A patient with neuroendocrine carcinoma of the urinary bladder and paraneoplastic degenerative parenccephalitis: A case report and review of the literature

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Abstract

Neuroendocrine carcinomas of the bladder (small cell, large cell, typical and atypical carcinoids) are rare and usually co exist with urothelial carcinoma. As in small cell carcinoma of the lung, various paraneoplastic neurologic disorders can occur although they are even less frequent. Here we report the case of a 63 year old man with small cell carcinoma of the urinary bladder and with a paraneoplastic neurologic disorder.

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1. Introduction

Neuroendocrine carcinomas can arise in almost all epithelium-containing organs, most commonly encountered in the respiratory and gastrointestinal tract. Among the histological patterns of urinary bladder tumors, neuroendocrine tumors can also be found. Although rare, they can be distinguished and differentiated as small cell carcinomas (SCUC), large cell neuroendocrine carcinomas (LCNEC), typical and atypical carcinoids. Since the first report of a case of SCUC by Cramer [1], the cumulative number reported has risen significantly. The estimated incidence is roughly 500 new cases annually [2].
What is even rarer is the co-existence of a paraneoplastic neurologic disorder (PND) in this setting. We know that the most common PND encountered in SCLC is the Lambert–Eaton myasthenic syndrome which affects 3% of patients. For other solid tumors the incidence of PND is less than 1% [3].

The purpose of this review is to present a case of SCUC with a PND.

2. Case report

A 63 year old man was referred to our institution with recurrent episodes of painless haematuria over an one month period. The patient had a history of diabetes mellitus, hypertension and hyperthyroidism. He reported moderate alcohol consumption and was a smoker of 80 pack years.

A cystoscopy revealed a bladder tumor and a biopsy specimen was obtained. Subsequently staging was performed with contrast enhanced total body computed tomography. No evidence of metastatic disease was found except an enlargement of an adjacent lymph node to the bladder. A radical cystoprostatectomy was performed which revealed a 4 cm mass that invaded the entire bladder wall, pericystic fat and blood vessels as well as an adjacent lymph node (T4N1M0).

The mass cytomorphologic features demonstrated small cells, hypercellularity, necrosis, atypical nuclear hyperchromatism and minimal cytoplasm (Figure 1). Immunohistochemical staining was positive for CK 20, CD 56, CK 7, CK 8/18, CEA, TTF-1, S-100, synaptophysin, chromogranin and negative for PSA (Figures 2 and 3). Ki-67 was positive in 60% of the neoplastic cells. It was defined as a small cell carcinoma of the urinary bladder, high grade, with neuroendocrine differentiation. In light of these findings, the patient underwent a bronchoscopy which revealed macroscopically normal mucosa. Brushing and washing cytology samples were analyzed with no signs of malignancy. An octeotide scintigraphy did not identify any systemic lesions.

One month after surgery the patient was admitted to hospital due to dysarthria, ataxia, opsoclonus, instability and muscle weakness. On physical examination he had positive Romberg sign, nystagmus in all directions, positive Barre sign on his left upper extremity (LUE), decreased muscle strength (2/5) on his right lower extremity (RLE) and a negative Babinski sign. He was alert and oriented and had no fever. Review of the other systems revealed no abnormality. The patient's lab work (complete blood count, liver function tests, electrolytes, C-reactive protein, D-Dimers, partial thromboplastin time, international normalized ratio) were unremarkable. A brain MRI revealed chronic ischemic changes. He underwent a diagnostic lumbar puncture and cerebrospinal fluid (CSF) was sent for analysis. There was mild leukocytosis, PCR for HSV being negative. CSF cytology was negative for malignant cells. The autoantibodies Anti-Yo and Anti-Hu were detected in the CSF. Based on the presenting symptoms, the work up and the findings, a neurological consultation was ordered and a diagnosis of paraneoplastic degenerative parencephalitis was deduced.

One month later, it was decided to administer 6 courses of adjuvant-like chemotherapy with carboplatin AUC 5 day 1 and etoposide 100 mg/m²/day Days 1-3 q 21 days.

Upon completion of cycle 3 there was a significant improvement in his neurological symptoms with only a persistent muscle weakness on his RLE (2/5) and opsoclonus. Restaging performed with total body contrast enhanced computer tomography revealed no signs of recurrence. An additional three courses of carboplatin and etoposide were administered uneventfully (Table 1).

One month after completion of his therapy the patient is still alive with no sign of recurrence, apart from a mild muscle weakness on his RLE (4/5).
3. Discussion

Small cell carcinoma of the bladder is a rare, aggressive, poorly differentiated neuroendocrine neoplasm that is similar in clinical behavior to small cell carcinoma of the lung. Because of its similarity to lung cancer, paraneoplastic syndromes can arise in this setting, even though rarely. The last 20 years the incidence of SCUC has risen significantly from 0.05 to 0.14 cases per 100,000 population, although a report/publication bias cannot be excluded. They alone account for 0.48 – 1% of all bladder carcinomas [2]. A past history of smoking has been associated with the disease, men being affected more commonly than women (4:1) and whites more commonly than non-whites (9:1). Median age of diagnosis is 73 years and median overall survival is 11 months, though with varying range. Two- and five year survival is observed in 13.5% and 8% of cases. Extrapolating from SCLC, due to data limitation in the literature, PND possibly account for less than 1% of SCUC cases [3].

Presenting symptoms are similar to other bladder tumors, most notably gross haematuria, pelvic pain and urinary obstruction. The vast majority presented with poorly differentiated (33%) or undifferentiated (43%) tumors. The most common sites involved were the lateral wall (16%) or the bladder dome (10%). Twenty-four percent of patients had distant metastases at the time of diagnosis, and another 5% had multiple lymph node metastases (N2 or N3) [4].

The diagnosis of SCUC depends on histopathological recognition and reactivity for neuroendocrine markers such as synaptophysin and chromogranin-A [5]. 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. The typical microscopic features are characterized by hypercellularity, necrosis, nuclear chromatin crush artefact and mitoses. 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 9.5, thyroid transcription factor-1, p53 and Ki67 [5].

No randomized clinical trials upon which to base definitive recommendations for the management of patients with small cell carcinoma of the bladder exist.

For patients with localized disease and a good performance status a combined modality approach that includes neoadjuvant or adjuvant chemotherapy using a platinum-based regimen, most notably carboplatin plus etoposide, coupled to cystectomy [6,7] rather than radiotherapy which should be reserved for non surgical candidates [8]. There are however several case series suggesting that the neoadjuvant approach with a platinum based c regimen may have a more favorable outcome [9].

For disseminated disease a chemotherapy regimen active in SCLC should be administered [10,11]. Controversy remains
whether prophylactic cranial irradiation should be applied to patients with limited disease or disseminated disease with a good response [12].

Paraneoplastic neurologic syndromes are a heterogeneous group of disorders caused by mechanisms other than metastases, metabolic and nutritional deficits, infections, coagulopathy, or side effects of cancer treatment. These syndromes may affect any part of the nervous system from cerebral cortex to neuromuscular junction and muscle [13]. The pathogenesis is unclear although it is believed that an immunologic response is directed against shared antigens that are ectopically expressed by the tumor, but otherwise exclusively expressed by the nervous system [14].

Well and partially characterized paraneoplastic antibodies (Anti-Hu, Anti-Yo, Anti-Ri, Anti-Zic 4, PCA2, ANNA-3, mGluR1, Anti-Tr, Anti-recoverinα, Anti-amphiphysin, Anti-CV2) can be detected in the serum and CSF of many, but not all, patients with paraneoplastic syndromes and are highly suggestive of PND [15,16]. Patients suspected of having a PND should be examined for paraneoplastic antibodies in their serum or CSF. These characterized paraneoplastic antibodies rarely if ever occur in normal individuals [16,17]. Absence of these antibodies does not exclude a PND, however its diagnosis requires the absence of the metastatic and nonmetastatic complications noted earlier [17]. Imaging with MRI, PET/CT can assist in the diagnosis [18].

Since the majority of the PNDs are immune mediated the general approach to therapy is removal of the antigen source by treatment of the underlying tumor and suppression of the immune response through immunomodulation and/or immunosuppression [19]. Prompt oncologic treatment and immunotherapy may be beneficial especially if instituted during symptom progression and not later. Of great interest is the fact that the oncologic outcome does not differ in patients with or without a diagnosed PND [20].

4. Conclusion

In this case we had detected Anti-Hu and Anti-Yo antibodies in the CSF of a patient with a recently resected localized small cell carcinoma of the urinary bladder and various neurological symptoms following surgery. Based on the literature we administered 6 courses of etoposide and platinum-based chemotherapy with a rapid neurological improvement. The fact that two months after the completion of chemotherapy muscle weakness persists may be due late-onset of chemotherapy, when the neurological deficits were already established.

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

References


