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Case Report

Rare Case of Lineage Switch from Acute Myeloid Leukemia to Acute Precursor B Lymphoblastic Leukemia in A 3-Year-Old

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NOVELTY – Only two pediatric case reports of lineage switch from Acute Myeloid Leukemia (AML) to Precursor B Lymphoblastic Leukemia (Pre B ALL) have been reported in literature till date. Here we report a rare case and review of literature of lineage switch from AML to Pre-B ALL in a three-year-old. Clinicians should be aware of such a switch and its early recognition can lead to the use of appropriate therapy and allow such patients to achieve remission.

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Abstract

Lineage switch defines as an acute leukemia that initially presents with either lymphoid or myeloid phenotype, and then converts to the other one when recurs, while keeping the same genotype. This is associated with poor prognosis and accounts for 0.6% of paediatric leukemia. Hence, we report a rare case of lineage switch from acute myeloid leukemia to precursor B lymphoblastic leukemia in a three-year-old boy.

Keywords: Pediatric leukemia; Lineage switch; Childhood

Abbreviations: SMNs: Subsequent Malignant Neoplasms; AML: Acute Myeloid Leukemia; ALL: Acute Lymphoblastic Leukemia; Pre-B ALL: Precursor B Lymphoblastic Leukemia; MPO: Myeloperoxidase; CD: Cluster of Differentiation; BCR-ABL 1: Breakpoint Cluster-Ableson; PML RARA: Promyelocytic Leukemia Retinoic Acid Receptor Alpha; NPM1: Nucleophosmin1; FLT3: FMS Like Tyrosine Kinase 3; HIDAC: High Dose Cytarabine; FISH: Fluorescent In Situ Hydridisation; ICiCLe: Indian Colloborative Childhood Leukemia Group; FAB: French American British; WHO: World Health Organisation BiTE: Bispecific T-cell Engager

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Introduction

Subsequent Malignant Neoplasms (SMNs) are defined as histologically distinct malignancies developing at least 2 months after completion of treatment for the primary malignancy [1]. Lineage switch defines as an acute leukemia that initially presents with either lymphoid or myeloid phenotype, and then converts to the other one when recurs, while keeping the same genotype. This is associated with poor prognosis and accounts for 0.6% of paediatric leukemia [2-4]. Only a few cases of Acute Myeloid Leukemia (AML) converting to Acute Lymphoblastic Leukemia (ALL) have been reported [5]. Here we report a case of a three-year-old child initially treated as acute myeloid leukemia presenting five months post therapy as Precursor B lymphoblastic leukemia (Pre B ALL).

Case Report

We report a case of a three-year-old boy who presented in July 2022 with symptoms of fever and bony pains of three months duration. On examination, he had pallor with liver palpable three centimetres below right costal margin and spleen palpable five centimetres below left costal margin. The initial laboratory findings revealed a white blood cell count of 1.150 x 10^3/µL with 10% blasts in the peripheral blood, 5.2 gram/decilitre haemoglobin, and a platelet count of 10 x 10^3/µL.

Bone marrow was hypercellular with 30% blasts which were medium to large with high N:C ratio, fine chromatin, 0-2 nucleoli and moderate cytoplasm with few cells showing cytoplasmic granules. Bone marrow flow cytometry was positive for Myeloperoxidase (MPO), Cluster of Differentiation (CD)13, CD33, CD117, CD14, CD64, CD11c and HLA DR. Bone marrow cytogenetics revealed 46, XY karyotype. AML multi-gene panel was negative for AML1-ETO, CBFB-MYH11, Breakpoint Cluster-Ableson1 (BCR-ABL1), Promyelocytic Leukemia Retinoic Acid Receptor Alpha (PML RARA), C-KIT, Nucleophosmin1(NPM1) and FMS Like Tyrosine kinase 3(FLT3). A diagnosis of Acute Myeloid Leukaemia Non M3 was made.

He was treated with two cycles of induction with Injection Daunomycin 60milligram per metre square on day 3,5,7 and Injection Cytarabine 100 milligram per metre square for 7days as 24hour infusion. Post two induction bone marrow and minimal residual disease was negative. This was followed by three cycles of High Dose Cytarabine (HIDAC) and completed the therapy on 13/12/2022. Bone marrow and minimal residual disease was negative following each cycle.

Post completion of therapy child was on regular follow up. In May 2023 i.e. five months after last chemotherapy, child presented with fever and bilateral leg pain. On examination, liver was palpable three centimetres below right costal margin and spleen eight centimetres below left costal margin. Peripheral smear was done which showed eosinophilia with thrombocytopenia. Bone marrow examination was done which showed 20% blasts. Flow cytometry was positive for HLADR, CD34, CD19. Cytogenectics showed a solitary metaphase of near tetraploidy/endoduplication. Based on correlation with morphology, final diagnosis of Relapsed acute leukemia with lineage switch from myeloid to Precursor B lymphoid was considered. In view of eosinophilia, FGFR1, PDGFRA, PDGFRB, MLL rearrangement by Fluorescent In Situ Hydridisation (FISH) was looked for which was negative. At "relapse," the Philadelphia chromosome was not present, ruling out chronic myeloid leukemia presenting in two morphologically different blast phases.

Child was started on induction with 3 drugs as per Indian Colloborative Childhood leukemia group (ICiCLe) protocol. Daunomycin was avoided as child had already received 360milligram per metre square in AML induction. Post induction bone marrow and minimal residual disease was negative and child is on further continuation therapy.

Discussion

The frequency of lineage switch at relapse was initially estimated at 6.7% using French American British (FAB) lineage assignment criteria; however this is an overestimate when advancement in immunophenotyping and more stringent lineage criteria by World Health Organisation (WHO) is considered [6-9]. The characterisation of the lineage of an acute leukemia typically requires flow cytometry and occasionally immunohistochemistry [10]. Blasts that express a combination of markers CD19, CD79a, and cytoplasmic CD22 generally define B lymphoblastic leukemias whereas blasts expressing cytoplasmic CD3 typically represent T-lymmphoblastic leukemia. Acute myeloid leukemia is defined by myeloperoxidase (MPO) or monocytic markers like CD64, CD11c, CD14 in association with other markers like CD117, CD13, CD33. Definition of lineage switch therefore requires loss of the markers of one lineage and gain of markers associated with another. Several mechanisms have been explained for lineage switch but the exact mechanism still remains unclear. One mechanism is stem cell plasticity in the original clone which gets changed into a new phenotype with or without change in genotype. Another possible mechanism is clonal selection. There may be multiple neoplastic population called as subclone where major apparent leukemic clone will be removed by chemotherapy which will lead to expansion of sub clone with different phenotype resulting in lineage switch [11,12]. Other possible explanation is due to the effects of therapy which is very unlikely in our case due to the short time interval between the first and second leukemia. Chemotherapy associated secondary AML have a mean latency of two years and monocytic subtypes with associated MLL gene translocations are more common [13,14].

Studies have shown that lineage commitment of plastic hematopoietic progenitors can be multidirectional and reversible upon specific signals provided by intrinsic and environmental cues. Aberrant functions of specific fusions genes and surrounding microenvironment cues might cause leukemia phenotype conversion through modulation of plasticity within the leukemia's initiating cells [12].

Myeloid form can develop from already committed B-cell progenitor either directly through differentiation or indirectly through dedifferentiation and redifferentiation. This might be due to reprogramming of a malignant pluripotent stem cell [15].

Rossi, *et al*. during their study reported a large cohort of 1482 patients with pediatric leukemia's, found incidence of phenotypic lineage switch in 0.6% cases (9/1482). Among them ALL to AML (7/9) switch is more common than AML to B-ALL (2/9). Rossi, et al. found a correlation between presence of MLL fusion genes and development of lineage switch [3].

Ascota et al reported a four-year-old girl with AML who relapsed as B-ALL after nine months since the initial diagnosis [11].

Therapies targeting CD19 like Bispecific T-cell Engager (BiTE) (Blinatumomab) and CD19- recognising Chimeric Antigen Receptor T cells (CAR-T) have been shown to be associated with

lineage switch. Almbe et al. reported 12 of 163(7.4%) B-ALL treated with CAR-T therapy demonstrated lineage switch, with 75% of the lineage switched relapses harbouring KMT2Ar [16].

Conclusion

Lineage switch is extremely rare especially from myeloid to lymphoid. However, it should be kept in mind that this phenomenon exists and its frequency is probably underestimated because myeloperoxidase cytochemistry and immunophenotypic analyses were not systematically performed at relapse. Its early recognition led to the use of appropriate therapy and allowed such patients to achieve remission.

Author Statements

Data Availability Statement

Data available on request from the authors.

Patient Consent Statement

Parent's consent was obtained prior to submission of article.

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