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Case Report

An 'Uncommon early lineage switch' in an MLL rearranged adult B-lineage Acute Lymphoblastic Leukemia to Mixed-phenotypic acute leukemia (B/Myeloid)

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Case Report

Lineage switch is an infrequent phenomenon with an incidence of ~ 0.6% of all de novo leukemias and seen in almost 6% of relapsed cases. This phenomenon is observed following therapy or at the time of relapse. Switch in lineage tends to occur in younger patients and is associated with particularly poor outcomes [1]. Rearranged KMT2A gene [formerly known as Mixed leukemia lineage (MLL) gene] is found in 10% and 5% of adult and paediatric acute lymphoblastic leukemia (ALL) patients respectively has been strongly associated with lineage switch. The most common MLL rearrangement in ALL is seen with AF4 gene on 4th chromosome resulting in t (4;11) (q21;q23), AF4:MLL fusion gene and the resultant proteins are essential for leukemia maintenance [2].

Many cases of lineage switch have been reported in paediatric population with MLL rearranged ALL to acute myeloid leukemia (AML) and vice versa [3]; but has been rarely described in an adult patient [1, 4]. We, hereby describe an early lineage switch in a 57-year-old male patient with KMT2A rearranged CD10 negative B Cell ALL who after induction chemotherapy, switched to Mixed-phenotypic acute leukemia; KMT2A-rearranged.

A 57-year-old hypertensive male presented with complaints of easy fatigability and mild abdominal pain for which he was evaluated with CBC which was suggestive of anemia, thrombocytopenia and TLC: 59900 cells/ mm3 .Liver and Kidney function tests were normal. Peripheral blood and Bone marrow aspirate smears showed 73% and 78% blasts respectively, which on microscopic examination were large blasts with scant cytoplasm, round to oval notched nucleus with open chromatin and inconspicuous nucleoli. Flow cytometric studies on bone marrow aspirate sample demonstrated expression of CD19(Bright), cCD79a(Bright), CD22(Bright) CD38(Moderate), CD73(Dim), CD86(Dim)consistent with B-ALL(Figure 1A). Chromosome analysis revealed 46, XY (t 4; 11) (q21; 23) [20] and PCR studies also detected t 4;11 (q21;23) confirming AF4: MLL fusion. He was treated with UKALL induction therapy with consisting of Daunorubicin, Prednisolone, Vincristine and Peg-Asparaginase. His induction chemotherapy was tolerated with grade 2 febrile neutropenia. Post Induction therapy -1, peripheral smear showed 80% blasts of lymphoid morphology. In view of progressive nature of disease, he was salvaged with BCL 2 inhibitor, venetoclax along with UK ALL Phase II Induction therapy. Post 2 blocks of Phase II induction therapy, he presented with fever (37.7°C) and chills. On evaluation, peripheral smear showed presence of 97% blast, flow cytometric gating of population of interest shows a compact of dim CD 45, low side scatter consists of two populations a) one population (major) of blasts show strong CD19 expression along with dim to moderate CD 20 and cy CD79a expression. b) other population (minor) shows moderate cMPO expression with heterogenous expression of CD 14, CD 36, CD 33. (Figure 1B). Cytogenetics done again revealed 46, XY (t 4; 11) (q21;23) [20]. He was considered to have evolved to Mixed-phenotypic acute leukemia;KMT2A-rearranged possibly due to myeloid blast escape following ALL therapy. Thereafter, he received high dose Ara-C and Mitoxantrone (HAM) based salvage chemotherapy. Post chemotherapy he developed severe pancytopenia, sepsis with multi-organ dysfunction syndrome, subdural hematoma and succumbed on day 12 of therapy.

Discussion

Our clinical report illustrates an adult refractory B -ALL with t (4;11) (q21;23), AF4:MLL fusion who transformed to Mixed-phenotypic acute leukemia;KMT2A-rearranged during his second month of therapy. Lineage switch in MLL rearranged paediatric ALL is common, but in adults it is not well reported. During the literature review,

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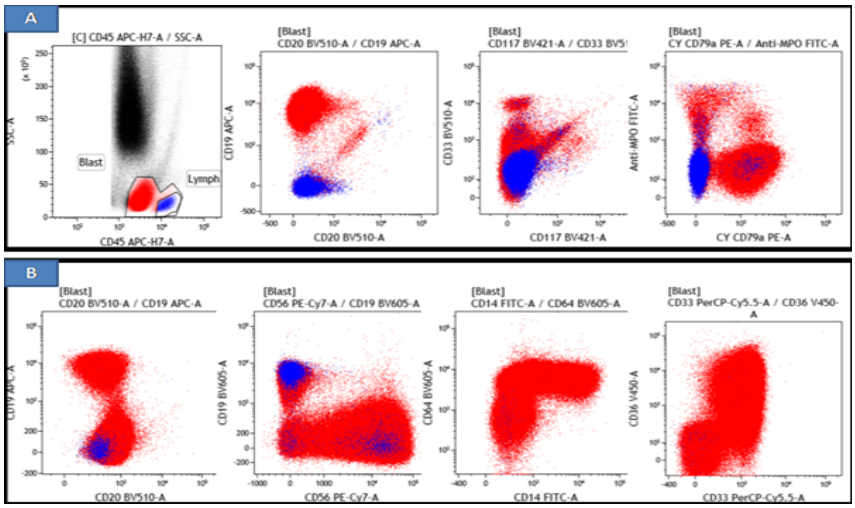
we found 2 cases of adult ALL harbouring t (4;11) transformed to AML [1, 4]. First case illustrated chemotherapy responsive MLL rearranged B-ALL who underwent allogeneic stem cell transplantation (Allo SCT) in remission after induction therapy, who transformed to AML post 100 days of Allo SCT [4]. Second case illustrated refractory MLL rearranged B-ALL adult that rapidly transformed to AML following initiation of blinatumomab therapy [1]. However there was no case found to have switched from B acute lymphoblastic leukemia to Mixed-phenotypic acute leukemia; KMT2A-rearranged .

Mechanism for lineage switch in MLL rearranged acute leukemia is not clear yet. Reports showing a strong trend of lineage switch involving B and myeloid lineages suggest that B myeloid progenitor might be involved in the mechanism of lineage switch. Studies reporting lineage switch post anti CD19 therapy; blinatumomab and CD19 chimeric antigen receptor (CAR-T), further advocates this theory [3].



In our case it is not possible to state that transformation occurred post Venetoclax therapy, as flow cytometric evaluation was not done prior to start of venetoclax therapy. Development of secondary AML as a result of therapy related process can be ruled out in view of early lineage switch (< 6 months of therapy) and consistent finding of the t (4;11) (q21;23) at diagnosis of B-ALL and transformation. The (4;11) rearrangement detected at diagnosis, and phenotypic switch suggests that the original clone harboured a bi-lineage potential. If further genetic studies including NGS or gene expression studies done at baseline could have predicted the bi lineage potential is also unclear as the case reported by Haddox C et al did not show any change in the baseline NGS and the NGS performed during relapse.

In conclusion, haematologists should be cognizant while treating MLL rearranged B -ALL adults for a lineage switch. It also underlies the importance of repeat evaluation of the disease if there is no response to standard therapy.

Declarations

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Funding information is not applicable to this study.

Conflict of Interest

All authors declare no conflict of interest to declare.

Compliance with Ethical Standards

Ethical Approval Statement: All authors stated that the study has been approved by the appropriate institutional review board and have been performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

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