Very High Prostate Specific Antigen in an Asymptomatic Patient Leading to Diagnosing Metastatic Prostate Cancer in a Primary Health Care Center in Jeddah, Saudi Arabia

Abstract

Background: Prostate-specific antigen (PSA) is a key marker for prostate cancer (PCa) screening, diagnosis, and monitoring, though elevated levels can also stem from benign conditions like benign prostatic hyperplasia (BPH) or prostatitis. While PSA levels above 4.0 ng/mL warrant concern, the 4.0-10.0 ng/mL range is a "gray zone" with limited diagnostic clarity. Levels exceeding 10 ng/mL strongly suggest PCa, and those above 100 ng/mL often indicate advanced or metastatic disease. However, exceptionally high PSA can occur without malignancy, as seen in cases of severe prostatitis, emphasizing the need for a comprehensive diagnostic approach including clinical evaluation, imaging, and biopsy to avoid misdiagnosis or overtreatment. PSA kinetics like velocity and doubling time may offer further insights, though their utility with extremely high PSA is debated.

Our case report aims to present an asymptomatic patient with an unusually elevated PSA level that was then diagnosed to have metastatic PCa, to explore the challenges in differential diagnosis and management, and to contribute to the existing literature emphasizing the critical need for careful PSA interpretation and evidence-based approaches to prevent misdiagnosis and overtreatment.

Case presentation: A 68-year-old male with a history of Type 2 Diabetes Mellitus, Hypertension, and Bronchial Asthma presented for a routine check-up in March 2021, asymptomatic. An incidental **screening PSA** revealed an extremely elevated level of **211.66 ng/mL**. Subsequent investigations, including an abdomen and pelvis CT, showed an enlarged prostate, left external iliac lymphadenopathy, and **diffuse bone metastasis**, alongside dysmorphic liver features consistent with Hepatitis B-related cirrhosis. An extra-rectal prostate biopsy confirmed **Prostatic Acinar Carcinoma**. Despite multiple lines of chemotherapy (Abiraterone with Prednisolone and Androgen Deprivation Therapy, Docetaxel, Enzalutamide, Cabazetaxel) from March 2021 to April 2024, the patient's condition showed minimal improvement, leading to a diagnosis of **Castration-resistant Prostate Cancer with bone and lymph node metastasis**. PSA levels fluctuated throughout treatment, initially decreasing then rising significantly. Due to disease progression and declining health, he was transferred to palliative care and passed away in July 2024.

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Discussion: PSA testing is crucial for prostate cancer detection and monitoring, despite limitations in specificity. While guidelines recommend individualized screening, our case demonstrates how incidental PSA testing can reveal advanced, asymptomatic metastatic castration-resistant prostate cancer (CRPC). This aggressive disease, characterized by progression despite androgen deprivation therapy and common metastasis to bone and lymph nodes, presents significant management challenges. Current treatments for metastatic CRPC include androgen receptor signaling inhibitors, taxane-based chemotherapy, and radiopharmaceuticals, with selection guided by disease characteristics and patient status. The case underscores the complexity of metastatic CRPC, the evolving treatment landscape, and the increasing role of genomic profiling in personalized therapy. It emphasizes the need for careful PSA interpretation and a comprehensive approach to managing advanced prostate cancer.

Conclusion: This case highlights the diagnostic complexity of markedly elevated PSA levels in an asymptomatic patient and the necessity of a thorough clinical evaluation. The incidental discovery of metastatic castration resistant prostate cancer (CRPC) In this patient highlights both the potential utility and limitations of PSA testing. Incorporating PSA assessment into primary healthcare settings when guided by risk factors and clinical suspicion can facilitate earlier detection of significant pathology. This report reinforces the need for Individualized screening strategies, careful interpretation of PSA values, and clinical vigilance in both specialized and primary care contexts.

Introduction:

Prostate-specific antigen (PSA) is a glycoprotein secreted by both normal and malignant prostate epithelial cells, and its measurement in serum has become a cornerstone in the screening, diagnosis, and monitoring of prostate cancer (PCa) \[1]. Elevated PSA levels are commonly associated with prostate malignancy, but they may also result from benign conditions such as benign prostatic hyperplasia (BPH), prostatitis, urinary tract infection, or even recent ejaculation or prostate manipulation \[2,3].

A serum PSA level above 4.0 ng/mL traditionally raises concern for the presence of prostate cancer, although levels between 4.0 and 10.0 ng/mL fall into a "gray zone" where specificity and sensitivity are limited \[4]. PSA levels greater than 10 ng/mL are

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generally associated with a significantly increased likelihood of prostate cancer \[5]. However, PSA levels in the extremely high range (above 100 ng/mL) are unusual and typically suggest advanced or metastatic disease \[6]. In some cases, extreme PSA elevation has been reported in the absence of confirmed malignancy, raising questions about potential diagnostic pitfalls and the necessity for thorough clinical evaluation \[7].

Several case reports in the literature describe unusually high PSA levels without confirmed prostate cancer. For example, Patel et al. reported a case where a patient presented with a PSA level exceeding 1,000 ng/mL, but histopathology revealed no malignancy and instead showed florid granulomatous prostatitis \[8]. Another report by Kim et al. highlighted a case of a 68-year-old male with a PSA of 546 ng/mL, later found to have high-grade prostatitis but no evidence of carcinoma on biopsy \[9]. These cases underline the importance of a comprehensive diagnostic workup that includes clinical history, digital rectal examination (DRE), imaging, and prostate biopsy before concluding the presence of malignancy.

Moreover, PSA kinetics such as PSA velocity (rate of change over time) and PSA doubling time may aid in distinguishing between benign and malignant causes of PSA elevation \[10]. However, their clinical utility remains controversial, especially in cases of extremely high PSA levels without other supporting evidence of cancer \[11].

Given these complexities, our case report details a patient with an unusually elevated PSA level, exploring the differential diagnosis, diagnostic challenges, and management decisions. We aim to contribute to the growing body of literature that underscores the need for careful interpretation of PSA values and to advocate for evidence-based approaches to avoid overtreatment or misdiagnosis.

Case Presentation:

This is a case of a 68 year old male who is known to have Type 2 Diabetes Mellitus, Hypertension and Bronchial Asthma who is a non-smoker. He presented to the Primary Health Care (PHC) clinic back in March of 2021 asking for general routine laboratory workup. At that visit, he did not complain of any symptoms and general systemic review questions were all negative, including lower urinary tract symptoms.

His daughter then came back for follow up on April 2021 asking for lab results, all results were reassuring except for an extremely elevated level of Prostate Specific Antigen (PSA) which was 211.66 ng/mL (reference range: ~ 4 ng/mL). At that time, PSA

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level was ordered as a screening method for Prostate Cancer even though the patient did not show any symptoms for it or have any family history of any types of malignancy.

After seeing this PSA level result, an immediate referral to the Urology Surgery department was made.

He was then seen by Urology Surgery and they ordered an abdomen and pelvis CT for him and referred him to the Medical Oncology department.

Abdomen and pelvis CT showed the prostate to be enlarged and measured 4.9 x 4.4 x 3.2 cm with an estimated volume of 35.8 ml and demonstrated heterogenous enhancement. The left external iliac lymph node group measuring 1.5 cm. Dysmorphic features of liver were seen. Also, diffuse bone metastasis was seen.

Dysmorphic features of the liver were then correlated with a positive Hepatitis B virus serology with cirrhosis.

His later visit to the Medical Oncology clinic resulted in the decision to take an extra-rectal prostate biopsy.

Biopsy results showed Prostatic Acinar Carcinoma. The patient was then started on chemotherapy and went through multiple cycles including:

- Abiraterone with Prednisolone and Androgen Deprivation Therapy on March 2021
- Six cycles of Docetaxel on the 24th of May 2023
- Enzalutamide on the 11th of July 2023
- Five cycles of Cabazetaxel on the 7th of April 2024

All these cycles resulted in minimal improvement of the patient's general condition and was then labeled as Castration-resistant Prostate Cancer with bone and lymph nodes metastasis.

During the treatment for his disease, monitoring for Prostate Cancer was done by measuring PSA levels, shown in figures 1 and 2 is the trend for PSA and Free PSA (FPSA) readings respectfully.

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Figure 1

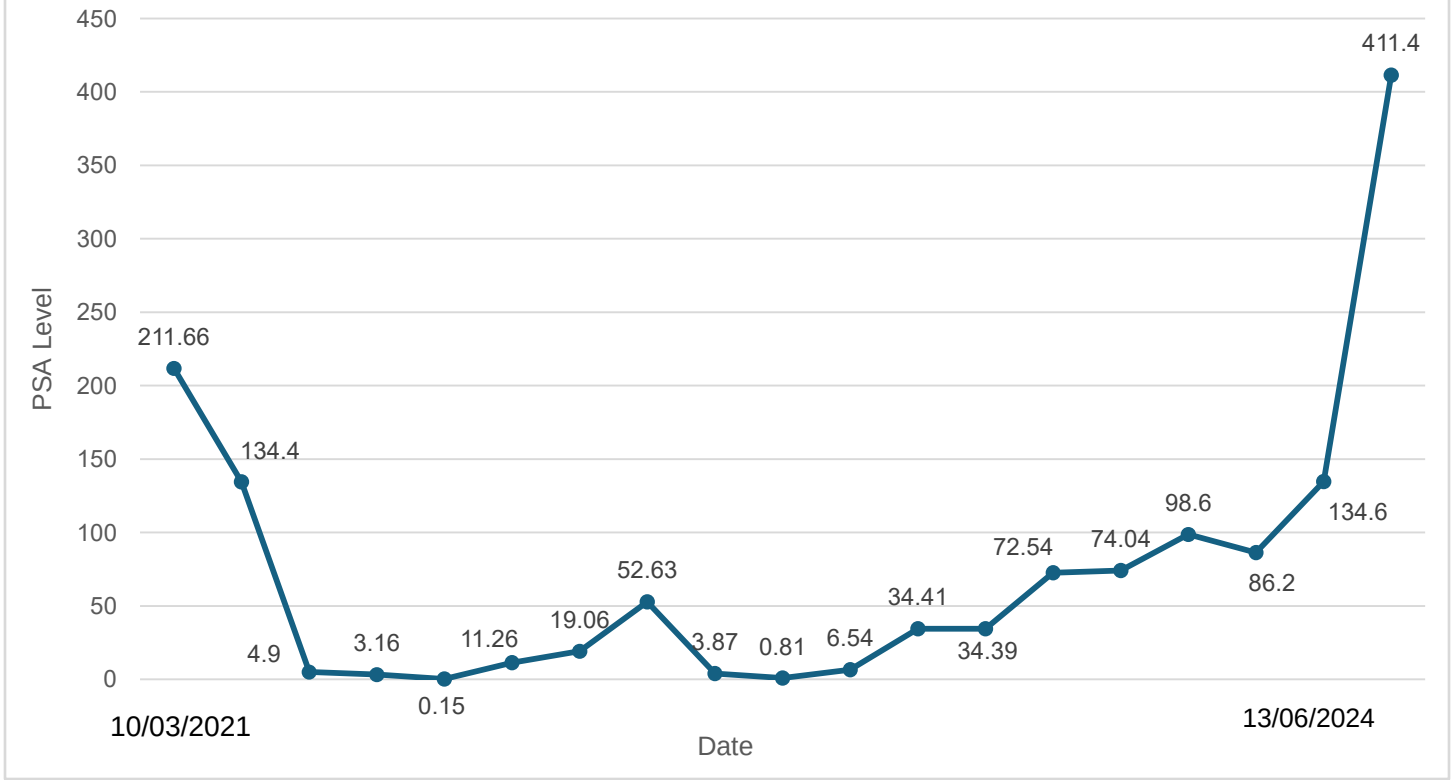
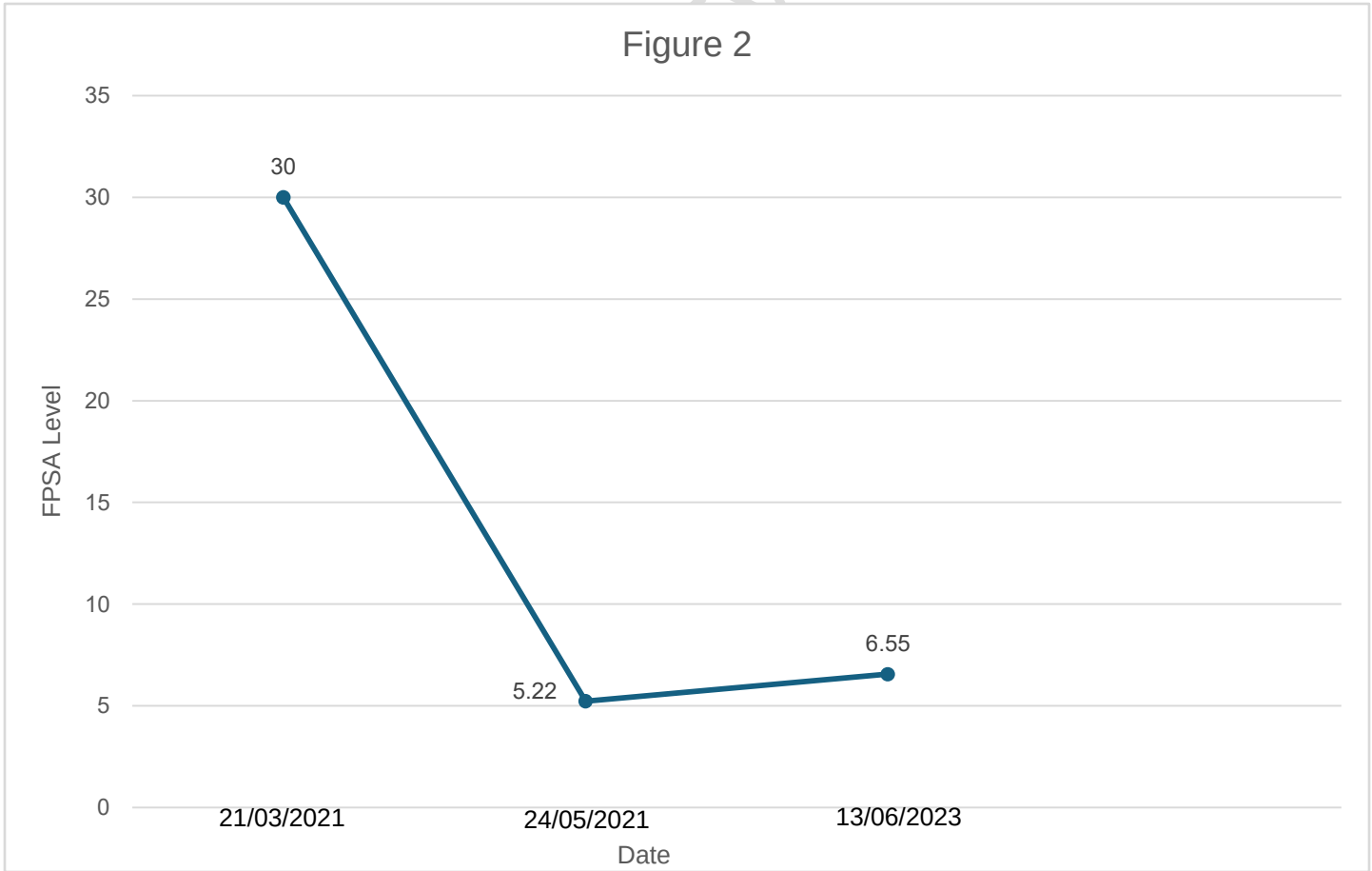


Figure 2



The patient was then transferred to Palliative Care due to poor response and general decline of his health condition due to progression of primary disease.

He was then admitted for the first time to the Palliative Care ward and stayed there for about one month with no improvement in his health condition. On the 9th of July 2024, the patient was found non-responsive with no pulse, no audible heartbeat, blood pressure undetectable and pupils fixed dilated, his death was announced then.

Discussion:

Prostate-specific antigen (PSA) testing plays a central role in the detection, monitoring, and management of prostate cancer. PSA is a serine protease produced by both normal and malignant prostate epithelial cells. While it is not specific to prostate cancer, its elevation often prompts further diagnostic evaluation. The sensitivity of PSA testing for prostate cancer ranges from 70% to 80%, while specificity is lower, approximately 60%, due to elevations seen in benign prostatic hyperplasia, prostatitis, and other non-malignant conditions (12, 2).

Despite its limitations, PSA remains the cornerstone of initial prostate cancer workup. Elevated PSA levels in asymptomatic individuals often lead to the detection of early-stage prostate cancer. However, this benefit must be weighed against the potential for overdiagnosis and overtreatment of indolent tumors. Data from large trials such as the European Randomized Study of Screening for Prostate Cancer (ERSPC) showed a relative reduction in prostate cancer mortality of about 20% among men undergoing regular PSA screening (13).

Guidelines regarding PSA screening vary. The U.S. Preventive Services Task Force (USPSTF) recommends that men aged 55 to 69 years engage in shared decision-making with their clinicians about PSA-based screening (14). The American Urological Association (AUA) advises similar individualized decision-making for men in the same age range, while discouraging routine screening in men over 70 or those with less than 10-15 years life expectancy (15). Meanwhile, the National Comprehensive Cancer Network (NCCN) provides risk-stratified screening protocols based on family history, race, and age (16).

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In this case, PSA testing—though not part of routine screening—contributed to the incidental diagnosis of metastatic prostate cancer. This highlights the dual nature of PSA: while not a perfect test, it remains a valuable biomarker in clinical practice when interpreted within context. Elevated PSA, especially in conjunction with clinical symptoms or abnormal digital rectal examination (DRE), warrants further investigation with imaging and histopathological confirmation.

Castration-resistant prostate cancer (CRPC) with metastasis remains a significant challenge in the management of advanced prostate cancer. The incidental diagnosis of metastatic CRPC, as seen in our patient, underscores the complexity and heterogeneity of this disease. Despite ongoing efforts to implement evidence-based screening protocols, incidental findings continue to occur, often revealing advanced disease at initial presentation.

CRPC is defined by disease progression despite androgen deprivation therapy (ADT), with castrate levels of testosterone (<50 ng/dL) (16). Once prostate cancer progresses to the castration-resistant stage, it typically demonstrates a more aggressive course and a higher likelihood of metastasis, commonly to bone and lymph nodes (17). Our patient exhibited metastatic lesions in both sites, reflecting the typical dissemination pattern.

The management of metastatic CRPC has evolved significantly over the past decade. Therapeutic options now include androgen receptor signaling inhibitors (such as abiraterone and enzalutamide), taxane-based chemotherapy (docetaxel and cabazitaxel), radiopharmaceuticals (radium-223 for bone metastases), and novel agents targeting DNA repair pathways (e.g., PARP inhibitors in BRCA-mutated cases) (18, 19). Treatment selection must consider disease burden, symptomatology, performance status, prior therapies, and molecular characteristics of the tumor (20).

Bone metastases are present in approximately 90% of men with advanced CRPC and are associated with significant morbidity, including skeletal-related events (SREs) (21). In this context, bone-modifying agents such as zoledronic acid and denosumab are recommended to reduce the risk of SREs (22). Our patient was initiated on bisphosphonate therapy as part of supportive care.

Although PSA screening for prostate cancer remains controversial due to concerns about overdiagnosis and overtreatment, some data suggest potential mortality benefits in appropriately selected populations (23). However, leading guidelines such as those from the US Preventive Services Task Force (USPSTF) recommend individualized decision-making regarding PSA testing, especially in men aged 55–69 years (24). This case highlights that incidental PSA testing, while not routinely recommended, can

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uncover advanced disease in asymptomatic individuals.

Genomic profiling is gaining increasing importance in the management of metastatic CRPC, particularly for identifying actionable mutations. Recent data support the use of next-generation sequencing to guide personalized therapy, including PARP inhibitors for patients with homologous recombination repair gene mutations (24). While our patient's molecular analysis is pending, future treatment will be guided by these findings.

In conclusion, this case emphasizes the importance of maintaining a high index of suspicion in patients with nonspecific symptoms and highlights the multifaceted approach required for managing metastatic CRPC. Ongoing research into biomarkers, novel therapies, and optimal sequencing of treatments continues to shape the evolving landscape of prostate cancer care.

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