

Synchronous Occurrence of Metastatic Prostate Adenocarcinoma and Plasma Cell Myeloma in the Bone Marrow: A Rare Case Report

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ABSTRACT

Simultaneous occurrence of plasma cell myeloma and prostate adenocarcinoma is rare, with only a few cases reported in the literature. The mechanism of co-occurrence of these malignancies is poorly understood. It has been suggested by some studies that Bone Marrow Microenvironment (BMME) plays a crucial role. We describe a rare case of synchronous occurrence of metastatic prostate cancer and plasma cell myeloma in bone marrow biopsy. A 73-year-old male presented with complaints of fatigue, low back ache and weight loss. Routine haematological and biochemical investigations showed anaemia with increased Erythrocyte Sedimentation Rate (ESR), raised creatinine and reversal of Albumin/Globulin ratio. Serum Protein Electrophoresis (SPE) showed M peak in the gamma fraction (2.30 g/dL). Serum Immunofixation Electrophoresis (IFE) showed two bands in the IgA region corresponding to the two bands in the kappa region. With clinical diagnosis of plasma cell myeloma, bone marrow study was done. Bone marrow aspirate showed around 20% plasma cells. Bone marrow biopsy showed clonal expansion of plasma cells with kappa light chain restriction. Same biopsy also showed tiny foci of metastatic carcinoma with surrounding fibrosis. Further evaluation revealed enlarged hard prostate with raised serum Prostate Specific Antigen (PSA) level, concerning for concomitant prostate carcinoma. On immunohistochemical study, carcinoma cells in bone marrow biopsy showed strong nuclear positivity for NKX3.1, confirming prostatic origin of metastatic carcinoma. The association between these two disorders is poorly understood. It has been suggested that BMME may play a crucial role.

Keywords: Metastasis, Monoclonal gammopathy, Serum electrophoresis, Tumour microenvironment

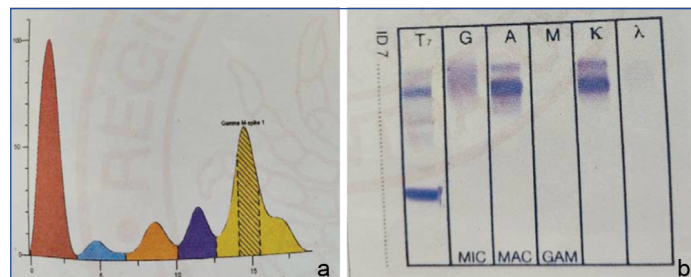
CASE REPORT

A 73-year-old man presented with complaints of fatigue, low backache and weight loss of two-month duration. Routine haematological and biochemical investigations were done. Complete haemogram revealed a haemoglobin level of 9.4 g/dL, indicating anaemia (reference range: 13.8-17.5 g/dL). The total leucocyte count was 6,500/mm³, which was within normal limits (reference range: 3,600-10,000/mm³). The platelet count was 2.5×10⁹/L (or 2.5 lac/mm³), also within the normal range (reference range: 1.5-4.5×10⁹/L). Thus, the haematological findings were significant for anaemia with normal leucocyte and platelet counts. Differential leucocyte count showed 64.6% polymorphs, 23.9% lymphocytes, 8.6% monocytes, 2.3% eosinophils, 0.6% basophils. ESR was elevated, 92 mm/hour (reference range: 20 mm/hour). Peripheral smear examination showed normocytic normochromic anaemia. Urine was negative for Bence Jones Protein (BJP) and Twenty-four-hour urinary protein excretion was elevated at 420 mg/day (reference range: <150 mg/day), indicating proteinuria. Serum albumin was mildly reduced at 3.45 g/dL (reference range: 3.5-5.0 g/dL), while total protein was within normal limits at 7.73 g/dL (reference range: 6.0-8.3 g/dL). Alkaline phosphatase (81 IU/L) and uric acid (5.71 mg/dL) were within normal reference ranges. Lactate Dehydrogenase (LDH) was marginally decreased at 139 IU/L (reference range: 140-280 IU/L). Renal function tests showed elevated serum creatinine of 1.77 mg/dL (reference range: 0.6-1.1 mg/dL) with blood urea of 40 mg/dL, which was within the upper normal range (reference range: 19.2-42.8 mg/dL).

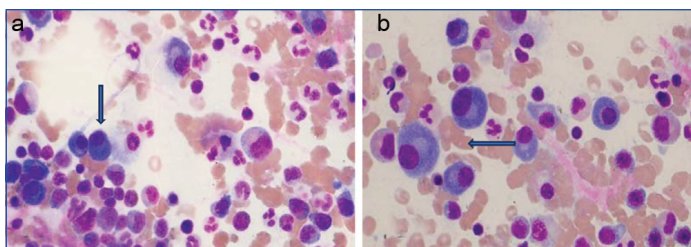
Serum immunoglobulin analysis demonstrated markedly elevated IgA levels (3285 mg/dL) (reference range: 90-450 mg/dL), with normal IgG (1055 mg/dL) and IgM (107 mg/dL) concentrations. Serum free light chain assay revealed elevated free kappa (44.8 mg/L)

and free lambda (33.6 mg/L) levels (reference ranges: 3.3-19.4 mg/L and 5.7-23.6 mg/L, respectively), kappa/lambda ratio=1.33. Serum electrophoresis showed M-band concentration of 2.30 g/dL [Table/Fig-1a], which was later shown by IFE to be IgA and kappa paraproteins [Table/Fig-1a,b]. Bone marrow aspiration and biopsy was done with a clinical diagnosis of plasma cell myeloma. Bone marrow aspirate showed 20% plasma cells [Table/Fig-2a,b]. Bone marrow biopsy showed plasmacytosis (35% plasma cells) [Table/Fig-3a]. Same bone marrow biopsy showed foci of infiltration by large atypical cuboidal to columnar cells arranged in a glandular pattern [Table/Fig-3b]. Immunohistochemistry performed on bone marrow biopsy to highlight plasma cells by CD138 showed strong membranous staining [Table/Fig-4a] for demonstrating clonality by kappa and lambda showed the plasma cells to be monoclonal for Kappa [Table/Fig-4b]. On further immunostaining large atypical cells showed strong positivity for cytokeratin [Table/Fig-5a].

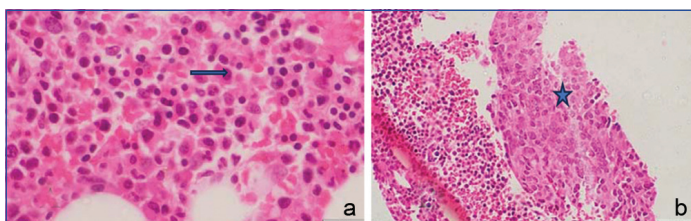
Further clinical examination and metastatic work up was done. Per rectal examination revealed a hard nodular growth in the prostate



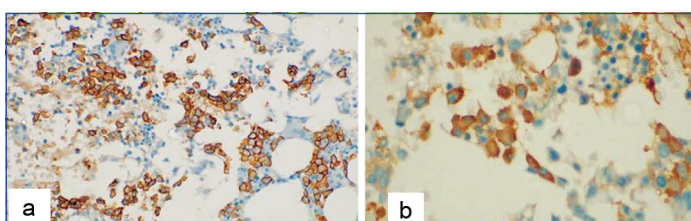
[Table/Fig-1]: a) Protein electrophoresis. An M-peak is seen in the gamma fraction; b) Serum Immunofixation Electrophoresis (IFE). It shows 2 bands in the IgA region corresponding to the two bands in the kappa region.



[Table/Fig-2]: a) Bone marrow aspirate showing scattered plasma cells along with few other haematopoietic cells (MGG, x1000); b) Trephine imprint smear showing plasma cells (MGG, x1000).

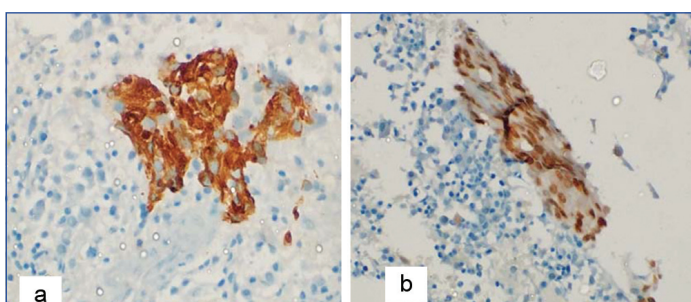


[Table/Fig-3]: a) Show interstitial infiltration of plasma cells (H&E, x400); b) Trephine biopsy shows marrow spaces infiltration large cells (H&E, x400).



[Table/Fig-4]: Bone marrow immunohistochemical staining: a) CD138 staining. Small collection and scattered plasma cells (Around 35%) (IHC, x200); b) Kappa staining. The plasma cells are kappa positive and lambda negative, Kappa light chain restriction (IHC, x400).

gland. Ultrasound of prostate showed grade III prostatomegaly. Serum PSA level was markedly increased- 476 ng/L. On further immunostaining, the metastatic carcinoma in the bone marrow biopsy showed strong nuclear positivity or NKX 3.1 [Table/Fig-5b], confirming a prostatic primary. Prostatic biopsy was not done for the patient considering the age and associated multiple comorbidities. Moreover, the clinical findings (Hard prostate, elevated PSA levels), immunohistochemistry proving a prostatic primary metastasis have sufficed the diagnosis of prostatic primary.



[Table/Fig-5]: a) Bone marrow immunohistochemical staining. Cluster of large atypical cell are showing cytokeratin positivity (IHC, x400); b) Positivity for NKX3.1 (IHC, x400).

A final diagnosis of bone marrow showing synchronous occurrence of metastatic prostatic carcinoma and plasma cell myeloma was made. The patient was diagnosed with dual malignancies- metastatic prostate adenocarcinoma and multiple myeloma International Staging System (ISS) stage II was commenced on treatment with androgen deprivation therapy for prostatic adenocarcinoma (leuprolide acetate 11.25 mg intramuscularly every 3 months), weekly CyBORd induction chemotherapy for multiple myeloma (cyclophosphamide 500 mg/m², bortezomib 1.3 mg/m² subcutaneously, dexamethasone 40 mg intravenously), and monthly zoledronic acid (4 mg intravenously). Reassessment at two months demonstrated a partial response, and the same regimen was continued for two more months. Given transplant ineligibility, the patient was planned to continue on

maintenance chemotherapy. The patient succumbed to the disease after 16 weeks of induction chemotherapy due to sepsis.

DISCUSSION

Synchronous Multiple Primary Cancers (SMPC) indicate diagnosis of two or more distinct primary malignant tumours occurring within a relatively short-time frame, typically within six months [1]. Co-existent malignancies are usually associated with common genetic, infectious, environmental, or occupational factors but some synchronous malignancies may be coincidental. They are less common than metachronous tumours, defined as more than six months' time interval between the diagnosis.

Coexistence of prostate cancer and plasma cell myeloma is rarer. Synchronous bone marrow involvement by both these malignancies is even rarer, with isolated case reports [2]. An association between prostate carcinoma and plasma cell myeloma has been hypothesised based on similarities in the tumour BMME of both malignancies [3]. The mechanism by which plasma cell myeloma and prostate cancer influence each other's development has been studied. There are possible common biological pathways leading to co-stimulatory mechanisms, like Interleukin-2 (IL-2), Insulin-Like Growth Factor 1 (IGF-1), Stromal Cell-Derived Factor 1 (SDF-1), and Vascular Endothelial Growth Factor (VEGF) [4]. Growth factors and antiapoptotic cytokines, such as IL-6 and IGF 1, which are commonly released by myeloma cells might play a role in prostatic proliferation by activation of the RAS-MAPK pathway and suppressing apoptosis. VEGF secreted by myeloma cells lines, is an important mediator of angiogenesis and overexpression of the same in prostate cancer patients correlates with poor survival [2,5]. Myeloma induced immunodeficiency might be a factor contributing to more aggressive phenotype and accelerated progression of prostate cancer [4].

The incidence of simultaneous diagnosis of prostate cancer and lymphoid malignancies is reported to be approximately 1.2% [5], but synchronous occurrence of prostate adenocarcinoma and plasma cell myeloma is very rare with isolated case reports [2,3,5].

Prostatic carcinoma and plasma cell myeloma can present with bone lesions. Early prostate cancer may not be symptomatic. Bone pain due to metastasis may be the initial presentation of advanced prostatic carcinoma. Metastasis mechanisms in prostate cancer include local, haematogenous, and lymphatic spread which can lead to atypical presentations. Metastatic prostate cancer to bone marrow with synchronous plasma cell myeloma is exceptional [4].

SDF-1 which is a chemoattractant which causes selective adhesion of myeloma cells to bone has recently been implicated in the pathogenesis of metastatic prostate cancer cells to bone [6]. Thus, it may be possible that the development of MM in our patient as a secondary malignant disease enhanced the progression of prostate cancer and metastasis to the bone.

Immune dysfunctions caused by plasma cell myeloma may lead to the accelerated progression of latent or clinically insignificant prostate cancers, resulting in a more aggressive phenotype with increased PSA levels or palpable masses. c-MYC dysregulation is observed in a significant proportion (45-90%) of advanced myeloma cells, and c-MYC amplification is associated with a higher grade of malignancy and worse prognosis in prostate cancer patients [7]. The new techniques like DNA microarrays, proteomic pattern analysis, and comparative genomic hybridisation offer paths to explore more additional link between prostate cancer and plasma cell myeloma.

Nevertheless, monoclonal gammopathy could be observed not only due to neoplastic B-cell proliferation but also as part of immunologic changes in patients with malignant tumour of epithelial origin [6]. In patients with epithelial neoplasia, a host's reaction is known to occur that involves T killers, T helpers, and B lymphocytes, and the low levels of M protein might be a result of lymphoid B-cell activation and antitumour immune response [8].

Thus, in a study of Kao J et al., among 700 consecutive patients with prostate cancer, there were 4 cases of MM that preceded the diagnosis of prostate cancer [4].

Comparison of similar reported cases from the literature has been tabulated [Table/Fig-6] [2,3,5,9-11].

We report a rare case of synchronous occurrence of metastatic prostate adenocarcinoma and plasma cell myeloma in an elderly male. For the diagnosis of plasma cell myeloma 10% or more clonal plasma cells on bone marrow examination/plasmacytoma and one or more myeloma defining events is required. In our case, findings in favour of plasma cell myeloma were anaemia, raised ESR, renal insufficiency and presence of 35% clonal plasma cells which showed monoclonality for kappa light chain. IFE confirmed the presence of M-band for IgA and kappa.

A timeline figure illustrating the disease course has been shown [Table/Fig-7].

A similar case was reported by Sehgal T et al., in which bone marrow examination revealed infiltration by malignant epithelial cells, which were arranged in a glandular fashion along with 12% plasma cells on aspirate smear [2]. Findings in favour of plasma cell myeloma in their case were anaemia, multiple osteolytic bony lesions in skull and vertebra and presence of 12% clonal plasma cells which showed monoclonality for lambda light chain. IFE confirmed the presence of M-band for IgA and lambda.

Treatment Implications and Recommendations

There are no defined guidelines regarding the treatment of synchronous malignancies. The treatment sequence and modalities are decided based on the stage of diseases, symptoms,

Author, year	Age (Years)	Clinical findings suspicious of multiple myeloma	Clinical findings suspicious of prostate carcinoma	Treatment received	Follow-up
Sehgal T et al., [2] 2014	62	Multiple osteolytic lesions in skull and vertebra. Haemogram showed anaemia. Serum Protein Electrophoresis (SPE) which showed M-band concentration of 0.50 g/dL, which was later shown by Immunofixation Electrophoresis (IFE) to be IgA and lambda paraproteins	Back pain with radiation of pain to legs MRI spine showed diffuse marrow infiltration. Elevated PSA levels (122 ng/mL)	Vincristine, endoxan and prednisolone, melphalan, and prednisone followed by hormonal therapy	Stable at 4 months follow-up
Kim NY et al., [3] 2011	58	Lower back pain, tingling sensation of the gluteal region, thigh and non-traumatic L3 vertebra fracture	Hesitancy, mild voiding difficulties, residual urine sensation and elevated PSA levels (62 ng/mL)	Radiation therapy on the L3 vertebra, androgen deprivation therapy with bicalutamide, goserelin as well as bisphosphonate	No evidence of disease recurrence at 37 months follow-up after diagnosis
Andres D et al., [9] 2018	71	Pain and swelling in the left thigh with difficulty in walking. Routine blood investigations showed normocytic anaemia, increased serum creatinine, and elevated globulin levels. MRI showed a large lytic lesion in femur. SPE showed an IgA-kappa monoclonal M-spike	CT demonstrated diffuse osteoblastic metastatic lesions, including multiple sclerotic lesions throughout the spine. Pelvic imaging also demonstrated asymmetric enhancement of the left anterior prostate. PSA level was 90 ng/mL	Distal femur resection with endoprosthetic reconstruction. Stable at 2-year follow-up. Bicalutamide and leuprolide, Cyclophosphamide, bortezomib, and dexamethasone followed by autologous haematopoietic stem cell transplantation with melphalan conditioning	Stable at 2-year follow-up
Vyas Y et al., [5] 2020	83	Low back pain. Investigations showed anaemia, normocytic normochromic anaemia. MRI showing osteolytic lesions in the skull and vertebrae	Urinary incontinence. PSA level was 140 ng/L. Transrectal ultrasound showed hypoechoic prostatic mass	Not available	Not available
Dass J et al., [10] 2020	70	Prolonged prothrombin time with lack of yellowness of plasma and serum showing a coagulum. Haemogram showed severe anaemia. Serum Protein Electrophoresis (SPE) showed an M-band of 4.37 g/dL which was typed as IgA λ on immunofixation	Bone scan done revealed multiple lytic lesions suggesting skeletal metastases	Zoledronic acid for skeletal metastasis and anti-androgen therapy (triptorelin) Refused multiple myeloma treatment	Expired
Upadhyay AK et al., [11] 2023	62	Lower back pain radiating to the left lower limb for three months, weight loss. Routine investigations showed significant anaemia and raised ESR	Magnetic Resonance Imaging (MRI) for the Lumbosacral Spine (LS) with whole spine screening and prostate revealed prostatomegaly and patchy to diffuse areas of altered signal intensity affected multiple vertebrae suggesting possible metastasis from the primary prostate. Serum PSA was 21.52 ng/mL	Bortezomib, cyclophosphamide and dexamethasone. Zoledronic acid was added Leuprolide for prostate cancer	Stable and planned for maintenance of bortezomib and radical intent radiation therapy for prostate cancer after three months
Current study	73	Back pain, fatigue and weight loss. Routine blood investigations showed normocytic anaemia, raised ESR, raised creatinine and reversal of Albumin/Globulin ratio. SPE showed M peak in the gamma fraction	Per rectal examination revealed enlarged hard prostate. PSA levels (476 ng/L)	Leuprolide for prostate cancer. Bortezomib, cyclophosphamide dexamethasone for multiple myeloma and Zoledronic acid for skeletal metastasis Planned for maintenance chemotherapy as the patient is transplant ineligible	Expired

[Table/Fig-6]: Comparison with similar reported cases of multiple myeloma and prostate cancer diagnosed together from the literature [2,3,5,9-11].

TASK	7 April 2025	18 April 2025	21 April 2025	29 April 2025	10 October 2025
Initial symptoms (First consultation)					
Diagnostic test (Bone marrow biopsy and serum electrophoresis)					

Initial diagnosis					
Final diagnosis (Multidisciplinary tumour board meeting)					
Treatment plan decided					
Treatment initiation for multiple myeloma and carcinoma prostate					
Succumbed to disease while on treatment					

[Table/Fig-7]: A timeline figure illustrating the disease course.

aggressiveness of diseases, co-morbidities, expected survival, available treatment options, interaction among treatment modalities, performance status and comorbidities of patients [11]. Treatment generally focuses on managing the more advanced or symptomatic malignancy first often with a combination of systemic therapy for MM and hormone therapy for prostate cancer, as their treatment plans typically do not conflict. A multidisciplinary team is essential to determine the sequence of therapy, such as starting chemotherapy to stabilise the patient before definitive radiation therapy for prostate cancer. Induction chemotherapy followed by autologous stem cell transplant in transplant-eligible cases is the standard of care for managing MM [12]. In our case, the patient was symptomatic for multiple myeloma and remained asymptomatic for prostatic carcinoma. Treatment is prioritised based on the most symptomatic disease and is usually initiated based on which cancer is more advanced or causing greater morbidity. After discussing the case in multidisciplinary tumour board, patient was started on treatment of multiple myeloma with the CyBorD regime and androgen deprivation therapy for prostatic adenocarcinoma.

Awareness of the possible interconnection between MM and prostate carcinoma is necessary so that appropriate treatment can be administered. In addition, the finding of two unrelated malignancies will have a significant impact on treatment of the patient.

There was a possibility of missing the diagnosis of metastatic deposit in the bone marrow if the marrow biopsy was not done as the atypical cell clusters were absent in the bone marrow aspirate. Prostate cancer and myeloma cell deposits can be seen together in bone marrow as in our case. A detailed and careful bone marrow examination and immunohistochemistry are warranted if there is suspicion of synchronous deposits in bone marrow.

CONCLUSION(S)

In summary, we report a rare case of synchronous plasma cell myeloma and metastatic prostate adenocarcinoma in the same

bone marrow biopsy which is extremely rare, very often rendering diagnostic and therapeutic challenge. A bone marrow examination including a biopsy is mandatory to confirm or refute a second malignancy. The pathogenesis of this co-existence should be further explored. Awareness of the possible interconnection between MM and prostate carcinoma is necessary so that appropriate treatment can be administered.

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