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 (36%; 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. Cyto genetic analysis revealed an aberrant karyotype with the presence of der(6)(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.

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.

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)(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.

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

<table>
<thead>
<tr>
<th>Gene</th>
<th>Variant type</th>
<th>DNA</th>
<th>Protein</th>
<th>VAF (variant allele frequency)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RUNX1</td>
<td>Missense variant</td>
<td>c.307C&gt;G</td>
<td>p.(Pro103Ala)</td>
<td>42.7%</td>
</tr>
<tr>
<td>SRSF2</td>
<td>Missense variant in hotspot (P95H)</td>
<td>c.284C&gt;A</td>
<td>p.(Pro95Hist)</td>
<td>34.7%</td>
</tr>
<tr>
<td>CALR</td>
<td>Frameshift variant in hotspot (type I)</td>
<td>c.1099_1150del</td>
<td>p.(Leu367Thrfs*46)</td>
<td>24.5%</td>
</tr>
</tbody>
</table>

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.