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APL-like Subset Within *NPM1*-mutated Acute Myeloid Leukemia: A Distinct Phenotypic Signature Correlating With Early-onset Vascular Complications

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INTRODUCTION

NPM1 mutations represent the most common genetic alteration in adult acute myeloid leukemia (AML), often in co-occurrence with *FLT3*-ITD and mutations in genes influencing DNA methylation (*DNMT3A*, *IDH1*, *IDH2* and *TET2*).

There is growing evidence of **distinct immunophenotypic subsets driven by co-occurring genetic mutations in NPM1-mutated AML**, potentially accounting for the heterogeneity of clinical presentations and outcome.

Mason et al have described a subtype of *NPM1*-mutated AML, displaying an **immunophenotypic profile resembling that of acute promyelocytic leukemia, and as such defined as APL-like[1].**

AIMS

- We studied the characteristics of patients with APL-like *NPM1*-mutated AML, focusing on **the incidence of vascular events at disease onset.**
- We investigated **the impact of some markers (blood counts, coagulation parameters and LDH) reported to correlate with coagulopathy in APL**.

METHODS

- The study cohort included **patients diagnosed with *NPM1*-mutated AML** at our Centre according to conventional criteria.
- APL-like subgroup definition relied on **negativity for both CD34 and HLA-DR.**
- Vascular events were defined according to the revised **WHO bleeding scale** and to the **CTCAE grading of thromboembolic events.**

RESULTS

- From April 2007 to May 2023, **139** patients with a diagnosis of *NPM1*-mutated AML were enrolled, of whom **31 (22,3%) featured by APL-like phenotype**
- APL-like patients were older (64 y) with respect to non-APL-like (57 y, P=0.002) *NPM1*-mutated patients.
- **Vascular complications (n=22 bleeding events and n=2 thrombotic events), were significantly more frequent in the APL-like (n=10, 34.5%) than non-APL-like (n=16, 13.6%, P=0.015) group.** In terms of grading, there was a non-significant trend for the occurrence of vascular G3-G4 events in APL-like (3/31, 9.7%) vs non-APL-like (3/108, 2.8%, P=0.12).
- A trend for higher incidence of **abnormal coagulopathy-related parameters (including INR ≥1.5 and/or fibrinogen) was found in APL-like patients** (27.6% versus 15.7%, P=0.175). **D-dimer levels** were significantly higher in APL-like (median 5998 ng/ml) versus non-APL-like (2287 ng/ml, P=.005) patients. The **D-dimer/fibrinogen ratio (DD/FBG),** showed higher level in APL-like (median 16.84) vs non-APL-like (4.4, P=.017) pts.
- In multivariate analysis, **APL-like phenotype maintained an independent value (OR=2.67, P=0.007) on DD level from WBC count (OR=2.37, P=0.017),** thus suggesting an intrinsic biological effect. Also, **APL-like subset kept an independent impact (OR=2.77, P=0.041) on the incidence of vascular events from age (OR=1.01, P=0.61).**
- The analysis of molecular data demonstrated a **significant enrichment in mutations of both *IDH1* (P=0.002) and *IDH2* (P=.001) genes in APL-like vs non-APL-like patients**. No difference in the incidence of *TET2* mutations was observed (18.8% and 25% in APL-like and non-APL-like, respectively, P=0.744).
- As regards outcome, **complete remission rate was 85.7% and 78.9% in APL- and non-APL-like (P=0.43**). We did not observe any significant difference between APL- and non-APL-like patients in disease-free (13.2 vs 22.0 months; P=0.83) or overall (15.9 vs 15.1 months, respectively; P=0.38) survival.

CONCLUSIONS

✓ Our findings suggest **APL-like signature to be a potential predictor of susceptibility to vascular events**

✓ Our results deserve validation in a larger patient set and might indicate the utility of an **intensive monitoring and supportive care to prevent early vascular events in this patient category.**

REFERENCES

1. *Mason EF et al. A distinct immunophenotype identifies a subset of NPM1-mutated AML with TET2 or IDH1/2 mutations and improved outcome. Am J Hematol. 2018 Aug;93(4):504-510.*

	Overall	NPM1 APL-like		NPM1 non-APL like		p
Total %	139	31/139	22.30%	108/139	77.7%	
Age ys	59 (47-66)	64	57-70	57	45-66	**0.002**
Female %	77/139 (55.4%)	13/31	41.9%	64/108	59.3%	
Male %	62/139 (44.6%)	18/31	58.1%	44/108	40.7%	0.103
WBC (x 10^9)	38 (12.4-81.6)	38.3	12.3-117	37.75	12.56-68.73	0.575
Hb (g/dl)	8.9 (7.9-9.9)	8.9	7.65-9.83	8.9	7.85-10.05	0.882
Plt (x10^9)	50 (32-79)	48.5	30.25-102	50	33-82.5	0.824
PT (s)	68 (60-77)	70	57.75-79	68	61-77	0.975
INR	1.3 (1.2-1.4)	1.25	1.2-1.5	1.3	1.2 -1.4	0.640
INR ≥1.3-<1.5%	52/133 (39.1%)	7/30	23.3%	45/103	43.7%	0.056
INR ≥1,5 %	20/133 (15%)	8/30	26.7%	12/103	11.7%	0.077
Fibrinogen (mg/dl)	414 (307-486)	405	210-537	421	317-488	0.495
Antithrombin III	91 (81-97)	93	86.5-97	91	80-97	0.178
D dimer ng/ml	2617 (929.3-12042)	5998	1377-28237	2287	842-6760	**0.005**
D dimer ≥ 4000 %	50/131 (38.2%)	18/30	60%	32/101	31.7%	**0.009**
DD/FBG (all cases)	6.45 (1.85-35.15)	16.84	3.22.-102.1	4.4	4.4-30	**0.017**
DD/FBG (cases with vascular complications)	47.91 (6.95-349.28)	191.78	14.58-558.52	16.41	3.85-233.61	0.084
Coagulopathy %	24/131 (18.3%)	8/29	27.6%	16/102	15.7%	0.175
Vascular complications %	24/132 (18.2%)	10/29	34.5%	14/103	13.6%	**0.015**
Bleeding (BC)	22/24 (91.67%)	9/29	31,03%	14/103	13.59%	
Thrombotic (TC)	2/24 (8.33%)	1/29	3.45%	1/103	0.97%	
WHO grading BC%						
G1-G2	18/24 (75%)	7/10	70%	11/14	78.6%	
G3-G4	4/24 (16.7%)	2/10	20%	2/14	14.3%	0.665
CTCAE TC%	0	0	0%	0	0%	
G1-G2	2/24 (8.3)	1/10	10%	1/14	1/14 (7.1%)	
G3-G4						
DIC Score	3 (2-4)	3.5	2.75-5	3	2-4	0.295
IDH1	11/85 (12.9%)	7/19	36.8%	4/66	6.1%	**0.002**
IDH2	16/91 (17.6%)	10/21	47.6%	6/70	8.6%	**0.001**
TET2	16/68 (23.5%)	3/16	18.8%	13/52	25%	0,744
CR1 %	99/132 (75%)	21/26	80.8%	78/106	73.6%	0.614
CR % anytime	109/131 (83.2%)	24/26	92.3%	85/105	81%	0.243
Relapse	60/113 (53.1%)	15/25	60%	45/88	50.1%	0.500

Table 1 *Clinical, molecular and treatment characteristics of 123 patients with NPM1 mutated AML*