Scientific Reports in Medicine

Case Report

Refractory thrombocytopenia after 177Lu-PSMA therapy: bone marrow infiltration (myelophthisis) versus treatment toxicity

Yasemin Aydinalp Camadan[1], Ertugrul Bayram[2], Tugba Toyran[3] , Tolga Köseci[4], Isa Burak Guney[5], Ismail Oguz Kara[6], Berksoy Sahin[7]

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Abstract

Lutetium is a radiopharmaceutical used effectively to treat metastatic castration-resistant prostate cancer (mCRPC). Myelosuppression can occur after lutetium therapy, and it can be difficult to distinguish between treatment-related toxicity and bone marrow infiltration (myelophthisis), especially in patients with extensive bone metastases.

A 60-year-old male patient with metastatic castration-resistant prostate cancer was scheduled for 177Lu-PSMA therapy after progression on docetaxel and abiraterone. Thrombocytopenia developed after the first course. At the same time, the patient developed infective endocarditis. Although platelet counts temporarily improved with infection management, severe thrombocytopenia recurred after the second 177Lu-PSMA cycle.

Bone marrow biopsy revealed infiltration by prostate adenocarcinoma. It was determined that the patient's thrombocytopenia was caused by cancer infiltration of the bone marrow and the resulting myelophthisis.

Hematologic toxicity is a recognized complication of 177Lu-PSMA therapy in patients with mCRPC and extensive skeletal involvement, bone marrow is essential to differentiate between effects caused by treatment and myelophthisis in cases of refractory cytopenia.

Keywords: Lutetium, Myelophthisis, Prostate cancer, Thrombocytopenia.

[1]University of Health Sciences, Sanlıurfa Mehmet Akif İnan Education and Research Hospital, Departmant of Medical Oncology, Sanlıurfa, Turkey
Email: yaseminaydinalp23@gmail.com
ORCID iD: 0000-0003-2435-368X

[2]Department of Medical Oncology, Cukurova University Faculty of Medicine, Adana, Turkey
Email: ertugrulbayram84@gmail.com
ORCID iD: 0000-0001-8713-7613

[3]Department of Pathology, Cukurova University Faculty of Medicine, Adana, Turkey
Email: tugbaolcan@hotmail.com
ORCID iD: 0000-0001-9135-0265

[4]Department of Medical Oncology, Cukurova University Faculty of Medicine, Adana, Turkey
Email: drtolgakoseci@gmail.com
ORCID iD: 0000-0002-8696-0525

[5]Department of Nuclear Medicine, Cukurova University Faculty of Medicine, Adana, Turkey
Email:isaburak@gmail.com
ORCID iD: 0000-0002-7642-9546

[6]Department of Medical Oncology, Cukurova University Faculty of Medicine, Adana, Turkey
Email:iokara@cu.edu.tr
ORCID iD: 0000-0003-4963-2028

[7]Department of Medical Oncology, Cukurova University Faculty of Medicine, Adana, Turkey
Email:berksoys@hotmail.com
ORCID iD: 0000-0002-3944-3891

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INTRODUCTION

Thrombocytopenia is a common hematological complication in cancer patients. Patients with cancer may develop thrombocytopenia for a variety of complex reasons. The most common causes of thrombocytopenia are systemic treatments, myelophthisis (marrow infiltration), tumor metastasis to the liver and spleen, liver failure, microangiopathic disorders such as disseminated intravascular coagulation, thrombotic thrombocytopenic purpura, or hemolytic uremic syndrome, infection, graft versus host disease, and other drugs (1).

Myelophthisis is a form of bone marrow failure resulting in anemia, thrombocytopenia, neutropenia, and pancytopenia of different severities. It happens when abnormal tissue replaces bone marrow precursor cells and their stroma, usually due to metastatic carcinomas. This condition generally appears in the later stages of the disease. The primary tumors most often linked to myelophthisis are solid cancers like lung, breast, and prostate cancers (2).

Prostate cancer includes a range of biological, clinical, and molecular characteristics. Metastatic castration-resistant prostate cancer (mCRPC) is characterized by disease progression despite androgen deprivation therapy (ADT). Recently, radioligand therapy (RLT) targeting the type II transmembrane glycoprotein prostate-specific membrane antigen (PSMA) has emerged as a new treatment option for patients whose disease is refractory to docetaxel and androgen receptor pathway inhibitors. Lutetium-177 (177Lu)-PSMA-617 delivers beta-particle radiation to PSMA-expressing cells and their surrounding microenvironment. Multiple retrospective and prospective studies have shown that 177Lu-PSMA-617 exhibits strong anti-tumor activity and is well tolerated in patients with mCRPC (3, 4).

In Lu-PSMA therapy, myelosuppression can be a dose-limiting factor. In the VISION study, approximately 25% of patients experienced significant (grade 3) hematological adverse events, including anemia in 68 patients (12.9%), leukopenia in 13 patients (2.5%), and thrombocytopenia in 42 patients (7.9%). Risk factors for myelosuppression during radionuclide therapy include bone malignancies, existing hematologic impairments, prior myelotoxic treatments, the activity dose per cycle, and treatment duration (5). In PSMA-RLT, bone marrow is identified as a tissue at risk, which may limit the amount of medication that can be given and its effectiveness. When cancer spreads to the bone marrow, hematological reserves may decrease. Due to insufficient bone marrow, patients may be unable to their current cytoreductive therapy, increasing the risk of disease progression (6). Deciding if myelosuppression is caused by treatment or disease progression can be difficult. The best approach to managing mCRPC with significant bone marrow involvement remains uncertain.

CASE REPORT

A 60-year-old male patient presented in May 2019 with nocturia and dysuria. His PSA level was measured at 4.9 ng/mL. The histopathological analysis of the prostate biopsy confirmed adenocarcinoma, with a Gleason Score of 9 (5+4). PSMA-PET/CT identified several bone metastases. The patient was started on maximum androgen blockade with goserelin and bicalutamide. Due to the extensive disease, he received six cycles of docetaxel (75 mg/m^2) and prednisone (10 mg/day) beginning in October 2019. By December 2020, his PSA level began to increase, indicating castration-resistant disease. Later, he was treated with abiraterone (1,000 mg/day), 10 mg/day prednisone, and denosumab, which led to a clinical response. In March 2021, he developed myocardial angina, resulting in the discontinuation of abiraterone.

By May 2021, the patient showed disease progression, including bone pain, radiographic progression, and increased PSA levels. Restaged 68Ga-PSMA PET/CT images are shown in Figure 1. Large, widespread PSMA-avid bone lesions were detected with 68Ga-PSMA PET/CT, with a maximum SUV of 47.34. The PSA level was 75 ng/mL.

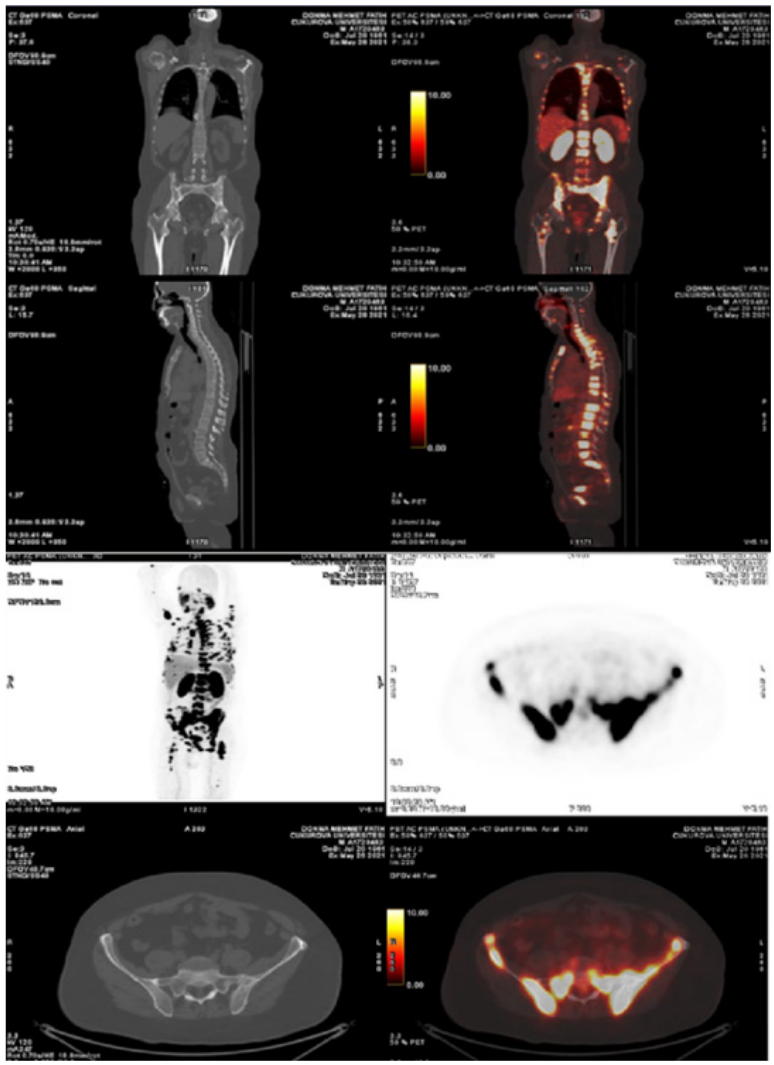

Figure 1: Restaged 68Ga-prostate-specific membrane antigen (PSMA) positron emission tomography (PET)/computed tomography (CT) images

Due to the high PSMA uptake in the bone lesions, the patient was treated with 177Lu-PSMA. Prior to treatment, the patient's laboratory parameters included a hemoglobin level of 9.9 g/dL, hematocrit of 28.5%, a platelet count of 105×10^9/L, and a white blood cell (WBC) count of 8.8×10^3/μL (neutrophils: 6.3×10^3/μL) (**Table 1**). In June 2021, following the first cycle of 177 Lu-PSMA therapy (200 mCi), the patient was hospitalized four days later due to fever. Laboratory evaluation showed a decline in hematological markers: hemoglobin 8.4 g/dL, hematocrit 24%, and platelets 63×10^9/L. Peripheral blood smear confirmed thrombocytopenia alongside anisocytosis and normochromic normocytic red blood cells. During this period, the patient developed mitral valve infective endocarditis, initially treated with meropenem and vancomycin. Following mitral valve replacement surgery, the antibiotic regimen was adjusted to daptomycin and fluconazole. After six weeks of therapy, laboratory values stabilized, with hemoglobin rising to 10.1 g/dL and platelets to 102×10^9/L. In August 2021, the patient, who showed improvement in laboratory parameters and overall clinical condition, received the second dose of 177 Lu-PSMA treatment (200 mCi). Ten days post-treatment, the patient presented with petechiae on the lower extremities and trunk. Laboratory tests confirmed severe thrombocytopenia with a platelet count of 5×10^9/L (**Figure 2**), while hemoglobin (10 g/dL) and WBC (4.2×10^3/μL). Peripheral

blood smear findings were consistent with the hemogram, showing no signs of hemolysis. Other biochemical parameters were largely within normal limits, including AST (40 U/L), ALT (15 U/L), total bilirubin (0.48 mg/dL), LDH (241 U/L), and creatinine (0.98 mg/dL). The patient had no history of heparin exposure, and inflammatory markers were low (procalcitonin: 0.17 ng/mL). Despite platelet transfusion, platelet levels did not increase.

Table 1: Laboratory Parameters During Treatment Course

Parameter (Unit)	Prior to Treatment	Post 1st Cycle	Prior to 2nd Cycle	Post 2nd Cycle
Hemoglobin(g/dL)	9.9	8.4	10.1	10.0
Hematocrit (%)	28.5	24.0	30.5	30
Platelets (x10⁹/L)	105	63	102	5
White Blood Cells (x10³/µL)	8.8	6.6	9.6	4.2
Neutrophils (x10³/µL)	6.3	5.6	7.3	1.3

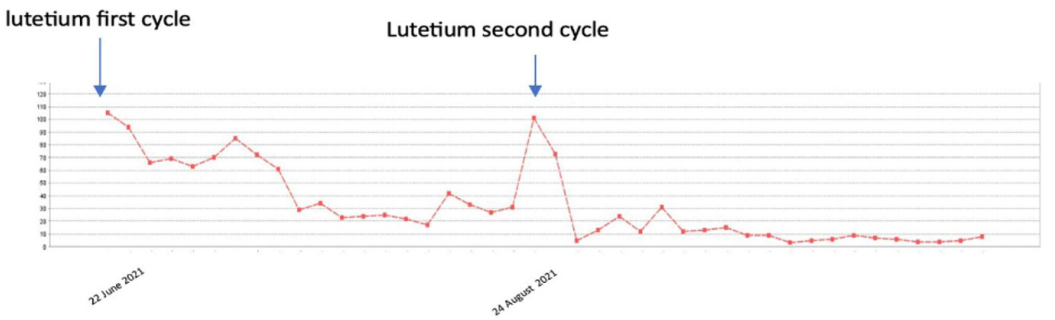

Figure 2: Platelet levels after lutetium therapy

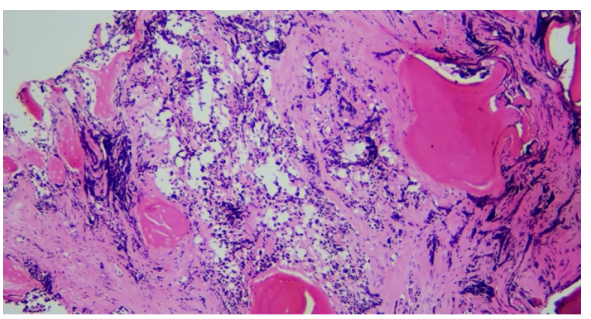

Figure 3A: Bone marrow biopsy, metastatic prostate carcinoma hematoxylin-eosin x200.

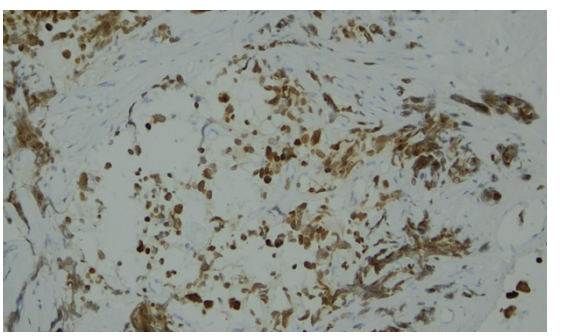

Figure 3B: Immunohistochemical stain NKX3.1 shows nuclear staining in tumor cells x200.

A biopsy and bone marrow aspiration were performed. Histopathologically, tumor clusters with extensive crush attenuation, large hyperchromatic nuclei, prominent nucleoli in some areas, eosinophilic cytoplasm, and glandular-structure-like areas were observed. (Figure 3A) Normal hematopoietic lineages, including megakaryocytes, were significantly depleted or obscured by the extensive fibroblastic activity and tumor infiltration, consistent with the patient's clinical thrombocytopenia. Immunohistochemical staining was used to determine the primary origin of the adenocarcinoma. The immunohistochemical staining of the biopsy revealed neoplastic cells that

were positive for keratin and NKX3.1 (Figure 3B) but negative for cytokeratin CK7, CK20, PSA, ERG, P63, TTF1, HMWK, Chromogranin, and sinaptofizin, indicating that cancer had spread to the prostate. During follow-up, the patient developed neutropenia and anemia. The patient died of neutropenic fever and sepsis.

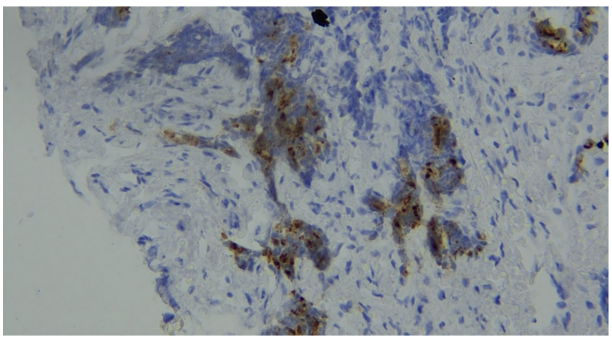

Figure 4: Immunohistochemical staining of the primary prostate biopsy specimen showing focal cytoplasmic PSA expression in neoplastic glandular structures (PSA, x200).

DISCUSSION

Myelophthisis is a rare and serious clinical problem that affects men with prostate cancer. When the disease spreads to the bone marrow, patients' hematological reserves may become compromised, potentially preventing them from receiving current cytoreductive therapy and increasing their risk of disease progression (7). In radionuclide therapy, blood-driven recirculating ß-irradiation and scatter radiation from bone metastases can cause or worsen myelosuppression (6). The use of RLT in this patient population has recently been studied retrospectively in a small number of trials. The findings of a study assessing the hematological safety of radioligand therapy with 177Lu-PSMA-617 in metastatic castration-resistant prostate cancer suggest that multiple cycles of RLT with 177Lu-PSMA-617 can be administered with acceptable rates of myelosuppression, with cytopenia being most often reversible, especially in earlier stages of disease progression (7). Platelet levels may normalize three to four months after PSMA-RLT treatment (8).

When there is a heavy burden of bone malignancies, previous chemotherapy with taxane-based drugs, or early stages of hematologic deterioration, significant new hematological adverse effects may appear (7). Our patient previously underwent treatment with docetaxel. Following that, he responded well to abiraterone treatment, but myocardial angina prevented the patient from completing the course of medication. In the third line lutetium therapy was administered. In a study that compared the effectiveness of Lu-PSMA treatment in patients with bone metastases based on the extent of bone involvement, the patients' survival showed a negative correlation with the degree of bone involvement. Response rates to therapy in patients with more than 20 bone lesions and widespread bone and bone marrow involvement were similar to those in the low-involvement group. However, it was found that these patients experienced higher rates of anemia and thrombocytopenia due to their treatment (9). Research examining potential links between hematological toxicity and treatment response in patients receiving PSMA-RLT found that patients with severe bone involvement and no post-treatment biochemical response experienced all grade 3 and 4 adverse events. (10) Our patient had multiple risk factors, including previous docetaxel treatment and widespread metastases in both the axial and appendicular skeleton.

In our patient, infectious endocarditis following the initial lutetium treatment complicated the cause of thrombocytopenia. The bone marrow biopsy was initially avoided because of the active infection and the improvement of cytopenia after treating the infection. However, after the second lutetium dose, thrombocytopenia recurred, and since there were no signs of new infection or toxic triggers, a bone marrow biopsy was performed. The biopsy confirmed the infiltration of prostate adenocarcinoma (myelophthisis) in addition to bone marrow fibrosis.

Table 2: Adverse Drug Reaction Probability Scale (Naranjo Algorithm)				
	Yes	**No**	**Do not know**	**Score**
1. Are there previous conclusive reports on this reaction?	+1	0	0	0
2. Did the adverse event appear after the suspected drug was administered?	+2	-1	0	+2
3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0	0
4. Did the adverse reaction reappear when the drug was readministered?	+2	-1	0	+2
5. Are there alternative causes (other than the drug) that could on their own have caused the reaction?	-1	+2	0	-1
6. Did the reaction reappear when a placebo was given?	-1	+1	0	0
7. Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	+1	0	0	0
8. Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	+1	0	0	0
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	0
10. Was the adverse event confirmed by any objective evidence?	+1	0	0	0
				Total score= 3

The immunohistochemical staining of the biopsy revealed neoplastic cells that were positive for keratin and NKX3.1 (Figure 3B) but negative for cytokeratin CK7, CK20, PSA, ERG, P63, TTF1, HMWK, Chromogranin, and Synaptophysin. The loss of PSA expression in the metastatic marrow lesion, despite its positivity in the primary tumor biopsy, is a significant finding. PSA is considered a highly specific marker for detecting metastases of prostate tumors, but its sensitivity is limited due to decreased or lost expression in higher-grade or metastatic tumors, making additional markers necessary. Pathologically, although PSA (Figure 4A) and NKX3.1 tested positive when applied immunohistochemically to the patient's first biopsy sample—where he was initially diagnosed with prostate adenocarcinoma—PSA was negative in the tumor that metastasized to the bone marrow, although NKX3.1 was positive. In the literature, the detection rate of prostate origin of metastasis for single markers was 100% for NKX3.1 and 80.8% for PSA. Therefore, it is emphasized that combining PSA with NKX3.1 demonstrates higher sensitivity (11). While PSA is highly specific for prostatic tissue, its expression is known to diminish or disappear in poorly differentiated and metastatic lesions. Recent large-scale tissue microarray studies have demonstrated that up to 15-20% of advanced castration-resistant cases exhibit partial or complete loss of PSA immunoreactivity. (12) Furthermore, in the setting of bone marrow metastasis, NKX3.1 has been shown to be a more robust and sensitive marker than PSA, maintaining positivity even when PSA is negative (13).

The Naranjo Adverse Drug Reaction (ADR) scale was used to assess the causal relationship between lutetium treatment and the development of refractory cytopenia. The clinical scenario resulted

in a Naranjo score of 3, indicating a 'possible' causal relationship between the radiopharmaceutical treatment and hematological toxicity in our patient (14). These findings suggest that, although underlying myelophytosis is the main factor, the treatment may have worsened bone marrow depletion.

Additionally, the presence of bone marrow fibrosis in this case highlights a rare but important consequence of metastatic prostate cancer adenocarcinoma. Due to tumor metastasis to the bone marrow, anemia and thrombocytopenia caused by fibrosis are typical (15). Causes of death due to marrow fibrosis include complications from progressive bone marrow failure, portal or pulmonary hypertension, infections, thrombosis, and bleeding (16).

CONCLUSION

Radionuclide therapies are an effective option for patients with metastatic castration-resistant prostate cancer (mCRPC) and are typically well tolerated. However, myelosuppression, especially in patients with extensive bone metastases, is the most critical and dose-limiting factor during treatment. Distinguishing treatment-related hematologic toxicity from bone marrow infiltration (myelophthisis) is crucial for clinical management. Bone marrow biopsy is essential for differential diagnosis. Our case highlights the significance of myelophthisis and the diagnostic value of bone marrow biopsy in patients who develop refractory cytopenia after lutetium therapy.

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Conflict of Interest

The authors declare that they have no conflict of interests regarding content of this article..

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Ethical Declaration

Informed consent was obtained from the participant and Helsinki Declaration rules were followed to conduct this study.

Authorship Contributions

Concept: YAC, EB, İBG, BŞ, Design: YAC, EB, İBG, BŞ, Supervising: İBG, BŞ, Financing and equipment: - Data collection and entry: YAC, EB, TT, İBG, BŞ Analysis and interpretation: YAC, Literature search: YAC, Writing: YAC, Critical review: YAC

Corresponding Author

Yasemin Aydinalp Camadan
University of Health Sciences, Sanlıurfa Mehmet Akif İnan Education and Research Hospital, Departmant of Medical Oncology, Sanlıurfa, Turkey
ORCID: 0000-0003-2435-368X

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