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Reduction of Testosterone with Leuprorelin Acetate below Normal Range as Treatment of Aging Related Metastasized Prostate Cancer Not an Optimal Longer-term Standard of Care

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Abstract

Background: The incidence and prevalence of prostate cancer is very high in aged individuals above 65 in the USA and across the globe, establishing it as a prominent aging-related disorder in men. Leuprolide acetate stands as a standard treatment for aging-related metastatic prostate cancer, aiming to lower testosterone levels to castrate levels.

Methods: This research report presents data from a patient with metastatic prostate cancer treated with leuprolide acetate to elucidate the agent's effectiveness and limitations in managing the metastatic prostate cancer. Additionally, curcumin, yellow spice gold from turmeric that works as an anticancer agent *via* multiple mechanisms including reduction in the androgen receptors and known to reduce PSA levels, was also taken as a supplement.

Results: Following the initial dose of Leuprolide acetate, significant reductions in testosterone and PSA levels were observed. However, castration-resistant prostate cancer developed after the second dose. Furthermore androgen depletion due to leuprolide acetate led to a substantial decline in hemoglobin levels, resulting in anemia.

Conclusion: Lowering testosterone levels below the normal range with leuprolide acetate for aging-related metastatic prostate cancer should not be viewed as an optimal long-term standard of care. Curcumin therapy is reported in some studies to reduce PSA levels, but did not seem to reduce PSA levels in the patient. Earlier surgical intervention and/or procedures like arterial embolization may offer superior protection, particularly in castration-resistant patients, compared to androgen suppression therapy.

Keywords: Prostate cancer • Curcumin • Testosterone

Introduction

Prostate cancer is a prevalent malignancy in the United States and globally, predominantly affecting men over the age of 65, with rare incidence in individuals under 40. Recent data from the American Cancer Society indicates that in 2025, approximately 313,780 individuals in the USA are projected to be diagnosed with prostate cancer, representing 15% of all new cancer cases and an estimated 35,770 (5.8% of all cancer deaths) deaths are expected [1]. Notably, roughly 60% of prostate cancer diagnoses occur in men aged 65 or older, establishing it as a significant age-related disorder in the male population. The incidence of prostate cancer is strongly correlated with age, becoming more common in individuals over 65, with a progressively increasing risk after the age of 50 [1].

Epidemiological studies outlined in the statistics by the National cancer institute referred above also indicate a higher prevalence in the Black population compared to other racial groups. Beyond age, several factors contribute to an elevated risk of prostate cancer, including dietary habits, exposure to specific chemicals, lifestyle choices, hormonal imbalances and genetic predispositions such as mutations in the BRCA1 and BRCA2 genes as reviewed in the recent articles, a book and references therein [2,3]. The number of cases with the prostate cancer are estimated to increase from 1.4 million in 2020 to 2.9 million in 2040 and due to various reasons discussed in this article published in the Lancet; these cases will progress to metastatic disease in many patients [4].

Various treatment modalities are available for prostate cancer [4,5]. Since 1944 androgen deprivation therapy (ADT) has been the cornerstone and first-line treatment for many stages of the disease [5]. However, the current standard treatment regimen presents several challenges. To optimize treatment strategies, a concise understanding of the etiology and progression of prostate cancer, as well as the advantages and limitations of ADT, is crucial. Comprehensive information regarding the epidemiology, etiology, pathogenesis and treatment options for prostate cancer is detailed in a book by Bott and Keng, along with numerous cited articles [3]. Many other publications also cover these aspects, including evolving insights into the pathogenesis and treatment approaches [4,5]. While a detailed discussion of the role of androgens and their receptors in prostate cancer pathogenesis is beyond the scope of this report, a brief overview is pertinent to its context.

In brief androgen levels are typically high in men during their twenties and thirties (approximately 300-1000 ng/dL) and naturally decline with age, generally remaining sufficient for reproductive function, but may result in hypogonadism in old age [6]. Given the significant inter-individual variability in normal androgen levels and the findings from recent studies indicating a weak direct correlation between blood testosterone levels and prostate cancer development, the predictive value of these hormone levels for disease progression is limited. Consequently, the role of testosterone/Androgen Receptors (ARs), rather than the circulating levels of androgens such as testosterone and its more active metabolite Dihydrotestosterone (DHT), is considered more critical in the progression of prostate cancer [2,4].

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In the early stages of the disease, prostate cancer cells retain sensitivity to androgen levels and androgens promote localized tumor growth through these ARs. As the disease advances and metastasizes to other organs, it is classified as "Advanced and Metastatic Hormone-Sensitive Prostate Cancer (mHSPC)", which is difficult to diagnose [7] because the cancer cells remain responsive to androgens and patients typically benefit from ADT [2,4]. However, with further disease progression, cancer cells can metastasize and continue to proliferate despite low androgen levels, a state termed Castration-Resistant Prostate Cancer (CRPC). The level of testosterone and Nadir PSA levels are monitored and compared to define if the prostate cancer developed is CRPC [8].

Traditionally, prostatectomy is the preferred treatment for localized prostate cancer, while ADT, with or without combination therapies, is the standard approach for metastatic disease [3-5]. Theranostic strategies involving radiation oncology are also employed, particularly for bone metastases [2]. Despite these therapeutic options, the involvement of multiple etiological factors and the dynamic changes in pathogenesis during disease transformation pose significant challenges in the effective management of prostate cancer. To illustrate these challenges, this report outlines the real-life clinical course of a 69-year-old male patient of Indian origin in the US who underwent ADT after being diagnosed with neuroendocrine carcinoma (C7A.8) and prostate cancer (C61) with metastatic well-differentiated neuroendocrine tumor (low Ki-67) and metastatic castration-sensitive prostate cancer (cT2cNxM1; Prostate cancer TNM staging AJCC UICC 8th edition) in November-December 2022.

Methodology

Treatment and data

The patient received two doses of leuprolide acetate, administered in January 2023 and July 2023, respectively. Although not part of the standard treatment protocol, it is noteworthy that the patient concurrently consumed oral curcumin with black pepper capsules (turmeric concentrate from You Theory; total daily dose=2250 mg/day) as a supplement until October 2024. This supplementation was discontinued for a six-month period after October 2024 and subsequently resumed in the last week of February 2025. The patient's decision to consume curcumin was based on its widely reported health benefits, particularly in the context of cancer, as supported by scientific literature. The levels of testosterone, Prostate-Specific Antigen (PSA) and hemoglobin before and during the treatment are detailed below. All these ranges have been evaluated if they are within the normal physiological range and/or within expected range after treatment.

Results

The patient was treated with the two doses of Lupron, the first one being administered in Jan 2023 and the second dose was administered in July 2023. Curcumin (Turmeric concentrate from You Theory; total daily dose=2250 mg/day) was administered daily until Octo 2024. It was discontinued for 6 months and was restarted again in the last week of Feb 2025.

The levels of testosterone, PSA and hemoglobin before starting the treatment, during the treatment are outlined below.

Following the initiation of leuprolide acetate treatment, the patient's hemoglobin levels exhibited a significant decline and did not return to baseline. On March 21st, 2025, the patient was hospitalized due to dizziness and subsequently discharged on March 22nd, 2025, after receiving a blood transfusion (Figure 1).

Leuprolide acetate treatment resulted in a significant reduction in Prostate-Specific Antigen (PSA) levels. However, approximately six months following the second dose, a significant increase in PSA was observed. In January 2025, subsequent to the arterial embolization procedure, PSA levels increased drastically, a transient effect anticipated to normalize over time. Nevertheless, even three months post-procedure, PSA levels continued to rise, reaching approximately 950 ng/mL in March 2025 (Figure 2).

Leuprolide acetate treatment resulted in a significant reduction in testosterone levels. Approximately one year following the second dose, testosterone levels returned to within the normal physiological range due to discontinuation of ADT and have remained stable within this range, even after the subsequent arterial embolization procedure. Although, within normal range, it is reducing after the arterial embolization treatment (Figure 3).

Following the first and second administrations of leuprolide acetate (administered as a six-monthly dose, totaling two doses per annum), testosterone levels decreased to below 50 ng/dL. Subsequent to the initial leuprolide acetate dose, prostate-specific antigen (PSA) levels were below 2 ng/mL, with a nadir PSA level of 0.26 ng/mL achieved three months post-treatment. However, despite sustained testosterone levels below 50 ng/dL after the second leuprolide acetate dose, PSA levels subsequently increased to above 3 ng/mL (Figure 4).

The X-Y plot illustrating testosterone levels (X-axis) against Prostate-Specific Antigen (PSA) levels (Y-axis) demonstrates a rise in PSA beyond the nadir achieved after the initial leuprolide acetate administration, consistent with the observations in Figure 4. These levels, as depicted in Figures 4 and 5,

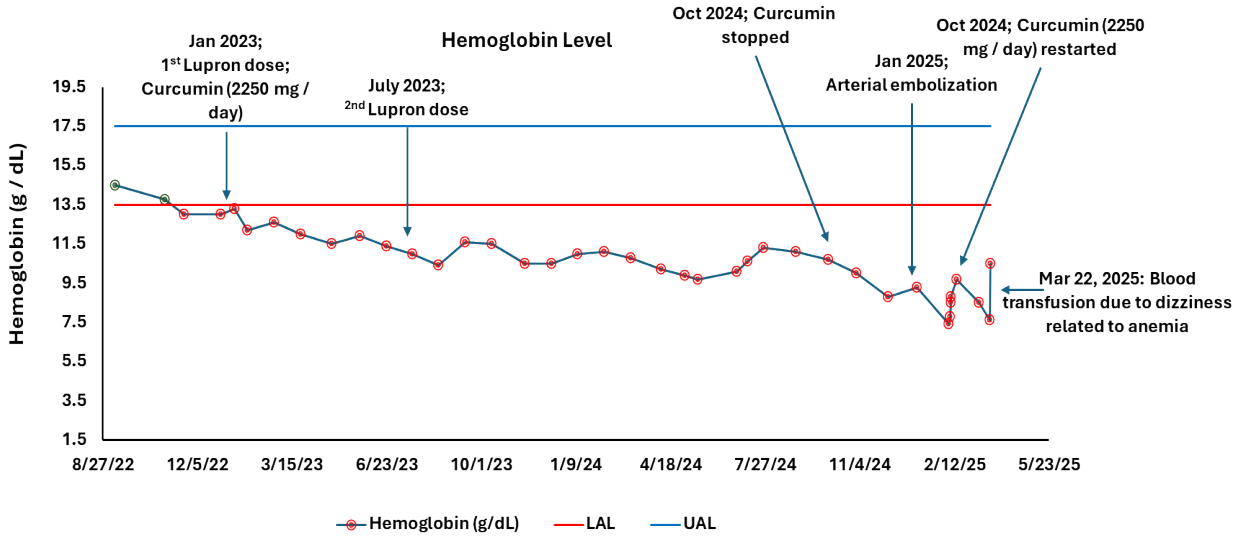

Figure 1. The level of hemoglobin in the patient's blood. LAL: Lower Acceptable Limit (g/dL); UAL: Upper Acceptable Limit (g/dL). The green color of the marker for data points indicates level within normal (acceptable) range, whereas red color of the marker indicates level beyond the acceptable range.

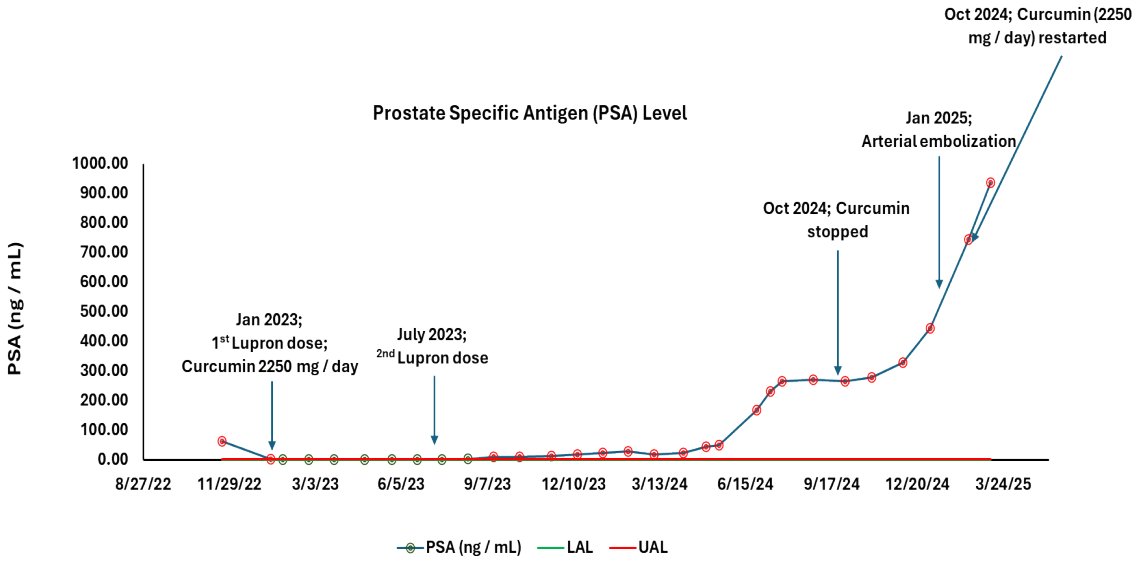

Figure 2. The level of PSA in the patient's blood. LAL: Lower Acceptable Limit (ng/mL); UAL: Upper Acceptable Limit (ng/mL). The green color of the marker for data points indicates level within normal (acceptable) range, whereas red color of the marker indicates level beyond the acceptable range.

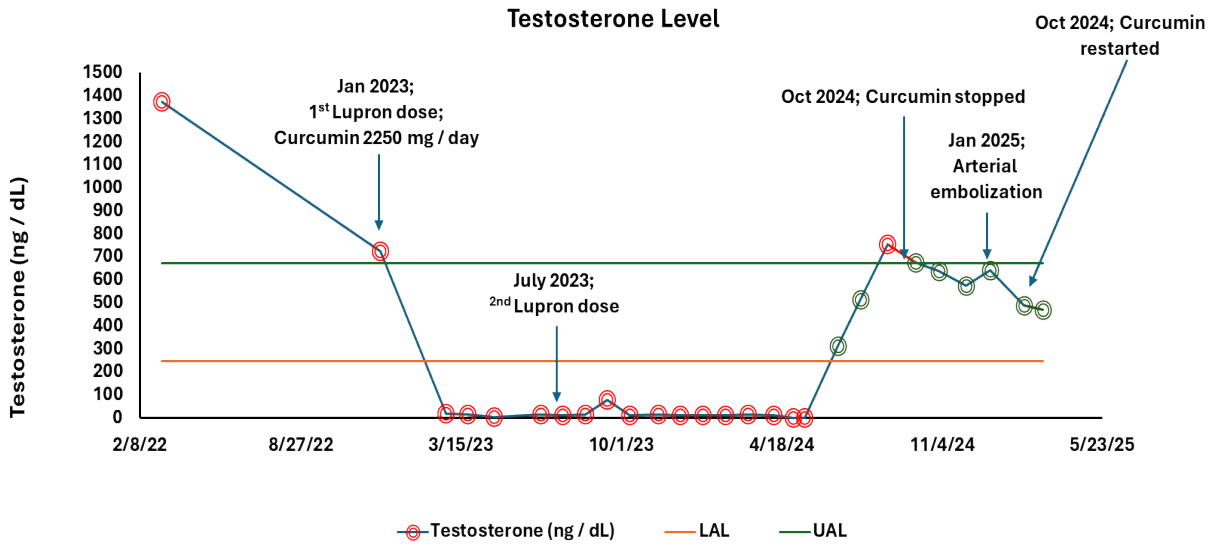

Figure 3. The level of testosterone in the patient's blood. LAL: Lower Acceptable Limit (ng/dL); UAL: Upper Acceptable Limit (ng/dL). The green color of the marker for data points indicates level within normal (acceptable) range, whereas red color of the marker indicates level beyond the acceptable range.

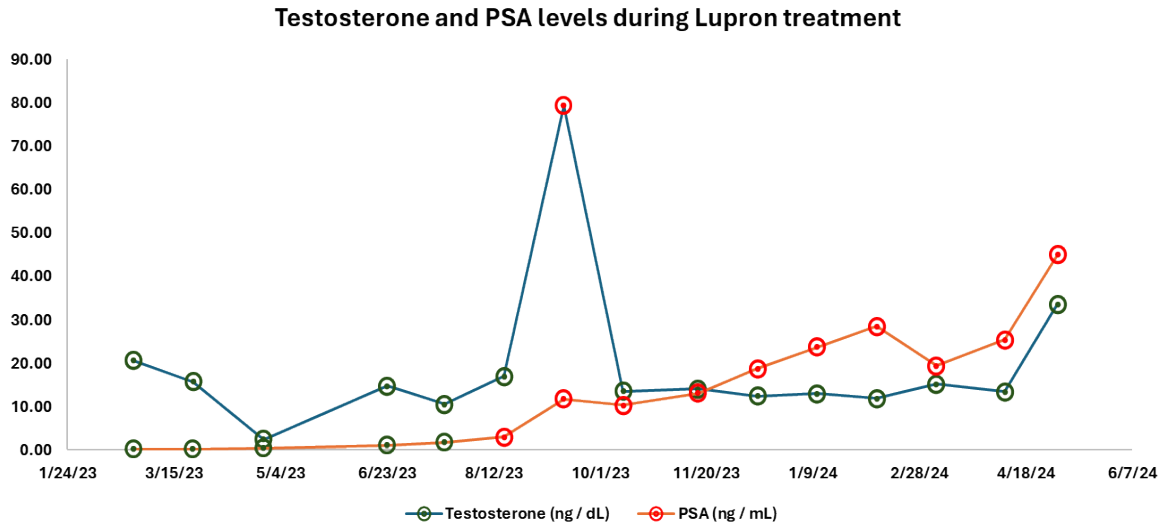

Figure 4. Relative comparison of PSA *vs*. testosterone levels in the patient's blood during Lupron treatment. The green color of the marker for data points indicates level considered acceptable for the success of therapy, whereas red color of the marker indicates level beyond the acceptable range.

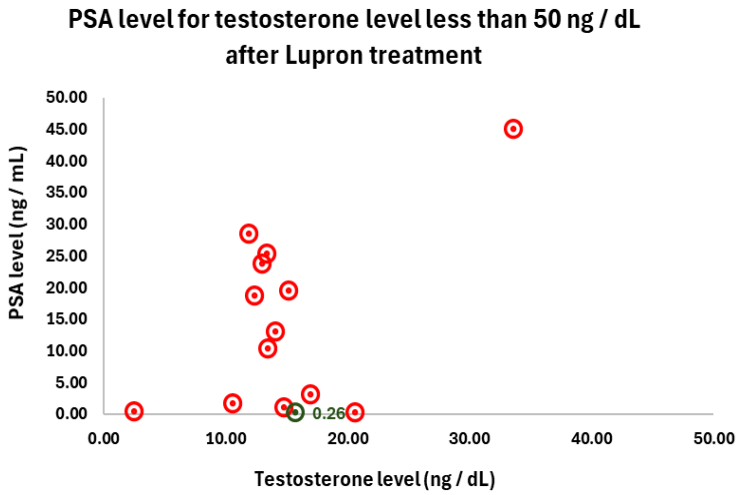

Figure 5. PSA level for testosterone below 50 ng/dL in the patient's blood during Lupron treatment. The green color of the marker for data point indicates nadir PSA level (i.e. the lowest PSA level obtained) after Lupron treatment.

suggest the development of castration-resistant prostate cancer in the patient, indicating a lack of sustained response to leuprolide acetate treatment. This biochemical evidence, potentially corroborated by radiographic findings and/or clinical symptoms, indicated cancer progression despite castrate levels of testosterone (<50 ng/dL or <1.7 nmol/L). Although, the prostate cancer was initially sensitive to ADT, it later transformed into the castration resistant form. Consequently, the patient was treated with Pluvicto®, a treatment approved by the US-FDA for castration-resistant prostate cancer. However, as shown in Figure 2, PSA levels remained elevated and continued to increase in the patient's blood despite this subsequent therapy (Figure 5).

Discussion

Prostate cancer is a complex, multifactorial disease in which Androgen Receptors (ARs) play a pivotal role. It represents a leading age-related disorder and a significant cause of mortality in males. The current and developing approaches for the various biomarkers is reviewed in detail in a recent review article [9]. Current biomarkers lack the necessary precision to accurately predict the progression of the disease to more aggressive stages, such as mHSPC and CRPC. Probably, this limitation complicates efforts to prevent disease advancement and to initiate timely and appropriate therapeutic interventions.

The Prostate cancer TNM staging system, as defined by the American Joint Committee on Cancer (AJCC) and the Union for International Cancer Control (UICC) in its 8th edition (effective for cases diagnosed on or after January 1, 2018), is a comprehensive system used to classify the extent of prostate cancer based on recent modifications [10]. TNM stands for Tumor, Nodes and Metastasis and it describes three key aspects of the cancer. This ICD-10 code were used to define the neuroendocrine tumor a (C7A.8) and malignant neoplasm of the prostate (C61; carcinoma of the prostate).

Hormone therapy, or Androgen Deprivation Therapy (ADT), has been a standard treatment for prostate cancer since its conceptualization by Huggins and Hodges in the 1940s [11]. The primary objective of hormone therapy is to reduce androgen levels or directly antagonize androgen receptor signaling. The principal androgens driving prostate cancer cell growth are testosterone and Dihydrotestosterone (DHT), primarily produced by the testes. However, the adrenal glands and the prostate cancer cells themselves can also synthesize these hormones. Consequently, orchiectomy, or surgical castration, is as effective as hormone therapy in reducing prostate tumor volume [3,5,11]. Nevertheless, many patients also go for ADT where patient selection is based on certain criteria [12].

Pharmacological interventions aimed at reducing androgen levels encompass various approaches, as detailed below

Luteinizing Hormone-Releasing Hormone (LHRH) agonists are among the most commonly prescribed pharmacotherapeutic agents [3,5,11,12]. These drugs effectively lower androgen levels to a similar extent as orchiectomy and include medications such as leuprolide acetate (Lupron, Eligard), leuprolide mesylate (Camcevi), goserelin (Zoladex) and triptorelin (Trelstar). The information of these agents and their product brochures is freely available on the internet. LHRH antagonists, including enzalutamide, apalutamide and darolutamide, are also utilized as hormonal therapies for prostate cancer treatment [11]. Additionally, agents such as abiraterone (a CYP17 inhibitor) and ketoconazole (an antifungal agent with known androgen-reducing properties) have demonstrated efficacy in lowering androgen levels [11].

In the present case, leuprolide acetate (Lupron) was selected as the primary treatment. Furthermore, the patient (GJK), a scientist with extensive research experience including numerous patents, publications (nearly one hundred) and citations (6000) and also a co-author of this article, decided to incorporate curcumin into his regimen based on its reported anticancer activity. The data presented herein expands upon a previously published short report concerning ADT and curcumin in the context of prostate cancer treatment [13]. Curcumin is tested in many chronic diseases and also in clinical trials [26] and tested in Kotwal's lab for complement inhibition. Although the potential efficacy of curcumin in treating prostate cancer was unknown to the patient at the initiation of its use, subsequent literature review indicated preclinical evidence supporting its anticancer properties in this disease. Laboratory studies suggest that curcumin may exert its effects in prostate cancer by modulating microRNA (miRNA)-mediated regulation of Androgen Receptor (AR) signaling [15]. Curcumin is also known to influence multiple cell signaling pathways, including AR, suggesting its potential therapeutic utility in Androgen-Dependent Prostate Cancer (ADPC) and androgen-independent prostate cancer (AIPC) [16]. Specifically, curcumin has been shown to reduce androgen-independent prostate cancer cells through the SAPK/JNK and MEK/ERK1/2 pathways, targeting NF-κB/p65 and MUC1-C [17]. *In vitro* studies indicate that curcumin may inhibit AR pathways at micromolar concentrations [18]. The curcumin analog Ca27 has also demonstrated beneficial anticancer activities in prostate cancer [19]. Clinically, curcumin has a well-established safety profile and is a widely consumed health supplement in the USA and globally. Based on this scientific rationale regarding the potential health benefits of curcumin, the patient self-administered 2250 mg of curcumin with black pepper in the form of a turmeric + black pepper concentrate (You Theory, USA). It is important to note that this was not part of the standard prescribed treatment but was taken concurrently with leuprolide acetate, informed by the available scientific literature suggesting its safety at higher doses and potential anticancer activity, although further validation is warranted. Denosumab (Xgeva) was also administered and radiation oncology treatment was employed as clinically indicated.

Testosterone and Prostate-Specific Antigen (PSA) levels served as key standard biochemical parameters for monitoring, alongside other standard imaging modalities such as PET/CT copper dotatate scans, whole-body bone

scans, CT and MRI. These imaging studies were performed as needed to monitor neuroendocrine tumor growth, metastases and bone health. It has been reported that leuprolide acetate treatment can lead to anemia and/or reduced hemoglobin levels in some individuals [20]. A similar reduction in hemoglobin levels was observed in this patient (Figure 1) and persisted despite the discontinuation of ADT.

While leuprolide acetate has the potential to exacerbate metabolic disorders, including diabetes and dyslipidemia, it was well-tolerated by this patient. However, shortly after the second dose of leuprolide acetate administration, despite sustained testosterone levels below 50 ng/dL, PSA levels subsequently increased to above 3 ng/mL, indicating the development of CRPC. Thus, leuprolide acetate treatment failed to prevent the progression of prostate cancer to CRPC in this patient within just six months of treatment (Figure 4). This rapid progression could be attributed to known mechanisms of cellular adaptation to low androgen levels. In contrast, medical literature typically reports that leuprolide treatment effectively controls both PSA and testosterone levels, with CRPC development taking considerably longer, with median times of approximately 140.7 months in low-risk groups and 20.5 months in high-risk groups [21]. However, in this specific patient, CRPC developed unusually early, within 6 to 9 months of initiating treatment. To the best of our knowledge, this represents an earlier onset of CRPC than typically reported. Furthermore, despite achieving low testosterone levels, PSA levels began to rise after the second dose of leuprolide acetate. Additionally, the patient's hemoglobin levels started to decline following leuprolide acetate treatment and remained low even after 18 months post-discontinuation, necessitating blood transfusions. This suggests a long-lasting effect of leuprolide acetate on hemoglobin levels in this patient, persisting well after cessation of therapy.

To the best of our knowledge, this case represents a rare occurrence in the medical literature, characterized by the rapid development of CRPC and long-term anemia shortly after the initial doses of ADT, with persistently low hemoglobin levels requiring blood transfusions months after treatment cessation. The development of CRPC following Combined Androgen Blockade (CAB) can be delayed with the use of abiraterone or enzalutamide [21-25]. These agents are frequently administered in conjunction with ADT. However, real-world data presented in a recent article in Prostate Cancer and Prostatic Diseases [24] indicates that overall survival with these agents as monotherapy is shorter, particularly in patients with pre-existing cardiovascular, diabetic and/or renal disorders. Consequently, novel therapeutic strategies are needed for the treatment of high-risk metastatic or CRPC. Moreover, the development of CRPC in this patient led to prostate gland enlargement, resulting in compression of adjacent organs and subsequent urinary retention and dysuria. Ultimately, the patient underwent Prostate Artery Embolization (PAE) to alleviate these symptoms. The patient was subsequently treated with PLUVICTO (lutetium Lu 177 vipivotide tetraxetan) for Prostate-Specific Membrane Antigen (PSMA)-positive metastatic Castration-Resistant Prostate Cancer (mCRPC) after prior Androgen Receptor Pathway Inhibition (ARPI), but PSA levels reached 231 ng/mL despite this treatment (Figures 2, 4 and 5). The patient requested discontinuation of PLUVICTO after three cycles in November 2024 due to its lack of efficacy. The patient was also on lanreotide for advanced or castration-resistant prostate cancer, targeting tumor growth and potentially reducing symptoms like bone pain, until February 2025. However, due to intolerable side effects and inability to adhere to the treatment, lanreotide was discontinued and the patient is currently only receiving denosumab (Xgeva).

Early surgical intervention, specifically radical prostatectomy (complete removal of the prostate gland), can be a life-saving option for localized prostate cancer. However, it is crucial to understand its role in comparison to Androgen Deprivation Therapy (ADT) and other pharmacotherapies. The decision regarding these treatments is complex and depends significantly on the socioeconomic factors, individual patient's age, fitness, cancer stage and grade, comorbidity etc [4].

Considering patient experiences and interactions with others who have undergone similar journeys with prostate cancer, many individuals have advocated for early prostatectomy. This review report also strongly recommends that various surgical options, preferably radical prostatectomy and/or artery embolization, should be discussed with patients at an early stage. Based on personal experience, there can be significant adverse events associated with pharmacotherapy, such as blood pressure fluctuations and anemia, where hemoglobin levels may not return to normal even after discontinuing treatment. Radical prostatectomy may potentially prevent at least these side effects of pharmacotherapy and/or the progression of the disease, although may not be suitable or useful in all the cases [4].

The real-world data discussed in this mini-review is critical, as it may assist physicians in making informed decisions for their patients and in discussing these approaches early in the disease course. Furthermore, this article, along with other case studies and reports, could also inform healthcare policymakers and/or insurance companies in making appropriate decisions for improved patient health and long-term prognosis, or in enhancing progression-free survival rates.

A comparable hormonal disorder in women is breast cancer, well-known for the "Angelina Jolie effect." Angelina Jolie publicly disclosed her decision to undergo a preventative double mastectomy at a relatively young age due to hereditary risks associated with the BRCA1 gene mutation [27]. In her 2013 New York Times op-ed, "My Medical Choice," she detailed her rationale. Her mother had passed away from ovarian cancer and Jolie learned she had an 87% risk of breast cancer and a 50% risk of ovarian cancer due to the gene mutation [27]. Her openness about her experience catalyzed the "Angelina Jolie effect," significantly increasing awareness in patients to prevent disease progression in high-risk patients [28,29].

Similar awareness should be promoted among aging individuals and/or their families to empower them to make informed decisions for themselves and their loved ones.

Conclusion

In conclusion, while ADT remains a standard first-line treatment for prostate cancer, it proved ineffective in controlling disease progression to CRPC in this particular patient with advanced disease. Furthermore, ADT failed to prevent prostate growth, leading to significant and poorly tolerated urinary complications. This case, along with other research, underscores the urgent need for the development of novel, safe and effective therapies to improve treatment adherence and achieve better control of prostate cancer. Early consideration of surgical intervention, either before or concurrently with ADT, may be warranted in certain cases.

Human and Animal Rights

Research involving humans

Not applicable. The patient himself is involved in writing this article based on the data generated for the various biochemical parameters as a part of standard treatment and follow-up.

Research involving animals

Not applicable.

Consent for Publication

The research article is the outcome of the original data of the patient and none of the Figures have been published elsewhere and it does not require any copyright to be obtained from any of the publishers.

Availability of Data and Materials

Data is taken from the patient's history on Norton MyChart app of the Norton Healthcare, Louisville, KY, USA. In the event of any doubt, data can be shared maintaining confidentiality agreements if required for any scientific scrutiny.

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Conflict of Interest

GK and APK work for InFlaMed Inc. However, this work is not related to InFlaMed Inc.

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