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– CASE REPORT –

NPM1-Mutated Acute Myeloid Leukemia with Uterine Myeloid Sarcoma: A Diagnostic Challenge

Daiana TUNARU[1], Gabriela Diana CANTOR[1], Ion DUMITRU[1], Ana-Maria ILINESCU[1], Florin NITU[1], Dan Sebastian SOARE[1], Cristina MAMBET[1], Georgiana ENE[1*]

Abstract

Introduction: *Acute myeloid leukemia(AML) NPM1+ represents a distinct entity, frequently associated with normal cytogenetics and favorable prognosis in the absence of other adverse mutations. In certain cases though the clinical and paraclinical presentation can appear as other forms of AML, especially APL variants, that imposes the initiation of treatment in an emergency setting due to the vital risk associated with severe coagulopathy.*

Methods: *This paper reports the case of a 56 years old patient, that came to the emergency department with a severe hemorrhagic syndrome, severe leukocytosis and severe bicytopenia with signs of disseminated intravascular coagulation (DIC) highly suggestive of APL. The peripheral blood smear outlined blasts with specific morphology – cup like cells- suggestive for AML NPM1+. Immunophenotyping exam confirmed the myeloid lineage SSC medium/high cMPO+, CD34 -, HLA-DR-, CD117+, CD33+ , CD64+ CD15+/-, CD9-, CD56- and molecular testing identified NPM1 mutation, PML-RARA negative. Imaging exams showed the presence of a tumor localized in the uterus, the biopsy confirming extramedullary involvement – myeloid sarcoma- with the same phenotyping profile. Additionally at the diagnosis the patient had multiple infectious complications (flu type A, and E.coli faringoamigdalitis).*

Results: *It is well-established that the morphological and immunophenotypic distinctions between APL and NPM1-mutated AML are exceedingly subtle. When clinical presentation also suggests APL, as observed in our case, establishing a timely diagnosis before cytogenetic and molecular test results become available can be challenging. The presence of disseminated intravascular coagulation (DIC) at presentation added complexity to the diagnostic process. Coagulopathy is a characteristic feature of acute promyelocytic leukemia (APL), frequently necessitating prompt initiation of all-trans retinoic acid therapy. Nonetheless, severe infections and sepsis are also well-established causes of DIC. In this case, the concurrent infectious pathology and APL-like morphological features resulted in significant diagnostic uncertainty. Although application of the ISTH DIC scoring system confirmed overt DIC, it was insufficient to distinguish between leukemia-associated and infection-induced mechanisms. Nevertheless, additional features can aid in the differential diagnosis. The white blood cell (WBC) count was markedly elevated, a finding that is atypical for acute promyelocytic leukaemia (APL). Importantly, increased median WBC counts and high percentages of bone marrow blasts have most frequently been reported in cases of acute myeloid leukaemia (AML) harbouring NPM1 mutations.*

Conclusion: *This atypical clinical presentation AML NPM1 positive with APL like coagulopathy and myeloid sarcoma outlines the challenges in differential diagnosis for acute leukemias accompanied at diagnosis with coagulopathies, and the importance of integrating morphology, immunophenotype and molecular data for avoiding therapeutical errors in a context of hematological emergency.*

Keywords: *Myeloid Sarcoma, AML NPM 1 postive, APL mimicry*

[1] Bone Marrow Transplantation Ward, University Emergency Hospital Bucharest, Bucharest, Romania

Corresponding author:
* **Georgiana ENE,** Bone Marrow Transplantation Ward, University Emergency Hospital Bucharest, Bucharest, Romania
Email: georgi_dap@yahoo.com

Introduction

Acute myeloid leukemia (AML) encompasses a diverse array of complex disorders originating from hematopoietic precursor cells with chromosomal anomalies or genetic mutations. The World Health Organization (WHO) classification system for AML integrates clinical presentation, morphological characteristics, immunophenotypic data, cytogenetic findings, and molecular profiles to define biologically uniform entities that possess clinical significance. While genetic mutations are used to classify hematologic disorders, links between specific immunophenotypes and genetic changes are less clear. NPM1 mutations are among the most frequent in AML, found in 27%-35% of adult cases overall and 45%-64% with a normal karyotype. NMP1 mutations typically occur later in leukaemia development, following earlier changes in preleukemic progenitor cells that act as founder events.

Myeloid sarcoma is a rare malignant neoplasm characterized by the extramedullary proliferation of myeloblasts, which may present at various anatomical locations beyond the bone marrow. It may occur *de novo*, with concurrent acute myeloid leukaemia (AML) or herald disease relapse

Involvement of the female reproductive tract is rare, with fewer than 1 percent of reported cases affecting the uterus or ovary according to the literature.

Acute promyelocytic leukemia (APL) represents a distinct subset of acute myeloid leukemia (AML), characterized by a favorable response to all-trans retinoic acid (ATRA)-based therapeutic regimens. APL constitutes a hematologic emergency due to its propensity for severe, potentially fatal disseminated intravascular coagulation (DIC), as evidenced by derangements in coagulation parameters and thrombocytopenia. Initial evaluation of acute promyelocytic leukemia (APL) is typically based on blast morphology and flow cytometric analysis. APL is known to exhibit a distinct immunophenotype, most notably lacking expression of CD34, HLA-DR, and CD11b. However, it should be noted that similar immunophenotypic profiles may also be observed in other subtypes of acute myeloid leukemia (AML). [1]

Therefore, although flow cytometry immunophenotyping contributes to the rapid preliminary diagnosis of APL cases, the final diagnosis requires molecular evidence of the PML–RARA transcript and/or cytogenetic evidence for t(15;17) or variant RARA translocations. Although uncommon, the "APL-like" immunophenotype pattern has been reported in a subset of de novo AML with mutation of the nucleophosmin (NPM1) gene.[2,3,4]

We present herein a case of AML with mutated NPM1 that showed APL-like immunophenotype and presented with coagulation parameters derangements frequently associated with APL, concomitant with uterine myeloid sarcoma. These similarities and complications pose a challenge in our daily practice sometimes leading to inappropriate ATRA therapy and difficulties in management.

Case Presentation

We report a rare case of NPM1-mutated AML presenting as uterine myeloid sarcoma that mimicked APL and was complicated by infection, with a focus on diagnostic challenges from the literature.

A 56-year-old woman presented to the emergency department with excessive non-menstrual genital bleeding and persistent high fever (39°C) while being evaluated for a uterine mass. Examination revealed widespread skin hemorrhage. Laboratory findings showed marked leukocytosis (120,000/mm³), severe bicytopenia (hemoglobin 7 g/dL, platelets 7,000/mm³), abnormal coagulation with low fibrinogen, and positive flu type A test. She was admitted to the Hematology Department Medullary Transplant Unit for further management.

DIC score

Disseminated intravascular coagulation (DIC) was diagnosed using the International Society on Thrombosis and Haemostasis (ISTH) point system, which considers PT, fibrinogen, D-dimer,and platelet counts; a score of 5 or more indicates DIC. [5]

Flow Cytometry

Multiparameter flow cytometry was conducted at the Flow Cytometry Laboratory, University Emergency Hospital Bucharest. Immunophenotypic data were collected for markers including CD3, cCD3, cCD79a, CD19, CD7, MPO, HLA-DR, CD34, CD117, CD16, CD11b, CD10, CD35, CD64, CD14, CD36, CD105, CD71, CD15, CD56, CD123, and CD9. Peripheral blood and bone marrow aspirate samples were analysed using a FACS Canto II cytometer, with at least 200,000 events per tube measured. Analytical gates were set according to internal protocols using forward scatter and CD45 to identify the general population. Further classification of immature cells and their maturation stages or aberrant expression was based on panel markers. Marker positivity was defined as a threshold of 20%, except for cMPO, which had a 2% threshold.

Morphologic examination and Immunohistochemical Analysis

Peripheral blood smear, bone marrow aspirate smear (Wright-Giemsa stained) and hematoxilin-and-eosin stained sections from the uterine tumour mass were reviewd. Peripherral blood and bone marrow blas percentages were recorded and the imunophenotype of the genital tumor.

Coventional cytogenetics and fluorescence in situ hybridization

Conventional cytogenetic analysis was perfomed on bone marrow aspirate specimen. At least 20 metaphases were analysed. Fluorescence in situ hybridisation (FISH) analyses were performed for 1p/1q, 5p/5q, 7p11/7q31, chromosome 8, t(9;22), 13q14/13q34, 20q, t(8;21), KMT2A(MLL), t(15;17), inv16/t(16;16) and RARA.

Molecular analysis

DNA from blood or bone marrow was analyzed by PCR to detect FLT3 ITD Signal Ratio, FLT3 TKD mutations, and NPM1 mutations. Patient RNA was reverse transcribed to cDNA for PML-RARA transcript quantification. Genomic DNA was screened for single-nucleotide variants, insertions/deletions, and copy number changes in 24 genes linked to AML, using NGS. Detected genomic alterations were identified and interpreted with bioinformatics tools and reference databases.

Literature review

This study presents a case of uterine myeloid sarcoma (MS) associated with NPM1-positive acute myeloid leukemia (AML), accompanied by a comprehensive review of the literature addressing diagnostic challenges, molecular features, and prognostic implications to inform optimal management strategies. A systematic search was conducted in PubMed, PMC, and relevant case databases using keywords such as “NPM1,” “acute myeloid leukemia,” “uterine myeloid sarcoma,” and “APL mimicry.” Extracted data were systematically categorized according to clinical presentation, molecular characteristics, and patient outcomes.

Results

The clinical and paraclinical features of the case are outlined in Table 1. The patient demonstrated laboratory abnormalities suggestive of a consumptive coagulopathy, including thrombocytopenia, prolonged prothrombin time, elevated fibrin-related markers, and reduced fibrinogen levels. Disseminated intravascular coagulation (DIC) was assessed using the International Society on Thrombosis and Haemostasis (ISTH) overt DIC scoring system. Based on platelet count, fibrin-related markers, prothrombin time prolongation, and fibrinogen level, the calculated ISTH score was **6**, consistent with **overt DIC.** Given the presence of DIC and morphologic features (figure 1) suggestive of acute promyelocytic leukemia, empirical treatment with all-trans retinoic acid was initiated pending molecular confirmation.

Case timeline	Diagnosis	After induction	After first consolid.	After second consolid.	First relapse	After salvage
Date	05.03.2025	28.04.2025	30.06.2025	20.08.2025	16.09.2025	16.12.2025
WBC count (/mmc)	120.500	2.400	11.100	9.900	5.600	4.600
PLT count (/mmc)	7000	168000	408000	44300	271000	304000
Blasts BM (%)	70	4	0	7	50	15
Blasts PB (%)	95	0	0	0	0	
PT (seg)	19	13,7	10,00	11,1	11	10,8
aPTT (seg)	44,3	38,7	33,7	61,7	45,7	34,2
Fibrinogen (g/L)	122	316	366	623	401	400
D-dimers (microg/ml)	2000	not done	not done	not done	not done	not done
DIC score	6	< 5	< 5	< 5	< 5	< 5
PML/RARA RT-PCR	negative	n/a	n/a	n/a	negative	n/a
FISH for t(15;17)	negative	n/a	n/a	n/a	negative	n/a
Detected mutations	NPM1+	negative	negative	negative	NPM1+	negative
Cytogenetics	trisomy 8, deletion(16)	n/a	n/a	n/a	trisomy 8, deletion(16)	n/a
Extramedular disease	yes	no	no	no	more extensive than at diagnosis	no
Phenotype	myeloid	n/a	n/a	n/a	myeloid	n/a

Table 1*: Clinical and pathological features of the patient during treatment timeline for APL-like AML and mutated NPM1 with genital MSAbbreviations: WBC – white blood cells, PLT- thrombocytes, BM- bone marrow, PB- perriferal blood, PT- thrombin time, aPTT- partialy activated thromboplastin time, DIC- diseminated intravascular coagulation, consolid.- consolidation therapy, n/a- not applicable*

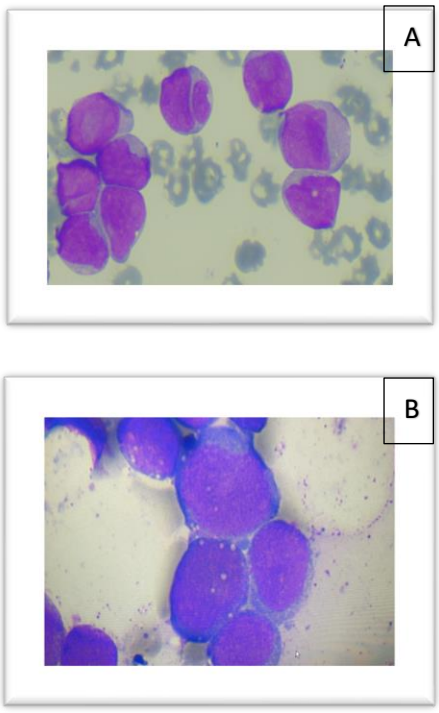

Figure 1 *Morphologic examination of (A) Perripheral blood and (B) Bone marrow at diganosis*

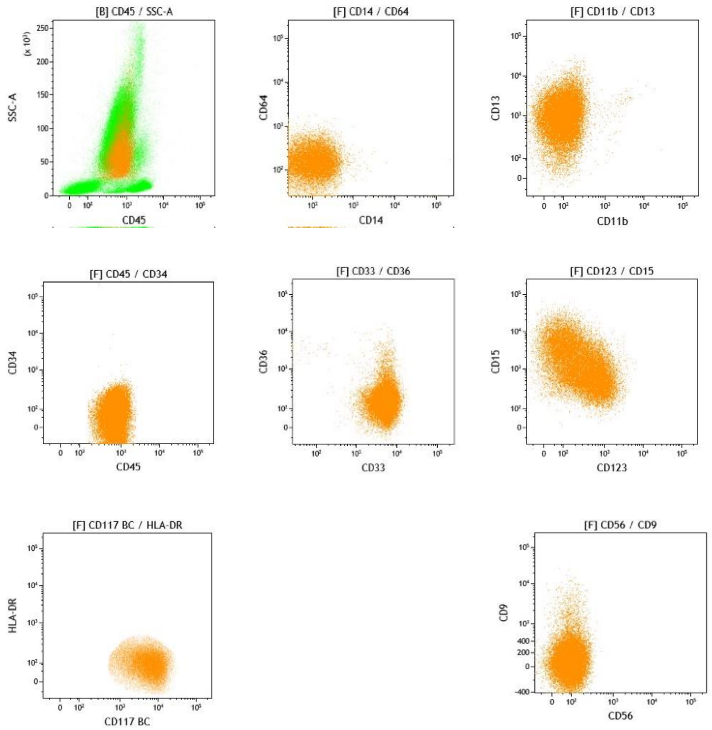

Figure 3 *Flow Cytometry analysis of the bone marrow at diagnosis*

Immunophenotype by Flow Cytometric Analisys and Immunohistochemistry findings

Blasts in thise case showed moderate to high side scatter, heterogenous expresion of CD13, homogenous expression of CD33, and positive for MPO, partial positive for CD117, and negative for both HLA-DR and CD34(figure 3). This immunophenotype pattern was suggestive of APL in the initial evaluation prior to FISH and molecular results. Immunohistochemistry showed and identical phenotyping profile of the genital tumour.

Cytogenetics/FISH/Molecular studies

APL was ruled out based on cytogenetic and molecular evidence given the absence of t(15;17) confirmed by FISH

exam and PML-RARA by RT-PCR. NPM1 mutation was detected instead in the absence of FLT3 ITD or TKD. Caryotype showed +8 and del(16)(q22) (figure 2)

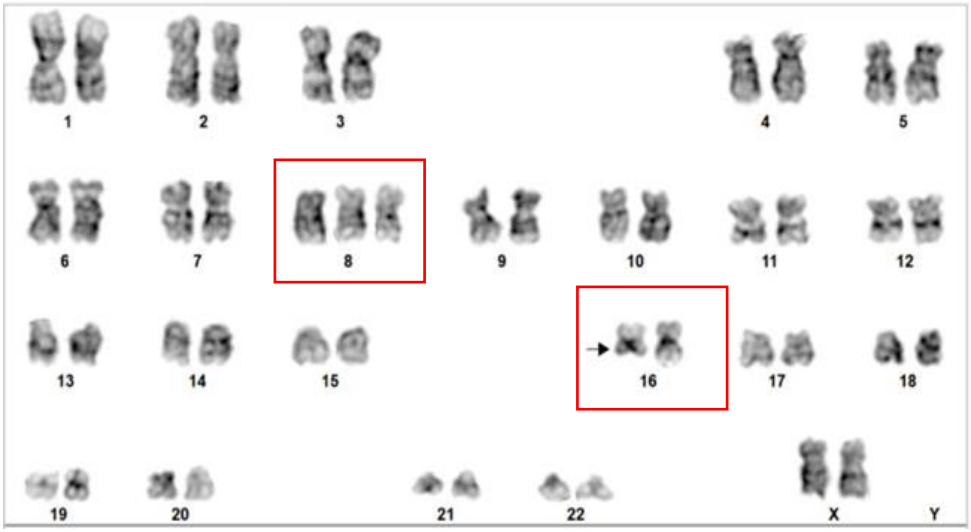

Figure 2 *Cytogenetic exam at diagnosis 47,XX, +8,del(16)(q22) [3]/46,XX[14] (ISCN 2020)*

Literature findings

Literature synthesis identified <50 uterine MS cases, with only isolated reports harboring NPM1 mutation. Several NPM1+ AML cases demonstrated APL-like immunophenotype (CD34-, HLA-DR-, MPO+, CD33+). Common co-mutations included **FLT3-ITD**, **TET2**, and **IDH1/2**.

In a case series of 11 patients, Garcia and colleagues note that the uterus was the most frequently involved gynaecologica site (8 patients); of whom three had cervical myeloid sarcoma [6] .Conversely, an eleven patient case series by Oliva and colleagues found that the ovary was the most commonly affected gynaecological site[7]. Involvement of the gynaecological tract in women who have succumbed to leukaemia is not uncommon, with uterine and ovarian involvement estimated in 40.8% and 36.4% respectively[8]. The mechanism by which myeloblasts can involve the reproductive tract is not well elucidated, and may reflect adhesion receptors such as CD56, or due to these sites serving as sanctuaries for leukaemic cells and allow them to evade systemic therapy [9]

Prognosis is generally poor, with 2 year survival rates of 6% reported[10]. The use of systemic therapy with agents used for treating AML is widely accepted

Haematopoietic stem cell transplant (HSCT) is associated with an improved outcome. In a case series by Pileri et al., MS patients treated with autologous or allogeneic HSCT corresponded with long term survivors compared with those treated with conventional chemotherapy (overall survival at 2 years 76% vs 0%)[11] .

Disscusion

This APL-like AML case described in this report exhibits CD34 and HLA-DR negativity, harbors an NPM1 mutation, and presented with disseminated intravascular coagulation (DIC) along with other coagulation abnormalities. It is well-established that the morphological and immunophenotypic distinctions between APL and NPM1-mutated AML are exceedingly subtle. When clinical presentation also suggests APL, as observed in our case, establishing a timely diagnosis before cytogenetic and molecular test results become available can be challenging.

Blasts in this case showed morphologic similarities with abnormal promielocytes of APL including bilobed nucleus, clearly visible cytoplasmic granules, and the presence of mostly single large Auer rods. The presence of significant number of blasts with cup-like nuclei, which has been previously reported for AML with mutated NPM1 could contribute to preferentialy suspect this diagnosis.

The immunophenotype profile is similar to that typically described for both APL and de novo NPM 1 mutated AML with myeloid differentiation: low to absent CD34 and HLA-DR, strong and homogenous expression of CD33, positivity for MPO.

The presence of disseminated intravascular coagulation (DIC) at presentation added complexity to the diagnostic process. Coagulopathy is a characteristic feature of acute promyelocytic leukemia (APL), frequently necessitating prompt initiation of all-trans retinoic acid therapy. Nonetheless, severe infections and sepsis are also well-established causes of DIC. In this case, the concurrent infectious pathology and APL-like morphological features resulted in significant diagnostic uncertainty. Although application of the ISTH DIC scoring system confirmed overt DIC, it was insufficient to distinguish between leukemia-associated and infection-induced mechanisms.

Nevertheless, additional features can aid in the differential diagnosis. The white blood cell (WBC) count was markedly elevated, a finding that is atypical for acute promyelocytic leukaemia (APL). Importantly, increased median WBC counts and high percentages of bone marrow blasts have most frequently been reported in cases of acute myeloid leukaemia (AML) harbouring NPM1 mutations.

Definitive differentiation between acute promyelocytic leukemia (APL) and NPM1-mutated acute myeloid leukemia (AML) requires comprehensive molecular analysis. The identification of the PML::RARA fusion gene is diagnostic for APL, whereas NPM1 mutations characterize a distinct biological and clinical subtype of AML. Timely molecular testing—including FISH or RT-PCR for PML::RARA and next-generation sequencing for recurrent AML-associated mutations—is critical for establishing an accurate diagnosis and informing optimal therapeutic decisions.

APL and NPM1-mutated AML require different treatments: APL needs immediate differentiation therapy with all-trans retinoic acid, while NPM1-mutated AML is treated with intensive chemotherapy or targeted approaches. Although ATRA can be used empirically in suspected APL, delayed diagnosis may postpone appropriate AML therapy, which can be critical in aggressive cases or those with extramedullary disease.

Extramedullary manifestations, including myeloid sarcoma, are infrequently observed in acute promyelocytic leukemia (APL) but demonstrate higher prevalence in NPM1-mutated acute myeloid leukemia (AML). Detection of extramedullary disease at initial presentation should raise suspicion for non-APL AML, even in cases exhibiting APL-like morphological features. Uterine involvement is exceedingly uncommon and may present challenges to prompt and accurate diagnosis.

This case underscores the importance of maintaining a comprehensive differential diagnosis when evaluating suspected acute promyelocytic leukemia (APL). While urgent assessment is warranted in instances presenting with APL-like characteristics, consideration of alternative acute myeloid leukemia (AML) subtypes remains crucial. Implementation of rapid molecular testing for PML::RARA, detailed mutational analysis, and multidisciplinary evaluation are critical measures to minimize misclassification and facilitate timely, optimal therapeutic intervention.

Conclusions

This case highlights the considerable diagnostic challenges presented by de novo NPM1-mutated acute myeloid leukemia (AML) accompanied by uterine myeloid sarcoma, acute promyelocytic leukemia (APL)-like morphological features, and disseminated intravascular coagulation (DIC). The presence of infection further confounded the clinical picture, complicating timely diagnosis and management. Notably, this report demonstrates that APL-like features and associated coagulopathy are not pathognomonic for acute promyelocytic leukemia, but can also occur in other subtypes of AML, such as those with NPM1 mutations. This case highlights the necessity of prompt molecular diagnostic testing and a multidisciplinary approach—including hematopathology, gynecology, and infectious disease specialists—to ensure accurate classification and to guide appropriate therapy in complex presentations resembling APL.

Ethics Statement and Conflict of Interest Disclosures

Financial support and sponsorship: All authors have declared that no financial support was received from any organization for the submitted work.

Ethics Consideration:

The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national laws. Written informed consent was provided by the participant in this study.

Conflict of interest:

No known conflict of interest correlated with this publication.

Availability of data and materials:

The data used and/or analyzed throughout this study are available from the corresponding authors upon reasonable request.

Competing interests:
The authors declared that they have no competing interests.
The use of generative AI and AI-assisted technologies:
AI technologies were used solely to refine English language and spelling.

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