Pancytopenia and Neuroendocrine Small Cell Carcinoma of the Bladder

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Abstract

Clinical Practice: Small cell neuroendocrine tumor of the bladder is a rare aggressive tumor with high metastatic potential. Despite aggressive multi-modal treatment, it has a high mortality rate.

Tumor infiltration of the bone marrow, myelophthisis, is uncommon and has a devastating prognosis. This is the second case described in scientific literature. In patients with bladder carcinoma and an alteration in any of the three blood series (red cells, white cells, platelets) that do not respond to transfusion, infiltration of the bone marrow must be established.

Keywords: Small cell neuroendocrine carcinoma of the bladder and myelophthisic anemia

Introduction

Small cell (oat cell) neuroendocrine tumors were first described in the bronchopulmonary tract [1]. Later, extra pulmonary locations such as in the urinary tract were published [2,3]. In the latter case, the urinary organ most commonly affected is the bladder, being the source of 20% of extra pulmonary neuroendocrine tumors. These have an incidence of 0.3–0.7% of all bladder cancers [4]. In more than 50% of the cases, it co-exists with other kinds of urinary tract tumors: urothelial carcinoma, in situ carcinoma, adenocarcinoma, squamous cell carcinoma, atypical carcinoid tumor, and sarcomatoid component.

Prognosis is poor. It has a great capacity for local progression and metastasis, even after radical treatment with neo- or adjuvant therapy.

Infiltration of the bone marrow by a small cell neuroendocrine bladder tumor is rare. This is the second case reported in the scientific literature.

Case Report

An 85 year old patient, a non-smoker with no surgical or medical history, presented on admission with a macroscopic hematuria that led to anemia: hemoglobin (Hb) 6g/dl. During his stay, he suffered a hemorrhagic shock, requiring immediate admission to the intensive care unit and hemostatic transurethral resection. Cystoscopy revealed a large blood clot and a solid lesion, 7cms in diameter, with infiltrating appearance, located on the lateral wall of the bladder. The histopathology study reported a neuroendocrine small cell carcinoma of the bladder that infiltrated muscle layers, with numerous points of necrosis and a limited urothelial carcinoma component. It was positive for CD 56 and synaptophysin, with a K167 proliferative index of almost 100%.

After surgery, the patient regained hemodynamic stability, but still had pancytopenia, with red cells, $3x\ 10^6/\mu L$; white cells, $2 \times 10^3/\mu L$; and platelets $13 \times 10^3 U/L$, which did not improve with transfusions. His baseline results had been normal a month earlier. A bone marrow aspiration was performed that showed infiltration by tumor cells (Figure 1).

Seven days after surgery, the patient had a febrile neutropenia with progressive hemodynamic instability, managed with palliative measures. The patient died three days later.

A literature search was made in Medline using the keywords "small cell neuroendocrine carcinoma of the bladder and myelophthisic anemia". The results of the literature review are presented.
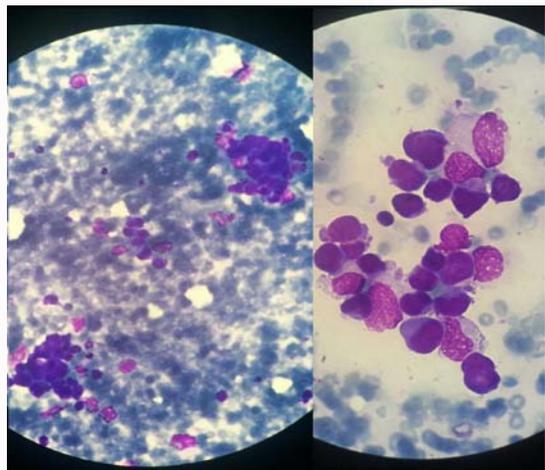
Figure 1: Destruction of the bone marrow environment and a leukoerythroblastic reaction.
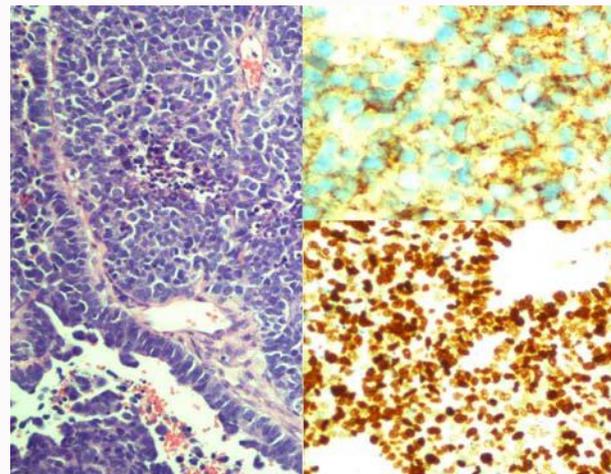

Figure 2: Small cells with a high mitotic index, hyperchromatic nuclei, small prominent nucleoli and scarce cytoplasm, Ki67.

Discussion

The World Health Organization (WHO) classifies neuroendocrine tumor as: neuroendocrine tumor grade 1, neuroendocrine tumor grade 2, neuroendocrine carcinoma (large cell and small cell), and mixed adenoneuroendocrine carcinoma (MANEC) [5,6]. Large cell neuroendocrine carcinoma of the bladder is rare, with only ten cases published in literature [5]. Small cell neuroendocrine carcinoma is more common and, to date, 400 cases have been reported [5]. The large series reported by Cheng et al. [7] consisted of 64 patients. The age of onset, male predilection, symptoms, and debut are similar to urothelial bladder tumors [2,3,5]. There is a higher prevalence in men than in women (5:1). It appears around the 7th decade of life, and is associated with the following risk factors: tobacco (70% of diagnosed patients are smokers), and exposure to chemical products. It may be associated, as in the case of squamous cell carcinoma of the bladder, with a history of kidney lithiasis, chronic cystitis, and urinary catheter (8,9).

The histogenesis of the neuroendocrine bladder tumor is controversial. There are three main theories. The first claims that the tumor originates from Kultschitzsky cells located in the urothelium (10). The second associates the origin to urothelial cell metaplasia (11). The third claims that it derives from a pluripotent stem cell of the bladder mucosa (12). This latter theory is the one supported by most authors because of the association of this neoplasm with other types of bladder tumors in up to 50% of the cases, with the most frequent being carcinoma in situ, followed by squamous cell carcinoma, and sarcomatoid carcinoma (13).

The clinical picture does not differ from other bladder tumors. As in the case of the patient being presented, 67 – 100% of the cases have a mono-symptomatic macroscopic hematuria. It can be accompanied by lower urinary tract symptoms, constitutional syndrome [5], and dilation of the upper urinary tract (up to 95% has muscle invasion at diagnosis). Paraneoplastic syndromes are rare, but may occur, with metabolic abnormalities (hypercalcemia, hyponatremia, hypokalemia), endocrine abnormalities (secretion of ADH, Cushing Syndrome), or neurological abnormalities (myasthenia gravis or Eaton Lambert Syndrome) (2,14). Many patients have symptoms caused by metastatic lesions (up to 67% of patients at the time of diagnosis.) (15,16). The most common parts of the body are: lymph nodes (56%), bone (44%), liver (33%), and lung (20%) (8).

Metastatic infiltration of the bone marrow due to this type of tumor is extremely rare (17). To the best of our knowledge, the present case is the second described in literature (18). Myelophthisis, or bone marrow infiltration by non-hematopoietic cells, was described by Reich in 1935, and may lead to different degrees of anemia, thrombocytopenia, and neutropenia (18). Here, a case with aplasia of the three cell series is presented. It occurs in 30% of solid tumors, with solid carcinomas being the most common (breast, lung, prostate, thyroid, kidney (18). It is exceptional in bladder tumors. The situation that triggers the event is unknown, but excess extra-tumor matrix metalloproteinases (MMP3, MMP-7, MMP-13) and vascular endothelial growth factor are involved. Tumor cells occupy the space of the trabecular bone, which leads to the destruction of the bone marrow environment (Figure 1) and a leukoerythroblastic reaction characterized by the presence of nucleated red blood cells, dacriocytosis with left shift neutrophilia, and giant platelets on the peripheral blood smear (18,19). The worst prognostic factors are: an initial Hb level less than 9g/dl, the presence of febrile neutropenia, and three or more concomitant visceral metastases. The patient presented had the first two features. There is no standard treatment for this condition. Both chemotherapy and radiotherapy show a similar survival rate (17,18). Half of the patients diagnosed with myelophthisis have a survival rate of less than 2 months.

As the symptoms and endoscopy findings are very vague, the diagnosis of neuroendocrine bladder tumor is achieved by histological and immunohistochemical study. Cryptoscopic findings in the present case were similar to those described in the literature: a solid mass a 4 to 10 cm solid mass with calcification and ulcerous necrotic areas. Up to 54% of the cases were on the bladder side walls, which suggest a urothelial carcinoma with a high degree of anaplasia [2,3,5]. The electronic microscope shows small cells with a high mitotic index, hyperchromatic nuclei, small prominent nucleoli and scarce cytoplasm. Necrotic areas are seen forming a "lumpy" material known as "starry sky". The basophilic material around the blood vessels is a common phenomenon called "Azzopardi phenomenon" (8,14,15). The most characteristic data, but not the most specific, is the presence of neurosecretory granules. At advanced stages, it is not possible to demonstrate this neuroendocrine difference because the cells are very difficult to differentiate.

Immunohistochemically, nearly 80% of the patients expressed positivity or neuron-specific enolase (NSE), but this marker is not very specific. Other, more specific, neuroendocrine markers include synaptophysin, which is positive in 64.3% of the cases, and CD 56 in 71.4% of the cases; these were positive in the patient presented (14,20). Positive results are also found for chromogranin A, in 28% of the cases; for Nuclear Transcription Factor Thyroid (TTF-1) in 30% of the cases (21); and epithelial markers (cytokeratin CAM 5.2, MNF 116, and EMA) (Figure 2).

Chromosome anomalies are related to small cell bladder neuroendocrine tumors, such as the deletions in the short arm of the chromosomes 4,5,10 and 13; DNA triploidy in the chromosomes 5p, 6p, 8q and alterations of the chromosome p53 and p16. Some of these abnormalities match with those described in transitional cell carcinoma (5, 16, 22). which supports the theory of histogenesis of the pluripotent stem cell (12).

Unlike most small cell tumors of other organs, immunohistochemical and genetic studies are not very specific for this type of bladder cancer, and are not pathognomonic. Therefore, WHO can only base its diagnosis on morphological criteria.

Differential diagnosis must be made with various pathologies. On the one hand, with bladder metastasis of the lung carcinoma, a lung focus must be ruled out via a CT scan, as well as a biopsy of the lesion. On the other hand, it must be differentiated from a lymphoma, which shows positivity for LCA, CD45, CD20, and also from a neuroendocrine prostate carcinoma with bladder infiltration, which is accompanied by an adenocarcinomatous component and high PSA, as well as from an embryonic rhabdomyosarcoma, more frequent in childhood, and positive for muscle specific vimentin, desmin and actin, and finally from the poorly differentiated transitional tumor, where the existence of small nuclei and positivity for NSE, synaptophysin, and other neuroendocrine markers point to small cell carcinoma (3,13).

Due to the low incidence of this disease and the advanced stage at the time of diagnosis, there are different options for treatment, but none has proved to be definitive. Most of these tumors have micrometastases at diagnosis, making surgical treatment on its own insufficient. Conservative treatment has no place, and is reserved for palliative therapy (2,3,9). Given the characteristics of the patient presented, with the hemodynamic instability and the advanced stage of the tumor, the palliative option was taken.

Treatment with a curative purpose is aggressive. The most common involves radical surgery plus adjuvant chemotherapy and/ or radiotherapy. The best results obtained combine radical surgery with adjuvant therapy, as we are dealing with a chemo sensitive tumor (2,3,5,9,24). As Mackey emphasized, the cisplatin based chemotherapy was the only factor that improved survival. The most commonly used regimen is the combination of cisplatin and etoposide for a pure neuroendocrine carcinoma, and the combination of methotrexate, vinblastine, cisplatin and doxorubicin for a neuroendocrine tumor associated with transitional cell carcinoma. Neoadjuvant therapy may be advantageous in comparison to adjuvant therapy because a large percentage of this patients has tumors with rapid growth rates, making complete resection difficult or imposible.

The worst prognosis factors are: poor histological differentiation, tumor size, involvement of bladder fat, the existence of neurovascularization, and micro metastases at the time of diagnosis. The latter being the main cause of death.

Despite aggressive treatment and therapy, the mortality rate is very high. Up to 3 times greater than high-grade urothelial carcinoma, with 60% of patients dying within 2 years of diagnosis. The average survival is 3- 35 months. The 5-year survival is 8%. No difference has been found in survival between pure and mixed tumors (3,15).

Conclusions

The small cell neuroendocrine bladder tumor is rare, very aggressive, and has high metastatic ability.

Despite multi-modal treatment with radical surgery and chemotherapy, with or without radiotherapy, it has an unfavorable evolution, ending the patient's life around two months from the time it is diagnosed.

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