendocrine system.[1] Although NETs most commonly originate in the gastrointestinal tract, they may originate anywhere in the body due to the wide distribution of the neuroendocrine system.[2] NETs of the urinary bladder comprise <1 % of all urinary bladder malignancies. According to the 2016 World Health Organization Classification of Urinary System and Male Genital Organ Classification system, NETs of the urinary bladder can be separated in four subtypes with crescent aggressiveness: well-differentiated neuroendocrine neoplasms (carcinoids), paragangliomas, large cell carcinoma, and small cell carcinoma (SmCC).[3]

SmCC of the urinary bladder is extremely rare with an estimated rate of 0.14 cases per 100000 people. SmCC predominantly affects patients in the 6th to 7th decades of life with a relative male preponderance from 2:1 to 5:1.[4,5] Hematuria with void symptoms is the most common clinical presentation. Rarely paraneoplastic syndromes can be present.[3] SmCC is highly aggressive with advanced disease common at the time of presentation. About 60% of patients present with metastatic disease at time of diagnosis and muscle invasive disease has been reported in about 95% of cases at surgery. Prognosis is therefore poor, with 5-year survival rates ranging from 8 to 40%.[6,7]

On imaging, CT urography has a sensitivity and specificity of over 90% for the diagnosis of bladder cancer in patients with hematuria. However, CT urography cannot be used as a replacement for diagnostic cystoscopy in most patients with suspected bladder cancer, particularly because of its low confidence in cases with flat lesions and lesions at the bladder base adjacent to a hypertrophic prostate gland. Due to its high soft-tissue contrast resolution, MR imaging has shown a more accurate staging of bladder carcinoma than CT, with the advantage of involving no ionizing resolution. MR imaging allows better differentiation of bladder wall layers and therefore it depicts better the intramural invasion as well as extravesical extension. The multiplanar capability of MR imaging allows image acquisition in different planes to minimize partial volume averaging and optimize imaging when evaluating the depth of bladder wall invasion. Moreover, the advances of functional sequences, particularly diffusion-weighted imaging (DWI) and dynamic contrast enhanced (DCE) MR imaging, have made multiparametric MR imaging feasible for the local staging of bladder cancer.[8]

Although SmCC remains difficult to distinguish on imaging from more common urothelial neoplasms such as urothelial carcinoma (UC), there are some features that reveal this diagnosis. SmCC tends to present itself as an aggressive solitary large bladder mass with a variable amount of necrosis, calcification, and enhancement. Unlike classic UC of the bladder that usually shows as a superficial neoplasm with focal asymmetric bladder wall thickening, SmCC tends to present itself as a polypoid intramural mass with a broad base and extension to the perivesical fat, with or without invasion of surrounding organs (such as seminal vesicles, ureters or vagina). Systemic disease with lymph node or liver metastases is common at the time of diagnosis or early in the course of disease.[9,10] Synchronous bladder or upper urinary tract lesions are uncommon and may help to differentiate SmCC from classic UC. Moreover, the presence of a large intraluminal bladder mass is seen in less than 20% of urothelial carcinomas and should raise suspicion for another form of bladder cancer, such as neuroendocrine carcinoma, squamous cell carcinoma adenocarcinoma or rhabdomyosarcoma.[5,11]

On pathology grounds, the diagnosis of bladder SmCC is based on morphology combined with immunohistochemistry to document neuroendocrine differentiation. On microscopic examination, SmCC consists of diffuse sheets or nests of small or intermediate fusiform cells with nuclear molding, scant cytoplasm, inconspicuous nucleoli, and evenly dispersed "salt-and-pepper chromatin". Frequent mitoses, crush artifact and geographic necrosis are indicative of its high proliferation rate. Vascular invasion is commonly present. Urinary bladder SmCC is frequently admixed with another histologic subtypes, most commonly conventional UC, including carcinoma *in situ*, followed by squamous cell carcinoma and adenocarcinoma and, rarely, even sarcomatoid carcinoma.[12]

Immunohistochemistry usually shows tumor positivity for neuroendocrine markers chromogranin A, synaptophysin, neuron-specific enolase, and CD56, and, less frequently, for TTF-1. Cytokeratins CAM 5.2 and CK7 are usually positive, whereas CK20 is negative (by contrast, this is positive in Merkel cell carcinoma and in about 40-70% of UC). Cell-cycle protein p16 is positive in up to 95% of SmCC and squamous-cell markers p63 and p40 are almost always negative. Therefore, the typical immunohistochemical profile of bladder SmCC is p16+, p63-, and CK20-, while high-grade UC's is usually p16-, p63+, and CK20+. Distinction between SmCC and lymphoma is made by a negative CD45 and positive neuroendocrine profile. Distinction with prostate origin of SmCC may be challenging but can be achieved by a negative prostate specific antigen (PSA) and a low staining rate of p501S.[3,12]

Because of the rarity of the disease and paucity of clinical studies there is no standard therapy for primary SmCC of the urinary bladder and multimodality treatment is often employed.[13,14] Survival mainly depends on the stage at presentation. Clinicopathological parameters such as age, gender, and the presence of nonsmall cell carcinoma components do not appear to impact on outcomes.[3] Options for treatment of limited disease include transurethral resection, radical cystectomy, and radiation. Simple transurethral resection may result in high recurrence rates and poor survival periods of 3-6 months, but some studies also reported no difference in the survival rates between patients who underwent radical cystectomy and those who did not.[13] Multimodal therapies using a combination of neoadjuvant (platinum-based) chemotherapy and radical cystectomy or radiation therapy may improve long-term survival. Other approaches combine partial cystectomy or radical cystectomy with adjuvant chemotherapy. In patients presenting extensive disease, chemotherapy (with cisplatin, gemcitabine, and paclitaxel) as first-line agents, combined or not with cystectomy, is the mainstay of treatment and extends the overall survival from 8 to 15 months. Despite chemotherapy and local treatment, distant metastases occur early within the first 6 months after presentation.[14]

Conclusions

SmCC of the urinary bladder is a rare and aggressive neoplasm with clinical presentation often indistinguishable from urothelial carcinoma. On imaging, the presence of a solitary, polypoid, broad base mass with aggressive features (perivesical fat and adjacent organs invasion, lymph nodes and distant metastases), should raise the suspicion for SmCC, and correct staging should be provided. Final diagnosis usually depends on the pathological and immunohistochemical analysis. Multimodality treatment is recommended but prognosis remains poor.

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Protection of human and animal subjects: The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).
Protecção de pessoas e animais: Os autores declaram que os procedimentos seguidos estavam de acordo com os regulamentos estabelecidos pelos responsáveis da Comissão de Investigação Clínica e Ética e de acordo com a Declaração de Helsínquia da Associação Médica Mundial.

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