Noonan Syndrome and Acute Myeloid Leukemia in Adults: The Importance of a Correct Multidisciplinary Approach during Childhood

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Editorial comment on the paper by Alhumaid et al. Comprehensive Genomic Analysis of Noonan Syndrome and Acute Myeloid Leukemia in Adults: A Review and Future Directions. A Case Report. Acta Haematol 2020;143:583–593

In this issue of *Acta Haematologica*, Alhumaid et al. [1] describe the rare case of an adult with Noonan syndrome (NS) who developed acute myeloid leukemia (AML) characterized by a combination of a germline mutation of *PTPN11* with somatic mutations of *NPM1*, *IDH1*, and *BCL6*. NS is an autosomal dominant disorder functionally characterized by hyperactivation of the RAS/MAPK signaling pathway, caused by mutations in various genes, the most frequent being *PTPN11*, mutated in about 50% of cases. The *PTPN11* gene encodes for the nonreceptor protein tyrosine phosphatase SHP-2, and germline and somatic mutations of *PTPN11* confer a gain-of-function of SHP-2. The NS phenotype is characterized by short stature, multiple dysmorphisms, congenital heart defects, cryptorchidism, coagulopathy, lymphatic dysplasia, and mild mental impairment. NS patients are at an increased risk of developing cancers (from 3.5 to 8 times in different series), the most frequent of which is juvenile myelomonocytic leukemia (JMML). Other cancers observed in NS are acute myelogenous leukemia (AML), acute lymphoblastic leukemia, rhabdomyosarcoma, and neuroblastoma. A myeloproliferative disorder similar to JMML but with a spontaneous remission has been described in NS [2].

The case report by Alhumaid et al. [1] suggests several considerations. First is the importance of an early diag-

nosis and a correct multidisciplinary approach during childhood. Among congenital syndromes, NS has the highest frequency of cardiac defects after trisomy 21, and the surgical correction of the atrial septal defect would have modified the clinical course of the reported patient. A correct transition from pediatric to adult care is critical in patients with chronic diseases.

A second point is the recommendation for cancer surveillance of RASopathies in patients with high-risk mutations. In this regard, Tartaglia et al. [3] analyzed germline and somatic *PTPN11* mutations and demonstrated that the cancer risk is related to the level of SHP-2 tyrosin phosphatase activity. In NS patients with high-risk mutations, clinical and laboratory surveillance every 3–6 months for the first 5 years is recommended [4]. A noninvasive functional evaluation of peripheral blood hematopoietic progenitors has also been suggested for high-risk subjects [5]. Cancer prevention strategies also play a role in subjects at risk of developing malignancies, with the focus on lifestyle and environmental factors. The *PTPN11* mutation p.Phe285Ser observed in the case report has been described in JMML, so the patient could be considered to be at risk of malignant transformation.

In adult AML, somatic mutations of *PTPN11* are often associated with *NPM1* mutations, according to the two-

hit theory of leukemogenesis, with those patients mutated in *PTPN11* but not in *NPM1* showing a poorer prognosis [6]. The presence of other co-occurring mutations may further influence the clinical course and prognosis [7]. The genomic analysis performed in the patient described by Alhumaid et al. [1] showed the presence of a combination of a germline mutation of *PTPN11* with somatic mutations of *NPM1*, *IDH1*, and *BCL6*. The disease relapse in the presence of this complex genomic profile could suggest an intensive treatment including allogeneic stem cell transplantation (HSCT). Successful HSCT has been reported in an adult NS patient with AML in second remission [8]. Unfortunately, the clinical conditions and comorbidities of the patient described by Alhumaid et al. [1] made this approach impossible.

Analysis of single-nucleotide polymorphisms and whole-genome sequencing now make it possible to revisit the classification of AML on a purely genomic basis, and to shift in the near future to precision medicine with targeted therapies of particular interest in patients with severe comorbidities.

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