Abstract. Small and large cell neuroendocrine carcinomas of the urinary bladder are rare and usually coexist with urothelial carcinoma in elderly patients. Here we report the clinical case of a young smoker who was referred to our institution for a primary pure neuroendocrine carcinoma of the bladder, and review the existing literature on small and large cell neuroendocrine carcinomas of the urinary bladder.

Neuroendocrine tumors can arise in almost all epithelium-containing organs and are commonly encountered in the respiratory and gastrointestinal tract. Among the different histological patterns of urinary bladder tumours, neuroendocrine tumours can also be found (1). They are very rare in this site and can be differentiated as small cell carcinomas (SCUCs), large cell neuroendocrine carcinomas (LCNECs) and typical and atypical carcinoid. Generally the neuroendocrine pattern has been found in coexistence with transitional, squamous or undifferentiated tumour cells. The presence of neuroendocrine cells alone or within transitional cells is essential in the differential diagnosis of neuroendocrine carcinoma from transitional cell carcinoma (TCC). Cramer reported the first case of an SCUC of urinary bladder in 1981 (2) and since that date 160 cases, less than 1% of all bladder tumours, have been reported in the literature (3-4). The incidence of LCNEC is very uncommon with only five cases of pure LCNEC reported to date in the literature (5-10). The purpose of this review is to present a new case of pure LCNEC and discuss the literature on the diagnosis and management of SCUC and LCNEC.

Case Report

A 37-year-old patient was referred to our institution with recurrent episodes of asymptomatic gross haematuria over a ten month period. The patient had a history of cigarette use. A complete abdominal ultrasound study seven months prior to the diagnosis was negative for neoplastic lesions of the urinary bladder. Subsequently a contrast enhanced total body computerized tomography (CT) scan revealed a 2.5x2 cm mass in the posterior wall of the urinary bladder with extension into perivesical fat. No evidence of metastatic disease was found except for retroperitoneal lymph node enlargement (Figure 1). A cystoscopy with the biopsy of the mass was carried out before the definitive treatment. The cytomorphologic features demonstrated atypical cells with abundant cytoplasm, large nuclei with coarse chromatin and a high mitotic index. Immunohistochemical staining showed that the tumour components were positive for cytokeratin 7 and for neuroendocrine markers such as neurone specific enolase (NSE), chromogranin and synaptophysin (Figure 2). The preoperative value of Sieric Chromogranin was 85 U/L. The patient underwent cystoprostatectomy with orthotopic neo-bladder reconstruction and pelvic lymphadenectomy. The subsequent surgical specimen confirmed the presence of a pure large cell neuroendocrine tumour of the bladder with lymph nodes positive for malignancy. A month after surgery Sieric Chromogranin decreased to 7 U/L and a [111In] DTPA-octreotide scintigraphy (Octreoscan) did not identify any systemic lesions. The patient was submitted to six cycles of adjuvant chemotherapy with carboplatin AUC 5 and etoposide 120 mg/m2/day. The treatment related toxicity was acceptable. Seven months later, a total body contrast enhanced CT showed only residual subcentimetric inter-aorto-caval lymph nodes. On the 18-fluorodeoxyglucose (18FDG)
positron emission tomography (PET), performed seven months later, there was no residual lymph node involvement. Twenty two months after surgery, the patient was still alive and without evidence of local or systemic recurrence.

Discussion

The unknown aetiology and natural history of neuroendocrine tumours of the urinary bladder represent a challenge for their diagnosis and the subsequent treatment. As a result of the rarity of this specific type of bladder neoplasm, there is no consensus of opinion among clinicians as to their optimum management, therefore different treatment strategies have been employed in order to improve their poor prognosis (11).

Small cell carcinoma of the urinary bladder. SCUC often coexists with conventional urothelial carcinoma and they alone account for 0.48-1% of all bladder carcinomas (12). The majority of these tumours appeared in males in their 7th and 8th decades of life with a male to female ratio of between 2:1 and 10:1 (11). These tumours are usually found in smokers. Abbas et al. reported that the mean survival is respectively 19.6 months, with 2 and 5 year of survival in 13.5% and in 8% of cases (13). The origin of SCUC is unknown and there is a hypothesis that they may arise from neuroendocrine cells within normal or metaplastic urothelium (3), or that the disease develops from undifferentiated or stem cells within the urothelium (11). The latter theory also explains the frequent association with other non-small cell carcinomas but fails to explain the low incidence of concomitant carcinoma in situ. The clinical presentation of SCUC is similar to other bladder tumours with gross haematuria as the most common presenting symptom (14). Other symptoms can be reported and may include local irritation, pelvic pain and urinary obstruction. Rarely, patients can develop distant metastases or paraneoplastic syndromes (11). The diagnosis of SCUC depends on histopathological recognition and reactivity for neuroendocrine markers as synaptophysin and chromogranin-A (14). The histological appearance on urine cytology includes isolated single cells, hypercellularity, nuclear moulding and nuclear hyperchromatism, with staining for neuroendocrine markers and a haemorrhagic, necrotic background (11); in mixed tumours however the identification of isolated neuroendocrine cells can be difficult (11). At cystoscopy, the tumour size can range from 4 to 10 centimetres and the tumour is usually located at the lateral and fundus of the bladder, while rarely occurring in the trigone within a bladder diverticulum (11) as result of the urachal remnant. Macroscopically, these tumors show polypoid lesions and are sometimes ulcerated (14). On CT the lesion appears as a defined mass with evident involvement of the perivesical fibroadipose tissue (14). In fact, these tumours, generally show a local extension (T3-T4) in 51-100% of cases and lymph node or bone, liver and brain involvement in 28-80% of patients. The typical microscopic features are characterized by hypercellularity, necrosis, nuclear chromatin crush artefact and mitoses (11). Immunohistochemical findings of SCUC include the expression of neural markers such as NSE in 87% of patients, chromogranin-A in only a third of cases, as well as CD44v6 and CK20. It is also possible to find an immunoreaction for synaptophysin, polypeptide glycoprotein...
Large cell neuroendocrine carcinomas. The aetiology, natural history, prognosis, clinical features and therapeutic management of LCNEC are the same as those for SCUC. Cytomorphology and immunocytochemistry are essential but not sufficient to differentiate a primary bladder LCNEC from a metastasis of pulmonary or gastrointestinal primary sites. In the case report cited, the histological pattern was defined adopting the criteria of Travis et al. used for histological characterization of lung neuroendocrine tumour (9). These criteria include cells of large size, polygonal shape, low nuclear to cytoplasm ratio, coarse chromatin, frequent nucleoli, high mitotic activity and immunohistochemical or ultrastructural evidence of neuroendocrine differentiation (9). Octreoscan and PET were performed in addition to the CT scan to help in the detection of other sites because neuroendocrine tumours are associated with the secretion of ectopic hormones and neuropeptides. \([^{111}\text{In}]\) DTPA-octreotide scintigraphy has been shown to be useful in identifying primary tumours and distant metastases in most patients with neuroendocrine tumours. The great advantage of octreotide scintigraphy is that it can cover all body regions that conventional CT or MRI does not examine (15). According to literature data regarding SCUCs, chemotherapy combined with surgery would appear to be the most important component of management (16, 17). We decided to follow the therapeutic modalities describe in the literature for three cases of LCNEC although the patients later died (1, 5). The patient underwent a radical cystoprostatectomy with orthotopic neo-bladder reconstruction because at cystoscopy the mass appeared to be at an advanced stage, though not involving the urethra. We did not believe sufficient local control would be achieved with tumor resection alone (6). We administered etoposide and platinum-based chemotherapy regimens because of their proven efficacy in patients with the more common and studied SCUC (7-9). Few reports have described cases of primary LCNEC and so it is difficult to make statements regarding optimal treatment and prognosis (1, 5). The management of neuroendocrine lesions must be very accurate and should involve pathologists, surgeons, radiotherapists, endocrinologists and oncologists. In our case, the patient was young and in a good state of health after two years from the diagnosis. Based on the present data, we conclude that neuroendocrine tumours of the urinary bladder, especially SCUCs, behave quite aggressively so once diagnosed they need a local radical treatment and adjuvant systemic chemotherapy.

References