Case Report

A testosterone-producing Leydig cell tumor metastasis during hormonal treatment of prostate cancer

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Abstract

We describe a patient with a testosterone-producing metastasis discovered during the follow-up of prostate cancer. The patient had a history of a Leydig cell tumor (LCT) in the right testicle for which he underwent radical orchiectomy at the age of 60 years. Within a year after orchiectomy, he was diagnosed with prostate cancer. He received a radical prostatectomy with pelvic lymph node dissection. Due to recurrent prostate cancer, he underwent salvage radiation to the prostatic fossa and pelvic lymph node stations with hormonal treatment for 3 years. After approximately 1.5 years of chemical castration, a significant increase in testosterone level occurred. Further, diagnostic evaluations and surgery revealed a testosterone-producing LCT metastasis in the retroperitoneum.

Keywords: Leydig cell tumor, metastasis, prostate cancer, testicular tumor, testosterone

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INTRODUCTION

Testicular malignancies are relatively rare and account for 1%–1.5% of all male malignancies and only 5% of all urologic tumors. About 95% of all primary testicular cancers are germ cell tumors.[1] Leydig cell tumors (LCTs) are the most common sex cordstromal tumors and comprise 1%–3% of all testicular cancers.[2] Only 10% of the LCTs classify as malignant.[1,2] The most prevalent sites of metastasis include the retroperitoneal lymph nodes (70%), liver (45%), lung (40%), and bone (25%).[1,3] In half of all patients with a primary LCT, an elevated testosterone level is found.[1,2]

CASE REPORT

In the outpatient department, a 65-year-old man was seen during follow-up after the treatment of a locally advanced prostate cancer. Laboratory findings revealed increasing levels of testosterone despite hormonal therapy.

His medical history mentioned a LCT in the right testicle for which he had undergone a radical orchiectomy in 2013. The tumor was 2.5 cm and radically excised. At pathologic examination, immunohistochemistry revealed the expression of melan-A, calretinin, and inhibin. Serum tumor markers for alpha-fetoprotein, beta-human chorionic gonadotropin, and lactate dehydrogenase were not elevated. These findings corresponded with the diagnosis of a pure LCT. Nine months later, he was evaluated for a positive family history for prostate cancer and elevated prostate-specific antigen (PSA). He was diagnosed with cT3bN0M0 prostate cancer with Gleason score 4 + 5 = 9

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and an initial PSA of 77 ng/ml. He received degarelix injections during 3 months followed by a nonnerve-sparing robotic-assisted radical prostatectomy (robot-assisted laparoscopic radical prostatectomy [RALP]) with lymph node dissection (LND) in 2014. A nice response to the degarelix injections was observed with a decrease in PSA level. However, before the surgery, PSA doubled from 42.6 to 96.36 ng/ml. The testosterone level before the surgery was low (<0.5 nmol/L). The pathological stage was ypT3b N0(0/13) Mx R1, Gleason score 4 + 5 = 9. After the surgery, PSA decreased to 0.52 ng/ml. Due to a new increase in PSA 7 months after RALP, a choline positron emission tomography–computed tomography (CT) was performed revealing local recurrence with bilateral lymph node metastasis around the external iliac vessels.

Considering his young age, he opted for locoregional treatment. He was treated with salvage external radiation to the prostatic fossa (70 Gy) and pelvic lymph nodes (56 Gy, in 35 fractions). In addition, he received goserelin injections initially planned for a period of 3 years. His PSA declined below the detectable level. Despite goserelin injections, an insufficient decrease in testosterone was observed (1.3 nmol/L) and bicalutamide was added. Due to the sustained increase in testosterone level, goserelin was replaced by leuprorelin. Nevertheless, the testosterone level continued to rise, and leuprorelin was substituted by degarelix. However, his testosterone level further increased from 5.0 to 22.9 nmol/L during a period of 5 months. His PSA level slightly increased along with the testosterone level from 0.05 to 0.14 ng/ml. Due to the lack of response to hormonal treatment, an ultrasound from the left testicle was performed showing no signs of pathology. Finally, CT scan of the abdomen/pelvis revealed a paracaval lymph node of 4 cm × 4 cm without malignant manifestations elsewhere [Figure 1]. The differential diagnosis included metastasis of LCT, prostate cancer, or pheochromocytoma. Working diagnosis was a LCT metastasis because of persistent elevated testosterone level and the absence of high cortisol or metanephrines in 24-h urine. An open retroperitoneal (paracaval) LND was performed. Immunohistochemistry of the paracaval lymph node revealed expression of the identical markers expressed by the primary LCT, and no expression of PSA was observed. Hence, the diagnosis of an LCT metastasis was confirmed. After retroperitoneal LND, the testosterone level declined from 35.1 to below detectable level. After the completion of the 3-year hormonal treatment, PSA remained low at first. However, 3 months after the completion of hormonal therapy, PSA increased to 15.8 ng/ml, whereas testosterone remained at castrate level. A gallium prostate-specific membrane antigen (PSMA) scan showed a solitary 2-cm pathologic lymph node with high PSMA uptake along the right common iliac vein. The lymph node was located at the border of the previous radiation field. Therefore, further radiation was not possible. He again received a salvage retroperitoneal lymph node excision. The lymph node was radically excised, and pathological examination revealed adenocarcinoma in concordance with prostate cancer. Figure 2a and b displays the histopathological examples of the patient's LCT nodal metastasis and prostate cancer nodal metastasis. A month after the surgery, PSA and testosterone levels were both undetectable. Figures 3 and 4a, b show the course of both diseases and the corresponding laboratory work. The patient remains under surveillance with PSA and testosterone measurements. He is in good clinical condition without any (lymph) edema.

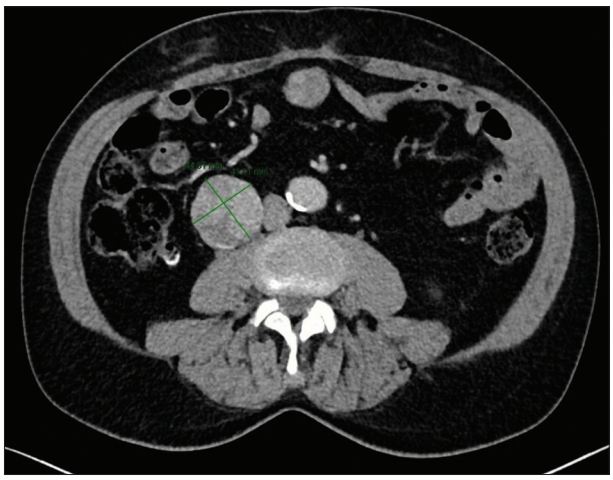

Figure 1: Computed tomography abdomen/pelvis – A transversal slice which demonstrates a paracaval mass of 4.1 cm × 4.3 cm with enhancement and calcifications in the lymph node wall

DISCUSSION

The cornerstone of hormonal therapy in prostate cancer is inhibiting the function of testosterone on the prostate cancer cell and thereby suppressing tumor proliferation. The proliferation of prostate cancer can be inhibited by blocking the androgen receptor on the prostate cancer cell or by

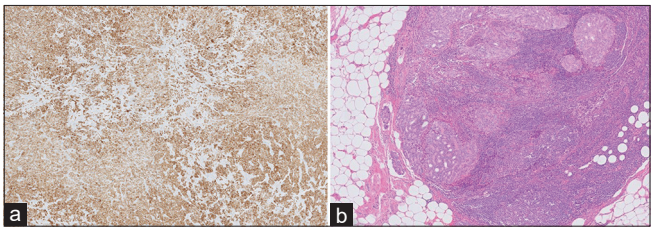

Figure 2: (a) A representative slide of the paracaval Leydig cell tumor metastasis (inhibin staining) showing high expression of inhibin removed in 2017. (b) Para-common iliac lymph node metastasis of prostate cancer: localized adenocarcinoma with a cribriform growth pattern removed in 2018

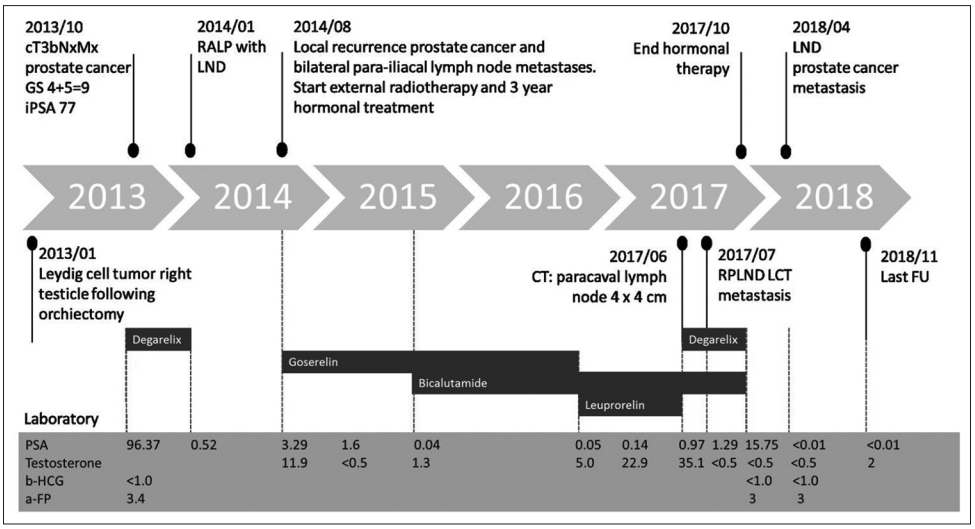

Figure 3: Course of the patient's diseases with concomitant laboratory findings. GS: Gleason score, RALP: Robot-assisted laparoscopic radical prostatectomy, LND: Lymph node dissection, RPLND: Retroperitoneal lymph node dissection, b-HCG: Beta-human chorionic gonadotropin, α-FP: Alpha-fetoprotein, FU: Follow-up

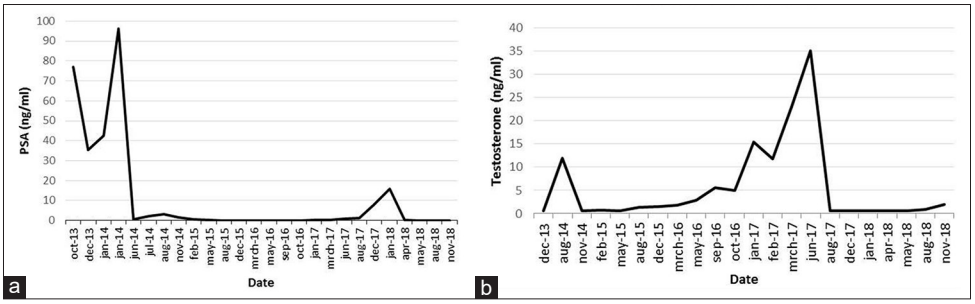

Figure 4: (a) Prostate-specific antigen curve. (b) Testosterone curve of the patient

restraining (testicular) testosterone production [Figure 5]. Testosterone production can be inhibited by luteinizing hormone-releasing hormone (LHRH) agonists, LHRH antagonists, or CYP17 inhibitors (impeding the synthesis of androgens).

Numerous studies have been performed investigating hormones and their possible role in the occurrence of prostate cancer. In particular, the influence of high testosterone levels on prostate cancer has been examined. This research showed that high serum concentrations of testosterone, dihydrotestosterone, or androgen derivatives were not associated with an increased risk of developing prostate cancer.[4] This may imply the absence of a causative relation between the high testosterone production of the LCT and the occurrence of prostate cancer in this patient.[5-7]

Another question that arises, in this case, is whether or not his testosterone level influenced the progression of his prostate cancer. The influence of testosterone levels on prostate cancer progression remains controversial. A relationship between testosterone levels and prostate cancer progression is not clear because contradictory results have been published on this subject.[8] The patient in our case report had a high-grade prostate cancer with an initial PSA of 77 ng/ml. His testosterone level at that time was within normal ranges (10 nmol/L). This makes progression of prostate cancer as a result of the primary LCT not likely.

After RALP, the patient initially had a rapidly rising PSA, which may be explained by local and nodal recurrence of prostate cancer. After the treatment, PSA level dropped to undetectable. Subsequently, testosterone began to rise along with a modest increase in PSA. In the end, this could only be explained by a testosterone-producing tumor because gonadotrophins were maximally suppressed, and an adrenal cause for testosterone production had been excluded. The LCT metastasis caused PSA to rise and might have had a counteractive effect on the hormonal treatment for prostate cancer. On the contrary, hormonal therapy might also have attributed to an enduring suppression of LCT progression.

We found only one case that described a patient with a hormone-producing retroperitoneal LCT metastasis in the literature. In this patient, a hormone-producing mass was discovered 7 years after the primary resection of

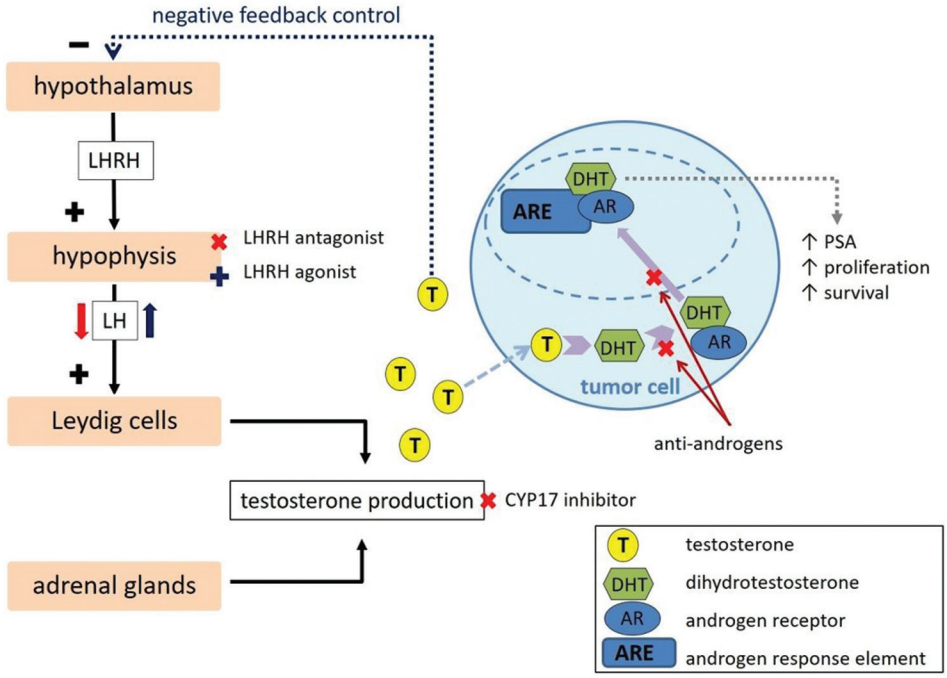

Figure 5: The effect of central regulation of luteinizing hormone secretion, the influence of testosterone on the prostate cancer cell, and mechanisms of androgen activation in the tumor cell. In addition, sites of action of hormonal therapy are illustrated

the LCT. This abdominal mass produced testosterone, estradiol, and cortisol.[9] LCTs in general do not metastasize, and according to our knowledge, this is the second case described in literature of a hormone-producing LCT metastasis and the first case discovered during hormonal treatment of prostate cancer.

CONCLUSION

LCT is a very rare testicular neoplasm of which only a fraction metastasizes and can be considered malignant. This case provides evidence that a LCT metastasis can produce ectopic testosterone and that this may interfere with the hormonal treatment of prostate cancer in the same individual.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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