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Case Report

Neuroendocrine Prostate Tumor: A Case Report and Literature Review

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Abstract
Neuroendocrine prostate cancer is a rare entity with a poor prognosis. It can present in a pure form (small or large cell neuroendocrine carcinoma) or mixed, that is to say associated with an adenocarcinomatous contingent. Rarely diagnosed de novo, primary large cell tumors are exceptional. The development of molecular analysis tools has provided important elements for understanding the origin of this histological subtype and the signaling pathways involved. This could also help to identify diagnostic and prognostic biomarkers as well as potential molecular targets. We report here the case of a 63-year-old patient diagnosed with mixed prostate cancer with large cell neuroendocrine component at a localized stage and detail the particularities of his management.
Keywords: Prostate Cancer, Neuroendocrine Tumor, Adenocarcinoma, PSA, Hormone Therapy, Surgery.

Introduction

Primary neuroendocrine neoplasia of the prostate is rare; large cell neuroendocrine tumors of the prostate constitute a rare histological entity whose progressive profile and treatment differ from those of conventional adenocarcinomas. The 2016 World Health Organization histological classification of prostate cancer includes well-differentiated carcinoid tumors and poorly differentiated small or large cell tumors in the neuroendocrine tumor category [1]. Primary large cell tumors are exceptional. Primary neuroendocrine tumors of the prostate can be pure or associated with an adenocarcinomatous component. Mixed forms have a better prognosis when diagnosed early and at a localized stage.

Observation

A 63-year-old patient was seen in consultation for the incidental discovery of a high PSA (prostate specific antigen) level. The patient had no particular history with the exception of high blood pressure controlled under treatment. The PSA level was 7.28 ng/ml (was correlated with a false increase in PSA since the patient had been treated a few days before for a urinary tract infection); 6 months later the PSA level was 10.37 ng/ml. Clinically, palpation revealed an enlarged, indurated prostate. Twelve ultrasound-guided biopsies were performed, suggesting an acinar adenocarcinoma associated with a large cell neuroendocrine carcinoma, Gleason score of 7 (3+4). A CT scan was performed and then completed with a PET scan (since the neuroendocrine component was predominant) showing metabolic hyper-uptake of the prostate with absence of secondary localizations.

The patient underwent a prostatectomy with lymph node dissection, the anatomo-pathological result of the operating specimen confirmed the result of the biopsies, and it was a mixed tumor with a predominant neuroendocrine component (confirmed by immunohistochemistry, with marking at synaptophysin and chromogranin A and a Ki67 of 70%. The tumor was classified pT4 N2 (2/13) (invasion by the neuroendocrine component).

The patient subsequently benefited from adjuvant treatment with chemotherapy followed by radiotherapy, the chemotherapy used was a combination of cisplatin + etoposide 3cures followed by radiotherapy to the pelvis. Note that the PSA level after surgery and adjuvant treatment was negative (0.02ng/ml), then the patient was placed under clinical radiological and biological monitoring. Currently one year later the PSA level is still negative (0.01 ng/ml) and there is no radiological recurrence.

Discussion

Neuroendocrine prostate cancer is a rare entity with a poor prognosis. It can present in a pure form (small or large cell neuroendocrine carcinoma) or mixed, that is to say associated with an adenocarcinomatous contingent. The first descriptions of cells of the neuroendocrine system are relatively recent, dating from the mid-20th century. In normal prostate glandular epithelium, there are rare neuroendocrine cells (less than 1%) scattered within secretory epithelial cells and basal cells [2]. Neuroendocrine cells are physiologically involved in the development of the prostate gland and the control of secretion via autocrine and paracrine mechanisms [3], they are recognizable by the absence of androgen receptors and the marking by certain immunohistochemical markers, such as chromogranin and synaptophysin.

Neuroendocrine cancer represents 0.1 to 10% of prostate cancers, depending on whether we consider "pure" or mixed variants, that is to say associated with an adenocarcinomatous contingent. The mixed form is observed more frequently (approximately 50–65% of cases) [2]. The presence of a neuroendocrine contingent has a poor prognosis [3] for both pure and mixed forms, the difference in survival between the two forms not being significant [4]. Epstein et al. [5] proposed a morphological, immunohistochemical and biological classification of neuroendocrine carcinomas of the prostate given the heterogeneity of these tumors. They identify adenocarcinoma with Paneth type neuroendocrine differentiation, carcinoid tumor, small cell neuroendocrine carcinoma, large cell neuroendocrine carcinoma and mixed type carcinoma combining adenocarcinoma/neuroendocrine carcinoma (large or small cells). This classification has been incorporated into the new World Health Organization (WHO) 2016 classification [6] focal neuroendocrine features of prostate adenocarcinoma correlate with high-grade and undifferentiated tumors. As adenocarcinoma and neuroendocrine cells may share hybrid immunohistochemical features in some cases, it is important to consider the classic morphological aspects of neuroendocrine tumor cells. Large neuroendocrine cancer cells are usually found in large nests with peripheral palisades [5].

Several hypotheses are discussed regarding the cell of origin of the neuroendocrine subtype of prostate cancer. One suggests that neuroendocrine cells derive from stem cells present in the basal layer of the prostate glands and that under the effect of pathological conditions such as "androgen depletion", these cells become malignant via paracrine signaling mechanisms [7-9]. Given the limited number of published cases and series, risk factors predisposing to the development of de novo neuroendocrine tumors have not been established [10]. The 2016 histological classification of tumors of the urinary and genital tract described three entities of neuroendocrine carcinoma of the prostate: neuroendocrine differentiation from adenocarcinoma, well-differentiated neuroendocrine tumors or carcinoid tumors, and poorly differentiated to small or large neuroendocrine tumor cells. The recognition of neuroendocrine tumors is based on morphological, functional and immunohistochemical criteria [1].

Pure forms, which do not secrete PSA, are often diagnosed at an advanced stage. Neuroendocrine tumors differ from adenocarcinoma by lack of PSA secretion, resistance to hormonal therapy, early metastasis, and rapid progression [11]. Small cell tumors are by far more common than large cell tumors which remain exceptional. The coexistence of the two forms within the same tumor can be observed [11]. Tu et al. report three cases of de novo pure large cell neuroendocrine tumors, diagnosed after transurethral resection of the prostate, with an unfavorable outcome under chemotherapy [10]. Evans et al. report a similar case with a tumor classified as pT3a after radical prostatectomy, the patient presenting a local and metastatic cerebral recurrence under adjuvant chemotherapy [12].

Therapeutic possibilities are similar to those for large cell neuroendocrine tumors of the lung and mainly involve chemotherapy given the resistance to hormonal therapy. The prognosis is generally unfavorable in locally advanced and metastatic stages, with very limited survival [13, 14].

The case that we report was diagnosed early and benefited from surgical treatment immediately followed by adjuvant treatment, with absence of recurrence after one year from the end of the adjuvant treatment. A fairly long median PFS compared to the cases reported in the literature, could confirm the need for early diagnosis.

Conclusion

Neuroendocrine carcinomas of the prostate are rare forms of prostate cancer with a poor prognosis. They encompass a multitude of entities with distinct tumor behavior and prognosis. A problem of therapeutic management therefore arises. Curative surgery should be considered in localized and locally advanced forms. The association with a hormone-sensitive adenocarcinoma component improves the prognosis. The

development of nuclear imaging modalities allows better monitoring and early diagnosis of recurrences, with largely optimized treatment.

Declarations

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