

CASE REPORT

An unusual case of phenotype switch between AML FAB subtypes

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Introduction

Acute promyelocytic leukemia (APML) is a distinct subtype of AML with specific clinical, morphologic, and genetic features which is treated differently than other AML subtypes. Patients in the low-risk group (platelet counts $>40 \times 10^9/L$ and WBC count $<10 \times 10^9/L$) and intermediate risk group (platelet counts $<40 \times 10^9/L$ and WBC count $<10 \times 10^9/L$) rarely experience relapse ($<3\%$), whereas patients in the high-risk group (WBC counts of greater than $10 \times 10^9/L$) are reported to have a relapse rate of $\sim 28\text{--}40\%$ [1]. Molecular monitoring of the minimal residual disease (MRD) by qualitative nested reverse transcription polymerase chain reaction (RT-PCR) and quantitative real-time PCR of promyelocytic leukemia/retinoic acid receptor- α (PML/RAR α) allows to follow the individual kinetics of MRD and to identify patients with an imminent hematological relapse. Till now, multiple case reports of lineage switch from Acute Lymphoblastic Leukemia (ALL) to AML and few reporting vice versa have been published [2, 3]. Herein, we report a case of APML which showed switch to AML-non-M3 after 2 years of arsenic and all-trans retinoic acid (ATRA) treatment. To the best of our knowledge, this is the first case of APML showing phenotypic

Key Clinical Message

Phenotypic switch between any leukemia subtypes is of concern to a treating physician and more so, in acute myelocytic leukemia (AML) as the mechanisms for switch and subsequent chemotherapy regimen to be used remain unclear. AML-non-M3 from AML-M3 subtype needs special mention as this has been unheard off.

Keywords

APML, children, flow cytometry, phenotypic switch.

switch to a AML-non-M3 and second case of switch between AML French American British (FAB) classification subgroups.

Case Report

A 5-year-old girl presented with fever, neck swelling, and weight loss for 2 months in April 2011 for which she was started on antitubercular drugs by a local physician. On examination, she had pallor, bilateral cervical lymphadenopathy, and hepatosplenomegaly (liver 3 cm and spleen 3 cm below costal margin). There were no signs of bleeding, focal neurological deficit, or gum hypertrophy. The hemoglobin was 71 gm/L, total leukocyte count was $8.1 \times 10^9/L$, and platelet count was $31 \times 10^9/L$. D-dimer test, prothrombin time (PT), and activated partial thromboplastin time (aPTT) were within normal limits. Peripheral blood smear showed 80% abnormal promyelocytes which were immunopositive for cMPO, CD45, CD33, CD117, CD2, CD13 (dim), and CD38 (dim) and immunonegative for CD34, HLADR, cCD79a, CD19, CD18, CD4, CD7, and cCD3. Bone marrow (BM) aspiration revealed near total replacement by abnormal promyelocytes (Fig. 1). Morphological and immunophenotypic features were consistent with APML microgranular variant.

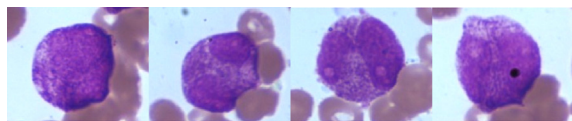


Figure 1. Peripheral blood smear showing abnormal promyelocytes at diagnosis (Jenner and Giemsa, 1000 \times).

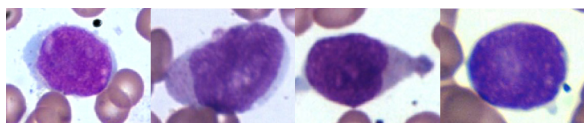


Figure 2. Peripheral blood smear showing abnormal myeloblasts (Jenner and Giemsa, 1000 \times).

No abnormal cells were noted on cerebrospinal fluid cytology. RT-PCR for PML/RAR α rearrangement showed a positive result. The patient was started on arsenic monotherapy (0.15 mg/kg per day) and after 60 days of induction, morphological remission in BM and absence of PML/RAR α transcripts on RT-PCR were reported. Induction was followed by one cycle of consolidation of 28 days with arsenic (0.15 mg/kg per day) and six cycles of maintenance; monthly cycle of arsenic for 10 days/month (0.15 mg/kg per day) and intrathecal methotrexate on day 1 (8 mg) till March 2012. The child was apparently well for 1 month, after which she again presented with fever. Five percent abnormal promyelocytes on peripheral blood smear and presence of PML/RAR α transcripts on RT-PCR were noted. At this time, treatment was initiated with ATRA (45 mg/m² per day) and daunomycin (1.5 mg/kg per day). Morphological remission in BM was reported after completion of 3 months of induction and thereafter consolidation with ATRA (0.15 mg/kg per day), daunorubicin, and cytarabine on day 1. Within 2 months of consolidation phase, patient relapsed again and the BM at this time was replaced by blasts which were immunopositive for cMPO, CD45, CD34, CD13, CD33, CD117, CD15, CD11b, CD56, CD19, CD64, CD2, CD65, CD7, HLADR, CD9, CD4, and CD133 and negative for CD38, cCD79a, and cCD3, suggestive of AML-non-M3 (Fig. 2). PML/RAR α by RT-PCR was negative. A diagnosis of switch to AML-non-M3 from AML-M3 was made. The prognosis was discussed with the family and the child was started on Medical Research Council's 10th AML (MRC AML10) protocol. The child succumbed to death after 2 months due to sepsis (febrile neutropenia), refractory shock, and ongoing myocardial dysfunction for which the child was on cardioprotective drugs.

Discussion

A lineage switch phenomenon is observed when acute leukemia that meet the standard FAB criteria for a lineage

(lymphoid or myeloid) at the time of initial diagnosis meet the criteria for opposite lineage at the time of relapse [4]. Most of the lineage switch cases are associated with poor outcome [2] – the bad prognostic factors being congenital acute leukemia (CAL) [5–7] – and chromosomal aberrations including rearrangements involving MLL gene (11q gene) [8, 9]. Conversion of AML to ALL or vice versa does not seem to have a role in prognosis [3, 4]. The case described earlier can be considered as phenotypic switch as leukemic clones have switched to different phenotype within the same lineage.

Hematopoietic system consists of progenitor stem cells that gradually lose multiple alternate potentials to commit to some lineage fates. Multiple potential mechanisms of lineage switch in acute leukemia in a nonhematological stem cell transplant case are proposed. The presence of early bipotential B-macrophage progenitors in the BM and the fact that MLL-positive B-ALL show gene expression profiles consistent with early hematopoietic progenitors have raised the possibility that early bipotential or oligopotential progenitor cells are target for leukemogenic translocations, and constitute the origin of lineage switching events [10]. Another possibility is that the ectopic expression or deletion of master regulators (such as RUNX1, SCL, Ikaros, GFI1 PU.1, GFI1, c/EBP α , c/EBF β , PU.1, and GATA-1 required for the commitment of myeloid cells, and Notch1, GATA3, and Pax5, which mediate T- and B-cell development) mostly result in lineage reprogramming with or without reversion of cells back to a multipotent stage which is potentiated in a changed microenvironment of the BM [11, 12]. Third possibility is that chemotherapy might suppress or eradicate the leukemic clone that is apparent at the time of diagnosis, thereby permitting the expansion of a clone with a different phenotype [13]. A review article in 2012 on lineage switch describes 18 pediatric case reports of lineage switch mostly occurring from ALL to AML-M4/M5 and vice versa mostly. Why specifically most lineage switch occurs between AML-M4/M5 has not been described [3].

Regarding phenotypic switch in AML between various subgroups, till now only one case report in 2002 has been published regarding switch from AML-M0 to AML-M7 on relapse [14]. Coming to our case which has been the switching from AML-M3 to AML-non-M3, there was no evidence of MLL/bilineage/biphenotypic markers at the time of diagnosis, no evidence of clonal change at the time of relapse, and no stem cell transplantation has been done. Other rare gene arrangements conferring poor prognosis in APML-like STAT 5B and NuMA could not be tested at diagnosis due to nonavailability of the same in our institution and poor financial status of the patient. Against a second malignancy, points are that ATRA and DNR used for APML treatment in this patient are not

leukemogenic and the child had not yet been declared cured from the treatment when this switch was noted. As such case has not been published till date and required genetic markers for understanding the mechanism of phenotypic switch could not be done in the described case, new management strategies could not be entertained.

In conclusion, though our current findings are insufficient to confirm the mechanism of switch from AML-M3 to AML-non-M3 and as it has been not previously documented, till now, it can be said that it is due to cellular reprogramming and redifferentiation to common myeloid precursors and thereafter AML-non-M3 in a favorable microenvironment of BM modified to some extent by chemotherapeutic agents used for treatment.

Conflict of Interest

None declared.

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