Unusual presentation of high-grade neuroendocrine carcinoma of the Urinary bladder with small-cell and large-cell features

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ABSTRACT

High-grade neuroendocrine carcinoma of the urinary bladder comprehends small-cell and large-cell variants. It is a rare and aggressive neoplasm, mostly diagnosed in advanced stages. It is more frequently encountered among Caucasian men in the sixth decade of life. Urinary symptoms are the most common clinical presentation. Diagnosis is generally not troublesome once the lesions are easily detectable by imaging exams and cystoscopy. This neoplasia is associated with tobacco smoking, and is frequently associated with other carcinomatous components such as urothelial carcinoma, adenocarcinoma, and sarcomatoid carcinoma. The authors report a case of an apparently healthy female patient who presented cervical lymph node enlargement not accompanied by systemic symptoms. The supraclavicular lymph node biopsy revealed metastatic small cell carcinoma. The computed tomography scan showed a bladder wall nodular thickening, enlarged lymph nodes along the iliac, periaortic, mediastinal, cervical and supraclavicular chains, as well as an insufflating lytic bone lesion in the right iliac wing. The positron emission tomography-fluorodeoxyglucose (PET-FDG) added to these findings, the presence of a paraesophageal lymph node, lymphadenomegaly in the gluteal region and a vertebral lytic lesion in T10. Resected specimen of the bladder tumor revealed a high-grade neuroendocrine carcinoma with small-cell and large-cell features.

Keywords: Carcinoma, Small Cell; Carcinoma, Neuroendocrine; Urinary Bladder Neoplasm; Lymphatic Diseases.

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CASE REPORTS

A 63-year-old female patient sought medical attention because of a left cervical bulging for the last 2 weeks and right flank pain radiating to the dorsum. She denied fever, weight loss, or any gastrointestinal or genitourinary complaints. The past medical history included hypertension and previous tabagism. The physical examination of the patient's cervical region showed the presence of enlarged lymph nodes along the left anterior and posterior cervical chains and a firm mass bulging on the left supraclavicular fossa corresponding to a cluster of enlarged lymph nodes. The cervical computed tomography (CT) scans showed lymphadenomegaly on the cervical (levels III and IV), supraclavicular and upper mediastinal regions, measuring up to 3.0 × 2.3 cm, determining contralateral deviation of the trachea (Figure 1).

The patient was submitted to a cervical lymph node biopsy, which revealed the presence of metastatic small-cell neuroendocrine carcinoma (Figure 2).

CT scans showed mediastinal (Figure 3), and periaortic (Figure 4), pericaval, common iliac, and right internal and external iliac chains (Figure 5) lymph node enlargements.

Some lymph nodes showed a heterogeneous aspect, which was probably related to necrotic liquefaction. On the right iliac wing, an insufflating, lytic lesion disrupting the cortical bone was present (Figure 6). No other bone lesions were found.

The CT scan showed a 2.0 cm-nodular bladder wall thickening on the right posterolateral wall (Figure 7). The ultrasonographic examination revealed a vegetating lesion at the same area, without evidence of muscular extension.
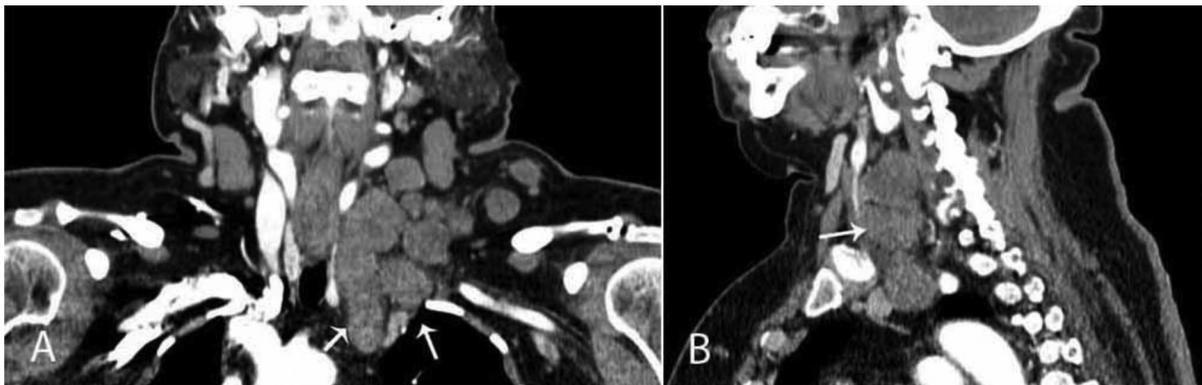

Figure 1 – Computed tomography (CT) of the cervical region. **A -** Coronal reformation; **B -** Sagittal reformation, showing lymphadenomegaly (arrows) on the left side of the neck and superior mediastinum.
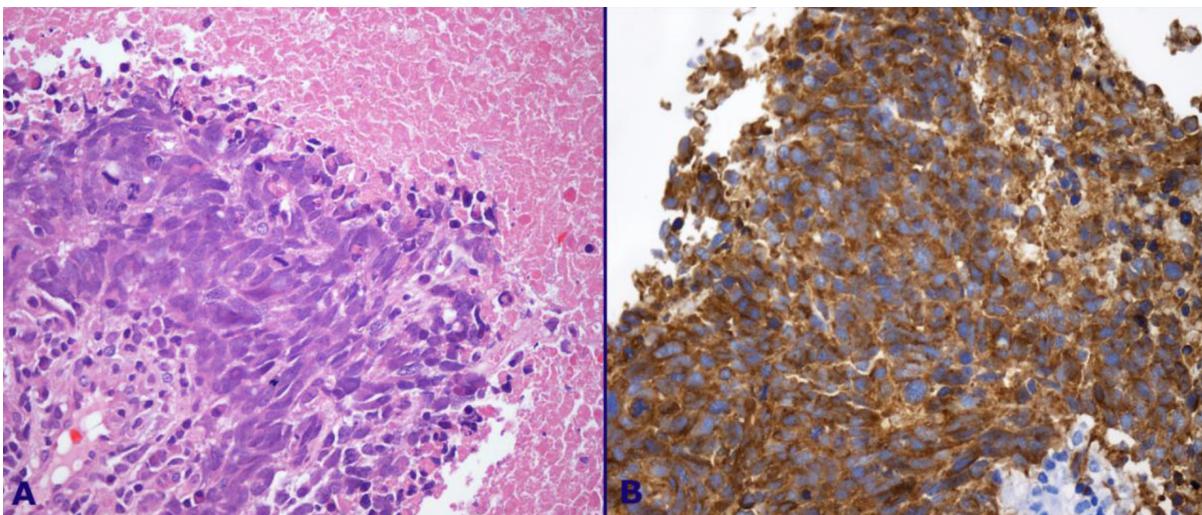

Figure 2 – Photomicrography of the lymph node biopsy with metastatic tumor. **A -** Small cells with nuclear molding, scant cytoplasm, and mitotic figures in a necrotic background (H&E, 400X); **B -** Positive immunohistochemistry staining for synaptophysin (400X).

Figure 3 – Axial computed tomography of the thorax showing mediastinal lymph nodes enlargement (arrows). **A -** Involving the pre vascular space; **B -** The carinal topography.
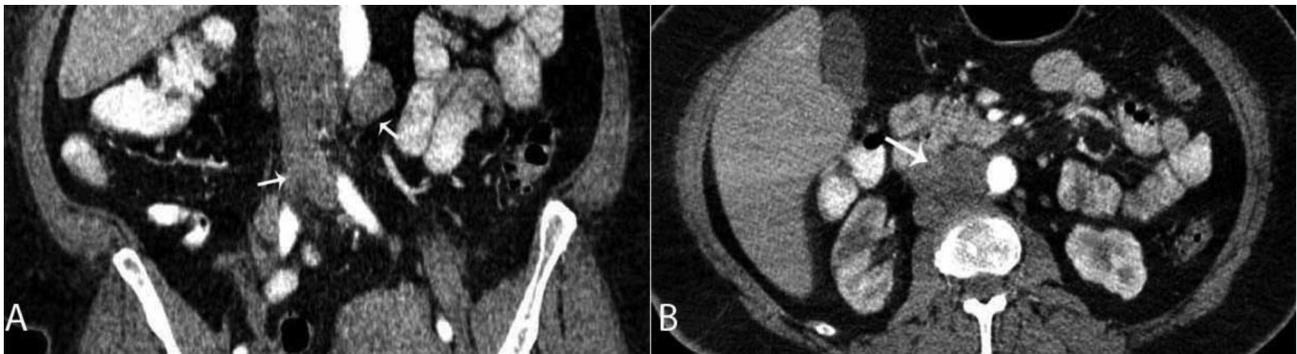

Figure 4 – CT of the abdomen. **A -** Coronal reformation; **B -** Axial plane – both showing periaortic lymphadenomegaly (arrows).
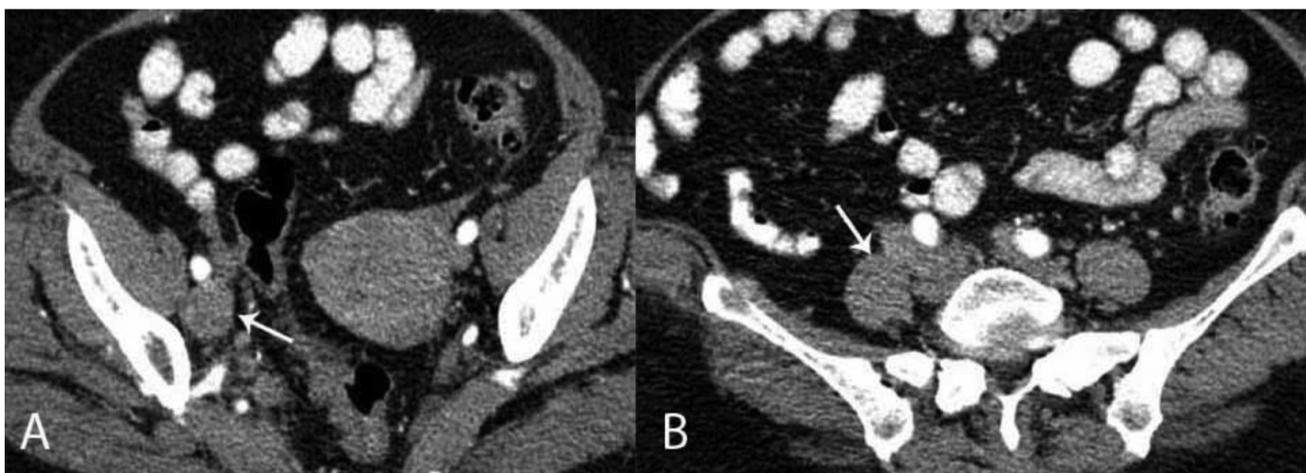

Figure 5 – Axial CT of the pelvis. **A -** Lymphadenomegaly along the external iliac chain; **B -** along the common iliac chain.

The patient underwent transurethral resection of the bladder lesion. The histopathological and immunohistochemical examination confirmed the diagnosis of a high-grade neuroendocrine carcinoma. The resected tumor was mostly composed of infiltrative, solid sheets of small and intermediate cells, often overlapping with scanty cytoplasm, similar to the metastatic sample on cervical lymph node (Figure 8A). Chromatin was granular with small or absent nucleoli and numerous mitotic figures were seen. In other areas (about 20%), tumor cells had larger and more pleomorphic nuclei,

Figure 6 – CT of the pelvis, bone window. **A -** Axial plane; **B** – Coronal reformation, both showing a lytic bone lesion (arrows) with a slight soft tissue involvement in the right iliac wing.
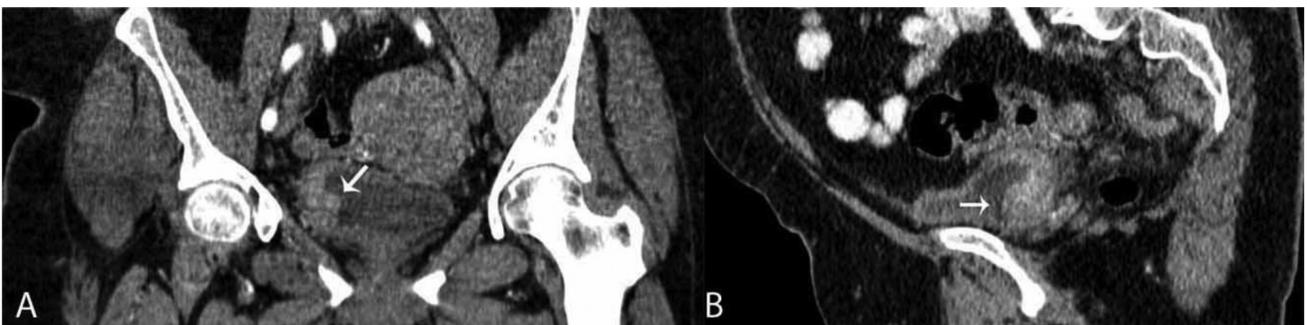

Figure 7 – CT of the pelvis. **A -** Coronal reformation; **B -** Sagittal reformation, both showing nodular thickening of the right posterolateral wall of the urinary bladder (arrows).

with prominent nucleoli and some multinucleated cells. These findings were interpreted as a large-cell neuroendocrine carcinoma component (Figure 8B, 8C, 8D).

Areas of adenocarcinoma with goblet cells and micropapillary urothelial carcinoma were present in about 10% of the specimen (Figure 9). Invasion of the urinary bladder muscular wall and lymphatics was evident on histology. The immunohistochemical staining of both pathological specimens are summarized in Table 1. The focal positivity for the p63 antibody in the metastasis was suggestive of a squamous or urothelial epithelium as the primary lesion. During the hospitalization, the patient did not present any urinary symptom or any compressive symptom associated with lymphadenopathy.

Complementary staging was held by a positron emission tomography-fluorodeoxyglucose (PET-FDG) examination from the base of the skull to the thighs, which revealed increased glycolytic metabolism in area of focal thickening of the urinary bladder wall, compatible with primary neoplastic lesion. There was an increase of glycolytic metabolism in multiple cervical lymph nodes, mediastinal, abdominal and pelvic lymph nodes, consistent with secondary involvement. PET-FDG also showed lytic bone lesions with increased glycolytic metabolism in the spine and the right iliac, compatible with secondary metastatic involvement. This exam seemed to be superior to CT alone by the demonstration of the paraesophageal lymph node, which was not enlarged (Figure 10A and B), the lymphadenomegaly between the right muscles gluteus maximus and gluteus medius (Figure 10C and D), as well as the presence of the vertebral lytic lesion in T10. The remaining lesions depicted on PET-FDG were also detected by the CT. Data obtained by PET-FDG were consistent with the poor differentiation and the high mitotic index (Ki-67 between 60%-70%). The primary neoplasm became evident after the administration of furosemide, when FDG diluted with urine, highlighted the bladder lesion (Figure 10 E and F).

With this diagnosis and staging, the patient was discharged for further treatment at an oncologic center.
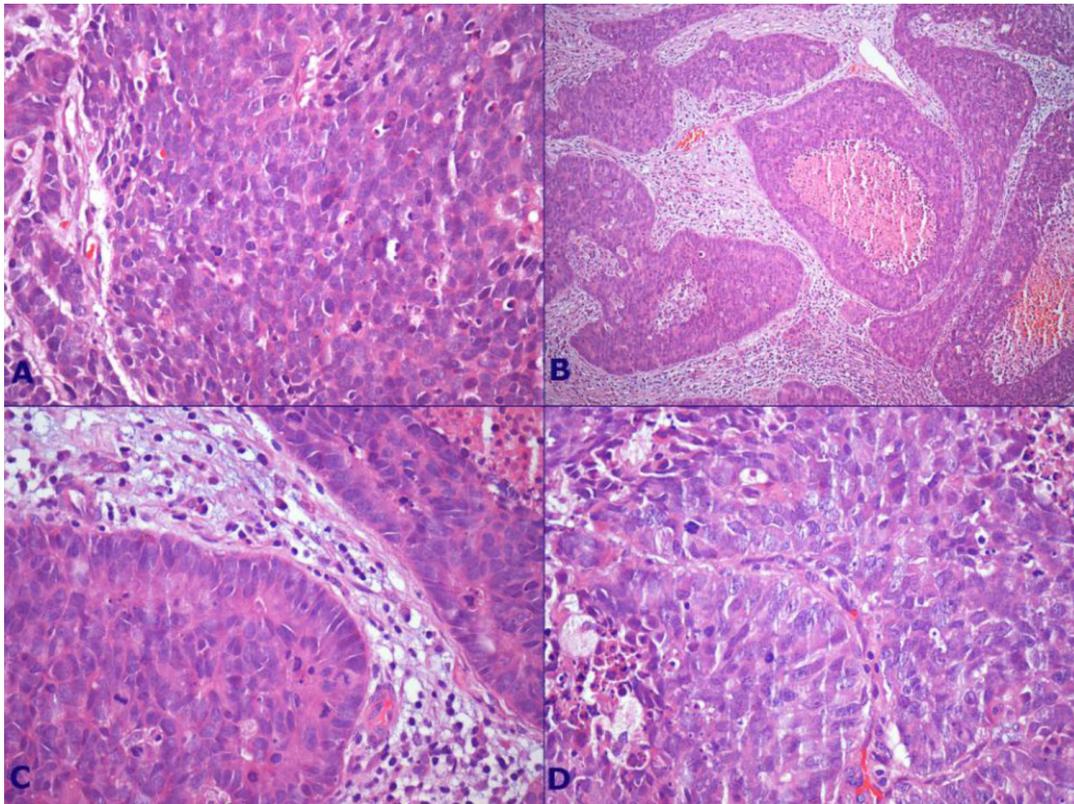
Figure 8 – Photomicrography of the bladder tumor. **A -** Areas of small-cell neuroendocrine carcinoma, (H&E, 400X); **B -** Areas of large-cell neuroendocrine carcinoma with comedonecrosis (H&E, 100X); **C -** Areas of large-cell neuroendocrine carcinoma with nuclear palisading with more abundant cytoplasm (H&E, 400X); **D** - Larger and more pleomorphic nuclei, with prominent nucleoli (H&E, 400X) were consistent with a large-cell neuroendocrine carcinoma component (compare to small-cell carcinoma in A).
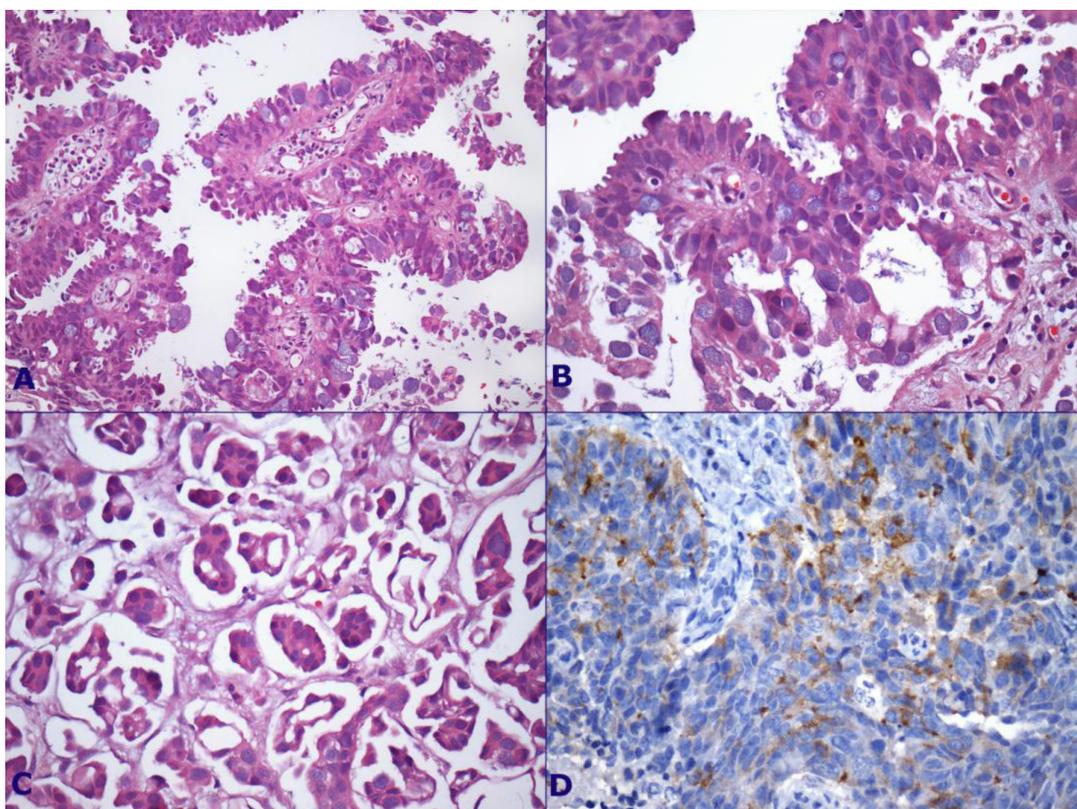

Figure 9 – Photomicrography of the bladder tumor. **A -** Adenocarcinoma component (H&E, 200X); **B -** Goblet cells in the adenocarcinoma component (H&E, 400X); **C -** Micropapillary component (H&E, 400X); **D -** Chromogranin-positive immunohistochemistry in solid areas with neuroendocrine pattern (400X).
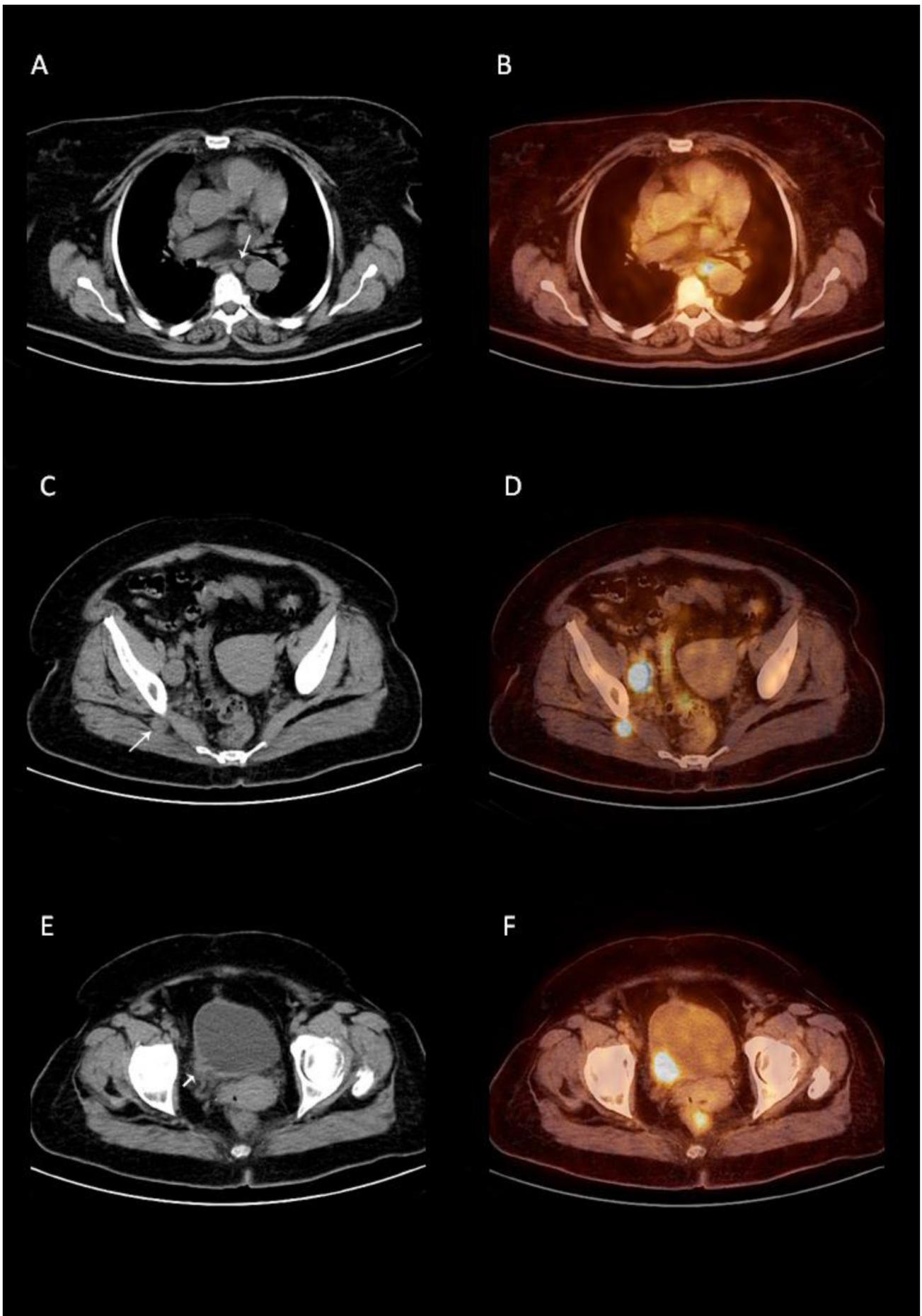
Figure 10 – PET-FDG image acquisition and CT. **A** and **B** disclose a metastatic paraesophageal lymph node (arrow); **C** and **D** show a metastatic lymph node between the gluteus maximus and gluteus medius muscles (arrow); **E** and **F** show the bladder lesion after furosemide administration (arrow).

Table 1 – Immunohistochemical panel

Antigen	Result	
	Lymph node metastasis	Urinary bladder primary
AE1 + AE3	Negative	Positive focal
Vimentin	Positive focal	NA
Chromogranin A	Positive focal	Positive focal
Synaptophysin	Positive	Positive
CK7	Negative	Positive (differentiated)
CK20	Negative	Positive (focal adenocarcinoma)
TTF-1	Negative	NA
CDX-2	Negative	NA
Ki67	Positive 60–70%	NA
p63	Positive focal	NA
EMA	Positive focal	NA
35Beta H11	Negative	Positive
CD99	Positive	NA
CD56	Positive	NA
S100	Negative	NA
CEA	NA	Positive (focal adenocarcinoma)

NA – non available.

DISCUSSION

Small-cell carcinoma (SmCC), also called undifferentiated carcinoma, anaplasic SmCC, neuroendocrine SmCC or "oat-cell" carcinoma, is a well-established histological variant of epithelial tumors of the lung, first described in 1926.[1] Since 1930, after the first description of an extrapulmonary small-cell carcinoma by Duguid et al.,[2] this neoplasia has been reported in many anatomical locations within the body like the esophagus, other organs of the gastrointestinal tract, head and neck and genitourinary tract.[3]

In the most recent consensus of the World Health Organization (WHO) and the International Agency for research on Cancer (IARC), neuroendocrine tumors (NETs), formerly called carcinoid tumors, are classified separately from neuroendocrine carcinomas (NECs) of low- and high-grade malignancy. "Atypical carcinoids," accompanied by local invasion, lymph node metastases, as well as distant metastases, correspond to low-grade NECs, whereas the classic small-cell carcinomas are classified as high-grade NECs.[4]

In 1981, Cramer et al.[5] reported the first case of small-cell carcinoma of the urinary bladder (SmCCB), in a 69-year-old man with urinary bladder irritability and hematuria. Despite the significant number of reports on this neoplasia variant since then, SmCCB remains rare and corresponds to 0.5-0.7% of all urinary bladder neoplasms.[6,7] The reported incidence is less than 1-9/1,000,000 inhabitant. From 1980 until 2011, fewer than 1000 cases of SmCCB have been reported.[7]

Similarly to the urothelial carcinoma of the urinary bladder (UCB), the SmCCB is more frequent among men than women (76% and 24%, respectively). Caucasians are involved in 91% of the cases with the median age at diagnosis of 73 years,[8] and 65% of the cases present a history of tobacco smoking.[9] The most common clinical features are related to the urinary tract, including hematuria, dysuria, nocturia, frequency, obstructive symptoms, and hypogastric and/or pelvic pain.[9] Among the NETs of the urinary bladder, a few cases of carcinoid tumors show immunoreactivity for polypeptides, such as calcitonin and subunit of β-human chorionic gonadotropin, without clinical expression.[10,11] Paraneoplastic syndromes, such as ectopic secretion of adrenocorticotropic hormone (ACTH) and hypercalcemia, are scarcely found among SmCCB,[12,13] differently from the SmCC of the lung.[7] In the case reported here, urinary symptoms and the lack of clinical and laboratory systemic involvement routinely found in advanced stage of neoplasias were noticeably absent. Considering the clinical presentation as isolated cervical and supraclavicular lymph adenomegaly in an apparently healthy patient, the diagnosis of bladder tumor was not raised among the differential diagnosis. Only after the incidental finding of the urinary bladder wall thickening on CT examination was this diagnosis taken into account. The histopathological examination of the lymph node biopsy could only provide the diagnosis of metastatic small-cell carcinoma of unknown origin. The sole epidemiological data favoring urinary bladder neoplasm was tabagism.

The biological behavior of SmCCB is characterized by its higher aggressiveness and consequently by a poorer prognosis when compared to the urothelial carcinoma of the bladder.[6] Therefore, SmCCB usually presents at diagnosis as an advanced metastatic undifferentiated disease (high-grade). In a series of 88 cases conducted at the MD Anderson Cancer Center over 18 years,[14] only 4.5% (n = 4 patients) were diagnosed in early

stage (Ta/T1), while 40.1% (n = 36) were T2; 28.3% (n = 25) as T3-T4a (stage III), and 26.1% (n = 23) as T4b-M1 (stage IV). The spreading pattern typically involves the lymph nodes, the liver, and bones, which is similar to urothelial carcinoma of the bladder.[9] Central nervous system metastases are less frequent when compared with SmCC of the lung.[15]

In the case reported here, it was surprising that regional disease or contiguity dissemination was not observed facing the presence of extensive lymphatic spread. The lymphatic involvement ascended from the right internal and external iliac chain to the retroperitoneal, mediastinal, and supraclavicular chains. At the moment of the diagnosis, hepatic or pulmonary metastases were not present at CT, PET-FDG and neither by biochemical determinations. The finding of a lytic and insufflating bone lesion at the right iliac wing detected by CT, and a vertebral lesion on PET-FDG represented the sole extranodal metastases. The neuroendocrine carcinoma (NEC) staging usually do not benefit from PET-FDG, due to their mild avidity for glucose, which show a low glycolytic metabolism. In this case it was useful because of the high mitotic index expressed by the tumor. On the other hand, when somatostatin-analog tracers labeled with gallium-68 are used, the PET scan hast a better impact.

Small, round cells with hyperchromatic nucleus, nucleolus and chromatin dispersed in a "salt and pepper" discernible pattern, scanty cytoplasm, and organelles, characterize the small-cell carcinoma on light microscopy. Mitotic rate is usually high, as well as tumor necrosis and crush artifact.[7] Pathogenesis of SmCCB is still obscure. However, several hypotheses were proposed to explain its origin. The strongest theory suggests that the origin of SmCCB may be a multipotential common stem cell that has the ability to differentiate into various cell types depending on the influence of a specific transformation or progression-related gene. This may explain the coexistence of SmCCB with transitional cell carcinoma and the heterogeneity of the immunohistochemical staining (cytokeratin and endocrine markers).[7]

Many other histological types may coexist in the same tumor: adenocarcinoma, squamous cell carcinoma, and sarcomatoid urothelial carcinoma.[15,16] The detection of this coexistence is important because it is associated with the prognosis. Patients with the mixed component have a median survival time, independently if metastatic or non-metastatic disease of two to three times higher than pure SmCCB histology.[17]

Immunohistochemistry is of paramount importance in the diagnosis of neuroendocrine SmCCB. In this setting, positive reactions to epithelial and neuroendocrine markers range from 30% to 100% of cases. It is remarkable the positivity to chromogranin A (22-89%), synaptophysin (67-76%), CD56 and cytokeratin 8-18 (CK8-18), and some of these tumors may express TTF-1 (33%). Less specific are cytokeratin 7 (CK7) (60%) and epithelial membrane antigen (EMA) (80%).[6,7,18] In the case reported here, most of the tumor was represented by SmCCB associated with large-cell neuroendocrine carcinoma and a micropapillary urothelial carcinoma, showing a high mitotic activity. Besides the morphology, immunohistochemistry confirmed the diagnosis through the positive expression of chromogranin A, synaptophysin and CD56.

The 5-year survival rate for patients with SmCCB ranged from 8% to 40%, no matter the staging. When properly staged, advanced disease presents a 5-year survival of 4-10.5%.[13,18]

Large-cell neuroendocrine carcinoma of the urinary bladder is an even rarer lesion, with many overlapping clinical and pathological features with SmCCB including presentation at advanced stages and poor prognosis.[19,20]

In summary, we present an exceedingly rare case of a high-grade neuroendocrine carcinoma of the urinary bladder with small and large cell features, which presented clinically with cervical lymph node enlargement and no urinary symptoms.

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