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A Patient (46XX) With Congenital Adrenal Hyperplasia and Prostate Cancer: A Case Report

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Congenital adrenal hyperplasia (CAH) can affect sex characteristics. The most common cause of CAH is 21-hydroxylase deficiency, and the cornerstone of treatment is glucocorticoid replacement in adrenocorticotropic hormone-suppressive dosages. A 64-year-old patient (46XX) with CAH resulting from 21-hydroxylase deficiency had been treated with dexamethasone and testosterone since diagnosis at age 12 and was phenotypically male. At age 62, he was diagnosed with prostate carcinoma. The patient received curative treatment with external beam radiotherapy. Genotypically female patients with CAH can develop prostate carcinoma when receiving long-term testosterone replacement therapy.

Freeform/Key Words: 46XX, CAH, prostate carcinoma, testosterone replacement

The most common cause of congenital adrenal hyperplasia (CAH) is 21-hydroxylase deficiency, which causes both cortisol deficiency and androgen excess as a result of increased pituitary adrenocorticotropic hormone secretion. Excessive adrenal androgens cause virilization. This can vary from clitoromegaly to completely masculinized external genitalia and can lead to wrong assignment of sex at birth. Patients with CAH are treated with glucocorticosteroids to compensate for cortisol deficiency and to suppress adrenal androgen excess, thereby preventing virilization in female patients.

We describe a karyotypic female (46XX) patient with CAH and complete virilization who developed prostate carcinoma on long-term testosterone replacement.

1. Case Presentation

The patient, phenotypically male and raised as a boy, was diagnosed with CAH at the age of 12 years. Chromosomal analysis revealed an XX karyotype and, because of the late onset of the disease, the patient continued as male. The uterus and adnexa were surgically removed, and dexamethasone and testosterone replacement was instituted. Other notable medical history included a low anterior resection at age 60 because of adenocarcinoma (pT1N0) of the sigmoid.

Prostate specific antigen (PSA) measurements were performed annually according to the protocol for testosterone replacement. PSA levels gradually increased from 1.4 ng/mL in 2009 to 4.6 ng/mL (reference, <4 ng/mL) in 2015 (Fig. 1). Pelvic magnetic resonance imaging showed an 8-mm soft-tissue mass encircling the urethra that, considering the location, could be consistent with a rudimentary prostate. No vesiculae seminales or testes were visible.

Abbreviations: CAH, congenital adrenal hyperplasia; PSA, prostate-specific antigen.

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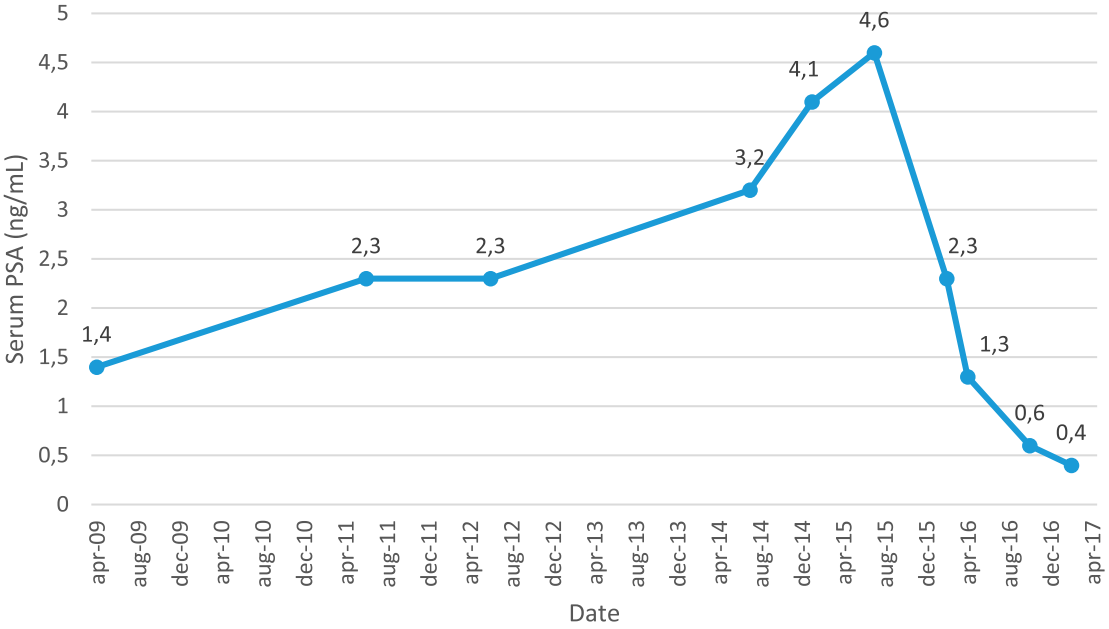

Figure 1. Serum PSA over time. Decreasing PSA after start of radiotherapy (September 2015).

A positron emission tomography/computed tomography scan using a prostate-specific membrane antigen ligand (^{68}Ga) showed a ^{68}Ga– prostate-specific membrane antigen ligand–enhancing lesion on the right side of the mass; it was highly suspected to be prostate carcinoma. There were no signs of lymph node metastasis or distant metastasis. Biopsies confirmed the diagnosis of Gleason 4 + 3 = 7 adenocarcinoma of the prostate (Fig. 2).

The patient was treated with curative external beam radiotherapy. Other than mild irritative lower urinary tract symptoms, there were no side effects. Eighteen months after treatment, the patient's PSA level was 0.4 ng/mL (Fig. 1).

Because the contributing role of testosterone replacement in this specific case was unknown, testosterone dose was lowered. This resulted in erectile dysfunction. After restoration of the initial dose, erectile dysfunction disappeared.

2. Discussion

To our knowledge, this is the second case reporting the development of prostate carcinoma in a karyotypic female patient with CAH [1]. However, this patient received exogenous androgen therapy and develops prostate carcinoma.

The presence of prostate tissue in female patients with CAH has been described in a limited number of cases [2]. The Skene gland, a *para*-urethral gland in females homologous to the prostate gland [3], can develop into tissue that is histologically identical to the male prostate in the presence of androgen excess [1].

In addition to dexamethasone, testosterone replacement was initiated in our patient because, at the time, given the late diagnosis of CAH, it was considered best to continue life as a male. In male patients with hypogonadism and testosterone deficiency, testosterone replacement therapy improves muscle mass, strength, and bone mineral density, and has positive effects on sexual function and desire [4]. Despite these desired effects, a study from 2010 including 229 urologists and 84 endocrinologists reported that doctors have reservations about testosterone replacement in hypogonadal men. In 11% of the patients, testosterone replacement was not provided, with concerns about the development of prostate cancer being the predominant reason (55%) [5]. An analysis of 18 prospective studies reported no association between the risk of prostate cancer and serum testosterone concentration, however [6].

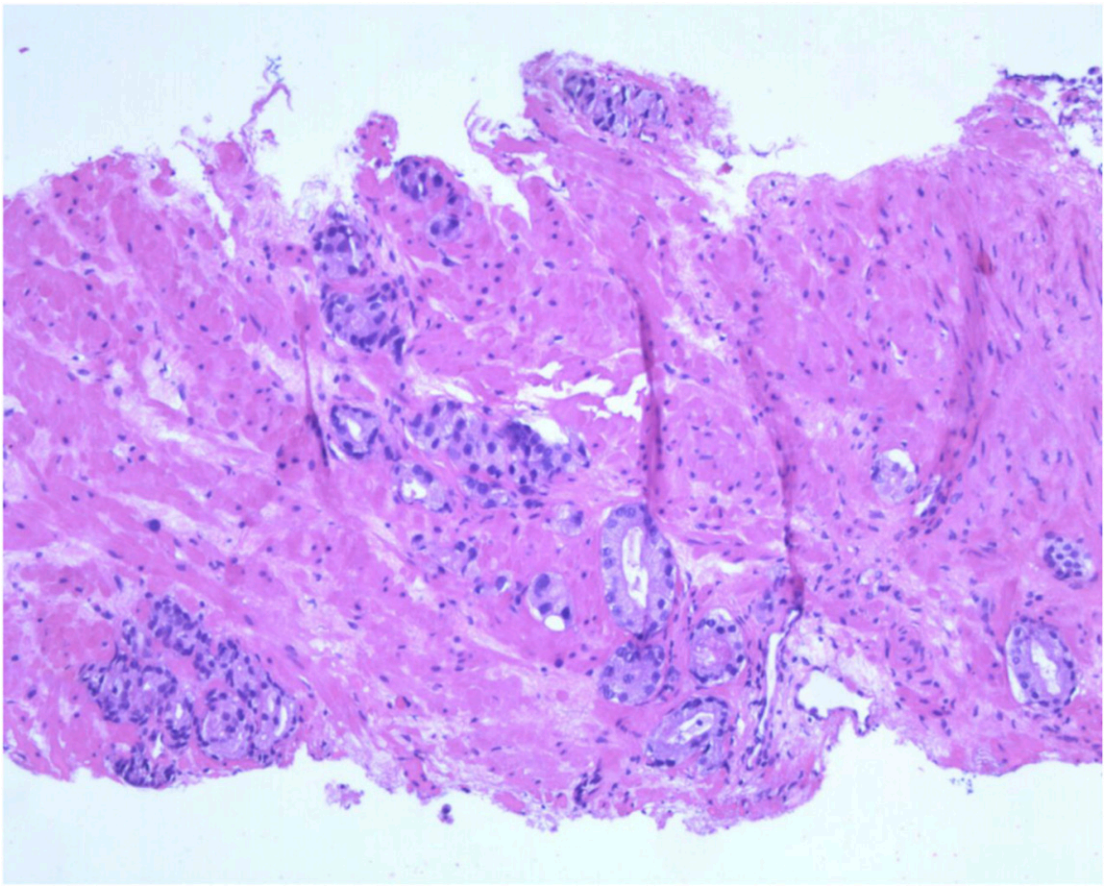

Figure 2. Biopsy specimen with Gleason 4 + 3 = 7 adenocarcinoma. Note the nucleomegaly, prominent nucleoli, and the absence of basal cells.

This can be explained by "the saturation model," which states that prostate growth is insensitive to testosterone concentrations above the near-castrate range [7], and is in line with studies on long-term testosterone replacement in hypogonadal men, which show no increased risk of prostate carcinoma [8, 9].

In addition, the available data indicate that, with careful monitoring, testosterone therapy in men with a history of prostate cancer also seems safe [10].

Our patient had received testosterone replacement for more than five decades, resulting in testosterone concentrations that were always within the normal reference ranges for men, adjusted for age. This contrasts sharply with the only other reported case [1], in which the patient had been exposed to high endogenous testosterone concentrations for 62 years. Therefore, in sporadic cases of genotypically female patients with CAH in whom testosterone replacement is indicated, we advocate screening for detectable circulating PSA. In the event of a positive result, periodic measurement of PSA in these specific cases can provide guidance to the treating physician for defining the optimal interval for PSA measurement during long-term follow-up.

3. Conclusion

We describe a case of prostate carcinoma in a karyotypic female patient (46XX) with CAH who received testosterone replacement to conserve male phenotype. The patient underwent curative treatment via external beam radiotherapy. To date, 18 months after treatment, serum PSA levels continue to decrease.

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