Synchronous association of acute myeloid leukemia with minimal differentiation (AML-M0) and multiple myeloma: a case report and literature review.

Abstract:

Introduction

The synchronous coexistence of acute myeloid leukemia (AML) and multiple myeloma (MM) in a patient who has never received cytotoxic therapy is an exceptional condition. Most reported associations involve secondary acute myeloid leukemia occurring after treatment for multiple myeloma. The pathophysiology and therapeutic management of this dual hematological malignancy remain poorly defined.

Case report

We report the case of a 67-year-old man with no significant medical history who was admitted for severe deterioration of general condition and profound bicytopenia. Bone marrow aspiration revealed a dual marrow infiltration consisting of 34% blasts and 32% plasma cells. Flow cytometry immunophenotyping confirmed acute myeloid leukemia with minimal differentiation (AML-M0), showing expression of CD34, CD117, HLA-DR, CD33, CD13, and CD11c, associated with a clonal plasma cell proliferation consistent with multiple myeloma. The clinical course was rapidly unfavorable, complicated by disseminated intravascular coagulation, severe infection, and acute respiratory failure, preventing initiation of specific treatment.

Conclusion

This case highlights the major diagnostic value of combining bone marrow cytology with immunophenotyping in complex hematological malignancies. The synchronous association of AML-M0 and multiple myeloma represents a rare entity with poor prognosis, requiring a multidisciplinary diagnostic approach and individualized therapeutic strategy.

Keywords:

Acute myeloid leukemia; AML-M0; Multiple myeloma; Flow cytometry; Immunophenotyping; Dual hematological malignancy; Bone marrow diagnosis.

Introduction

Multiple myeloma (MM) and acute myeloid leukemia (AML) are two distinct clonal hematological malignancies arising from plasma cells and myeloid progenitors, respectively. Their coexistence in the same patient is an exceptional event. In most reported cases, AML occurs as a secondary malignancy following treatment for multiple myeloma, particularly after exposure to alkylating agents or topoisomerase II inhibitors **(1,4).**

The synchronous occurrence of de novo AML and MM in a patient without previous exposure to cytotoxic therapy is extremely rare. Only a few dozen cases have been reported, mainly as isolated case reports, limiting current knowledge regarding their pathogenesis, therapeutic management, and prognosis **(5–7).** Several mechanisms have been proposed, including the independent emergence of two malignant clones, the presence of a common hematopoietic stem cell precursor, and the contribution of genetic abnormalities and bone marrow microenvironment alterations. However, no single mechanism has been clearly established to date **(5,6).**

AML with minimal differentiation (AML-M0), according to the French-American-British (FAB) classification, is a rare subtype characterized by minimal expression of myeloid differentiation markers and negativity for myeloperoxidase (MPO). Its diagnosis relies mainly on flow cytometry immunophenotyping, complemented by cytogenetic and molecular investigations according to current classification systems **(2–4).**

We report a case of synchronous AML-M0 and multiple myeloma diagnosed simultaneously in a patient with no history of cytotoxic treatment. This observation emphasizes the importance of bone marrow cytology and immunophenotyping in the diagnosis of this dual hematological malignancy and discusses the therapeutic challenges associated with this exceptional condition.

Case Presentation

Clinical findings

A 67-year-old man with no significant past medical history was admitted for deterioration of general condition associated with unquantified weight loss. Initial physical examination revealed hepatomegaly measuring 14 cm. Laboratory investigations demonstrated severe bicytopenia, including profound anemia (hemoglobin level: 4.6 g/dl) and severe thrombocytopenia (platelet count: 20×10^9/L), prompting bone marrow evaluation.

Hematological diagnosis

The complete blood count confirmed bicytopenia and revealed 9% circulating blasts. Bone marrow aspiration showed a hypercellular marrow with dual pathological infiltration consisting of:

- A blast population accounting for 34% of bone marrow cells, negative for myeloperoxidase staining on cytochemistry;
- A plasma cell proliferation representing 32% of bone marrow cellularity.

Bone marrow flow cytometry immunophenotyping identified a blast population representing 38% of analyzed events, expressing CD34, CD117, HLA-DR, CD33, CD13, and CD11c. This immunophenotypic profile, combined with the absence of morphological differentiation and myeloperoxidase negativity, supported the diagnosis of acute myeloid leukemia with minimal differentiation (AML-M0 according to the FAB classification).

The plasma cell population study confirmed a clonal plasma cell proliferation consistent with multiple myeloma. Immunological assessment revealed a free light chain κ/λ ratio of 0.40, and serum protein electrophoresis showed a profile compatible with an inflammatory syndrome associated with restricted heterogeneity of the gamma-globulin fraction (Figure 1).

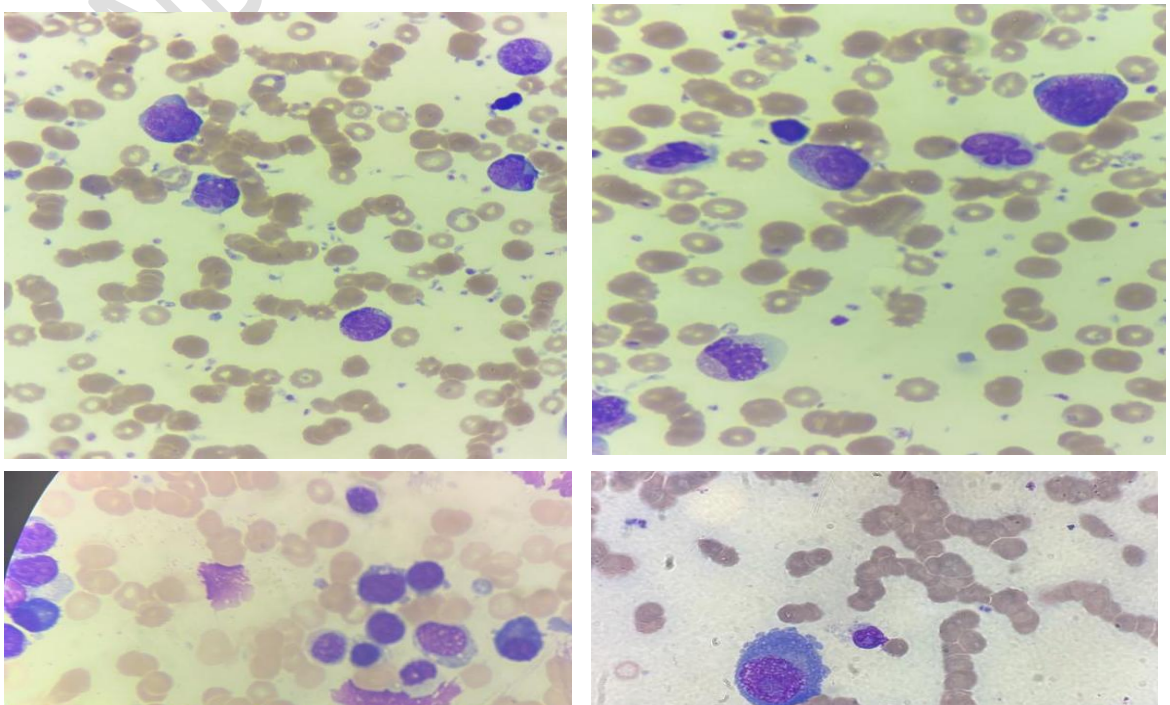

Figure 1. *Bone marrow aspirate showing a blastic proliferation (34% myeloperoxidase-negative blasts) associated with bone marrow plasmacytosis (32% plasma cells).*

Clinical course and complications

During hospitalization, the patient developed febrile hypoxemic pneumonia (39.6°C), initially treated with empirical antibiotic therapy. Subsequently, clinical deterioration occurred with the onset of hemorrhagic manifestations, progressive disseminated intravascular coagulation (DIC) (prothrombin time decreasing from 67% to 18%, fibrinogen level: 1.2 g/L), and acute respiratory failure.

Upon admission to the intensive care unit, bilateral pleural effusion was identified. The patient was somnolent without focal neurological deficits, and brain computed tomography showed no abnormalities. Hepatocellular involvement was observed, characterized by cholestatic jaundice and decreased factor V activity (54%). A transient functional renal impairment was also noted (serum creatinine: 14 mg/L). Genital ulceration prompted investigation for a sexually transmitted infection.

Thoracic computed tomography angiography revealed bilateral pleural effusion associated with diffuse interstitial syndrome, without evidence of pulmonary embolism.

Therapeutic management and clinical outcome

Given the patient's clinical instability, disseminated intravascular coagulation, severe infection, and acute respiratory failure, no specific treatment for AML or multiple myeloma could be initiated.

Management was based exclusively on supportive measures, including:

- Daily transfusion support with packed red blood cells, platelet concentrates, and fresh frozen plasma;
- Broad-spectrum empirical antibiotic therapy, subsequently modified due to the occurrence of a drug-induced skin reaction;
- Correction of electrolyte disturbances and appropriate fluid management, resulting in improvement of renal function.

Despite these supportive measures, the clinical course remained unfavorable, with progressive worsening of respiratory failure characterized by persistent hypoxemia (oxygen saturation 87% despite oxygen therapy at 15 L/min), requiring transfer to the medical intensive care unit.

Discussion

The synchronous association of acute myeloid leukemia (AML) and multiple myeloma (MM) at diagnosis represents an exceptionally rare clinical entity. These two clonal hematological malignancies arise from different cellular compartments, namely myeloid progenitors and

plasma cells, respectively. Most cases reported in the literature involve secondary acute myeloid leukemia occurring after treatment of multiple myeloma, particularly following exposure to alkylating agents or other cytotoxic therapies. Therapy-related AML (t-AML) represents a rare but severe complication, whose incidence has increased with the improvement in survival of patients with MM **(1,2).**

Conversely, the simultaneous occurrence of de novo AML and MM in a patient without previous cytotoxic exposure remains extremely uncommon. Available data are mainly derived from isolated case reports and small case series. Wang et al. reported in 2015 a case of synchronous AML/MM, highlighting the diagnostic and therapeutic difficulties associated with this rare condition **(3).** More recently, Feng et al. conducted a literature review confirming the exceptional nature of this association, with fewer than thirty reported cases, generally associated with poor prognosis and the absence of standardized therapeutic strategies **(4).**

The present case shares several characteristics with previously published reports, including advanced patient age, simultaneous diagnosis of both malignancies, and rapidly unfavorable clinical evolution. However, it presents an additional distinctive feature due to the presence of AML-M0, a rare subtype characterized by minimal differentiation.

From a diagnostic perspective, this case illustrates the importance of an integrated approach combining bone marrow morphology and immunophenotyping. Bone marrow aspiration identified two distinct abnormal cellular populations: a blast population accounting for 34% of marrow cells and a plasma cell proliferation representing 32% of marrow elements. The identification of such dual infiltration should prompt investigation for the coexistence of two neoplastic processes rather than being interpreted as a secondary reactive plasmacytosis.

AML-M0 corresponds to AML with minimal differentiation according to the FAB classification. It is characterized by the absence of morphological evidence of myeloid maturation and negativity for myeloperoxidase staining by cytochemistry. Current World Health Organization (WHO) classifications and European LeukemiaNet (ELN) recommendations emphasize the essential role of immunophenotyping, cytogenetic studies, and molecular analyses in AML diagnosis and prognostic stratification **(6,7).**

In our case, expression of CD34, CD117, HLA-DR, CD33, CD13, and CD11c allowed identification of an immature myeloid blast population and confirmed the diagnosis of AML-M0. Flow cytometry is particularly valuable in such complex situations, as it enables discrimination between different pathological cell populations and prevents diagnostic errors based solely on morphological examination **(6–8).**

The coexistence of plasma cell and myeloid proliferations also raises important pathogenetic questions. Several mechanisms have been proposed. The first hypothesis involves the independent development of two distinct malignant clones, promoted by age-related marrow changes and progressive accumulation of genetic abnormalities. A second hypothesis suggests the existence of a common hematopoietic stem cell capable of subsequently differentiating into two separate malignant lineages. Finally, alterations in the bone marrow microenvironment, pro-inflammatory cytokines, and age-related clonal hematopoiesis may contribute to the emergence of multiple pathological clones **(3,4,9).**

Molecular analyses performed in some reported cases have occasionally identified shared genetic abnormalities between the two proliferations; however, no unique pathogenic mechanism has been demonstrated to date.

From a therapeutic standpoint, management of this association remains particularly challenging due to the absence of specific recommendations. Treatment decisions must be individualized according to patient age, performance status, AML biological characteristics, and myeloma profile.

In patients who are not candidates for intensive chemotherapy, combinations based on hypomethylating agents and venetoclax have transformed the management of AML in elderly or frail patients, achieving higher response rates compared with conventional approaches **(7,10).** Similarly, therapeutic advances in MM, including proteasome inhibitors, immunomodulatory drugs, and anti-CD38 monoclonal antibodies, have considerably improved disease outcomes **(1,11).**

A few case reports have described combined therapeutic approaches targeting both malignant clones. Bories et al. reported a patient with synchronous AML and MM successfully treated with azacitidine, lenalidomide, and daratumumab, suggesting the potential benefit of a strategy adapted to both tumor components **(12).** However, clinical experience remains extremely limited, and no consensus treatment regimen can currently be recommended.

In our patient, despite rapid diagnosis achieved through the combination of bone marrow cytology and immunophenotyping, no specific therapy could be initiated because of the severity of the initial presentation. Disseminated intravascular coagulation, severe infection, acute respiratory failure, and marked deterioration of general condition required exclusively supportive management. This outcome is consistent with published data describing poor prognosis in synchronous AML/MM cases, particularly when diagnosis is associated with infectious or hemorrhagic complications **(3,4).**

This report has some limitations, particularly the absence of cytogenetic and molecular analyses, which would have allowed better characterization of AML and exploration of a possible clonal relationship between the blast and plasma cell populations. Nevertheless, it is of particular interest because of the exceptional coexistence of AML-M0 and MM at diagnosis.

It emphasizes the essential role of multiparametric bone marrow assessment combining morphology, immunophenotyping, and, whenever possible, molecular investigations in the management of complex hematological malignancies.

Conclusion

The synchronous association of AML with minimal differentiation (AML-M0) and multiple myeloma represents an extremely rare hematological entity characterized by major diagnostic and therapeutic challenges. Our observation highlights the importance of comprehensive bone marrow evaluation combining cytological analysis and flow cytometry immunophenotyping, allowing simultaneous recognition and characterization of both malignant populations, particularly in poorly differentiated AML subtypes.

This dual hematological malignancy also represents a therapeutic challenge due to the absence of standardized treatment strategies and the frequent frailty of patients at diagnosis. Clinical outcomes remain generally unfavorable, especially when severe complications such as infection, disseminated intravascular coagulation, or multiorgan failure are present.

The publication of additional cases, together with comprehensive cytogenetic and molecular studies, is essential to improve understanding of the biological mechanisms underlying this coexistence, clarify potential clonal relationships between the two proliferations, and develop tailored therapeutic approaches.

This case therefore emphasizes the need for multidisciplinary management and early diagnosis based on an integrated approach to complex hematological malignancies.

Conflict of Interest

The authors declare that they have no competing interests.

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