A CASE REPORT OF ACUTE PANMYELOSIS WITH MYELOFIBROSIS (APMF) WITH A DISTINCT MOLECULAR PATTERN

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CASE

A 67-year-old man presented with persisting fatigue and unexplained weight loss. The peripheral blood examination showed anemia (hemoglobin 8,6 g/dL; normal range 12,9-17,3 g/dL) with normal platelet and white blood cell counts, and a blastic population (35%; figure 1A).

In contrast to the hypocellular bone marrow aspirate (figure 1B), the biopsy revealed a markedly hypercellular marrow, with proliferation of the three lineages (i.e. panmyelosis) and 50% blasts (figure 1C). The megakaryocytes showed dysplastic features and a reticulin staining revealed myelofibrosis (grade 2-3; figure 1D). The blastic population showed expression of CD34, CD117, HLA-DR, CD13 and CD33, in the absence of cyMPO, T/B/NK cell and monocytic markers (figure 2). According to the WHO 2016 classification, the diagnosis of an acute panmyelosis with myelofibrosis (APMF) was made. Next-generation sequencing (NGS) showed mutations in three genes: *RUNX1, SRSF2* and *CALR*. Also, *WT1* and *EVI1* overexpression were found. Cytogenetic analysis revealed an aberrant karyotype with the presence of der(6)t(1;6)(q21;p21).
Due to co-morbidities, low intensity chemotherapy (cytarabine) was started but discontinued after one cycle because of complications. Further treatment was palliative.

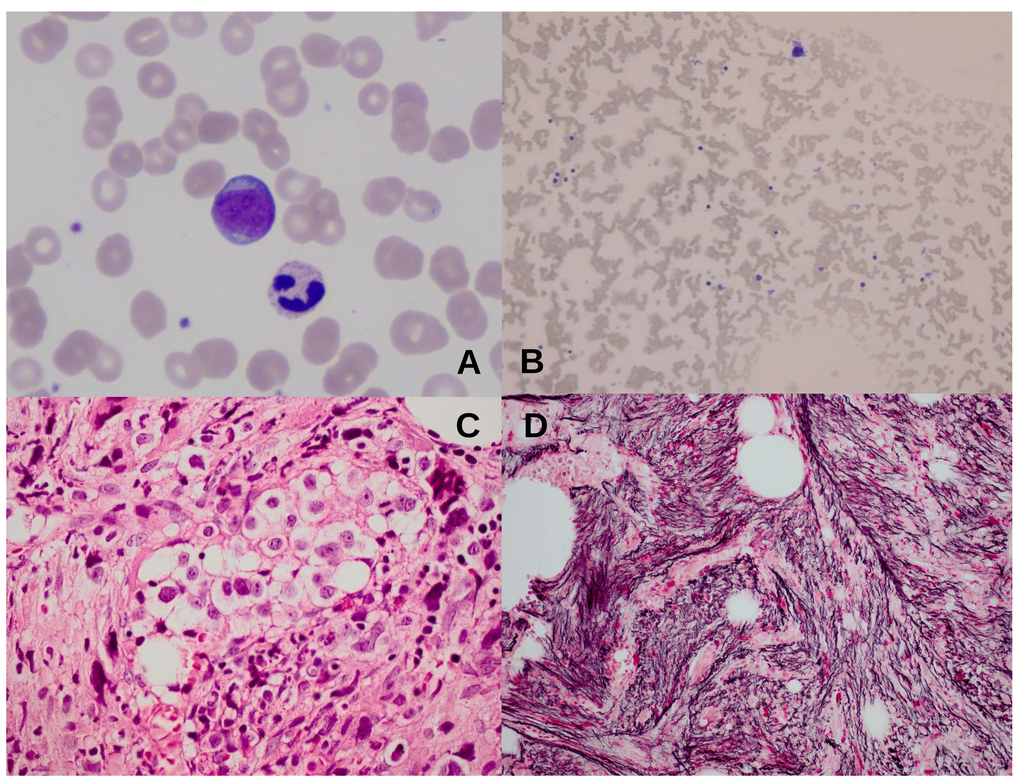

Figure 1. A. Blast in peripheral blood smear (x40).
B. Hypocellular bone marrow aspirate (x10).
C. Hypercellular bone marrow biopsy showing a focus of blasts and dysplastic megakaryocytes of small size with atypical hyposegmented nuclei (hematoxylin and eosin, x40).
D. Reticulin staining showing an obvious increase of coarse reticulin fibres (x20).

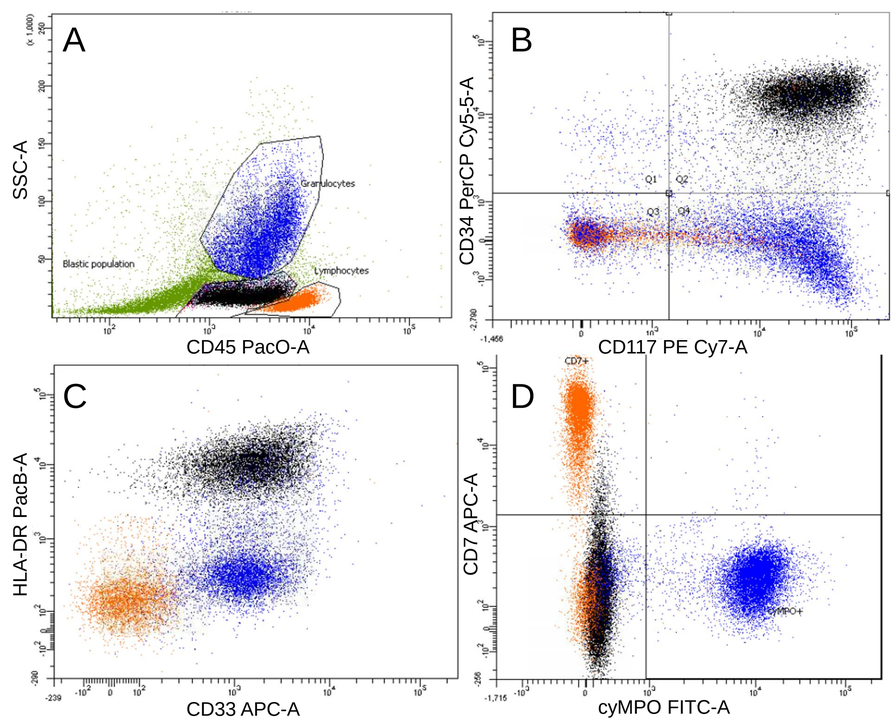

Figure 2. Immunophenotyping of the bone marrow aspirate. Black: blasts; blue: granulocytes; orange: lymphocytes. The monocytes were absent, concordant with the cytomorphology.
A. SSC versus CD45. The green population is debris.
B. CD34 versus CD117. The majority of the granulocytes express CD117, i.e. immature granulocytes.
C. HLA-DR versus CD33.
D. CD7 versus cyMPO

DISCUSSION

APMF is a rare type of acute myeloid leukemia (AML), although prevalence might be underestimated due to the challenging diagnosis. The differential diagnosis includes acute megakaryoblastic leukemia, other AML with dysplastic changes, myelodysplastic syndrome with excess blasts and primary myelofibrosis (PMF). Very little is known about the genetic profile of APMF.

We performed NGS analysis on the bone marrow sample of genes that are relevant in AML and in myeloproliferative disorders, considering the myelofibrosis. Following genes were included: *ASXL1, CEBPA, DNMT3A, FLT3, IDH1, IDH2, KIT, NPM1, NRAS, RUNX1, SF3B1, SRSF2, TET2, TP53, U2AF1, JAK2, CALR* and *MPL*. We detected three variants with this targeted NGS analysis, presented in table 1.

Table 1. Overview of the detected variants in the bone marrow sample of the patient with APMF

Gene	Variant type	DNA	Protein	VAF (variant allele frequency)
RUNX1	Missense variant	c.307C>G	p.(Pro103Ala)	42.7%
SRSF2	Missense variant in hotspot (P95H)	c.284C>A	p.(Pro95His)	34.7%
CALR	Frameshift variant in hotspot (type I)	c.1099_1150del	p.(Leu367Thrfs*46)	24.5%

The combination of a *RUNX1* and *SRSF2* variant is known to correlate with a poor prognosis in AML (Gaidzik et al., Leukemia 2016). Frameshift mutations in *CALR* occur in myeloproliferative disorders and especially type I is associated with myelofibrosis. Additionally, der(6)t(1;6)(q21;p21) has already been described in PMF (Hussein et al., European Journal of Haematology 2009). These findings are compatible with the APMF diagnosis.

CONCLUSION

APMF is a rare AML entity with a challenging diagnosis. Genetic alterations associated with this disease are not well studied. The variants present in this patient underly the biology of the disease and can be of added value to confirm the diagnosis.

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