Abstract: PB2422

Title: AML WITH PLASMACYTOID DENDRITIC CELL EXPANSION IN TWO CHILDREN WITH UNDERLYING CONGENITAL BONE MARROW FAILURE SYNDROME

Abstract Type: Publication Only

Topic: Acute myeloid leukemia - Biology & translational research

Background:

A subtype of acute myeloid leukemia with expansion of plasmacytoid dendritic cells (pDC-AML), associated with a high frequency of clonal *RUNX1* mutation and poor clinical outcome, has previously been described in two series of adult patients (Zalmei et al, 2021; Xiao et al, 2021). The occurrence and biology of this disease in children are unknown.

Aims:

The aim of this study was to characterize the immunophenotypic, genetic and clinical characteristics of two AML cases with pDC expansion and inherited bone marrow failure (BMF)/myelodysplastic neoplasm (MDS) syndromes.

Methods:

We describe two patients, age 16y (Pt1) and 11y (Pt2) presenting with AML. Comprehensive immunophenotyping was performed using multiparameter flow cytometry (FCM). Cytogenetics was done by karyotyping and fluorescent in-situ hybridization. A targeted NGS-panel and WGS were used to identify somatic and germline gene variants, respectively. Treatment response (measurable residual disease, MRD) was measured in BM samples by FCM using standardized and patient-specific antibody combinations. The patients were treated according to NOPHO–DBH AML2012.

Results:

Both patients presented with similar immunophenotypic profiles of the AML leukemic cells (Figure 1A-B). The leukemic cells were comprised of three subpopulations including an immature CD34+ cell subset, monocytic cells, and precursor pDCs, in accordance with known pDC-AML characteristics. Somatic pathogenic *RUNX1* mutations were detected in both cases. Karyotyping revealed normal female karyotype in Pt1, and monosomy 7 in Pt2 (Figure 1C).

The MRD response kinetics differed in the two patients. Pt1 had undetectable MRD from the first follow-up sample on day 22 and at all time points, whereas Pt2 had slowly decreasing MRD and displayed undetectable MRD (<0.1%) prior to the pre-consolidation time point.

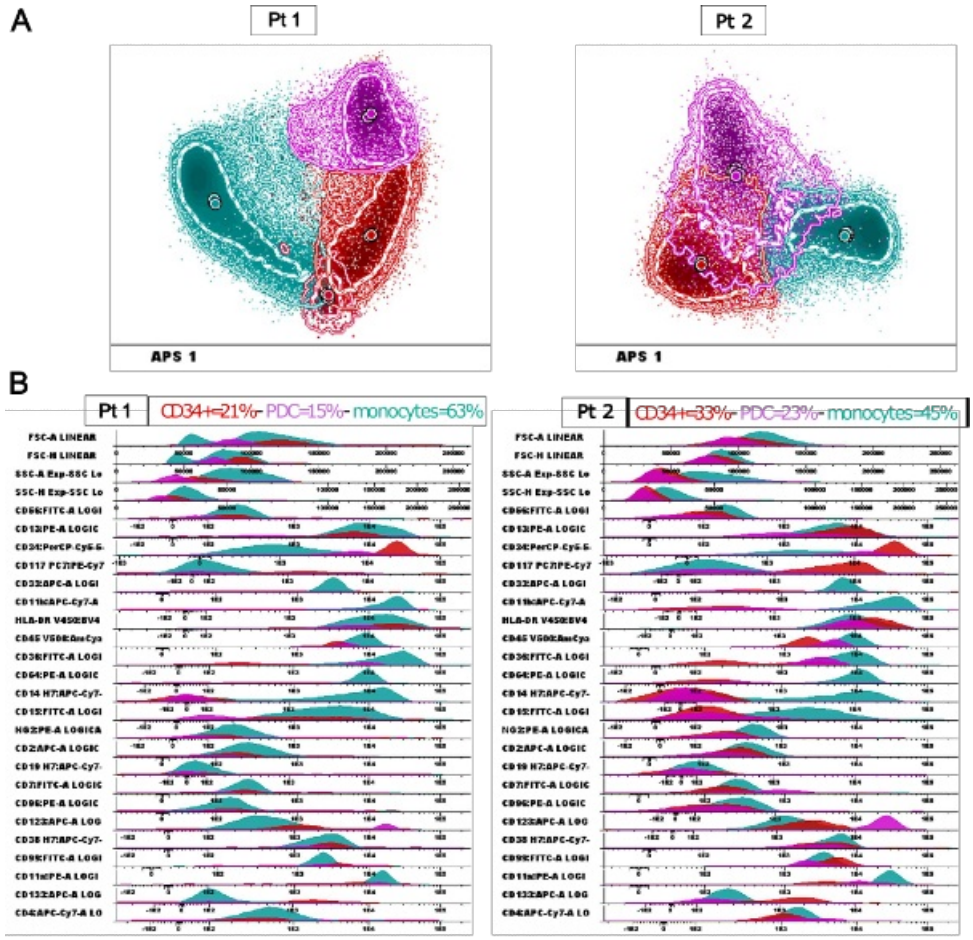
Pt1 experienced a long period of aplasia after each induction course and did not achieve complete hematologic recovery, suggesting an underlying bone marrow failure syndrome. Indeed, WGS revealed compound heterozygous pathogenic variants in the *SBDS* gene confirming the diagnosis of Shwachman-Diamond syndrome (SDS). Targeted NGS after chemotherapy courses just pre-HSCT found a somatic pathogenic *TP53* variant (Figure 1C). Re-analysis of the diagnostic BM identified this variant at subclonal level. Pt1 received HSCT from a 10/10 allele matched-unrelated-donor resulting in full donor chimerism and is currently 22 months post-HSCT; to our knowledge this is the first long-term surviving SDS patient after fully developed AML.

Similarly, Pt2 also showed a slow hematologic recovery but in addition had sustained B-NK-cell lymphopenia and monocytopenia. This triad of findings raised the suspicion of GATA2 deficiency syndrome. A heterozygous germline de novo variant, a 250 kb deletion on chromosome 3, including *GATA2* and *RPN1*, was detected confirming the diagnosis of this MDS/AML predisposing syndrome (Figure 1C). Despite clinical and peripheral

hematological recovery, the patient succumbed to sudden death due to pulmonary hemorrhage at 7 weeks after the last consolidation course.

Summary/Conclusion:

To the best of our knowledge, this is the first report of pDC-AML with *RUNX1* mutations in children and of pDC-AML with underlying BMF/MDS syndromes. These case presentations expand our knowledge on the heterogeneity of disease manifestations in predisposing hematologic malignancy syndromes. The findings suggest that investigations for germline gene variants are warranted in children with pDC-AML immunophenotype and that somatic *TP53* variants are indicative for underlying SDS.



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	Patient 1	Patient 2
Karyotype	46,XX Normal	45,XY -7[10]/ 46,XY[7]
Germline mutations	*SBDS* compound heterozygous mutations, c.184A>T, c.258+2T>C Pathogen ic	Heterozygous 250 kb deletion on chromosome 3, involving: *GATA2*, *DNAJB8*, *RPN1*
Somatic *RUNX1* mutations	*RUNX1* c.245delinsCAC p. (Leu82Profs*41) Pathogenic . VAF 70%	*RUNX1* in-frame insertion Ser141_Ala142insHisHis IleTrp Unknown clinical significance . VAF 4% *RUNX1* nonsense variant 498insGTAG;p.(Ser167*) Unknown variant but likely pathogen. VAF 4%
Other somatic mutations	*TP53* missense variant c.524G>A; p.(Arg175His) Pathogenic . VAF 0.8% *EZH2* variant c.2051G>A p.(Arg684His) Likely pathogenic . VAF 1.1% Pre-HSCT sample : *TP53* c.524G>A; p.(Arg175His) . VAF 16%	*EZH2* missense va riant c.1955C>A;p. (Ser652Tyr) Unknown clinical significance . VAF 7%.

Figure 1. Immunophenotypic profiles and genetic characteristics

Flowcytometric immunophenotyping found that the two patients' bone marrow at the time of AML diagnosis were dominated by side scatter-low/CD45dim blast area cells comprising 43% (pt1) and 58% (pt2) of all live cells, respectively. Three subpopulations formed a maturation continuum between immature myeloid blasts (red), expanded (precursor) pDCs (magenta) and monocytic cells (turquoise). A. Dimensional reduction with Infinicyte APS tool. B. Histograms showing expression patterns for the individual markers in the three subpopulations. C. Summary of genetic characteristics (karyotyping, FISH, targeted-NGS and WGS).

Keywords: AML, Bone marrow failure, Immunophenotype