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POSTER ABSTRACTS

613.ACUTE MYELOID LEUKEMIAS: CLINICAL AND EPIDEMIOLOGICAL

APL-like Subset within *NPM1*-Mutated Acute Myeloid Leukemia: A Distinct Phenotypic Signature Correlating with Early-Onset Vascular Complications

Francesca Crupi[1], *Gaia Ciolli*[1], *Matteo Piccini, MD*[1], *Sara Bencini*[2], *Giacomo Gianfaldoni*[3], *Benedetta Peruzzi*[4], *Roberto Caporale*[4], *Barbara Scappini*[1], *Laura Fasano*[1], *Elisa Quinti*[1], *Andrea Pasquini*[1], *Jessica Caroprese*[1], *Fabiana Pancani*[1,5], *Leonardo Signori*[1,5], *Chiara Maccari*[6,7], *Vivian Paradiso*[1], *Francesco Annunziato*[4], *Paola Guglielmelli, MDPhD*[1,8], *Alessandro Maria Vannucchi*[1,9], *Francesco Mannelli*[1,9]

[1] SOD Ematologia, Università di Firenze, AOU Careggi, Firenze, Italy
[2] Centro Diagnostico di Citofluorimetria e Immunoterapia, AOU Careggi, Florence, Italy
[3] AOU Careggi, Florence, Italy
[4] Centro Diagnostico di Citofluorimetria e Immunoterapia, AOU Careggi, Firenze, Italy
[5] Centro Ricerca e Innovazione Malattie Mieloproliferative (CRIMM), AOU Careggi, Firenze, Italy
[6] Department of Experimental and Clinical Medicine, University of Florence, Florence, Italy
[7] CRIMM, Center for Research and Innovation of Myeloproliferative Neoplasms, Azienda Ospedaliero-Universitaria Careggi, Florence, Italy
[8] Azienda Ospedaliero-Universitaria Careggi, Florence, Italy
[9] CRIMM, Center for Research and Innovation of Myeloproliferative Neoplasms, Azienda Ospedaliero-Universitaria Careggi, Firenze, Italy

Background: *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*). Whether these genetic alterations correlate with distinct immunophenotypic and clinical features is still a matter of debate. 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, specifically, the negativity for both CD34 and HLA-DR, and as such defined APL-like.
Aims: We studied the characteristics of a series of patients with APL-like *NPM1*-mutated AML, focusing on the incidence of vascular events at disease onset, and 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 morphological, immunophenotypic, cytogenetic and molecular criteria. Vascular events were defined according to the revised World Health Organization (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. Their characteristics are detailed in Table 1. APL-like patients were older (64 y) compared to non-APL-like (57 y, P=0.002) *NPM1*-mutated patients; no further difference emerged for baseline blood count parameters. 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. There was a trend for more severe (G3-G4) vascular events in APL-like (3/31, 9.7%) vs non-APL-like (3/108, 2.8%, P=0.12). Also, abnormal coagulopathy-related parameters, including INR ≥1.5 and/or fibrinogen below normal level) were more frequent in APL-like patients (27.6% versus 15.7%,). D-dimer levels resulted significantly higher in APL-like patients (median 5998 ng/ml versus 2287 ng/ml, P=.005). The D-dimer/fibrinogen ratio (DD/FBG) showed significantly higher level in APL-like (median 16.84) vs non-APL-like (4.4, P=.017) patients. Of note, in multivariate analysis, APL-like phenotype maintained a value (OR=2.67, P=0.007) on DD levels from WBC count (OR=2.37, P=0.017), thus suggesting an effect independent from leukocytosis. Also, APL-like subset maintained an age-independent impact (OR=2.77, P=0.041) on the rate of vascular events. Among the 85 patients with full molecular information, there was a significant enrichment *IDH1* (36.8%, P=0.002) and *IDH2* (47.6%, P=.001) mutations in APL-like vs non-APL-like (6.1% and 8.6%, respectively) 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 within *NPM1*-mutated AML. 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, especially hemorrhagic, events in this patient category.

Disclosures Guglielmelli: *GSK:* Speakers Bureau; *Abbvie:* Other: Other member of advisory board, speaker at meeting, Speakers Bureau; *Novartis:* Other: Other member of advisory board, speaker at meeting, Speakers Bureau. **Vannucchi:** *BMS:* Honoraria; *Roche:* Honoraria; *Abbvie:* Honoraria; *AOP:* Honoraria; *GSK:* Honoraria; *Novartis:* Honoraria; *Incyte:* Honoraria.

	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**
WBC (x 10^9)	38 (12.4-81.6)	38.3	12.3-117	37.75	12.56-68.73	0.575
WBC≥ 25 (x10^9) %	108/139 (63.4%)	18/31	58.1%	67/108	62%	0.682
Hb g/dl	8.9 (7.9-9.9)	8.9	7.65-9.83	8.9	7.85-10.05	0.882
Fibrinogen (mg/dl)	414 (307-486)	405	210-537	421	317-488	0.495
AT III low %[2]	7/114 (6.1%)	0/25	0%	7/89	7.9%	0.344
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 (only 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 %[3]	24/131 (18.3%)	8/29	27.6%	16/102	15.7%	0.175
Vascular complications%[4]	24/132 (18.2%)	10/29	34.5%	14/103	13.6%	**0.015**
Bleeding (BC) Thrombotic (TC)	22/24 (91.67%) 2/24 (8.33%)	9/29 1/29	31.03% 3.45%	14/103 1/103	13.59% 0.97%	
WHO grading BC% G1-G2 G3-G4 CTCAE TC% G1-G2 G3-G4	 18/24 (75%) 4/24 (16.7%) 0 2/24 (8.3)	 7/10 2/10 0 1/10	 70% 20% 0% 10%	 11/14 2/14 0 1/14	 78.6% 14.3% 0% 1/14 (7.1%)	0.665
Days before vascular events (median)	4.5 (1-10.5)	8	(1.5-12.25)	3	(0.5-8)	0.247
Vascular events within 15 days % over 15 days %	 19/24 (79.2) 5/24 (20.8%)	 8/10 2/10	 80% 20%	 11/14 3/14	 78.6 21.4%	1
DIC Score[5]	3 (2-4)	3.5	2.75-5	3	2-4	0.295
DIC score≥5 %	25/129 (19.4%)	8/30	26.7%	17/99	17.2%	0293
FLT3 any TKD ITD	80/136 (58.8%) 20/136 (14.7%) 67/136 (49.3%)	19/30 2/30 18/30	63.3% 6.7% 60%	61/106 18/106 49/106	57.5% 17 % 46.2%	0.363 0.243 0.217
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
DNMT3A	18/91 (52.7%)	6/18	33.3%	42/73	57.5%	0.112
Karyotype (normal)%	92/110 (83.63%)	19/31	61.3%	73/108	67.6%	0.164

Figure 1

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