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JCIMCR OPEN ACCESS Journal of Clinical Images and Medical Case Reports

ISSN 2766-7820

Case Report

Open Access, Volume 6

Non-secretory multiple myeloma: Diagnostic challenges and the value of imaging and immunohistochemistry

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Received: Sep 25, 2025

Accepted: Oct 20, 2025

Published: Oct 27, 2025

Archived: www.jcimcr.org

DOI: www.doi.org/10.52768/2766-7820/3821

Abstract

Background: Non-Secretory Multiple Myeloma (NSMM) is a rare variant of multiple myeloma, representing 3-5% of cases. Its diagnosis is challenging due to the absence of detectable monoclonal protein in serum or urine.

Case presentation: A 42-year-old female presented with progressive generalizes body pain, anaemia. Imaging revealed multiple lytic lesions, but serum protein electrophoresis and immunofixation were negative. Serum free light chains were normal. Bone marrow is inspirable, H/E stain of trephine biopsy is inconclusive. Immunohistochemistry revealed infiltration by CD138 lambda restricted plasma cells.

Conclusion: This case highlights the importance of bone marrow studies particularly immunohistochemistry and advanced imaging in diagnosing NSMM. Despite the absence of measurable M-protein, inspirable bone marrow and inconclusive trephine biopsy, immunohistochemistry solve the mystery of lytic lesions that appear in X-rays and CT scan.

Keywords: Non-secretory multiple myeloma; Lytic lesions; Immunohistochemistry; Bone marrow biopsy.

Introduction

Multiple Myeloma (MM) is a malignant plasma cell disorder that accounts for 10% of hematologic malignancies. The diagnosis of MM traditionally relies on the detection of Monoclonal protein (M-protein) in serum or urine. However, in 3-5% of patients, no measurable M-protein is detected, defining a subgroup known as Non-Secretory Multiple Myeloma (NSMM).

The absence of M-protein complicates both diagnosis and monitoring. Patients typically present with the same CRAB features (hypercalcemia, renal impairment, anaemia, bone lesions) as secretory myeloma. Confirmation requires bone marrow biopsy with immunophenotyping and imaging such as CT and X-rays.

We report a rare case of NSMM, emphasizing the diagnostic difficulties and how the diagnosis can be made in the absence of typical presenting features.

Case presentation

A 42-year-old female presented with a 1-week history of worsening bilateral upper limb pain and shortness of breath. There was no history of weight loss, fever, or night sweats.

Examination: Revealed pallor and spinal tenderness, but no lymphadenopathy or organomegaly.

Laboratory investigations:

- Hemoglobin: 8.7 g/dL

- WBC: 18.7×10^9/L
- Platelets: 265×10^9/L
- Serum corrected calcium: 2.9 mmol/L
- Serum creatinine: 1937 micromol/l (49-90)
- Serum protein electrophoresis: normal
- Beta-2 microglobulin: 47.3 mg/l (0.9-2)
- Normal protein electrophoresis

Imaging: Skeletal survey demonstrated lytic lesions in vertebrae, pelvis, and skull.

Diagnosis: Non-secretory multiple myeloma.

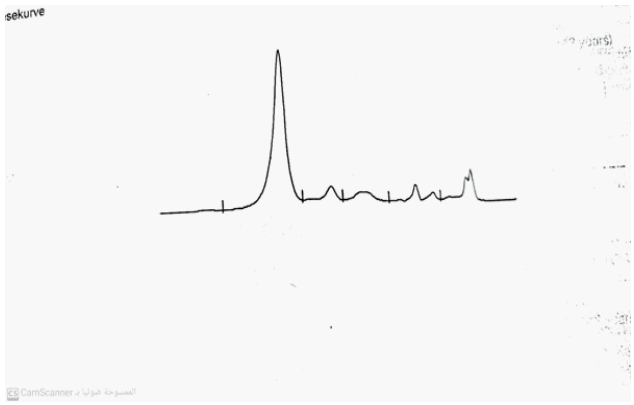

Figure 1: Graph.

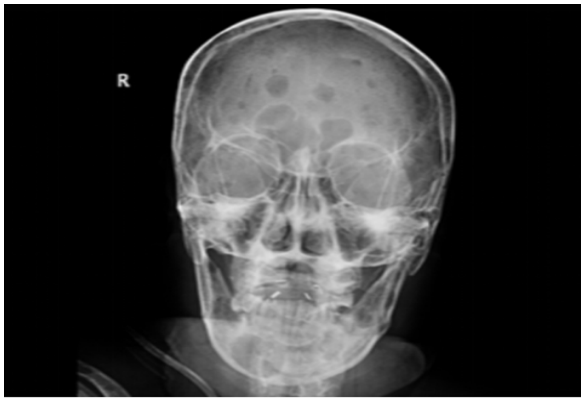

Figure 2: Skull X-ray showed lytic lesions.

Discussion

The diagnosis of NSMM remains one of the greatest challenges in hematopathology, particularly in patients presenting with negative or inconclusive standard diagnostic tools. Conventionally, the diagnosis of Multiple Myeloma (MM) relies on the triad of serum/urine protein studies, bone marrow examination, and radiologic evidence of lytic bone disease. However, when bone marrow aspiration yields a dry tap, the Hematoxylin and Eosin (H&E) stained trephine biopsy is inconclusive, and Serum Protein Electrophoresis (SPEP) appears normal, the role of advanced imaging and Immunohistochemistry (IHC) becomes indispensable.

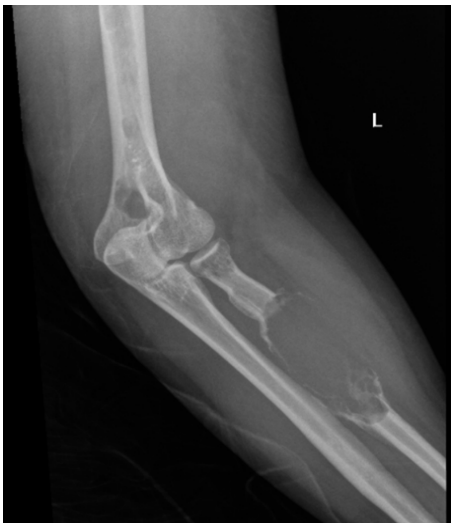

Figure 3: Expansile aggressive lytic lesion with thinning and destructive cortex of proximal shaft of radius.
Bone marrow aspiration is inspirable (dry tab).
Bone marrow biopsy: is inconclusive.

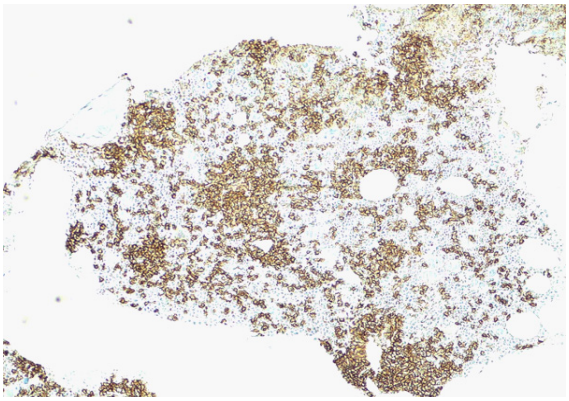

Figure 4: CD138: Positive

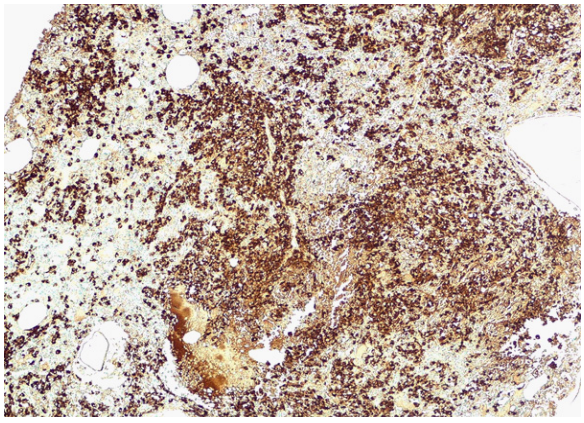

Figure 5: Lambda light chain: Positive

Challenges in diagnosis of NSMM

In NSMM, plasma cells either fail to secrete detectable immunoglobulin or produce quantities below the detection threshold of conventional electrophoretic techniques. Approximately 1-5% of all myeloma cases fall into this category. The absence of a detectable Monoclonal (M) protein in the serum or urine excludes one of the most sensitive and commonly used diagnostic parameters, thereby complicating diagnosis.

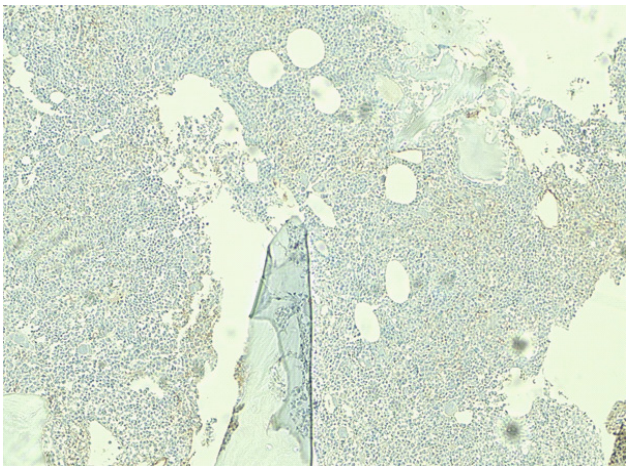

Figure 6: LamKappa light chain: Negative

Additionally, bone marrow aspiration may be uninformative due to fibrosis, patchy infiltration, or technical difficulties, resulting in a "dry tap." Similarly, routine H&E evaluation of the trephine biopsy may not clearly reveal the clonal plasma cell infiltrate, especially when the infiltration is subtle, interstitial, or masked by reactive changes.

Importance of imaging

Imaging modalities, particularly whole-body low-dose CT, MRI, and PET/CT, play a pivotal role in this diagnostic dilemma.

- **MRI:** Highly sensitive in detecting marrow infiltration, even in the absence of lytic lesions. Diffuse marrow signal changes or focal lesions may guide the pathologist to suspect plasma cell neoplasm.

- **PET/CT with FDG:** Provides functional information about metabolically active lesions, detecting disease sites not visible on skeletal surveys or CT alone. PET/CT is particularly helpful in differentiating between active myeloma lesions and osteoporotic changes.

- **Low-dose CT:** More sensitive than conventional skeletal surveys in detecting lytic bone lesions, which remain one of the CRAB (calcium elevation, renal failure, anemia, bone lesions) defining features of myeloma.

Thus, imaging can direct attention to disease activity and support the diagnosis when traditional laboratory findings are inconclusive.

Role of Immunohistochemistry (IHC) in trephine biopsy

When H&E sections are nondiagnostic, IHC staining is indispensable in revealing and characterizing plasma cell infiltrates. Specific markers provide both diagnostic confirmation and clonality assessment:

- CD138: Sensitive markers for identifying plasma cells, especially when morphology is subtle.

- Kappa and Lambda light chain restriction: Demonstrates clonality of plasma cells, which is critical for confirming malignancy.

IHC can thus uncover small or diffuse plasma cell infiltrates not appreciable on H&E and establish clonality, transforming an "inconclusive" trephine into a diagnostic specimen.

Integrative diagnostic approach

In cases of NSMM with inconclusive marrow morphology and negative protein electrophoresis, the integration of advanced imaging and IHC provides a reliable pathway toward diagnosis:

- Imaging demonstrates the extent and pattern of skeletal or marrow involvement, supplying indirect but highly suggestive evidence of myeloma.

- IHC confirms the presence and monoclonal nature of plasma cells, validating the histopathological diagnosis despite negative H&E findings.

Together, these modalities bridge the diagnostic gap left by the limitations of aspiration cytology, electrophoresis, and routine morphology.

Clinical implications

The accurate diagnosis of NSMM is not merely academic-it carries substantial therapeutic and prognostic consequences. Without M-protein as a biomarker, disease monitoring and response assessment in NSMM rely heavily on imaging findings and bone marrow evaluation using IHC or flow cytometry. Failure to utilize these advanced techniques risks misdiagnosis, delayed treatment initiation, and underestimation of disease burden.

Conclusion

Non-secretory multiple myeloma is a rare, diagnostically challenging entity. Clinicians should suspect NSMM in patients with CRAB features and lytic lesions but negative serum and urine studies. Bone marrow biopsy with flow cytometry and advanced imaging are essential for diagnosis and disease monitoring. With novel therapeutic approaches, NSMM patients can achieve long-term remission comparable to secretory myeloma.

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