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Acute Myeloid Leukemia Post Cytotoxic Therapy in Pediatric B-ALL: A Case Report

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ABSTRACT

Myeloid neoplasms post cytotoxic therapy (MN-pCT)", previously referred as therapy related AML (t-AML) is a serious complication of cytotoxic cancer treatment for various solid and some hematologic malignancies, though it's uncommon after B-cell Acute Lymphoblastic Leukemia(B-ALL) treatment. This case, involving an 11-year-old boy presenting with AML with emergence of KMT2A (MLL) gene rearrangement while on treatment for ALL, underscores the need for heightened awareness of MN-pCT in ALL survivors. The patient developed AML with monocytic differentiation 18 months after initial B-ALL treatment. The molecular investigation revealed a KMT2A (MLL) gene rearrangement at relapse, which was absent at the time of initial B-ALL diagnosis. This case emphasizes to be aware of MN-pCT development in ALL survivors and optimize monitoring and management decisions.

Keywords: Acute Lymphoblastic Leukemia; Acute Myeloid leukemia; Flow cytometry; Cytotoxic therapy; KMT2Ar

INTRODUCTION

Leukemias represent a major group of hematologic malignancies, with B-ALL being the most common childhood cancer [1,2]. While treatment outcomes have dramatically improved, late complications such as MN-pCT remain a concern. These accounts for 10-20% of new AML diagnoses and is associated with previous exposure to cytotoxic agents or radiation. Secondary AML following ALL therapy is particularly rare, with limited cases reported [3,4]. We present a unique case of AML with monocytic differentiation, emerging during maintenance therapy for B-ALL in a pediatric patient.

CASE PRESENTATION

An 11-year-old boy presented with progressive fatigue for two weeks. on examination, he was hemodynamically stable with no organomegaly or lymphadenopathy. He was diagnosed with B-cell ALL based on peripheral smear morphology (Figure 1), Immunophenotyping (CD19+, CD10+, CD34+, Tdt+, CD22+, cytoplasmic CD79a + and negative for myeloid and Tcell markers), and detection of the ETV6-RUNX1 fusion by FISH.

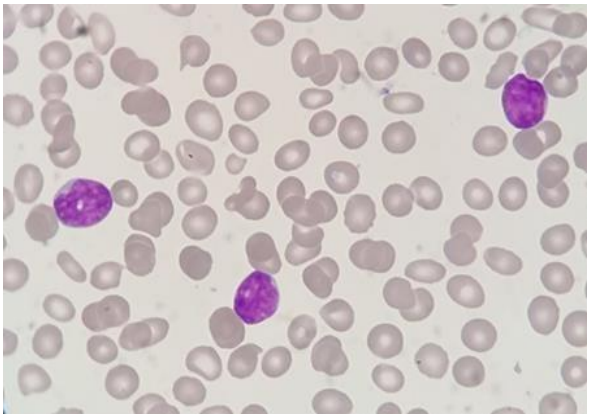
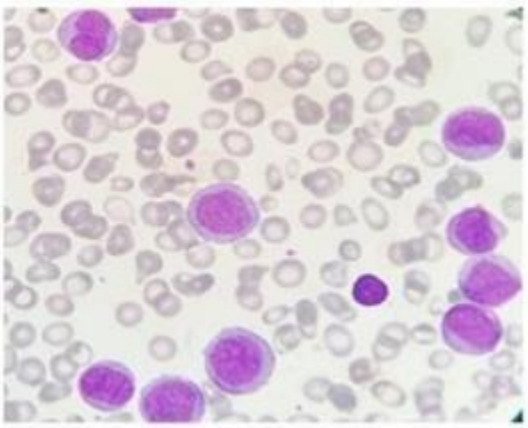


Figure 1: Peripheral smear showing 53% blasts with high N/C ratio, scanty cytoplasm, open chromatin, inconspicuous nucleoli.

He was regarded as high risk ALL (in view of his age) and treated under the COG AALL1732 protocol. Despite initial complications, including sepsis during induction, he achieved Minimal/ measurable (MRD) negativity by flow cytometry and FISH for ETV6-RUNX1 was negative, post induction. He completed consolidation and interim maintenance.

During maintenance phase III, he developed leukocytosis (WBC 16 $\times 10^{9}$/L) and monocytosis (3520 cells/ ul). A follow-up smear revealed 22% monocytic cells with immature forms. Although initially stable, he later presented with worsening leukocytosis (WBC 102×10^{9}/L) over the next 10 days, anemia, thrombocytopenia, gingival bleeding, and gum hypertrophy and 60% promonocytes on morphology (Figure 2). Flow cytometry (Figure 2) indicated a predominant population of promonocytes and immature monocytes in dim CD45 and merging onto monocytic region with a distinctive immunophenotype: CD64+, CD33+, CD11b+/−, CD14−, HLA-DR bright, and loss of CD13. A small population of CD34+, CD117+, CD13+ dim CD33, myeloid blasts was also identified.



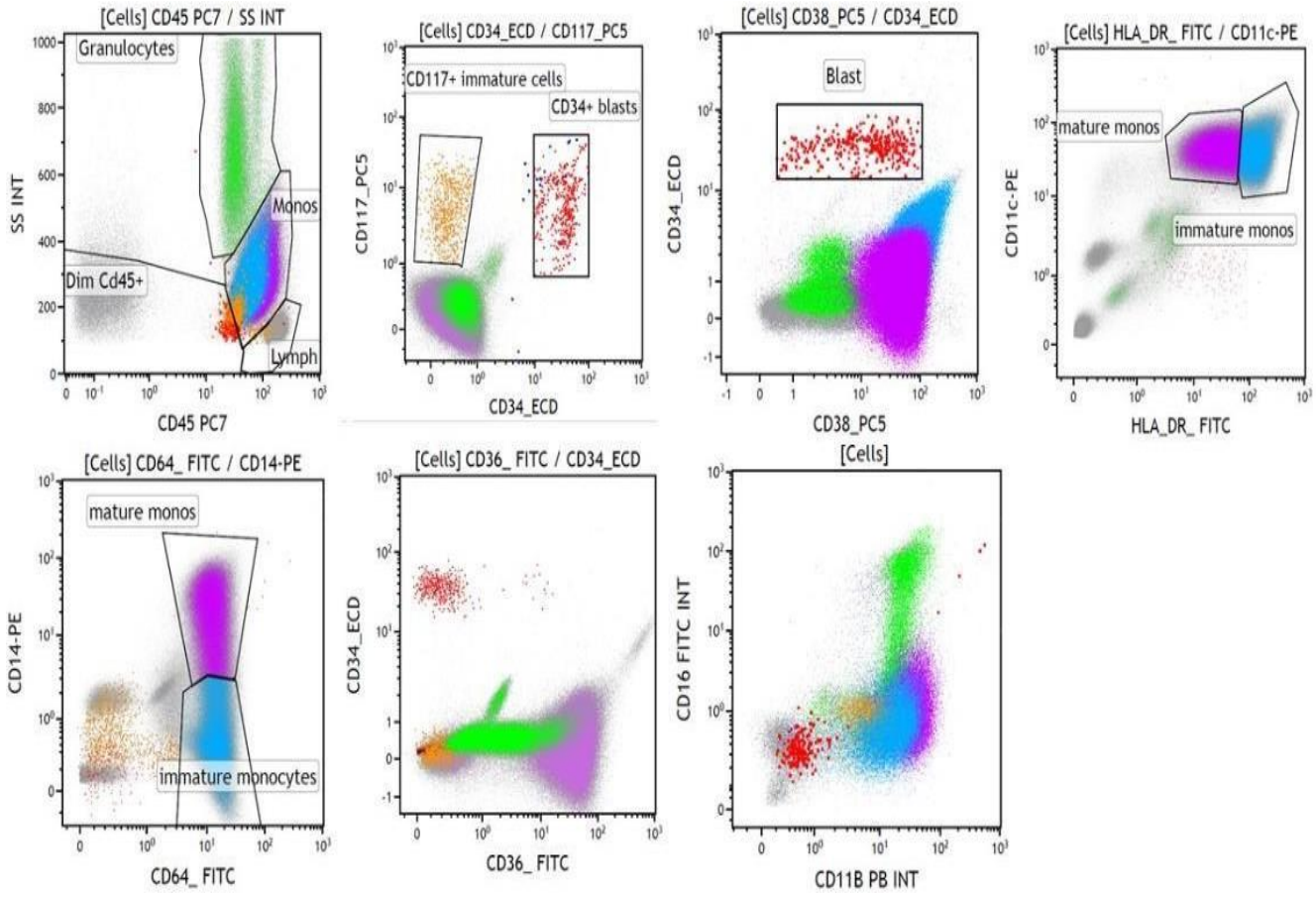


Figure 2: Peripheral smear showing 60% promonocytes on morphology and Flow cytometry showing predominance of monocytes with scant blasts, maturing towards monocytic lineage.

Bone marrow analysis revealed 81% blasts/promonocytes. Morphology and immunophenotype was consistent with AML with monocytic differentiation. FISH analysis detected KMT2A (11q23) rearrangement (KMT2Ar) not present at initial ALL diagnosis. NGS performed at this time, revealed a TP53 mutation (p.Arg196Gln, VAF 8%). The patient deteriorated rapidly and succumbed to the disease within one month of diagnosis.

The following table (Table 1) summarizes the Morphology, Immunophenotyping and Genetics findings at initial diagnosis, Follow up and at relapse.

Table 1: The morphology, immunophenotype and genetic findings at initial diagnosis, follow up and relapse.

Clinical data	Initial Diagnosis	Follow up	Relapse
Bone marrow blast count	90% lymphoblasts	Less than 2% blasts/hematogones	81% blasts/Promonocytes
Flow cytometry	Blasts negative for CD45. The blasts expressed CD34 and Tdt, CD19(moderate -bright), CD10 (bright), surface CD22, CD38 (moderate) cytoplasmic CD79a and partial cytoplasmic CD22.	MRD undetectable (<0.01%)	Small population of blasts in dim CD45 merging onto monocytic region. CD33 (bright), Overexpressed HLA-DR, CD36, aberrant under expression of CD11c, CD11b, CD64, CD38, CD4
			(aberrant dim – negative) and CD13 (aberrant dim to negative) and while it was negative for CD14, MPO, CD34. Along with A small population of CD34+, CD117+, CD13+ dim CD33 myeloid blasts.
Cytogenetics	Baseline cytogenetics normal	Not done	Not done
FISH	FISH analysis targeting CDKN2A(P16), BCR/ABL1, KMT2A(MLL), TCF3, pericentromeric region of chromosomes 4,10,17 was normal in all nuclei examined, however showed ETV6-RUNX1 fusion.	FISH analysis targeting KMT2A(MLL) CDKN2A(P16), BCR/ABL1, ETV6/RUNX1, TCF3, pericentromeric region of chromosomes 4,10,17 was normal in all nuclei examined.	FISH analysis showed KMT2A(MLL)gene rearrangement, nuc ish 11q23.
			FISH analysis targeting CDKN2A(P16), BCR/ABL1, TCF3, pericentromeric region of chromosomes 4,10,17 was normal in all nuclei examined. NGS showed TP53(VAF 8%) and KRAS
Lumbar puncture	No blasts	No blasts	Not done
Final Diagnosis	B-ALL	MRD undetected in B-ALL	AML with Monocytic differentiation

DISCUSSION

Myeloid neoplasms post cytotoxic therapy (MN-pCT)" typically arises after chemotherapy or radiotherapy for various solid malignancies. MN – pCT following ALL is rare, especially in pediatric patients [5]. Our case represents a unique instance of AML with monocytic differentiation arising during maintenance therapy for B-ALL, supported by emergence of KMT2A rearrangement.

Mn-pCT is categorized as 2 types first occurring secondary to alkylating agents and radiation (long latency, unbalanced karyotypes), and other associated with topoisomerase II (TOP 2) inhibitors (shorter latency, balanced translocations such as KMT2A). Our patient received doxorubicin and daunorubicin, intercalating agents, both of which target TOP2 and are known to induce KMT2A rearrangements through DNA cleavage and faulty repair mechanisms [4,6-8].

Most frequent primary malignancy in case of MN-pCT is breast cancer followed by Non-Hodgkin's lymphoma [5]. As per a review of primary malignancies in t-AML by Kayser et al showed hematologic malignancies were noted in 55 of 179 (27.5%) of their patients. ALL was noted in just 2 of 179 patients [4]. Our patient had MN-pCT while on treatment for ALL. These usually occur after 2-5 yrs. of therapy of de novo ALL [4] as in our patient, it occurred 18 months later. Wong et al reported cytogenetics evaluation of their t-AML cases as 23% had MLL rearrangements like in our case, 23% had complex cytogenetics, and 36% normal cytogenetics [9].Kayser et al also revealed that treatment with the intercalating agents was significantly associated with the induction of cytogenetic abnormalities, particularly MLL gene rearrangement [4] like noted in our patient. The presence of the KMT2A rearrangement in AML, and its absence in the initial B-ALL, strongly suggests the AML developed because of treatment. The KMT2A rearrangement in the AML could be a result of such treatment-induced mutations

It is to be noted that a majority of reported KMT2Ar leukemias exhibit myelomonocytic or monocytic immunophenotype, at relapse. Our patient showed blasts with monocytic differentiation [6,10].

NGS is not always part of the standard diagnostic workup in pediatric B-ALL and therefore, was not performed at the time of diagnosis for our patient. NGS performed at relapse showed TP53 mutation (VAF 8%). AML with TP53 mutation requires the presence of a somatic TP53 mutation with a variant-allele frequency [VAF] of >10% [8], however our patient had VAF <10%. Wong et al and Ok et al showed, although TP53 mutation is more frequently found in t-AML as compared to de novo AML however mutation burden may not be different, suggesting presence of TP53 alone cannot lead to development of t-AML. This led to the conclusion that chemotherapy does not directly induce TP53 mutations [9,11]. The identification of TP53 mutation in our patient, at the development of AML, could suggest possible clonal selection present from before or emergence of a pre-existing treatment-resistant clone. However, the presence of KMT2Ar is of high significance [8] and hence this case is better categorized AML with KMT2A rearrangement post cytotoxic therapy.

Not much is known about interplay of TP53 mutation and KMT2A rearrangement [8] Jeevitha et al showed TP53 mutations are associated with de novo resistance to revumenib [12]. Revumenib and other menin inhibitors have shown promising activity against AMLs with KMT2A-rearrangements. Presence of TP53 mutations in patients with KMT2A rearrangements can impact treatment decisions.

Patients with MN-pCT usually harbor a poor prognosis [3] as was noted in our patient that he worsened and succumbed within a months' time from this diagnosis.

CONCLUSION

This case highlights a rare but clinically significant complication of ALL therapy. AML with monocytic differentiation can develop post treatment for ALL. Addition of Myeloid markers while doing flow cytometric MRD studies for ALL may assist in detecting these cases early as they are emerging. Prompt diagnosis and treatment are essential for improving outcomes in MN-pCT.

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