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Research Article

PSMA PET Avidity Beyond Metastasis. A Case Report Highlighting Second Primary Malignancies in Prostate Cancer - A Report of Two Cases

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Abstract: *Introduction:* Prostate cancer characteristically spreads to bone, so skeletal lesions in a man with a raised prostate-specific antigen (PSA) are routinely attributed to osseous metastases. This reflex is usually correct but occasionally wrong, and when it is wrong it can conceal a biologically distinct second primary whose treatment differs entirely. Multiple primary malignant neoplasms (MPMNs) are recognised more often as cancer survival lengthens and imaging grows more sensitive, yet the bone lesions that accompany them are easily misassigned to a single known tumour. Prostate-specific membrane antigen (PSMA) PET/CT offers a way out of this trap: because tracer uptake closely tracks prostatic disease, the scan can both confirm a prostatic origin for skeletal lesions and, just as usefully, exclude it.**Case presentation**. We describe two men in whom PSMA PET/CT was pivotal. In Case 1 (metachronous), a 57-year-old man previously treated for poorly differentiated, TP53-mutant, PD-L1–negative carcinoma of the lung re-presented months later with severe back pain and a serum prostate-specific antigen (PSA) >400 ng/mL but no urinary symptoms. PSMA PET/CT demonstrated a PSMA-avid prostatic lesion together with PSMA-avid axial and appendicular skeletal lesions; prostate biopsy confirmed adenocarcinoma (Gleason 4+5=9). PSMA imaging established a metachronous prostatic primary and confirmed that the skeletal disease originated from prostate cancer rather than the prior lung malignancy. In Case 2 (synchronous), a 79-year-old man presented with dysuria, back pain and a serum PSA of 141.5 ng/mL, with magnetic resonance imaging showing extensive marrow infiltration of the lumbosacral spine, sacrum and iliac bones. PSMA PET/CT revealed a focal PSMA-avid prostatic lesion (SUVmax 39.1) but, strikingly, no skeletal PSMA uptake. This discordance prompted a haematological work-up that revealed an IgG-kappa monoclonal (M) protein with a markedly elevated serum free kappa light chain and kappa/lambda ratio, establishing synchronous multiple myeloma alongside prostate adenocarcinoma. He was treated with a bortezomib–lenalidomide–dexamethasone (VRd) regimen together with androgen deprivation therapy using leuprolide.**Conclusion.** A second primary malignancy should be suspected whenever the imaging pattern is discordant with the expected behaviour of a known tumour, or when a patient's symptoms are not attributable to it. Because PSMA expression - though characteristic of prostate cancer - is not entirely prostate-specific, PSMA PET/CT findings must always be interpreted within the clinical and biochemical context. Used judiciously, PSMA PET/CT serves as both a confirmatory and exclusionary imaging tool, distinguishing prostatic from non-prostatic disease and directing appropriate, tumour-specific therapy.

Keywords: PSMA PET/CT; prostate cancer; multiple primary malignant neoplasms; synchronous malignancy; metachronous malignancy; multiple myeloma; second primary; molecular imagin

INTRODUCTION

The occurrence of more than one histologically distinct primary malignancy in a single individual - multiple primary malignant neoplasms (MPMNs) - was first recognised by Billroth in the late nineteenth century, and formal diagnostic criteria were subsequently codified by Warren and Gates in 1932. By these still widely accepted criteria, each tumour must be unequivocally malignant on histopathology, each must be histologically distinct, and the possibility that one lesion represents a metastasis of the other must be excluded.

MPMNs are conventionally classified by the interval between diagnoses. Tumours identified within six months of one another are termed synchronous, whereas a second tumour arising more than six months after the first is termed metachronous.

Reported incidence varies widely with population, ascertainment method and length of follow-up, ranging in the literature from approximately 0.7% to 11.7% of cancer patients. Indian institutional series have similarly reported double primary malignancies in well under 1% of cancer patients, with metachronous tumours generally outnumbering synchronous ones. Improved survivorship, heightened screening, an ageing population and the late effects of prior oncological therapy are all thought to contribute to the rising recognition of MPMNs.

Prostate cancer is among the most common malignancies in men beyond the fifth decade of life and characteristically metastasises to the axial skeleton. Consequently, when a man with prostate cancer is found to have bony lesions, those lesions are frequently - and reasonably - attributed to osseous metastatic spread. However, this assumption carries an important clinical risk: it can obscure a coexisting second primary whose management is entirely different.

Prostate-specific membrane antigen (PSMA) is a transmembrane glycoprotein with folate hydrolase activity that is strongly overexpressed by most prostatic adenocarcinomas. PSMA-targeted PET/CT has transformed prostate cancer imaging: in the randomised proPSMA trial, gallium-68 PSMA-11 PET/CT achieved an accuracy of 92% for detecting nodal or distant metastatic disease, compared with 65% for conventional CT and bone scintigraphy, with higher sensitivity (85% vs 38%) and specificity (98% vs 91%) and a lower radiation burden. Importantly, however, the label "prostate-specific" is a misnomer: PSMA is also expressed by the neovasculature of various non-prostatic tumours and in a spectrum of benign and malignant conditions, including bone-related and haematological disorders. This dual property - high but not absolute specificity for prostate cancer - is precisely what makes PSMA PET/CT so informative when interpreting skeletal disease in a man with prostate cancer.

We present two patients in whom PSMA PET/CT was decisive in the recognition of a second primary malignancy associated with prostate cancer - one metachronous and one synchronous - illustrating how the modality functioned, respectively, as a confirmatory and an exclusionary test, and how this distinction altered management.

Case Presentation

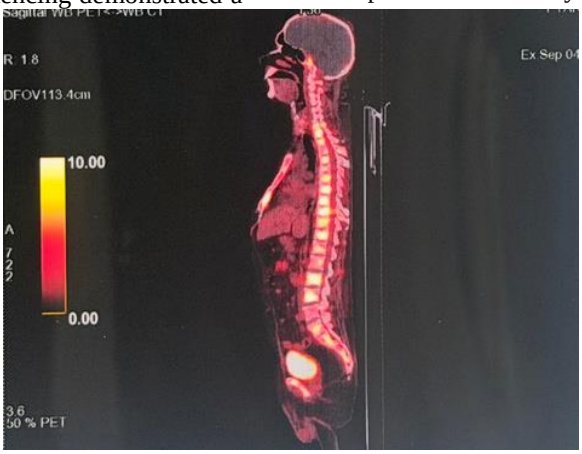
2.1 Case 1 - Metachronous prostate cancer in a patient treated for carcinoma of the lung

A 57-year-old man had previously been diagnosed with a poorly differentiated carcinoma of the lung. Molecular profiling by next-generation sequencing demonstrated a TP53 alteration, and programmed death-ligand 1 (PD-L1) expression was negative (tumour proportion score <1%). He had received six cycles of pemetrexed and carboplatin followed by five cycles of pemetrexed with denosumab as maintenance therapy.

More than six months after completing treatment, he re-presented with severe low back pain and difficulty in walking. Notably, he reported no urinary symptoms. Fluorodeoxyglucose (FDG) PET/CT performed in the context of his lung cancer follow-up demonstrated a primary lesion measuring approximately 2.0 × 2.6 cm, FDG-avid skeletal lesions, and FDG uptake within a mildly enlarged prostate. On the basis of FDG findings alone, the skeletal lesions could not be confidently assigned to either the known lung primary or a possible second source.

Biochemical evaluation revealed a markedly elevated serum PSA of >400 ng/mL (reference <4 ng/mL), a value far exceeding levels expected in lung carcinoma and strongly suggestive of an independent prostatic malignancy. Gallium-68 PSMA PET/CT was therefore performed. It demonstrated an intensely PSMA-avid prostatic lesion measuring approximately 3.0 × 3.4 × 3.0 cm - corresponding to the FDG-avid prostatic region noted previously - together with PSMA-avid lesions throughout the axial and appendicular skeleton. Magnetic resonance imaging confirmed a prostatic lesion (PI-RADS 5) with bilateral osseous metastatic involvement of the hips. Targeted prostate biopsy confirmed acinar adenocarcinoma with a Gleason score of 4+5=9 (Grade Group 5).

The PSMA-avidity of the skeletal lesions, concordant with the PSMA-avid prostatic primary and the markedly elevated PSA, established that the widespread bone disease arose from a newly diagnosed, metastatic prostate cancer rather than from the antecedent lung carcinoma. By the Warren–Gates criteria, and given an interval exceeding six months between the two histologically distinct malignancies, this represented a metachronous second primary. The diagnosis reframed the patient's skeletal symptoms and directed the addition of prostate-directed systemic therapy.



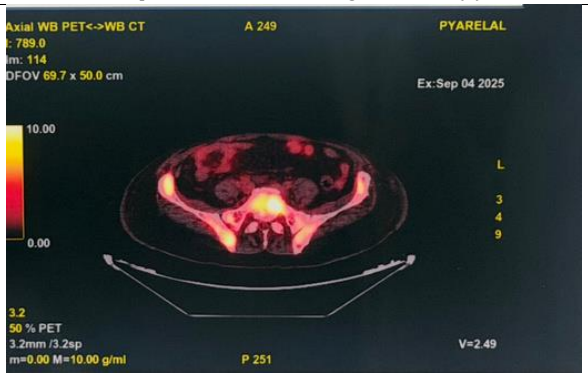


Figure 1. Imaging findings in Case 1. (A) 68Ga-PSMA-11 PET/CT whole-body maximum-intensity projection showing the intensely PSMA-avid prostatic primary together with PSMA-avid axial and appendicular skeletal lesions. (B) 68Ga-PSMA-11 PET/CT axial fused image at the level of the pelvis showing the intensely PSMA-avid prostatic lesion, confirming the prostatic origin of the skeletal disease and establishing a metachronous second primary malignancy.

2.2 Case 2 - Synchronous prostate cancer and multiple myeloma

A 79-year-old man presented with burning micturition, back pain and difficulty in walking. Serum PSA was elevated at 141.5 ng/mL (reference <4 ng/mL). Magnetic resonance imaging of the lumbosacral spine demonstrated diffuse marrow infiltration involving the lumbosacral spine, sacrum and iliac bones, with osteoporotic wedge deformities of the L1, L2 and L3 vertebral bodies.

At first inspection, the combination of an elevated PSA and extensive axial skeletal/marrow disease was highly suggestive of metastatic prostate cancer. However, laboratory evaluation revealed a constellation of findings atypical for prostate cancer alone, summarised in Table 1: mild macrocytic anaemia (haemoglobin 10 g/dL), thrombocytopenia, hypoalbuminaemia with a strikingly elevated serum globulin and a reversed albumin/globulin ratio (0.5), together with renal impairment (urea 79.16 mg/dL, creatinine 1.28 mg/dL) and hyperuricaemia. This biochemical profile - anaemia, renal dysfunction and a paraprotein-type globulin elevation - raised the possibility of a coexisting plasma-cell disorder.

Table 1. Baseline laboratory parameters at presentation (Case 2).

Investigation	Result	Reference interval
Haemoglobin	10 g/dL	13–17 g/dL
Mean corpuscular volume (MCV)	101.6 fL	83–100 fL
Total leukocyte count	10 × 10^3/µL	4.0–11.0 × 10^3/µL
Platelet count	98 × 10^3/µL	150–410 × 10^3/µL
Total bilirubin	0.7 mg/dL	0.3–1.2 mg/dL
SGOT (AST)	31 U/L	<35 U/L
SGPT (ALT)	23 U/L	<45 U/L
Alkaline phosphatase	42 U/L	45–129 U/L
Serum albumin	2.65 g/dL	3.2–4.8 g/dL
Serum globulin	5.32 g/dL	2.5–3.4 g/dL
Albumin/globulin (A/G) ratio	0.5	0.9–2.0
Serum urea	79.16 mg/dL	17–43 mg/dL
Serum creatinine	1.28 mg/dL	0.72–1.18 mg/dL
Serum uric acid	9.95 mg/dL	4.2–7.3 mg/dL
Serum PSA	141.5 ng/mL	<4 ng/mL

Values in bold lie outside the reference interval. The pattern of anaemia, hypoalbuminaemia, marked globulin elevation with reversed A/G ratio, and renal impairment is characteristic of a plasma-cell dyscrasia rather than of prostate cancer alone.

Gallium-68 PSMA PET/CT was performed to characterise the disease. It demonstrated a focal, intensely PSMA-avid lesion in the peripheral aspect of the left lobe of the prostate (SUVmax 39.1) but, critically, no PSMA uptake within the skeleton - i.e., no scintigraphic evidence of prostatic bone metastases despite the extensive marrow disease seen on MRI. This discordance between the extensive marrow infiltration on MRI and the absence of skeletal PSMA uptake indicated that the bone disease was not of prostatic origin and prompted a dedicated haematological evaluation.

Serum protein electrophoresis and immunofixation revealed a monoclonal (M) spike of IgG-kappa type. Serum free light chain assay showed a markedly elevated free kappa level with a grossly abnormal free kappa/lambda ratio (Table 2). Together with the anaemia, renal impairment and lytic/marrow-infiltrative skeletal disease, these findings confirmed multiple myeloma occurring synchronously with prostate adenocarcinoma.

Table 2. Serum free light chain assay (Case 2).

Parameter	Result	Reference interval
Free kappa	950.57 mg/L	3.30–19.40 mg/L
Free lambda	9.65 mg/L	5.71–26.30 mg/L
Free kappa/lambda ratio	98.5	0.35–2.42

A markedly elevated free kappa concentration with a free kappa/lambda ratio of 98.5 is diagnostic of a kappa-restricted clonal plasma-cell process, consistent with the IgG-kappa M-spike.

The patient was managed for both synchronous primaries. Multiple myeloma was treated with a bortezomib–lenalidomide–dexamethasone (VRd) regimen, while the prostate adenocarcinoma was managed with androgen deprivation therapy using injectable leuprolide. Had the skeletal disease been uncritically attributed to metastatic prostate cancer, the underlying myeloma - and its attendant renal and skeletal morbidity - might have gone unrecognised and untreated.

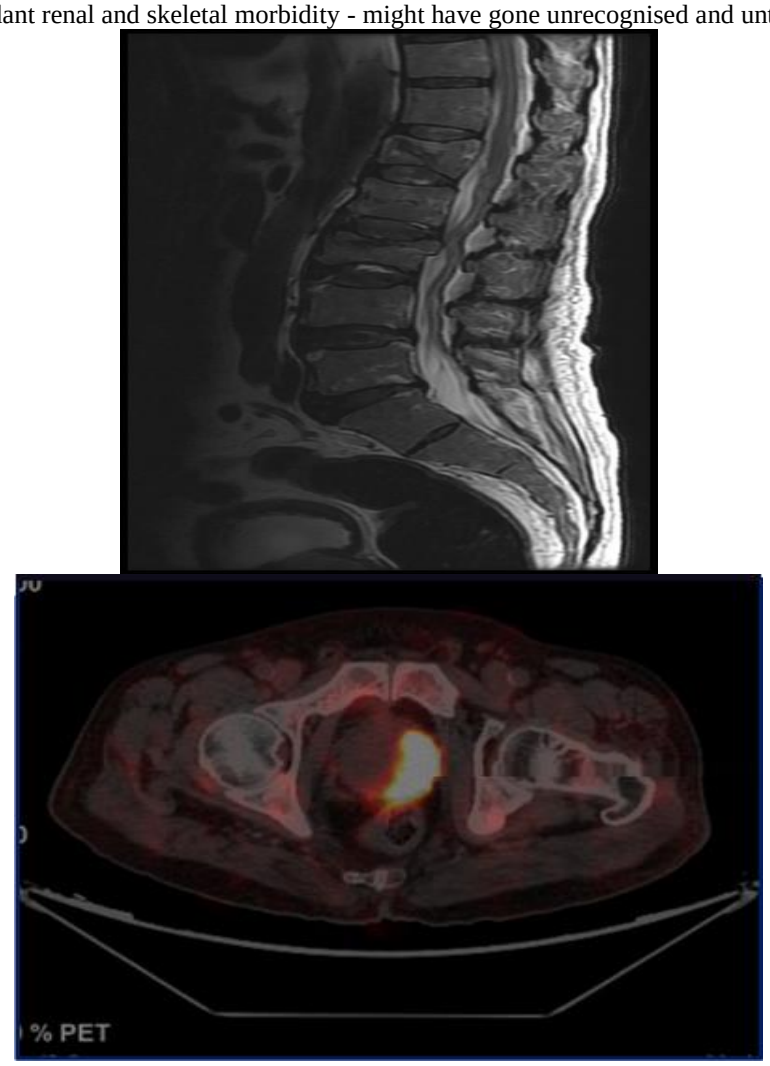


Figure 2. Imaging findings in Case 2. (A) Magnetic resonance imaging of the lumbosacral spine showing diffuse marrow infiltration of the lumbosacral spine, sacrum and iliac bones with osteoporotic wedging of L1–L3. (B) 68Ga-PSMA-11 PET/CT showing a focal PSMA-avid lesion in the left peripheral prostate (SUVmax 39.1) with no skeletal PSMA uptake, indicating a non-prostatic cause for the bone disease and prompting the diagnosis of synchronous multiple myeloma.

DISCUSSION

These two cases share a common diagnostic challenge: in each, a man with newly identified prostate cancer also harboured extensive skeletal disease, the origin of which determined both management and prognosis. The cases are instructive because PSMA PET/CT resolved the diagnostic dilemma in opposite ways - confirming prostatic origin in the first case and excluding it in the second - and in doing so revealed a second primary malignancy in each. To our knowledge, few reports have comparatively demonstrated the dual confirmatory and exclusionary diagnostic roles of PSMA PET/CT within a single series of synchronous and metachronous second primary malignancies.

The biological basis for this discriminatory power lies in the nature of PSMA itself. As a folate hydrolase strongly expressed by prostatic adenocarcinoma, PSMA provides an excellent target for molecular imaging, and the proPSMA trial demonstrated the superior accuracy of PSMA PET/CT over conventional CT and bone scintigraphy for staging high-risk prostate cancer. In Case 1, this sensitivity and target specificity allowed PSMA PET/CT to confirm both a prostatic primary and the prostatic origin of the skeletal lesions that FDG PET/CT could not confidently characterise - a setting in which FDG is particularly limited, since most prostate cancers show low FDG avidity. The markedly elevated PSA (>400 ng/mL) provided an important corroborating clue that the skeletal disease was unlikely to be attributable solely to the lung primary.

Case 2 illustrates the converse and more subtle point. Because PSMA expression is not exclusive to prostate tissue, the absence of PSMA uptake in morphologically abnormal regions may itself provide important diagnostic information. Here, extensive marrow infiltration on MRI without corresponding skeletal PSMA uptake argued against prostatic bone metastases and redirected the work-up towards a haematological cause, leading to identification of an IgG-kappa M-protein and a grossly elevated free kappa/lambda ratio diagnostic of multiple myeloma. Notably, myeloma may occasionally demonstrate PSMA uptake through neovascular expression, so findings must always be integrated with morphology, biochemistry and clinical context. Our case is instructive particularly because the bone disease was PSMA-negative: whereas Wang et al. reported a patient with treated prostate cancer in whom diffuse PSMA-avid osteolytic lesions proved to be multiple myeloma, in our patient it was the absence - rather than the presence - of skeletal PSMA uptake that unmasked the coexisting myeloma.

Both cases underline the value of suspecting a second primary whenever the clinical or imaging picture does not fit the expected behaviour of a known malignancy. In Case 1, the discordantly high PSA and the absence of urinary symptoms, in a patient whose skeletal disease was being ascribed to lung cancer, were the alerting features. In Case 2, it was the mismatch between MRI marrow disease and skeletal PSMA uptake, together with a biochemical profile uncharacteristic of prostate cancer. A high index of suspicion, anchored in the Warren–Gates framework, is essential to avoid attributing all disease to a single tumour.

From a resource-utilisation standpoint, these cases also highlight the limitations of substituting bone scintigraphy or FDG PET/CT for PSMA PET/CT as a cost-containment measure when the clinical question is whether skeletal disease is of prostatic origin. Bone scintigraphy reflects osteoblastic reaction non-specifically, and FDG PET/CT is limited in typically low-FDG-avid prostate cancer; neither reliably distinguishes prostatic from non-prostatic skeletal disease. PSMA PET/CT, interpreted in context, provides that discrimination and can prevent both over- and under-treatment. Recognising a second primary has direct therapeutic consequences - as seen in the addition of androgen deprivation therapy in Case 1 and the institution of myeloma-directed VRd therapy alongside androgen deprivation in Case 2 - and is best achieved through multidisciplinary team discussion.

This report is limited by its retrospective, two-patient design and the absence of long-term follow-up, so the conclusions are illustrative rather than statistical. Histological confirmation of every skeletal lesion was not undertaken, and imaging interpretation rested on integrating biochemical, morphological and molecular findings. Nonetheless, the cases offer a clear, reproducible lesson on how PSMA PET/CT should be interpreted when a second malignancy is possible.

CONCLUSION

A second primary malignancy is not an uncommon occurrence and should be actively considered whenever imaging findings do not conform to the typical pattern of spread of a known tumour, or when a patient's symptoms cannot be attributed to the recognised disease. In men with prostate cancer, PSMA PET/CT is a powerful tool for resolving such dilemmas - confirming prostatic origin where it exists and, just as valuably, excluding it where it does not - thereby unmasking synchronous or metachronous second primaries. PSMA is highly, but not absolutely, specific for prostate tissue. Therefore, imaging findings should always be interpreted alongside clinical history, biochemical parameters and

conventional imaging. Clinicians should remain alert to the possibility of coexisting malignancies in patients with atypical imaging or biochemical findings.

Clinical learning points

- Suspect a second primary malignancy when the imaging pattern or symptom profile is discordant with the expected behaviour of a known tumour.
- PSMA PET/CT functions both as a confirmatory test (demonstrating prostatic origin of skeletal disease) and as an exclusionary test (absence of uptake within morphologically abnormal bone lesions suggests a non-prostatic cause).
- PSMA is not exclusively prostate-specific; non-prostatic and haematological conditions - including multiple myeloma - may show uptake, so findings must be integrated with biochemistry and morphology.
- A markedly elevated PSA disproportionate to a known non-prostatic tumour, or a laboratory pattern of anaemia, reversed A/G ratio and renal impairment, should prompt evaluation for an independent primary.
- Bone scintigraphy and FDG PET/CT, often used as lower-cost alternatives, do not reliably distinguish prostatic from non-prostatic skeletal disease; PSMA PET/CT, interpreted in context, can.

Declarations

Ethics approval and consent to participate. All procedures described were part of routine clinical care and were performed in accordance with the ethical standards of the institutional research committee and with the 1964 Declaration of Helsinki and its later amendments. In keeping with institutional policy, formal ethics committee approval is not required for retrospective reports of individual cases; the report was undertaken with institutional approval.

Consent for publication. Written informed consent was obtained from both patients for publication of this case report and the accompanying clinical and imaging data. All images were anonymised before submission.

Availability of data and materials. The data supporting the findings of this report are available from the corresponding author on reasonable request.

Competing interests. The authors declare that they have no competing interests.

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Authors' contributions. SM conceptualised the report and drafted the manuscript. VV, AG, AA and DDL contributed to patient management, data acquisition and critical revision. All authors read and approved the final manuscript.

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