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Letter to the Editor

Acute basophilic leukemia with U2AF1 mutation

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Acute basophilic leukemia (ABL) is a rare form of acute leukemia (4–5% of all cases of acute non-lymphocytic leukemia) whose pathophysiology remains elusive [1,2]. Most cases have been reported to develop from other hematological disorders, such as chronic myeloid leukemia (CML) and myelodysplastic syndromes (MDS) [3–6]. *U2AF1* is a commonly (about 10%) mutated spliceosome gene in MDS [7], encoding for a RNA-binding protein that helps to direct the U2 small nuclear ribonucleoprotein particle (U2 snRNP) to the 3′ splice-acceptor site in pre-mRNA [8,9]. Here we report for the first time a case of ABL harboring a *U2AF1* mutation.

A 60-year-old man was admitted to our hematology department with anemia, thrombocytopenia and leukocytosis. Hemoglobin was 8,9 g/dl, platelet 61 × 10^9/L and total leukocyte count 15 × 10^9/L. Serum biochemistry and coagulation were unremarkable. Morphological examination on both peripheral blood (Fig. 1) as well as bone marrow revealed a large population of basophils with a variable degree of maturation ranging from blasts with coarse basophilic granules to mature basophil granulocytes, some of which with signs of degranulation. Bone marrow residual myeloid as well erythroid lineages were dysplastic while megakaryocytes were markedly reduced in number. Immunophenotyping on marrow blood confirmed the heterogeneous population of basophils with was positive for CD9, CD13, CD25, CD33, CD45 and CD123, among which the most immature fraction, corresponding to 15% of total cellularity, was CD22-/CD13+ and $CD123^{DIM}$ (Fig. 2). Conventional cytogenetic analysis performed on bone marrow aspirate revealed a normal karyotype and molecular studies investigating common fusion transcripts were negative. Amplicon-based next generation sequencing (NGS) targeting the coding regions of a panel of 30 genes associated with hematological malignancies was performed on whole bone marrow DNA using an Ion Torrent platform (Thermofisher). A *U2AF1* (NM_006758.2) c.470A > C (p.Gln157Pro) mutation at a variant allelic frequency (VAF) of 38% was identified. The patient was treated with a classical 3 + 7 approach with a poor response and is about to undergo a salvage treatment.

"Basophilic leukemia" was first described in 1906 by Jaochim in two patients with extreme basophilia and clinical features of myelocytic leukemia [10]. In the most recent WHO classifications of myeloid malignancies, ABL has been integrated as a distinct entity and defined as an acute myeloid leukemia (AML) in which primary differentiation is towards the basophil lineage [11]. Morphologically, this entity is quite heterogeneous as blasts can be either agranular or exhibit coarse basophilic granules in their cytoplasm and mature basophils may be present or not [2,12]. Blasts usually express a myeloid phenotype and are positive for CD9 and CD25, which are typical basophil associated markers [1,11]. ABL is not associated with any specific chromosomal abnormality [11] and the clinical course is usually rapid and associated with a poor prognosis. This is the first reported case of such a rare subtype of leukemia associated with a *U2AF1* mutation. During normal pre-mRNA splicing, the U2AF1 protein binds to the AG dinucleotide at the 3′ end of the intron, then assisting its cofactor U2AF2 in recruiting the U2 snRNP for spliceosome activation [13,14]. As in AML *U2AF1* mutations are associated with a lower complete remission rate after induction therapy [8,15], both the morphologic and the molecular profile observed in our patient imply an extremely negative prognosis. Further investigations should explore the potential functional links between this specific subtype of AML and this mutation which is responsible of a derangement involving the spliceosome machinery.

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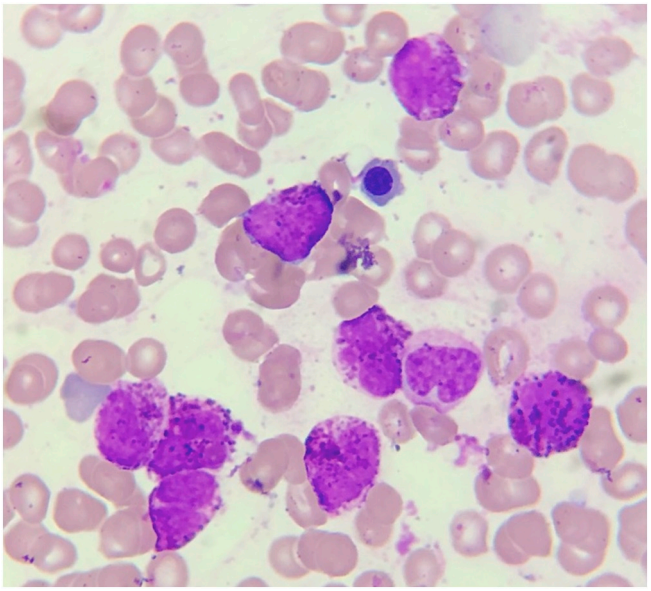

Fig. 1. Morphological examination on peripheral blood revealed a large population of basophils with a variable degree of maturation ranging from blasts with coarse basophilic granules to mature basophil granulocytes, some of which with signs of degranulation.

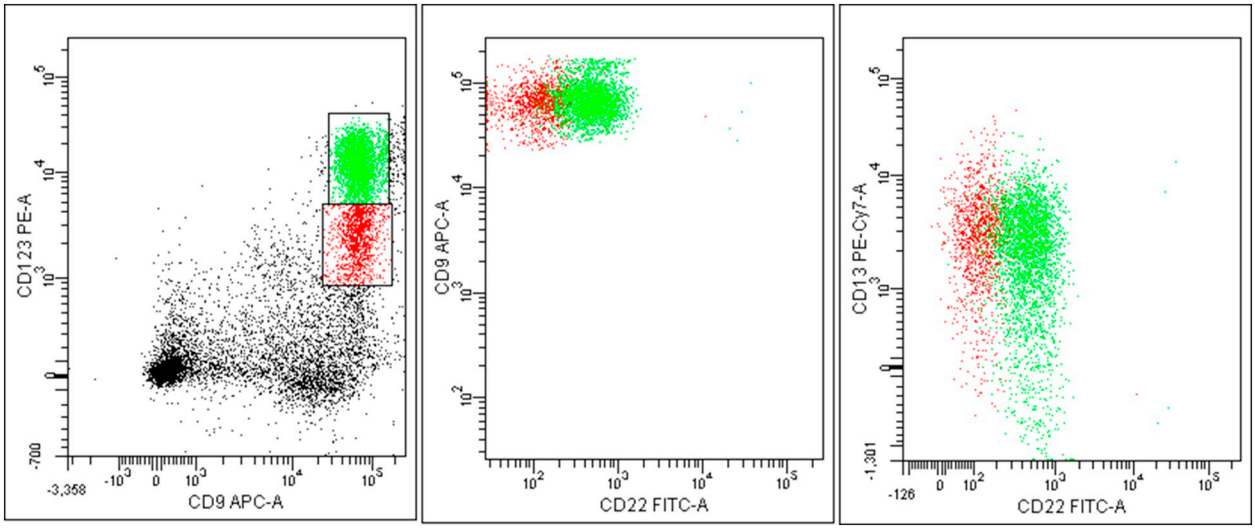

Fig. 2. Immunophenotyping on marrow blood confirmed the heterogeneous population of basophils with was positive for CD9, CD13, CD25, CD33, CD45 and CD123, among which the most immature fraction, corresponding to 15% of total cellularity, was CD22-/CD13+ and CD123^{DIM}. In the present plots the two different cell populations both positive for CD9 but with low (in red) or high intensity (in green) for CD123 (left panel), are shown to be negative for CD22 (middle panel) and positive for CD13 (right panel). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Conflicts of interests

Nothing to declare.

Authorship

AC, GM, RR, FL, GV and CF were involved in the diagnostic workflow and patient management; PV, SB, GP, AU, AP performed all laboratory studies; GC, GL and CF wrote tha manuscript; all authors reviewed the manuscript.

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