

Renal and Extramedullary Involvement Revealing Atypical Multiple Myeloma: A Case Report and a Literature Review

Atteinte rénale et extramédullaire révélant un myélome multiple atypique: A propos d'un cas et revue de la littérature

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ABSTRACT

Background: Multiple myeloma (MM) is a plasma cell malignancy with diverse clinical manifestations. Beyond the classic CRAB features (hypercalcemia, renal insufficiency, anemia, and lytic bone lesions), extramedullary involvement is rare and often life-threatening. This case highlighted atypical and severe pulmonary-pleural manifestations, emphasizing the diagnostic complexity of extramedullary disease.

Case presentation: A 67-year-old hypertensive man was admitted with fever, dyspnea, and hemoptysis. He presented with pleural effusion, biologically confirmed alveolar hemorrhage, nephrotic-range proteinuria, and osteolytic lesions. Cytology demonstrated pleural plasmacytic infiltration, and bone marrow aspiration showed 100% plasmacytosis. He was diagnosed with immunoglobulin G-kappa MM with pulmonary and pleural extramedullary disease and achieved partial remission with melphalan-dexamethasone, maintaining clinical improvement for 12 months.

Conclusion: This case illustrated rare, severe extramedullary manifestations of MM with renal dysfunction as a key clinical clue. It underscored the importance of early recognition and comprehensive diagnostic evaluation. Prognosis remains poor in aggressive variants despite timely treatment.

Keywords: Ascites, liver neoplasms, lung neoplasms, multiple myeloma, renal insufficiency, pleural effusion

RÉSUMÉ

Introduction: Le myélome multiple (MM) est une hémopathie maligne des plasmocytes aux manifestations cliniques variées. Au-delà des critères classiques CRAB (hypercalcémie, insuffisance rénale, anémie, lésions osseuses), l'atteinte extramédullaire est rare et souvent potentiellement fatale. Ce cas illustre des manifestations atypiques, soulignant les défis diagnostiques.

Observation clinique: Un homme hypertendu de 67 ans a consulté pour fièvre, dyspnée et hémoptysie. Il présentait un épanchement pleural, une hémorragie alvéolaire, une protéinurie de type néphrotique et des lésions ostéolytiques. La cytologie a objectivé une infiltration plasmocytaire pleurale, et la biopsie médullaire a montré une plasmocytose de 100%. Le diagnostic de MM immunoglobuline G-kappa avec atteinte extramédullaire pulmonaire et pleurale a été retenu. Le patient a obtenu une rémission partielle sous melphalan-dexaméthasone, avec maintien de l'amélioration clinique après 12 mois.

Conclusion: Ce cas illustre une forme extramédullaire rare et sévère du MM, dont l'insuffisance rénale représentait un signe d'appel majeur. Il souligne l'importance d'un diagnostic précoce et d'une évaluation complète. Le pronostic reste défavorable dans les formes agressives, malgré une prise en charge rapide.

Mots-clés: Ascite, épanchement pleural, insuffisance rénale, myélome multiple, néoplasmes du foie, néoplasmes pulmonaires

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INTRODUCTION

Multiple myeloma (MM) is a malignant plasma cell disorder characterized by the clonal proliferation of plasma cells within the bone marrow and the secretion of a monoclonal immunoglobulin, usually detectable in serum and/or urine (1). It accounts for approximately 10% of hematologic malignancies and predominantly affects older adults, with a median age at diagnosis of 65 years (1,2). According to the revised International Myeloma Working Group criteria, the diagnosis of MM requires $\geq 10\%$ clonal plasma cells in the bone marrow or a biopsy-proven plasmacytoma, together with one or more myeloma-defining events (3). These include the classic CRAB features: hypercalcemia, renal insufficiency, anemia, and lytic bone lesions (1).

Extramedullary disease (EMD) is defined by clonal plasma cell infiltration outside the bone marrow and can involve diverse sites such as the liver, spleen, lymph nodes, skin, pleura, soft tissues, central nervous system, upper aerodigestive tract and kidney (3,4). Because of its rarity, heterogeneous presentations, and frequent association with high-risk cytogenetics, EMD poses substantial diagnostic and therapeutic challenges. Standardized treatment strategies remain lacking. EMD is observed in only 1–2% of patients at diagnosis but develops in up to 8% during disease progression (1,5). Due to its rarity, heterogeneity, and association with high-risk cytogenetics, EMD poses significant diagnostic and therapeutic challenges (4). Current management is largely extrapolated from systemic MM protocols or guided by expert opinion, underscoring the urgent need for prospective studies and standardized treatment strategies (1).

Herein, we presented an atypical case of extramedullary MM, with myelomatous pleural effusion (MPE), with a brief literature review. This case was prepared in accordance with the CARE (CAsEReport) guidelines (6).

PATIENT INFORMATION

We reported the case of a 67-year-old man with a medical history of arterial hypertension, treated with captopril. He was admitted with fever at 38.6°, dyspnea, and hemoptysis.

CLINICAL FINDINGS

On admission, the patient weighed 66.5 kg and had a blood pressure of 110/60 mmHg. Chest auscultation revealed bilateral crackles. Urine dipstick testing was negative for proteinuria and hematuria.

Laboratory investigations demonstrated chronic renal impairment (serum creatinine at 202.4 $\mu\text{mol/L}$ (normal range: 60–110 $\mu\text{mol/L}$)), anemia (hemoglobin level at 8.4 g/dL (normal range: 13–17.5 g/dL)), and thrombocytopenia with a platelet count of 105 $\times 10^9/\text{L}$ (normal range: 150–400 $\times 10^9/\text{L}$). Serum proteins were markedly elevated at 136 g/L (normal range: 65–80 g/L), with albumin at 28.4 g/L (normal range: 35–50 g/L) and gamma globulin

at 95.06 g/L (normal range: 8–16 g/L). Inflammatory markers were increased (C-reactive protein at 153 mg/L (normal range: <5 mg/L), Erythrocyte sedimentation rate greater than 140 mm/h (normal range: <15–20 mm/h)). Lactate dehydrogenase was within normal limits at 158 U/L (normal range: 140–280 U/L), while corrected calcium was at 2.45 mmol/L (normal range: 2.2–2.6 mmol/L). A 24-hour urine collection revealed proteinuria at 7.9 g/day (normal range: <0.15 g/day), with detection of Bence Jones proteins.

TIMELINE AND CLINICAL COURSE

Chest X-ray at admission showed pneumonitis with right-sided pleural effusion. Chest Computed tomography confirmed bilateral ground-glass opacities, pleural thickening, right pleural effusion, and alveolar infiltrates. Bronchoscopy findings were unremarkable, but arterial blood gases revealed hypoxemia (Partial pressure of oxygen at 58 mmHg (normal range: 80–100 mmHg)) requiring oxygen therapy. The patient received levofloxacin for 10 days, which led to improvement of the pneumonitis, although the effusion persisted.

Thoracentesis yielded a slightly bloody exudate. Cytological analysis demonstrated plasma cell infiltration (Figure 1), while microbiological studies were negative. Immunoelectrophoresis of both serum and pleural fluid confirmed monoclonal Immunoglobulin (Ig) G kappa in the gamma region. Skeletal radiographs revealed multiple lytic lesions.

Due to persistent hemoptysis, a bronchoalveolar lavage was performed, showing siderophages, 69% lymphocytes, and a Cluster of differentiation 4 / Cluster of differentiation 8 ratio of 1.6. A gold score of 150 was consistent with alveolar hemorrhage. All microbiological studies including bacterial, viral, fungal, and tuberculosis testing were negative, effectively ruling out an infectious etiology. Autoimmune markers (Antinuclear antibodies, Antineutrophil cytoplasmic antibodies, Anti-glomerular basement membrane antibodies) and cryoglobulins were negative. Echocardiography demonstrated pulmonary arterial hypertension estimated at 70 mmHg (normal range: 10–20 mmHg).

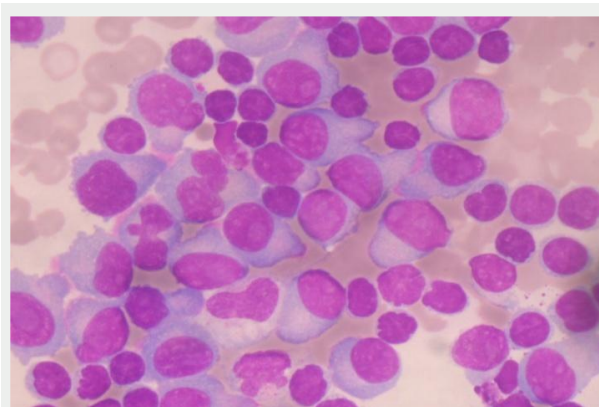


Figure 1. Cytology of pleural fluid (May-Grünwald Giemsa stain $\times 100$) showing plasmacytic infiltration

DIAGNOSTIC ASSESSMENT

- Bone marrow aspiration revealed 100% plasma cell infiltration, consistent with advanced MM (stage IIIB, Durie–Salmon classification).
- Cytology of pleural fluid confirmed plasmacytic infiltration.
- Serum and pleural immunoelectrophoresis showed monoclonal IgG kappa.
- Imaging demonstrated osteolytic lesions and pulmonary infiltrates.
- The Congo red staining of the salivary gland biopsy was negative, and the echocardiography showed no signs of amyloid cardiomyopathy, thereby ruling out systemic amyloidosis.

The final diagnosis was IgG kappa MM with pleural extramedullary involvement and associated alveolar hemorrhage.

THERAPEUTIC INTERVENTION

The patient was treated with a monthly regimen of melphalan (0.1 mg/kg/day) combined with pulse dexamethasone (20 mg/m²/day for four days). Treatment was continued for 12 months.

FOLLOW-UP AND OUTCOMES

After three months of therapy, the pleural effusion resolved, and respiratory symptoms improved significantly. At 12 months of follow-up, no recurrence of pleural effusion was observed. The patient maintained a partial response, with stable osteolytic lesions. Biologically, serum creatinine improved to 167.2 µmol/L, corrected calcium normalized to 2.12 mmol/L, and hemoglobin stabilized at 9.3 g/dL. Serum protein and albumin levels decreased to 91 g/L and 29 g/L, respectively, while gamma globulins were reduced to 48 g/L. Proteinuria improved markedly to 1.71 g/24h.

DISCUSSION

MM is usually confined to the bone marrow and skeleton. It rarely presents with an extramedullary localization. Yet, postmortem studies show up to 70% of patients have extra-skeletal disease (1,5). Its extramedullary spread remains poorly understood but is linked to reduced adhesion molecule expression (Very late antigen-4, Cluster of differentiation 44), loss of Cluster of differentiation 56, and impaired bone marrow homing due to downregulation of P-selectin, chemokine receptors (C-C chemokine receptor type 1, C-C chemokine receptor type 2, C-X-C chemokine receptor type 4), and its Stromal cell-derived factor 1 alpha. Altered tetraspanins and increased angiogenesis may further facilitate tumor escape and dissemination (5).

Table 1. Diagnostic exams and procedures performed at admission and during follow-up

Days	Exam / Procedure	Findings
Admission	Chest X-ray	-Pneumonitis with right-sided pleural effusion
1	Chest CT scan	-Bilateral ground-glass opacities -Pleural thickening -Right pleural effusion -Alveolar infiltrates
1	Arterial blood gases	-Hypoxemia (PaO ₂ = 58 mmHg)
2	Bronchoscopy	-Unremarkable
10	Thoracentesis	-Bloody exudates -Microbiology negative -Pleural fluid cytology: Plasma cell infiltration -Serum & pleural fluid immunoelectrophoresis: Monoclonal IgG kappa in gamma region
14	Bronchoalveolar lavage	-Siderophages -69% lymphocytes -CD4/CD8 ratio at 1.6 -GOLD score at 150
14	Autoimmune markers (ANA, ANCA, anti-GBM), cryoglobulins	-Negative
14	Tuberculosis tests & tumor markers	-Negative
14	Echocardiography	-Pulmonary arterial hypertension at 70 mmHg

ANCA: Antineutrophil cytoplasmic antibodies, **anti-GBM:** Anti-glomerular basement membrane antibodies. **CD4:** Cluster of differentiation 4; **CD8:** Cluster of differentiation 8, **ANA:** Antinuclear antibodies, **CT:** Computed tomography; **Ig:** Immunoglobulin; **PaO₂:** Partial pressure of oxygen.

Various studies have explored the clinical manifestations and potential pathways involved in extramedullary dissemination (7). In a study of 57 autopsied patients, Pasmantierand and Azar (8) classified MM-related tumor masses into three stages: intraskeletal (Stage I), paraskelatal from direct bone extension (Stage II), and extraskeletal from distant metastases (5). Soft-tissue plasmacytomas therefore arise either by contiguous spread after cortical breach or via hematogenous dissemination (3).

EMD most often involves the skin, muscles, pleura, lymph nodes, liver, and central nervous system, yet virtually any organ system may be affected (3,5). Liver involvement is clinically uncommon but more frequent in autopsy series, with infiltration in up to 30–40% of cases (9). Histopathologically, MM may involve the liver through diffuse plasma cell infiltration, extramedullary plasmacytomas, light chain deposition disease, or amyloidosis (10). Clinical manifestations are nonspecific, including hepatomegaly, splenomegaly, jaundice, or ascites (11), though some cases remain asymptomatic and detected as nodular or metastatic lesions on imaging (12,13). Such variability complicates diagnosis, as hepatic lesions can mimic primary or secondary liver disease. Extramedullary MM may also progress to plasma cell leukemia, the most aggressive form of the disease (14). Our patient developed widespread extramedullary involvement complicated by secondary plasma cell

leukemia, a terminal event with fatal outcome.

Pleural involvement in MM is an uncommon manifestation, reported in <1% of cases (2). The first description of MPE dates back to 1978 (2). Effusions in MM are more commonly secondary to sepsis, amyloidosis-related heart failure, renal failure, pulmonary embolism, or a second malignancy, while true pleural infiltration remains rare. Mechanisms include direct extension from adjacent bone or parenchymal lesions, implantation of tumor nodules on the pleura, or mediastinal lymph node obstruction (15). In our patient, cytological confirmation of pleural plasmacytosis supported local myelomatous involvement, a factor that may have contributed not only to the pleural effusion but also to the alveolar complications described below.

MPE is most often associated with aggressive disease and poor prognosis. IgG is the most frequent subtype, followed by IgA and light chain disease, whereas IgD, IgE, and IgM are exceedingly rare (5). Diagnosis requires detection of clonal plasma cells or identical monoclonal Ig in serum and pleural fluid, supported by flow cytometry or cytology (16). Reported treatments include multidrug regimens, autologous stem cell rescue, and pleurodesis, though responses are limited (17). Novel agents such as thalidomide or bortezomib have shown occasional responses, but overall survival is typically <4 months (16,17). In the present case, pleural plasmacytosis strongly supports local myelomatous involvement as a contributing mechanism. Although the thrombocytopenia was moderate ($105 \times 10^3/L$), this reduction in platelet count does not explain the severity of the pulmonary hemorrhage. Direct myelomatous infiltration of pulmonary structures remains the most plausible mechanism. Infectious causes were ruled out based on negative cultures, Polymerase Chain Reaction (PCR) testing, and the absence of clinical or radiological elements supporting infection after an initial antibiotic trial. Given that amyloidosis may cause renal dysfunction and pulmonary bleeding, Congo-red staining in the salivary gland biopsy was performed and was negative. Echocardiography also showed no features of amyloid cardiomyopathy, excluding systemic amyloidosis. The differential diagnosis included autoimmune vasculitis, infection, drug-induced lung injury, hypertensive crisis, cardiac causes, and hematologic disorders. Autoimmune tests, microbiology, and imaging were all non-contributory in this patient, and the presence of plasma cell infiltration favored a myelomatous origin. Our patient presented with both pleural effusion and alveolar hemorrhage, two adverse prognostic features. Nevertheless, melphalan and dexamethasone achieved clinical remission, with resolution of pulmonary hemorrhage within 15 days and sustained response over 12 months. Such survival beyond one year is rarely reported (17). The efficacy of Melphalan in patients with EMD is limited according to data from the literature (16,18). Also, traditional agents like thalidomide have moderate activity in MM but are often less effective against EMD (19). The introduction of newer therapies including proteasome inhibitors such as bortezomib, has improved response rates and prognosis even in high risk or extramedullary cases (20). This case

underscores the heterogeneity of MPE outcomes and highlights the potential for favorable responses, even in the presence of high-risk features, when timely diagnosis and treatment are achieved.

To conclude, extramedullary manifestations of MM are rare but clinically significant, often signaling aggressive disease biology and therapeutic resistance. Our case of MPE underscores the diagnostic challenges and poor outcomes associated with EMD. EMD is strongly linked to high-risk features, limited responsiveness to conventional regimens, and the absence of standardized treatment approaches. Early recognition, individualized therapy, and incorporation of novel agents remain essential to patient care. Ongoing translational research is crucial to clarify disease mechanisms and guide more effective strategies to improve prognosis in this high-risk subset of MM.

PATIENT'S PERSPECTIVE

The patient reported relief after treatment and expressed satisfaction with the improvement of his respiratory symptoms. He agreed to share his experience to highlight the importance of early recognition of unusual myeloma manifestations.

CONSENT

A written informed consent was obtained from the patient.

Conflicts of Interest

The authors declare no conflicts of interest.

DECLARATION. The authors wish to disclose that one artificial intelligence tools ChatGPT (ephemeral version) was used exclusively to enhance the clarity and coherence of the manuscript. This tool was employed solely for language refinement purposes, without altering the scientific content or interpretation of the findings.

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