CLINICAL VIGNETTE

"Difficult to Treat Post-operative Hypothyroidism in Papillary Thyroid Cancer and Prostate Cancer, Treated with Apalutamide and Androgen Deprivation Therapy"

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A 53-year-old male with benign renal cyst status post right partial robotic nephrectomy, pre-diabetes, hyperlipidemia, and papillary thyroid cancer, T1bN1b status post total thyroidectomy and 100 mCi I-131 in 2018 and left neck dissection and 205 mCi I-131 in 2019, presented to endocrinology for management of post-operative hypothyroidism. With levothyroxine 175 mcg daily, he achieved TSH 0.14 (0.4-4.5 uIU/mL) with corresponding thyroglobulin (Tg) level of 0.7 (1.4-29.2 ng/mL)**.** Ultrasound neck demonstrated small right lateral neck lymph nodes. American Thyroid Association criteria included intermediate risk for recurrence and TSH suppression goals were 0.1-0.5 uIU/mL.

Screening PSA was elevated at 7.3 (0-3.5 ng/mL), and he was diagnosed with Gleason 9 prostate cancer. Prostate specific membrane antigen PET imaging was negative for distant metastases. Pre-operatively, he was treated with leuprolide and apalutamide. TSH 3 months afterwards was remarkably elevated to 57.4, and levothyroxine was increased to 200 mcg daily. Six weeks later, TSH remained elevated at 51, and levothyroxine was increased to 250 mcg daily. Notably, thyroglobulin was 1.1 and 0.7 ng/mL, respectively, with undetectable thyroglobulin antibodies. Repeat thyroid ultrasound reamained negative for abnormal right neck lymph nodes. Repeat TSH 6 weeks afterwards was still elevated at 26, at which time levothyroxine was increased to 300 mcg daily. Given patient's significantly elevated TSH and scheduled robotic-assisted laparoscopic radical prostatectomy, urology discontinued apalutamide. After prostatectomy, his levothyroxine was decreased to 200 mcg. Repeat TSH 2 months later was suppressed at 0.062 uIU/mL.

Discussion

Prostate cancer remains the most common cancer in males after skin cancer, affecting approximately one in nine men, and is the second leading cause of cancer death in US men. First line systemic treatment includes androgen deprivation therapy (ADT) to decrease circulating androgen levels. ADT commonly is accomplished with luteinizing hormone releasing agonists, such as leuprolide, goserelin, histrelin, or triptorelin. In metastatic castration sensitive prostate cancer, addition of docetaxel or abiraterone to ADT has shown improved overall survival, and has become standard of care.[1] Newer agents, including apalutamide, are used with androgen deprivation therapy prior to bilateral orchiectomy.

Apalutamide acts as a selective androgen receptor inhibitor, limiting testosterone binding to the androgen receptor and impeding nuclear translocation and DNA transcription.[2] In phase III clinical trials, have examined efficacy of apalutamide in combination with androgen deprivation therapy in metastatic castration sensitive prostate cancer (TITAN) and high risk non-metastatic castration resistant prostate cancer (SPARTAN).[1] SPARTAN, reported significant metastasis-free survival in the apalutamide group compared to the control group.[3] In both SPARTAN and TITAN, thyroid functions were evaluated every 4 months.[1] In the SPARTAN trial, hypothyroidism was noted in 8% of the apalutamide group versus 2% in the control group. In the apalutamide group, one patient discontinued treatment another had dose reduction. No treatment disruptions occurred in the control group. Thyroid replacement requirements increased in patients with pre-existing hypothyroidism treated with apalutamide, with median time to first TSH elevation of 113 days.[3] In TITAN, 6.5% of the apalutamide group reported hypothyroidism versus 1.1% in the control group. No patients discontinued apalutamide due to hypothyroidism.[4] The proposed mechanism for the increased levothyroxine requirements is apalutamide interacting with thyroxine and levothyroxine, decreasing their efficacy.[3]

We present a unique patient with two concomitant malignancies, in which treatment of one malignancy resulted in loss of control of the other. Given the history of thyroid cancer, thyroid function and thyroglobulin levels are closely monitored. This patient's TSH levels were significantly uncontrolled due to his treatment with apalutamide. Clinicians should be aware that apalutamide can result in significant increased thyroid hormone requirements. This is particularly important in circumstances with rigorous TSH goals, such as treatment of thyroid cancer. Thyroid hormone requirements can normalize after cessation of apalutamide, as seen in our patient. However, generally levothyroxine doses can be increased to achieve euthyroidism, and apalutamide does not need to be discontinued.

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