Primary Large-Cell Neuro-Endocrine Carcinoma of the Bladder: The Study of Two Cases with the Literature Review

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Primary Large-Cell Neuro-Endocrine Carcinoma of the Bladder: The Study of Two Cases with the Literature Review

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Abstract

Primary large-cell neuro-endocrine carcinoma of the bladder is a rare aggressive tumor with a very poor prognosis. The authors report two new cases of primary large-cell neuro-endocrine carcinoma of the bladder and discuss the pathological and therapeutic aspects of this tumor in the light of a review of the literature.

Introduction

Neuroendocrine tumors can grow in all organs containing epithelia, moreover they are frequently encountered in respiratory and gastrointestinal tract. These tumors are subdivided into small cell carcinomas, typical carcinoid, atypical ones, and large cell carcinomas. These tumors represent less than 1% of all bladder tumors. At this level, they are represented mainly by small cell carcinomas. Large cell carcinoma of the bladder are extremely rare. Only seven cases have been reported in English literature so far. These tumors with high metastatic potential and poor prognosis, require immediate aggressive treatment. We report two cases of primary large-cell neuro-endocrine carcinoma of the bladder and we discuss it from the clinical, the pathological and the therapeutic perspective.

Case Report(s)

Case 1:
GA, age 74, chronic smoker, who had a surgery in 1981 for peritonitis with perforated ulcer, admitted in our training for terminal hematuria with blood clots associated with irritative symptoms of the low urinary tract. Clinical examination was unremarkable. Laboratory tests were normal. The ultrasound showed an echo pattern process tissue of 3 cm located in the antero upper face of the bladder. Cystoscopy found a tumor of the anterior side with a non-papillary necrosis appearance. We performed a transurethral resection of the tumor. The pathological examination was in favor of infiltrating neuroendocrine large cell carcinoma. A further immunohistochemical study confirmed this diagnosis with:
- ACL antibodies: positive
- anti-chromogranin antibodies: marking rather diffuse
- synaptophysin antibodies: intense and diffuse staining

A thoracoabdominal and pelvic CT was performed as a staging and was unremarkable. The patient was subsequently sent to the oncology department for chemotherapy based on cystplatine and gemcitabine. He died two months later.

Case 2:
B.N., aged 54 years, medically treated since 1977 with corticosteroids and immunosuppressants for a complicated lupus, admitted in our training to support a massive hematuria lasting for two months. Examination found the patient in poor general condition, presenting a slightly discolored conjunctiva with cushingoïde aspect. The abdomen is soft with the presence of a palpable, hard, hypogastric mass. The biological tests found an anemia with normal renal function. Ultrasound found an echo pattern process tissue located on the bladder floor without repercussions on the upper urinary tract. Endoscopy found a tumor in the trigone and in the right and left sides of the trigone with a non-papillary necrosis appearance. The patient therefore underwent a transurethral resection of the tumor considered to be complete by the operator. Pathological examination was in favor of a poorly differentiated carcinoma process (figure 1). Immunohistochemical complement was in favor of a neuroendocrine large cell carcinoma of the bladder with:
- chromogranin antibodies: positive
- synaptophysin antibodies: positive
- CK 7 Antibodies: negative

A thoracoabdominal and pelvic CT, as a staging, performed three weeks later objective a circumferential thickening of the bladder wall with a bilateral ureterohydronephrosis and presence of several lung nodules suggestive of secondary localization. The patient was subsequently sent to the...
medical oncology department for chemotherapy based on cisplatin and gemcitabine. She died before starting the first course from pulmonary embolism.

Discussion

Neuroendocrine tumors of the bladder are rare. Morphological criteria for neuroendocrine tumors are similar to those of other locations and are: organoid disposal and endocrinoid vascularization; the criteria for distinguishing between these tumors are the presence or absence of necrosis, mitotic count and cell size. The cells composing these tumors are characterized by the expression of immunohistochemical markers of neuroendocrine differentiation [1]. The large cell neuroendocrine carcinoma is a clinical-pathological entity originally proposed in 1991 by Travis [2]. These carcinomas are more often described in the lungs, although other localizations have been described such as the cervix, thymus, stomach and parotid gland. Histologically, it differs from small cell carcinomas by the large size of cells, a low volume ratio of nucleus and cytoplasm and frequent nucleoli [3]. The cells are large (nucleus > 33 mm or 3 small lymphocytes), the architecture is trabecular, solid or pseudo-rosette, sometimes with palisading. The mitotic activity is high (greater than 10 mitoses per 10 fields at high magnification). There are pockets of extensive necrosis and the tumor tends to be diffusely invasive. The immunohistochemical study confirmed the diagnosis by showing an expression of neuroendocrine classic markers such as the NSE, CD56, chromogranin A and synaptophysin [4]. To our knowledge, 13 cases of large cell neuroendocrine carcinoma of the bladder have been reported in the literature. However, as the entity of the large cell neuroendocrine carcinoma is not well established, it is possible that some cases have been recognized and have not been diagnosed as variants of neuroendocrine tumors. Indeed, Quek reported that about 25 cases of neuroendocrine tumors collected at their institution, five were found to be large cell carcinomas when the specimens were reviewed retrospectively [5].

These large cell carcinomas can be pure or composite emerging in a urothelial carcinoma. The pure form of the tumor is defined by the presence of more than 90% of tumor cells that express a neuroendocrine differentiation. The histogenesis of primary neuroendocrine carcinomas of the bladder is unknown. The difficulty lies in the fact that the bladder seems devoid of diffuse neuroendocrine system cells. Two hypothesis are proposed: the first suggests an origin from a totipotent stem cell transformation of normal urothelium [6,7], the second involves metaplasia of the normal urothelium or a dedifferentiation of a high grade transitional cell carcinoma [6, 8]. Five cases of large cell neuroendocrine carcinoma of the bladder reported contained another contingent than the neuroendocrinien one which can plead for the first hypothesis. The two cases reported in our study are pure large cell neuroendocrine carcinomas.

Almost all neuroendocrine tumors of the bladder are high grade of malignancy carcinomas with a poor prognosis because of their high metastatic potential [6, 5, 8, 9, 10]. Treatment modalities (surgery, chemotherapy and radiotherapy) are not well defined because of the rarity of these tumors. However, several studies of large cell lung carcinoma reported a relatively high response rate to standard chemotherapy regimens used to treat small cell carcinoma. A potential benefit of adjuvant chemotherapy has also been suggested. Thus, treatment of disseminated forms is based on chemotherapy with platinum [10, 11]. If cons-indication or failure of chemotherapy, radiotherapy is the best option for symptomatic tumors. Treatment of localized forms has to take account of the high frequency of micro-metastasis and is based on a combination of chemotherapy to radical surgery or radio-chemotherapy [10].

The evolution of neuroendocrine tumors of the bladder is often unfavorably relevant to the clinical stage at the moment of diagnosis that is more often advanced. However, early diagnosis and prompt treatment involving cystoprostatectomy and adjuvant chemotherapy can help to obtain a long-term control of disease. Indeed Akamatsu had good results after combining surgery and adjuvant chemotherapy with etoposide and carboplatin. The patient remained alive and did not recur after 14 months [3]. The two cases we reported have a rapidly fatal evolution after diagnosis without the benefit of radical cystoprostatectomy, or full courses of chemotherapy or radiotherapy.

Conclusion

Primary large cell neuroendocrine carcinomas of the bladder are rare, aggressive and often immediately metastatic. Only histological examination with immunohistochemical study of the resection material allows the diagnosis. The management is not codified given the small number of cases described in the literature.
References

Illustrations

Illustration 1

Figure 1

Tumoral proliferation made of sheets of cells with ovoid nuclei strongly nucleolated (HE, Gx400).
Illustration 2

Figure 2

Expression of the anti-chromogranin by tumor cells. (Gx400).
Illustration 3

Figure 3

Positive immunostaining with anti-synaptophysin (Gx400).
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