The intriguing occurrence of Acute Myeloid Leukemia in a case of Acute Lymphoblastic leukemia: Report of two cases

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Abstract:
The aim of this study is to study the two cases of acute lymphoblastic leukemia (ALL) who relapsed as acute myeloid leukemia (AML). Presented here are reports of two cases of pediatric ALL who developed change of lineage to AML at relapse. This change in phenotype, which involves the conversion of one phenotype to other phenotype during the course of disease or at relapse is a rare phenomenon rarely described in literature. The immunophenotypic and molecular findings are described. The present study emphasizes the need of immunophenotyping and molecular workup at relapse. Also adds to the repertoire of the published literature on this rare entity.

Keywords:
Acute lymphoblastic leukemia, acute myeloid leukemia, immunophenotyping, lineage change, molecular finding

Introduction
Lineage switch in acute leukemia is a rarely described entity in literature. It involves the conversion of one phenotype to other during disease or at relapse. Different case scenarios are described in literature wherein B-lymphoblastic leukemia (B-ALL) turned to acute myeloid leukemia (AML) and vice versa. These are more commonly described in the pediatric population, although cases in adults are also reported. Here, we present two interesting cases of phenotype switch.

Case Reports

Case 1
In the year 2014, a 3-year-old girl was evaluated elsewhere for fever on and off for 3 months. Examination findings revealed mild hepatosplenomegaly. Peripheral blood examination showed leukocytosis with the presence of blast, morphologically lymphoblast and negative for myeloperoxidase (MPO) cytochemical stain. Immunophenotyping characteristics are enumerated in Table 1. The diagnosis of B-ALL was rendered. Cytogenetics showed a normal 46XX karyotype; however, fluorescence in situ hybridization (FISH) revealed ETV6-RUNX 1 t(12,21) (p13.2;q22.1) translocation in 55% of the cells. Other mutation BCR-ABL, t(1,19), and MLL tested were negative by FISH. The patient was started on BFM95 protocol (prednisolone, daunorubicin, vincristine, L-asparaginase, and methotrexate). Remission was documented at the end of induction phase. The patient completed the consolidation and maintenance phase in 2016. In 2019, the patient presented at our center with fever, weakness, and loss of appetite for duration of
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20 days. Peripheral blood examination showed 14% blasts and 2% basophilia [Figure 1a]. Immunophenotyping showed two populations of CD45-positive cells showing myeloid antigens comprising of CD13, CD33, MPO.

Aberrant expression of CD79a and CD22 was seen on one population, whereas on other B markers were negative [Figure 2]. Cytogenetic evaluation revealed 46XX, add (17) (p13). Polymerase chain reaction (PCR) was done for BCR-ABL1, t(8,21), t(9,11), Inv16, fli3, Nucleophosmin 1 NPM was negative. The patient was started on FLAG protocol (Fludarabin, cytarabin, and granulocyte colony-stimulating factor [G-CSF]). The patient did not achieve remission at the end of induction phase. However, developed febrile neutropenia and succumbed to the infection.

Case 2

In 2015, a 5-year-old boy was evaluated elsewhere for on and off episodes of fever of 1-month duration. Immunophenotyping performed on peripheral blood

Figure 1: (a) Case 1 showing undifferentiated blast morphology, basophil (arrow) also included in the field (Leishman, ×400). (b) Case 2 showing predominance of blasts, cytoplasm shows the presence of fine granules (arrow) (Leishman, ×400)

Figure 2: Flowcytometry results of case one, wherein the gated blast population (red and green) show positive myeloid markers. Only red population shows aberrant CD22 and CD79a expression
showed B-ALL. Bone marrow showed 30% blasts. The patient came to our hospital for treatment, chemotherapy with MCP 841 protocol was initiated (Vincristine Daunomycin Methotrexate). Postinduction the patient achieved remission and later completed the consolidation phase with few episodes of hospitalization for fever and neutropenia. The maintenance regime was started with 6 mercaptopurine, methotrexate, cyclophosphamide followed by vincristine + L-asparaginase, which ended in May 2018. Subsequently, the patient developed leukopenia. He was treated with G-CSF/blood products/IV antibiotics and supportive care. The patient had persisting leukopenia for a period of 5 months duration and was admitted at our hospital for headache and vomiting for supportive care. Peripheral blood examination revealed 12% blasts. Magnetic resonance imaging brain was suggestive of focal cerebritis/infiltration, CSF examination was normal. Bone marrow examination showed a hypercellular marrow with 8% blasts. The blasts were negative for cytochemical stains MPO and periodic acid-schiff. The patient was advised weekly follow-up with supportive treatment. He defaulted and presented back to the hospital after 20 days, this time the peripheral blood examination showed rise in the blast count. Bone marrow done showed 81% blasts [Figure 1b]. Immunophenotyping done on peripheral blood revealed AML. None of the B- and T-cell markers were positive [Table 1]. Cytogenetics showed 46XY, der (18) dup (18) (q21q23) in all the 20 cells analyzed. Induction chemotherapy with mitoxantrone + cytarabine was started. However, the patient failed to achieve remission and reinduction was done. Simultaneously, the patient was counseled for stem cell transplant. At present, the patient is undergoing his second induction cycle.

**Discussion**

ALL represents the most common type of leukemia in children. The relapse of disease whenever occurs, the phenotype remains the same. Lineage switch at relapse though described in literature is a rare occurrence with the reported incidence being 6%–8%. More commonly, lineage switch described is ALL transforming to AML and mostly seen in the pediatric population, which was also seen in the two cases described in the present study [Table 1].

Various hypothesis have been laid to explain the phenomenon of lineage switch, most common ones being chemotherapy-induced selection of subclone resistant to therapy which proliferates, leading to phenotypic switch (which might explain the aberrant B markers in case 1), pluripotent nature/plasticity of stem cells capable of multilineage differentiation in accordance to external
stimuli and intrinsic environmental factors.\textsuperscript{1,3} Mutations occurring in very immature bipotential progenitor stem cells have also been suggested as a mechanism responsible for the phenotypic switch. Hence, high association of MLL gene abnormalities with lineage switches point to origin of MLL-ALL from immature precursors.

In case 1, the presence of basophilia raised the suspicion of association with chronic myeloid leukemia, in which sequential myeloid and lymphoid blast crisis is known,\textsuperscript{9} however was ruled out by real-time-PCR for BCR-ABL. Some authors have suggested the phenotypic switch as a part of the biologic spectrum of mixed phenotypic leukemia.\textsuperscript{4,8}

Transitional MDS like disease on marrow morphology seen in the second case, Wu et al.\textsuperscript{7} have described similar features in their two cases of phenotypic switch, wherein the initial karyotype associated with B-ALL was a complex followed by abnormalities indicative of MDS. Both these entities are associated with bad prognosis.\textsuperscript{4,8}

The authors cannot conclusively rule out therapy-related myeloid neoplasm in both cases, as the lineage switch occurred late in the course of disease 4½ and 3 years, respectively. However scenarios like the present one are described in literature, although rare.\textsuperscript{11} There is no clear evidence as to pointers at differentiating a lineage switch from therapy-related AML except presence of the initially described cytogenetic/molecular abnormalities at relapse.\textsuperscript{11} Therapy-related AML due to alkylating agents as in the present scenario are generally described at 5–7 years with high occurrence of molecular abnormalities such as monosomy 7 and del 5/monosomy 5,\textsuperscript{10} which were not seen in our cases.

From the present study, we conclude the need of systematic approach in the diagnostic algorithm of acute leukemia. These cases reemphasize the need of immunophenotypic and molecular studies in relapse cases so as to better understand the evolving science behind these elusive case scenarios.

The present study adds to the repertoire of cases published since single-center large study is difficult in view of rarity of these cases.

Declaration of patient consent
The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest
There are no conflicts of interest.

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