Case Series

Diagnostic challenges in multiple myeloma: A case series of atypical neurological, renal, and skeletal presentations

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ABSTRACT

Multiple myeloma (MM) is a clinically heterogeneous plasma-cell malignancy in which reliance on conventional diagnostic markers, including CRAB features and serum protein electrophoresis, may contribute to delayed or missed diagnosis. This case series describes four patients presenting with atypical, organ-predominant manifestations that obscured early recognition of MM. Presentations included non-compressive conus medullaris syndrome due to diffuse vertebral marrow infiltration, nephrotic syndrome secondary to Amyloid Light chain (AL) amyloidosis, delayed diagnosis of kappa light-chain myeloma with progressive osteolytic disease despite initially non-diagnostic monoclonal studies, and true non-secretory myeloma identified during evaluation for acute infection. In two cases, initial serum monoclonal protein studies were negative, contributing to diagnostic delay. Contemporary evidence emphasizes the need for early integration of serum-free light-chain assays, advanced imaging, and bone marrow evaluation in patients with high clinical suspicion, even when classical features are absent.

Key words: Conus medullaris syndrome, CRAB features, Light chain myeloma, Multiple myeloma, Serum protein electrophoresis

Multiple myeloma (MM) is a clonal plasma-cell malignancy with heterogeneous clinical manifestations. Although anemia, renal dysfunction, hypercalcemia, and osteolytic bone disease form the traditional diagnostic framework, exclusive reliance on CRAB (hypercalcemia, renal dysfunction, anemia, and bone lesions) features and serum protein electrophoresis (SPEP) may delay recognition in patients with organ-predominant, light-chain–restricted, or non-secretory disease. The revised International Myeloma Working Group (IMWG) criteria incorporate bone marrow plasmacytosis, advanced imaging, and biomarker-defined myeloma-defining events to facilitate earlier diagnosis. Despite these advances, delayed or missed diagnosis remains common in routine clinical practice, particularly when initial monoclonal protein studies are non-diagnostic or clinical manifestations are attributed to more prevalent non-malignant conditions [1].

In this case series, we describe four patients in whom MM presented with atypical neurological, renal, and skeletal manifestations, leading to diagnostic delay. Rather than emphasizing the rarity of phenotype, these cases are examined through the lens of recurring diagnostic dilemmas, including false reassurance from negative SPEP, misattribution of organ-predominant disease, and under-recognition of light-chain and non-secretory myeloma.

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CASE 1: KAPPA LIGHT-CHAIN MM PRESENTING WITH CONUS MEDULLARIS SYNDROME

A 54-year-old man presented with acute bladder and bowel dysfunction in the form of urinary and fecal incontinence, dribbling of urine, and inability to perceive bladder fullness of 5-day duration, accompanied by dull low back pain for 1 week. There was no history of limb weakness or sensory deficit in the extremities.

On admission, his pulse was 88/min, blood pressure 130/70 mmHg, and room air saturation was 98%. The patient had pallor, and neurological examination demonstrated saddle anesthesia with absent ankle and bulbocavernosus reflexes, consistent with conus medullaris syndrome, while motor strength and peripheral sensation were preserved.

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Initial laboratory evaluation (Table 1) revealed normocytic anemia, hypercalcemia, and markedly elevated erythrocyte sedimentation rate. Serum β_2-microglobulin was significantly elevated. Serum immunofixation studies identified an immunoglobulin G kappa monoclonal band (Fig. 1a). Magnetic resonance imaging (MRI) of the spine (Fig. 1b) showed diffuse vertebral marrow signal abnormality involving multiple levels without epidural mass or radiological spinal cord compression. Skeletal survey demonstrated generalized osteopenia without focal lytic lesions. Bone marrow examination revealed 40% clonal plasma cells with CD138 positivity, confirming a plasma cell neoplasm. In the absence of structural cord compression, the neurological deficit was attributed to infiltrative marrow disease involving the conus medullaris region. A diagnosis of kappa light-chain MM presenting with non-compressive conus medullaris syndrome was established. The patient was referred for definitive hematologic management.

CASE 2: MM WITH SECONDARY AL-TYPE AMYLOIDOSIS PRESENTING AS NEPHROTIC SYNDROME

A 68-year-old woman presented with progressive bilateral lower-limb edema and facial puffiness over 3 months. There were no symptoms suggestive of cardiac failure, chronic liver disease, infection, or systemic inflammatory disorder. On presentation, her pulse was 92/min, blood pressure 120/80 mmHg, and a respiratory rate of 16/min. Clinical examination revealed pallor, generalized anasarca, and an otherwise insignificant systemic examination.

Laboratory evaluation demonstrated nephrotic-range proteinuria with marked hypoalbuminemia and preserved renal function, along with mild normocytic anemia (Table 2). Given adult-onset nephrotic syndrome without an obvious secondary cause, a renal biopsy was performed.

Histopathology revealed acellular amorphous extracellular deposits showing Congo red positivity with apple-green birefringence on polarized microscopy (Fig. 2a and b). Immunofluorescence demonstrated lambda light-chain restriction, consistent with AL-type amyloidosis (Fig. 3). Subsequent hematologic evaluation revealed 20% clonal plasma cells on bone marrow examination with CD138 positivity. Serum free light-chain assay showed markedly elevated lambda light chains with a suppressed kappa/lambda ratio, and β_2-microglobulin levels were significantly increased. Positron emission tomography–computed tomography did not demonstrate overt lytic bone disease. In the setting of biopsy-proven AL amyloidosis with underlying clonal plasma-cell proliferation, a diagnosis of MM with secondary AL (lambda) amyloidosis presenting as nephrotic syndrome was established. The patient was transferred to hematology for further staging and initiation of systemic therapy.

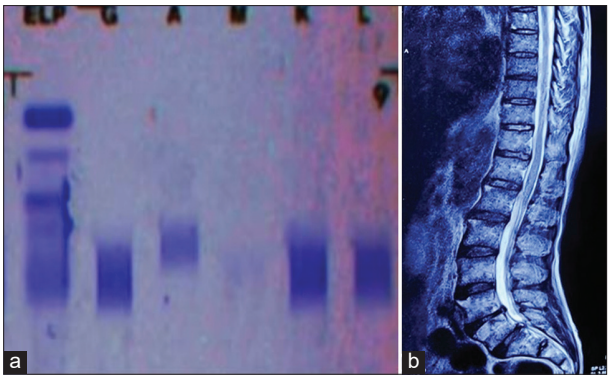

Figure 1: (a) Serum immunofixation electrophoresis showing immunoglobulin G band, Kappa and Lambda chain bands; (b) Magnetic resonance imaging of the spine showing altered bone marrow signal intensities and diffuse osteopenic changes in multiple vertebral levels (case 1)

CASE 3: DELAYED DIAGNOSIS OF KAPPA LIGHT-CHAIN MM WITH EXTENSIVE SKELETAL INVOLVEMENT

A 42-year-old man presented in a chronically debilitated state with progressive weight loss, generalized weakness, and recent-onset respiratory symptoms. He had sustained multiple long-bone fractures 2 years earlier, attributed at the time to trauma, with evaluation revealing anemia and diffuse osteopenia but normal serum calcium and non-diagnostic SPEP. No hematologic malignancy was identified at that time.

On the current presentation, pulse rate was 112/min, blood pressure 100/60 mmHg, and peripheral oxygen saturation 97% in room air. He was emaciated and markedly anemic, with kyphotic deformity and multiple

Table 1: Laboratory and diagnostic findings in case 1

Parameter	Result	Reference range
Hemoglobin	9.6 g/dL	13–17 g/dL
Total leukocyte count	6.400/mm^3	4.000–11.000/mm^3
Platelet count	2.11×10^5/mm^3	1.5–4.0×10^5/mm^3
Erythrocyte sedimentation rate	80 mm/h	<20 mm/h
Serum calcium	11.4 mg/dL	8.6–10.2 mg/dL
Serum creatinine	1.3 mg/dL	0.6–1.2 mg/dL
Serum albumin	3.1 g/dL	3.5–5.0 g/dL
Total serum protein	8.5 g/dL	6.0–8.0 g/dL
Beta-2 microglobulin	6180.55 ng/mL	0.7–1.8 mg/L
Serum protein studies	IgG kappa monoclonal band	-
MRI spine	Diffuse vertebral marrow infiltration; no cord compression	-
Skeletal survey	Generalized osteopenia; no focal lytic lesions	-
Bone marrow biopsy	40% plasma cells; CD138 positive	<10%

MRI: Magnetic resonance imaging, IgG: Immunoglobulin G

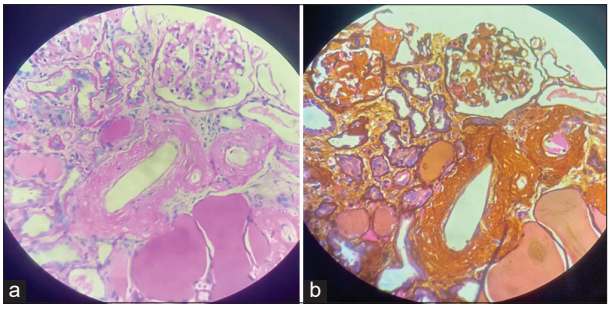

Figure 2: (a and b) Renal biopsy showing acellular amorphous deposits in glomeruli and focally on the interstitium which is Congo red positive giving apple green birefringence under polarized light (case 2)

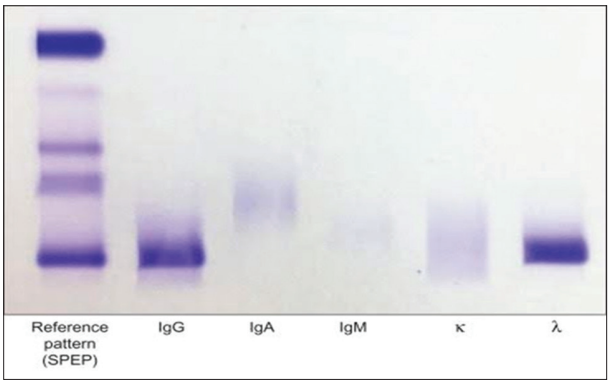

Figure 3: Serum immunofixation showing immunoglobulin G band and lambda chain bands (case 2)

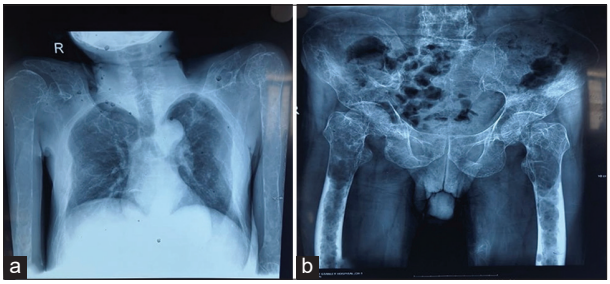

Figure 4: (a and b) Skeletal survey revealing multiple lytic lesions with diffuse osteopenia (case 3)

bony swellings involving the chest wall and shoulders. Imaging revealed diffuse osteopenia with multiple lytic lesions involving the ribs, spine, pelvis, and long bones (Fig. 4a and b).

Laboratory investigations demonstrated normocytic anemia and hypercalcemia with preserved renal function. Urinary testing for Bence–Jones protein was negative. SPEP showed hypogammaglobulinemia without a discrete M-spike (Table 3). Given the extent of skeletal involvement, further evaluation with serum immunofixation electrophoresis revealed kappa-restricted monoclonal light-chain disease, accompanied by elevated β_2-microglobulin levels. Bone marrow examination demonstrated approximately 10% atypical plasma cells with CD138 positivity, confirming clonal plasma-cell proliferation. A diagnosis of kappa light-chain MM with extensive osteolytic disease was established. The patient was treated with intravenous fluids and bisphosphonates for hypercalcemia. The patient was counseled regarding systemic therapy but declined treatment and was discharged against medical advice.

Table 2: Laboratory and diagnostic findings in case 2

Parameter	Result	Reference range
Hemoglobin	10.8 g/dL	12–15 g/dL
Total leukocyte count	7.000/mm^3	4.000–11.000/mm^3
Platelet count	2.3×10^5/mm^3	1.5–4.0×10^5/mm^3
Serum creatinine	0.9 mg/dL	0.6–1.2 mg/dL
Serum albumin	2.2 g/dL	3.5–5.0 g/dL
Total serum protein	6.8 g/dL	6.0–8.0 g/dL
24-h urine protein	4.8 g/day	<0.15 g/day
Serum calcium	8.9 mg/dL	8.6–10.2 mg/dL
Beta-2 microglobulin	10433 ng/mL	0.7–1.8 mg/L
Kappa free light chain	37 mg/L	3.3–19.4 mg/L
Lambda free light chain	1007.93 mg/L	5.7–26.3 mg/L
Kappa/Lambda ratio	<0.1	0.26–1.65
Renal biopsy	Congo red positive; lambda restricted	-
Bone marrow biopsy	20% plasma cells; CD138 positive	<10%
PET-CT	No hypermetabolic lytic lesions	-

PET-CT: Positron emission tomography-computed tomography

Table 3: Laboratory and diagnostic findings in case 3

Parameter	Result	Reference range
Hemoglobin	8.3 g/dL	14–17 g/dL
Total leukocyte count	8,200/mm^3	4.000–11.000/mm^3
Platelet count	2.4 lakhs	1.5–4.0 lakhs
Erythrocyte sedimentation rate	40 mm/h	Up to 20 mm/h
Serum calcium	12.3 mg/dL	8.5–10.5 mg/dL
Serum phosphorus	3.4 mg/dL	2.5–4.5 mg/dL
Blood urea	42 mg/dL	15–45 mg/dL
Serum creatinine	1.1 mg/dL	0.6–1.2 mg/dL
Serum sodium	132 mmoL/L	135–145 mmoL/L
Serum potassium	4.1 mmoL/L	3.5–5.1 mmoL/L
Serum albumin	3.48 g/dL	3.5–5.0 g/dL
Total protein	6.95 g/dL	6.0–8.3 g/dL
Serum parathyroid hormone	17.04 pg/mL	15–65 pg/mL
Thyroid-stimulating hormone	3.1 mIU/L	0.5–4.5 mIU/L
Free T4	1.4 ng/dL	0.8–1.8 ng/dL
Serum lactate dehydrogenase	376 U/L	135-225 U/L
Alkaline phosphatase	160 U/L	44–147 U/L
Urine Bence–Jones protein	Negative	Negative
C-reactive protein	Negative	Negative
Peripheral smear	Normocytic normochromic anemia	Normal morphology

Table 4: Laboratory and diagnostic findings in case 4

Parameter	Day 1	Day 2	Day 3/latest
Total leukocyte count/(uL)	26.000	17.500	11.500
Hemoglobin (g/dL)	7.9	7.6	7.7
Platelet count ($\times 10^5$/uL)	4.2	3.5	3.8
Erythrocyte sedimentation rate (30 min)	62 mm	NA	NA
Erythrocyte sedimentation rate (1 h)	132 mm	NA	NA
Peripheral smear	Neutrophilic leukocytosis; normocytic normochromic anemia	NA	NA
Reticulocyte count (%)	0.6	NA	NA
Reticulocyte production index	0.24	NA	NA
Blood urea (mg/dL)	45	40	33
Serum creatinine (mg/dL)	1.2	0.8	0.7
Serum calcium (mg/dL)	9.9	NA	NA
Corrected calcium (mg/dL)	11.2	NA	NA
Serum albumin (g/dL)	2.3	NA	NA
Liver function tests	Normal	NA	NA
Urine routine examination	Plenty of pus cells; no albumin, no sugar	NA	NA
Urine culture	*Klebsiella pneumoniae*	NA	NA
Urinary Bence–Jones protein	Negative	NA	NA
Serum protein electrophoresis	No M-band	NA	NA
Immunofixation electrophoresis	Negative	NA	NA
Bone marrow plasma cells (%)	12	NA	NA

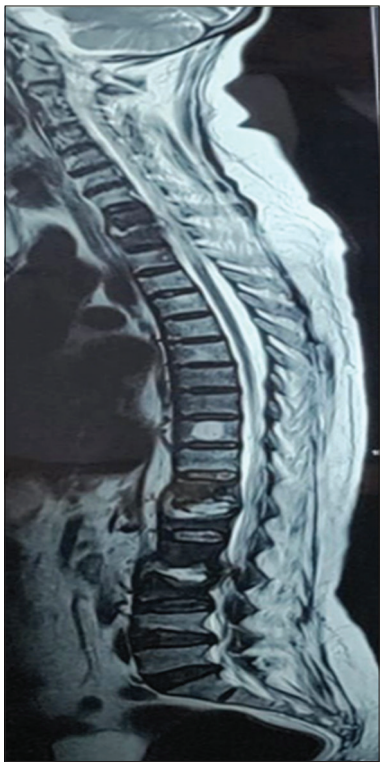

Figure 5: Magnetic resonance imaging of the spine showing altered signal intensity with bulging of the posterior cortex involving multiple vertebrae (T12, L1, 2, 3) with diffuse T2 hypointensity in C7, T1, T2 vertebral body (case 4)

CASE 4: NON-SECRETORY MM IN A 60-YEAR-OLD WOMAN

A 60-year-old woman with no significant comorbidities presented with acute febrile illness and altered sensorium. Initial vitals of the patient showed a pulse rate of 90/min, blood pressure 130/90 mmHg, and a Glasgow Coma Scale of 14/15 (E4V4M6), and the patient was subsequently diagnosed with right-sided acute pyelonephritis based on imaging and urine culture. She improved clinically with intravenous antibiotics. During hospitalization, she reported a 3-month history of persistent low back pain. Examination revealed localized lumbar spine tenderness. MRI of the spine demonstrated multiple focal vertebral lesions with altered marrow signal intensity involving the cervical and thoracolumbar spine, without features of degenerative disease (Fig. 5).

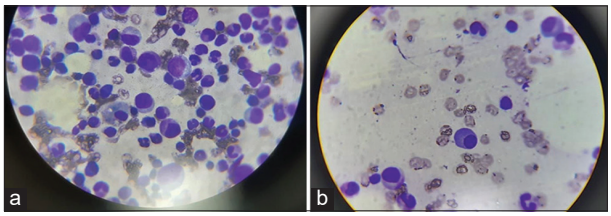

Figure 6: (a and b) Bone marrow biopsy showing hypercellular marrow with 12% plasma cells (case 4)

Laboratory evaluation showed persistent normocytic anemia, markedly elevated erythrocyte sedimentation rate, hypoalbuminemia, and mild hypercalcemia. Renal function normalized following resolution of sepsis. SPEP, immunofixation, and 24-h urine studies were negative for monoclonal protein, including Bence–Jones protein (Table 4). Given the unexplained cytopenia and multifocal vertebral lesions, a bone marrow examination was performed, revealing a hypercellular marrow with approximately 12% clonal plasma cells (Fig. 6a and b). In the presence of multifocal skeletal involvement and myeloma-defining clinical features despite absent measurable monoclonal protein, a diagnosis of

non-secretory MM was established. Definitive oncologic management was planned under hematology follow-up.

DISCUSSION

MM exhibits substantial clinical heterogeneity and may present with organ-predominant manifestations beyond classic CRAB features, contributing to clinically meaningful diagnostic delay. In this series, the focus is shifted from description of atypical phenotypes to identification of recurring diagnostic failure patterns encountered in routine clinical practice. Across the four cases, delayed or obscured diagnosis arose from four reproducible mechanisms: (a) False reassurance from negative or non-diagnostic SPEP; (b) misattribution of organ-predominant disease to more common non-malignant condition; (c) failure to recognize infiltrative, non-compressive neurological involvement; and (d) under-recognition of light-chain–restricted and true non-secretory MM.

Central nervous system involvement in MM is uncommon, occurring in less than 1% of cases, and is typically attributed to epidural plasmacytoma or vertebral collapse causing mechanical compression. In contrast, Case 1 illustrates a presentation that may mislead clinical assessment, as the absence of a discrete epidural mass or vertebral collapse on MRI can bias clinicians toward non-malignant etiologies of conus medullaris syndrome. The presence of systemic red flags, including anemia, hypercalcemia, and markedly elevated β_2-microglobulin, should prompt early consideration of an underlying plasma-cell dyscrasia even when overt radiological compression is absent. Acute conus medullaris or cauda equina syndromes with diffuse vertebral marrow signal abnormality, therefore, represent a high-risk diagnostic context in which reliance on structural compression alone may delay recognition of MM. Neurological dysfunction in such settings may arise from infiltrative marrow disease without overt mechanical compression, warranting early integration of bone marrow evaluation and hematologic work-up [2,3].

Case 2 exemplifies an organ-predominant presentation that may mislead clinical assessment, in which nephrotic syndrome due to AL amyloidosis preceded overt skeletal or hematologic features of MM. The clinical profile of heavy proteinuria with marked hypoalbuminemia and preserved renal function is characteristic of glomerular amyloid deposition rather than myeloma cast nephropathy, predisposing to an initial nephrology-centered diagnostic pathway [4-6].

Although renal involvement occurs in approximately two-thirds of patients with systemic AL amyloidosis, with 50–75% presenting with nephrotic-range proteinuria [7,8], only 10–20% of patients with AL amyloidosis meet criteria for overt MM at presentation [9]. In this context, renal biopsy served as the diagnostic inflection point, prompting targeted hematologic evaluation and establishing the underlying plasma-cell dyscrasia.

This case highlights adult-onset nephrotic syndrome due to AL amyloidosis as a high-risk diagnostic context in which reliance on organ-specific evaluation alone may delay recognition of MM. Early integration of bone marrow examination and serum free light-chain analysis is therefore warranted even in the absence of myeloma-defining skeletal lesions [7-9].

Case 3 illustrates a recurring diagnostic pitfall in light-chain–predominant MM, in which early skeletal manifestations are misattributed to trauma or degenerative bone disease and negative SPEP provides false reassurance. Initial evaluation following fractures revealed anemia and osteopenia with normal serum calcium and non-diagnostic SPEP, delaying consideration of an underlying plasma-cell dyscrasia.

As the disease evolved, the subsequent development of extensive osteolytic lesions, hypercalcemia, and markedly elevated kappa-restricted free light chains unmasked active myeloma, underscoring the limited sensitivity of single-time-point monoclonal protein studies in light-chain–restricted disease.

This case highlights unexplained fractures or progressive osteopenia with initially negative monoclonal studies as a high-risk diagnostic context in which reliance on baseline SPEP alone may delay recognition of MM. Longitudinal reassessment with repeat immunofixation, serum free light-chain analysis, advanced skeletal imaging, and bone marrow examination is therefore warranted [1,4,5,10].

Case 4 illustrates a critical diagnostic pitfall in true non-secretory MM, in which reliance on monoclonal protein-based screening may falsely exclude plasma-cell dyscrasia. In this patient, normal SPEP, negative immunofixation, and absence of urinary Bence–Jones protein initially obscured the diagnosis. However, the presence of anemia, mild hypercalcemia, multifocal vertebral lesions on MRI, and >10% clonal plasma cells on bone marrow examination fulfilled the IMWG criteria for symptomatic disease [11].

True non-secretory myeloma is uncommon and accounts for only 1–3% of cases [5,6]. Unlike oligo-secretory disease, diagnosis depends primarily on bone marrow evaluation and advanced imaging rather than biochemical markers. The incidental identification of vertebral lesions during evaluation for intercurrent infection in this case highlights how systemic stressors may unmask otherwise occult disease.

This case underscores that unexplained cytopenias with focal skeletal lesions constitute a high-risk diagnostic context in which the absence of measurable monoclonal protein should not defer marrow evaluation. Early integration of imaging and bone marrow examination is therefore warranted when clinical suspicion persists [1,4,5,6].

CONCLUSION

MM should be actively considered in patients with

unexplained neurological deficits, nephrotic syndrome, or progressive skeletal disease, even when SPEP is negative. Early consideration of plasma-cell dyscrasia and timely use of bone marrow examination, serum free light-chain analysis, and advanced imaging are essential in such settings and facilitate earlier initiation of therapy.

REFERENCES

1. Rajkumar SV, Dimopoulos MA, Palumbo A, Blade J, Merlini G, Mateos MV, *et al*. International myeloma working group updated criteria for the diagnosis of multiple myeloma. Lancet Oncol 2014;15:e538-48.
2. Egan PA, Elder PT, Deighan WI, O'Connor SJ, Alexander HD. Multiple myeloma with central nervous system relapse. Haematologica 2020;105:1715-24.
3. Tosev G. Extramedullary multiple myeloma with central nervous system involvement. J Neurooncol 2019;13:1-12.
4. Bladé J, Beksac M, Caers J, Jurczyszyn A, Von Lilienfeld-Toal M, Moreau P, *et al*. Extramedullary disease in multiple myeloma: A systematic literature review. Blood Cancer J 2022;12:45.
5. Albano F, De Larrea CF, Rosiñol L. Extramedullary involvement in multiple myeloma: Incidence and clinical implications. Haematologica 2024;109:1234-43.
6. Katodritou E, Terpos E, Kastritis E. Central nervous system multiple myeloma: A real-world multi-institutional study of the Greek myeloma study group. Leuk Lymphoma 2023;64:671-80.
7. Nasr SH, Valeri AM, Sethi S, Fidler ME, Cornell LD, Gertz MA, *et al*. Clinicopathologic correlations in multiple myeloma: A case series of 190 patients with kidney biopsies. Am J Kidney Dis 2012;59:786-94.
8. Muchtar E, Gertz MA, Kyle RA, Lacy MQ, Dingli D, Leung N, *et al*. A modern primer on light chain amyloidosis in 592 patients with mass spectrometry-verified typing. Mayo Clin Proc 2019;94:472-83.
9. Gertz MA, Dispenzieri A. Systemic amyloidosis recognition, prognosis, and therapy: A systematic review. JAMA 2020;324:79-89.
10. Landgren O, Rajkumar SV. New developments in diagnosis, prognosis, and assessment of response in multiple myeloma. Clin Cancer Res 2016;22:5428-33.
11. Zamagni E, Cavo M. The role of imaging techniques in the management of multiple myeloma. Br J Haematol 2012;159:499-513.

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