The Tyr Phenomenon: A Hypocalcemic Response in High-Volume Treatment Responders to ^{177}Lu-Prostate-Specific Membrane Antigen Therapy

Shejil Kumar*[1], Megan Crumbaker*[2], Christopher Harvey[2], Sarennya Pathmanandavel[2], Nikieth John[2,3], Mina M. Swiha[2,4], Michelle M. McDonald[5,6], Roderick Clifton-Bligh[1,6], Adrian Lee[7–9], Patricia Bastick[10], William Counter[2], Andrew Nguyen[2,3], and Louise Emmett[2,3,5]

[1]Department of Endocrinology, Royal North Shore Hospital, Sydney, New South Wales, Australia; [2]Department of Theranostics and Nuclear Medicine, St. Vincent's Hospital, Sydney, New South Wales, Australia; [3]St. Vincent's Clinical School, University of New South Wales, Sydney, New South Wales, Australia; [4]Schulich School of Medicine and Dentistry, University of Western Ontario, London, Ontario, Canada; [5]Garvan Institute of Medical Research, Sydney, New South Wales, Australia; [6]School of Medical Science, Faculty of Medicine and Health, University of Sydney, Sydney, New South Wales, Australia; [7]Department of Medical Oncology, Royal North Shore Hospital, Sydney, New South Wales, Australia; [8]Northern Clinical School, Faculty of Medicine and Health, University of Sydney, Sydney, New South Wales, Australia; [9]Genesis Care, Sydney, New South Wales, Australia; and [10]St. George Hospital, Sydney, New South Wales, Australia

^{177}Lu-prostate-specific membrane antigen (PSMA) is an effective treatment for metastatic castration-resistant prostate cancer. Rarer treatment-related adverse events have not yet been described. **Methods:** We present case reviews of 2 men with a marked hypocalcemic osteosclerotic response to ^{177}Lu-PSMA-I&T therapy. A clinical dataset of ^{177}Lu-PSMA-I&T therapy was evaluated to estimate the incidence and clinical association with hypocalcemia. **Results:** Forty-one of the 127 men (32%) had a serum calcium drop, and 6 (5%) developed clinical hypocalcemia during ^{177}Lu-PSMA therapy. The baseline total tumor volume was significantly higher in those who developed hypocalcemia (median, 3,249 cm^3 [interquartile range, 1,856–3,852] vs. 465 [interquartile range 135–1,172]; $P = 0.002$). The mean prostate-specific antigen response in those with hypocalcemia was 78% (SD, 24%). **Conclusion:** Hypocalcemia may occur in response to ^{177}Lu-PSMA-I&T, particularly with both high-volume bone metastases and a significant prostate-specific antigen response, and may be severe, requiring corticosteroids. Further evaluation of ^{177}Lu-PSMA–induced hypocalcemia is required to better understand mechanisms, optimal treatments, and repercussions from any subsequent osteosclerotic response.

Key Words: hypocalcemia; metastatic prostate cancer; ^{177}Lu-PSMA

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In metastatic castration-resistant prostate cancer (mCRPC), ^{177}Lu-prostate-specific membrane antigen (PSMA) is an effective treatment that is generally associated with few adverse events (*1*,*2*). We report 2 cases in which men treated with ^{177}Lu-PSMA-I&T for mCRPC developed clinically significant hypocalcemia on therapy; examine the incidence of ^{177}Lu-PSMA-I&T–associated hypocalcemia in a clinical dataset; and discuss potential mechanisms, treatment strategies, and potential long-term consequences of this phenomenon.

MATERIALS AND METHODS

Men with mCRPC who had disease progression despite at least 1 line of androgen receptor signaling inhibition and who were either ineligible for taxane chemotherapy or for whom it had failed were considered for treatment with ^{177}Lu-PSMA-I&T in a clinical treatment program (2022/ETH00924). All men received a minimum of 2 doses of ^{177}Lu-PSMA-I&T at 6-wk intervals. A median of 8.0 GBq (interquartile range [IQR], 8.0–8.5 GBq) was administered at each dose via a slow intravenous injection. Before each dose and at 3-wk intervals, blood was collected for biomarkers including hemoglobin, platelets, lactate dehydrogenase, calcium, alkaline phosphatase, albumin, and prostate-specific antigen (PSA).

RESULTS

Case One

A 71-y-old man with progressive, symptomatic mCRPC and widespread, highly PSMA-avid bony metastases on ^{68}Ga-PSMA-11 PET/CT commenced treatment with 8.5 GBq of ^{177}Lu-PSMA-I&T

TABLE 1
Case Characteristics at Initiation of ^{177}Lu-PSMA-I&T

Characteristic	Case 1	Case 2
Age	71	81
Metastatic sites	Bone	Bone
Time since diagnosis	13 mo	17 y
Time on denosumab	11 mo	8 y
Prior lines of therapy	Goserelin, abiraterone, docetaxel, denosumab	Goserelin, docetaxel, abiraterone, denosumab

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For correspondence or reprints, contact Louise Emmett (louise.emmett@svha.org.au).
*Contributed equally to this work.
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TABLE 2
Case Characteristics During ^{177}Lu-PSMA-I&T Treatment

Characteristic	Case 1		Case 2	
	Dose 1	Dose 2	Dose 1	Dose 2
PSA (0.3–6.5 μg/L)	540	31	4,960	723
Hemoglobin (128–175 g/L)	117	104	89	82
Platelets (150–450 × 10^9/L)	97	150	241	108
Alkaline phosphatase (35–110 U/L)	195	2,049	311	240
Estimated glomerular filtration rate (>60 mL/min/1.73 m^2)	>90	>90	49	73
Parathyroid hormone (1.6–7.2 pmol/L)	NA	27.7	NA	42
25-hydroxyvitamin D_3 (50–140 nmol/L)	88	55	NA	87
Corrected calcium (2.15–2.55 mmol/L)	2.29	1.54	2.11	1.68

NA = not applicable.

and showed a marked biochemical response (PSA, 540 to 31 μg/L) after 4 doses 6 wk apart. He received 2 additional doses after a treatment break. He was originally diagnosed 11 mo beforehand with high-volume de novo metastatic prostate adenocarcinoma and progressed on 3 lines of systemic therapy (Tables 1 and 2. He was on goserelin and denosumab, 120 mg monthly, at the initiation of ^{177}Lu-PSMA-I&T. He had normal serum calcium concentrations during the 11 mo that he was taking denosumab before ^{177}Lu-PSMA-I&T. He developed hypocalcemia after the first dose of ^{177}Lu-PSMA-I&T, which worsened despite calcium replacement and cessation of denosumab (Fig. 1). The hypocalcemia was associated with an increased alkaline phosphatase level and serum N-terminal propeptide of type 1 collagen (P1NP) concentration (744 μg/L; reference range, 15–115 μg/L; Fig. 1). The serum parathyroid hormone concentration was appropriately elevated (27.7 pmol/L; reference range, 1.6–7.2). He commenced prednisone, 60 mg daily, to suppress the exaggerated osteoblastic response, in addition to calcitriol and an increased dose of calcium carbonate. The level of serum P1NP normalized within 6 wk of commencing prednisone, whereas the level of serum C-terminal telopeptide of type 1 collagen (CTx) did not increase until 10 mo after ^{177}Lu-PSMA-I&T commencement (to 2,150 ng/L; reference range, 100–750 ng/L), consistent with a postdenosumab cessation rebound (Fig. 1). A baseline dual-energy x-ray absorptiometry bone mineral

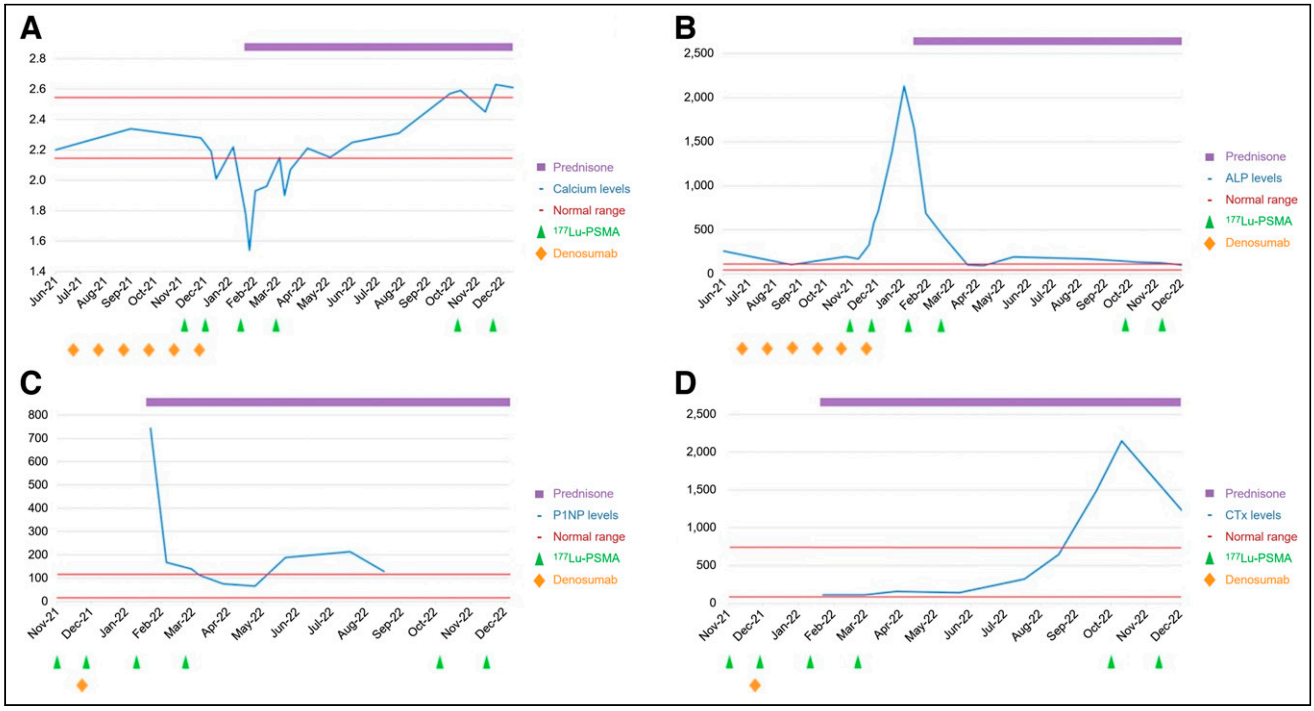

FIGURE 1. Case 1, showing first serum calcium (A) and serum alkaline phosphatase (B) for 6 mo before and during ^{177}Lu-PSMA therapy and second serum P1NP (C) and serum CTx (D) during hypocalcemic response to ^{177}Lu-PSMA and recovery phase.

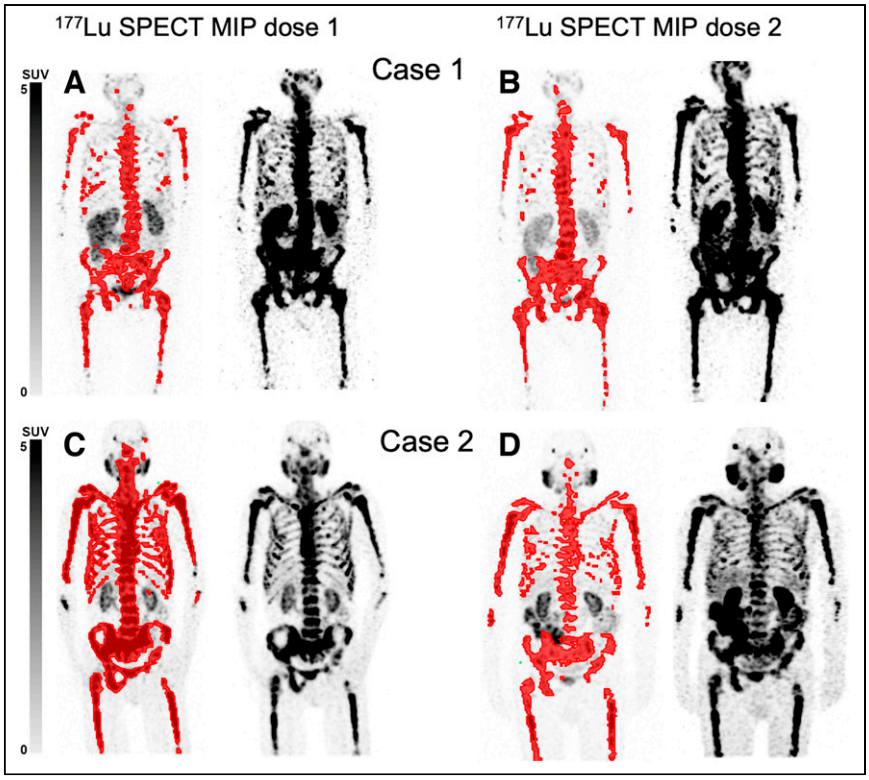

FIGURE 2. (A and B) Case 1, treated with ^{177}Lu-PSMA-I&T dose 1 (A) (PSA, 540 μg/L, and total tumor volume, 1,923 cm^3, on ^{177}Lu SPECT) and dose 2 (B), with marked PSA response (PSA, 31 μg/L) but persistent high-volume disease on ^{177}Lu-PSMA SPECT (total tumor volume, 1,606 cm^3). (C and D) Case 2, treated with ^{177}Lu-PSMA-I&T dose 1 (C) (PSA, 4,960 μg/L, and total tumor volume, 3,453 cm^3) and dose 2 (D), with marked PSA response (PSA, 723 μg/L) and significant reduction in total tumor volume (1,247 cm^3). Both patients developed clinically significant hypocalcemia after dose 1 ^{177}Lu-PSMA, requiring high-dose steroid treatment.

density scan at the onset of hypocalcemia demonstrated a generalized high bone mass (lumbar spine T-score, +9.5; left femoral neck T-score, +4.2), and serial ^{177}Lu-PSMA SPECT/CT imaging showed persistently high-volume PSMA-avid disease (Fig. 2). A tetracycline-labeled transiliac bone biopsy was attempted; however, the results were nondiagnostic because of difficulty in sampling the sclerotic bone. He remains clinically well and normocalcemic on prednisone, 10 mg; calcium carbonate, 1,200 mg twice per day; and calcitriol, 0.25 μg twice per day, after 6 doses of ^{177}Lu-PSMA-I&T (total dose, 47.5 GBq) and 18 mo after his initial dose. He commenced treatment with ^{225}Ac-PSMA-617 on a trial basis at clinical and radiographic progression, 17 mo after ^{177}Lu-PSMA-I&T initiation.

Case Two

An 81-y-old man with progressive mCRPC and intensely PSMA-avid large-volume skeletal metastases on ^{68}Ga-PSMA-11 PET/CT commenced ^{177}Lu-PSMA-I&T after progression despite multiple lines of treatment (Tables 1 and 2). At ^{177}Lu-PSMA-I&T initiation, he was on goserelin but had ceased taking denosumab (120 mg monthly) for transient hypocalcemia that had resolved with calcium carbonate, 600 mg daily, and calcitriol, 0.25 μg twice per day. Despite ongoing cessation of denosumab for more than 6 wk, he presented with fatigue and severe hypocalcemia (1.68 mmol/L) 1 wk after his first dose of ^{177}Lu-PSMA-I&T. The parathyroid hormone level was appropriately elevated (42 pmol/L). Calcium carbonate was increased to 1,200 mg 3 times per day, and the hypocalcemia resolved. Severe hypocalcemia recurred 1 mo later—again, after the second dose of treatment. These recurrent episodes were managed with intravenous calcium gluconate, reuptitration of calcium carbonate, 50 mg of prednisone daily, and cessation of ^{177}Lu-PSMA-I&T. He had a good biochemical response to treatment (PSA, from 4,960 to 730 ng/mL), with a significant reduction of total tumor volume on SPECT (Fig. 2). However, he required a slow prednisone wean with ongoing calcium carbonate, 1,200 mg daily, and calcitriol, 0.25 μg twice per day. He developed PSA progression and clinical progression 4 mo after his initial ^{177}Lu-PSMA-I&T, having received only 2 doses because of recurrent hypocalcemia requiring hospitalization.

Clinical Dataset

Review of a clinical dataset of 127 patients treated with ^{177}Lu-PSMA-I&T (*3*) demonstrated that 41 (32%) had a fall in serum calcium of any magnitude at any point between starting treatment and administration of dose 3 (12 wk). Six patients (5%) developed new-onset hypocalcemia (serum corrected calcium falling below the reference range) in the first 12 wk of treatment. The mean PSA response in those with hypocalcemia was 78% (SD, 24%), with 1 patient showing no PSA response to treatment. Baseline SPECT total tumor volume was significantly higher in those who had a reduction in calcium than in those who maintained their calcium level (median, 1,017 cm^3 [IQR, 331–1,831 cm^3] vs. 369 cm^3 (IQR, 96–1,035 cm^3); $P = 0.01$) and

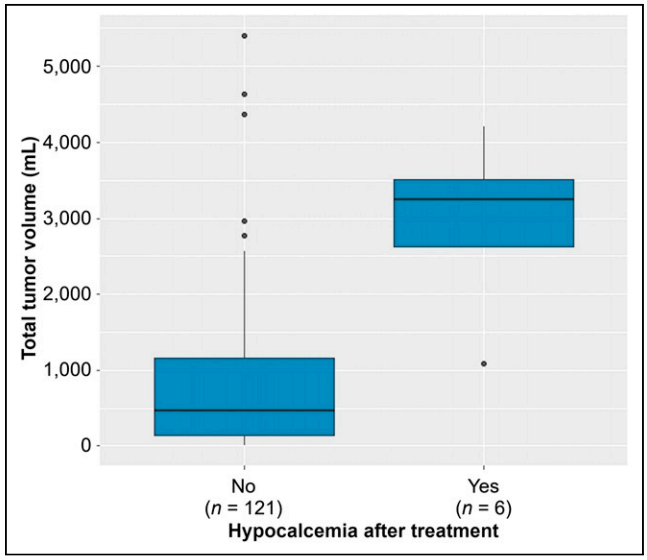

FIGURE 3. Box plot showing relationship between first-dose ^{177}Lu-PSMA-I&T SPECT total tumor volume and development of posttreatment hypocalcemia. Baseline total tumor volume was significantly higher in patients who developed posttreatment hypocalcemia ($P = 0.002$).

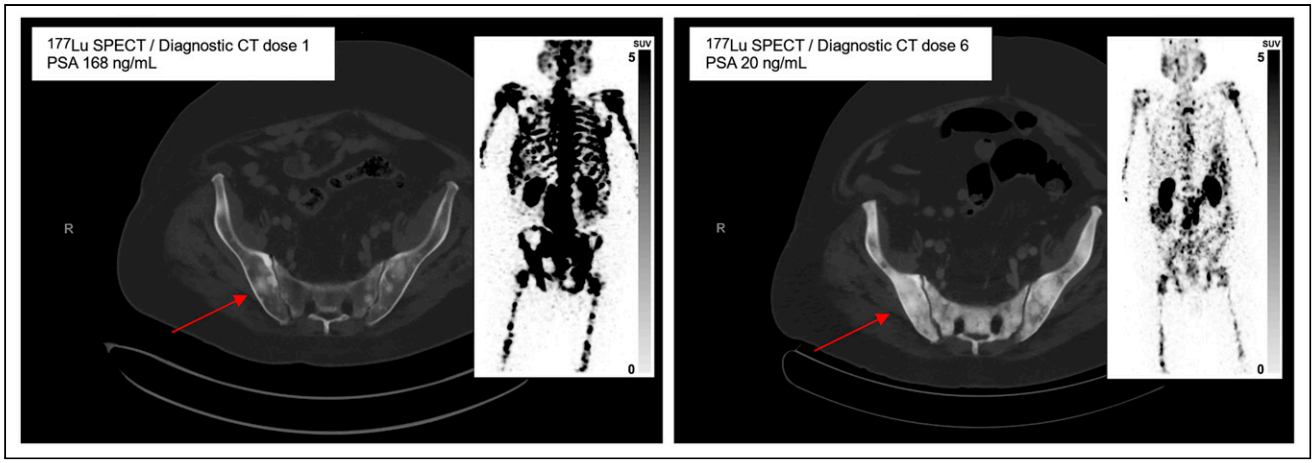

FIGURE 4. ^{177}Lu-PSMA SPECT/CT images for 1 of 6 cases treated with ^{177}Lu-PSMA-I&T who developed hypocalcemia. Images within 24 h after dose 1 (left) and dose 6 (right) show significant reduction in cancer volume with concomitant marked osteosclerotic response (arrows).

in those who developed hypocalcemia than in those who did not (median, 3,249 cm^3 (IQR, 1,856–3,852 cm^3) vs. 465 cm^3 (IQR, 135–1,172 cm^3); $P = 0.002$) (Fig. 3). Some patients with hypocalcemia after treatment developed marked osteosclerosis subsequently, despite an excellent biochemical and imaging treatment response (Fig. 4).

DISCUSSION

To our knowledge, this is the first report of clinically significant hypocalcemia developing in response to successful ^{177}Lu-PSMA-I&T treatment. All men impacted had high-volume disease at baseline, and the 2 cases we presented experienced more than a 90% reduction in PSA in response to ^{177}Lu-PSMA-I&T. Tyr is a Norse god who sacrificed his hand to control a powerful wolf god. Similarly, hypocalcemia and osteosclerosis appears to be an adverse consequence of an excellent treatment response.

On the basis of the biochemistry results in our cases, the severe hypocalcemia was independent of parathyroid hormone or systemic controls of serum calcium. The hypocalcemia appeared to be triggered by a direct local tumor effect on bone by ^{177}Lu-PSMA rather than denosumab, given that both patients had normal calcium levels until receiving ^{177}Lu-PSMA-I&T. In case 1, serum alkaline phosphatase and P1NP were markedly elevated at the onset of severe hypocalcemia, indicating an exaggerated osteoblastic response. Serum CTx (a bone resorption marker) was within the reference range but was higher than expected for a patient receiving high-dose denosumab, given the fact that denosumab suppresses CTx within days and remains suppressed during treatment (*4*,*5*). Given the markedly exaggerated P1NP levels in relation to CTx, we hypothesize that the ^{177}Lu-PSMA-I&T triggered an uncoupling of bone turnover favoring bone formation over resorption. The resulting increased skeletal demand for calcium for bone formation and mineralization depleted the circulating calcium stores, resulting in severe hypocalcemia similar to that seen in hungry bone syndrome (*6*).

Prostate cancer is known to cause sclerotic bone metastases, with an increase in sclerotic foci well recognized in response to effective therapy (*7*). This phenomenon is a major reason that CT is not used to analyze bone lesions on RECIST and that new lesions found on bone scans during the first few months of treatment are not considered to be disease progression. However, the mechanism by which prostate cancer induces osteosclerosis in response to treatment is not fully understood, and although significant concomitant hypocalcemia has been reported with rapid cancer progression (*8*), it has not been described after exceptional responses to treatment. Treatment-induced hypocalcemia in prostate cancer has been reported as an adverse reaction to only high-dose denosumab and bisphosphonates (*5*).

With increasing use of ^{177}Lu-PSMA therapy, this is an important phenomenon to recognize, particularly as it may require escalated therapy to manage, such as glucocorticoid therapy. In the patients who had an unrecognized hypocalcemic response to ^{177}Lu-PSMA-I&T in our clinical dataset, there was a significant increase in sclerotic disease volume. This increase has the potential to reduce the available marrow reserve and may lead to early induction of marrow failure with subsequent treatments, particularly with ^{177}Lu-PSMA therapy potentially moving to earlier in the disease course.

Supraphysiologic glucocorticoid administration suppresses bone formation by inhibiting osteoblast differentiation and proliferation and inducing osteoblast apoptosis (*9*). Hence, management of these patients required high-dose glucocorticoids to dampen the exaggerated osteoblastic response and help normalize calcium levels. The underlying mechanism by which ^{177}Lu-PSMA drives this exaggerated osteoblastic response and results in hypocalcemia is unclear and may be the release of osteoblastogenic growth factors by metastatic prostate cancer cells and cells within the bone tumor microenvironment. Further prospective evaluation of such cases, with close monitoring of calcium and bone turnover markers and tetracycline-labeled bone biopsy using techniques such as micro-CT, histomorphometry, and immunohistochemistry, will likely enhance understanding and identify factors that select patients who need prophylactic treatment, thereby preventing the hypocalcemic and sclerotic events.

CONCLUSION

Clinically significant hypocalcemia and osteosclerosis are a rare but important side effect of ^{177}Lu-PSMA-I&T therapy in men with high-volume osseous metastatic disease and a significant treatment response. Importantly, calcium and calcitriol supplementation were insufficient in managing the hypocalcemia, and oral prednisone was required. Further work delineating the mechanism in the tumor microenvironment is required to fully understand

and develop effective management options for patients with this phenomenon.

DISCLOSURE

No potential conflict of interest relevant to this article was reported.

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KEY POINTS

QUESTION: Are good responders to ^{177}Lu-PSMA at risk for clinically significant hypocalcemia?

PERTINENT FINDINGS: We found that patients with high-volume bone metastases and a significant PSA response are at a higher risk of developing hypocalcemia.

IMPLICATIONS FOR PATIENT CARE: Although hypocalcemia is a rare side effect of ^{177}Lu-PSMA, it can be clinically significant and may require treatment.

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