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LINEAGE SWITCH OF ADULT B-CELL ACUTE LYMPHOBLASTIC LEUKAEMIA TO ACUTE MYELOID LEUKAEMIA FOLLOWING B-CELL-DIRECTED THERAPY

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ABSTRACT

Background: Blinatumomab and inotuzumab ozogamicin (InO) are B-cell targeted agents used in the frontline and relapsed/refractory treatment of B-cell acute lymphoblastic leukaemia (B-ALL). Blinatumomab, a bispecific T-cell engager that targets CD19 and CD3, and InO, an antibody-drug conjugate targeting CD22, have both shown efficacy. However, recent reports have noted lineage conversion as a complication when these agents are used individually or sequentially. We present a rare case of this phenomenon in a 79-year-old male patient.

Case description: A 79-year-old male with refractory B-ALL underwent a lineage switch to acute myeloid leukaemia following treatment with blinatumomab and InO. The patient initially achieved remission after initial therapy but relapsed and was subsequently treated with blinatumomab. Due to adverse effects, the treatment was discontinued. He was then treated with InO but again relapsed. A subsequent bone marrow biopsy revealed morphologic evidence of residual B-ALL, but with the presence of acute monocytic leukaemia. Fluorescence in situ hybridisation (FISH) analysis demonstrated an additional copy of KMT2A in a large percentage of cells which was a feature present since the initial diagnosis. Unfortunately, the patient's condition deteriorated, and he died.

Conclusion: This case underscores potential complication of lineage switch following treatment with B-cell directed therapies. Although such therapies have improved outcomes in B-cell malignancies, clinicians should remain aware of rare risks such as lineage transformation. Timely recognition is essential to guide appropriate clinical management.

KEYWORDS

Leukaemia, antibodies, bispecific

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LEARNING POINTS

- Lineage switch is a rare complication observed after B-cell targeted therapies; however, evidence remains limited.
- Specific genetic alterations, such as KMT2A abnormalities, may predispose leukemic clones to lineage plasticity.
- Close monitoring for immunophenotypic evolution is essential for timely recognition and clinical management of lineage switch.

INTRODUCTION

Bispecific T-cell engagers have represented a dramatic change in treatment outcomes for many different types of haematologic malignancies in the refractory setting[1]. For instance, blinatumomab is commonly used to treat relapsed/refractory B-cell acute lymphoblastic leukaemia (B-ALL) and measurable residual disease (MRD)-positive B-ALL, more recently incorporated as part of the consolidation treatment in the frontline setting for patients with MRD-negative B-ALL after initial complete response[2]. It specifically attaches to both CD3 and CD19, molecules highly expressed in both T cells and B-cell precursor leukemic cells respectively. This medication has been demonstrated to be highly effective, but relapse remains an issue for a considerable subset of patients receiving this therapy, in addition to medication-related systemic toxicities[3].

Lineage switch following CD19-targeted therapies has also emerged as a concern in the treatment of B-ALL. This phenomenon is particularly notable in the context of recent advances in immunotherapy and targeted-based treatments[3]. Some chromosomal aberrations associated with lineage switch in adult acute leukaemia include t(4;11)(q21;q23) and rearrangement with KMT2A/AFF1 fusion protein[3]. Previous studies suggest that approximately 20% of patients that have relapsed post-blinatumomab treatment in the paediatric population are characterised by loss of CD19 antigen from leukemic cells. A subset of those CD19 negative patients have been found to have acquisition of myeloid distinctive antigens; however, mechanisms are still unknown[3]. Highlighting the clinical implications of this, we present the case of an adult patient with refractory B-ALL with an additional KMT2A chromosome copy who transformed to acute myeloid leukaemia following therapy with blinatumomab and inotuzumab ozogamicin (InO).

CASE DESCRIPTION

A 79-year-old male presented for evaluation of anaemia and leukopenia on complete blood count. He reported increased fatigue, weight loss and weakness for the previous few weeks. A peripheral blood smear review demonstrated 29% blasts with flow cytometric analysis showing blast positivity for CD19, CD10, CD22, TdT, CD45 (dim), CD79A, CD20 (spectrum), CD34 (subset) and negativity for myeloperoxidase and T-cell associated antigens. This was consistent with B-ALL *(Fig. 1)*. Subsequent bone marrow biopsy confirmed the diagnosis with 78% blasts on an aspirate smear review. Cytogenetics showed an abnormal karyotype including 58–61,XX,i(Y)(q10),+1,+1,+6,+6,+8,+10,+11,+14,+18,+19,+19,+21,+21, +mar[cp20], most consistent with a high hyper diploid B-ALL. Fluorescence in situ hybridisation (FISH) analysis revealed an extra copy of the KMT2A gene region (due to the extra copy of chromosome 11), but no rearrangement of KMT2A.

Due to advanced age and comorbidities, the patient was treated with low intensity chemotherapy based on the EWALL protocol[4], achieving complete remission at the end of induction. He then proceeded to consolidation without consideration of allogeneic transplantation. The patient finished his two cycles of consolidation therapy with evidence of morphologic remission. Bone marrow biopsy was performed six months after diagnosis with no evidence of leukaemia. The patient later transitioned to maintenance therapy, receiving three cycles of 6-mercaptopurine and vincristine.

Nine months after initial diagnosis, a peripheral blood smear review and flow cytometric analysis demonstrated 16% B lymphoblasts present, consistent with residual or recurrent B-ALL with blasts comprising 16% of analysed events and expressing CD19, CD10, CD20 (variable), CD22,

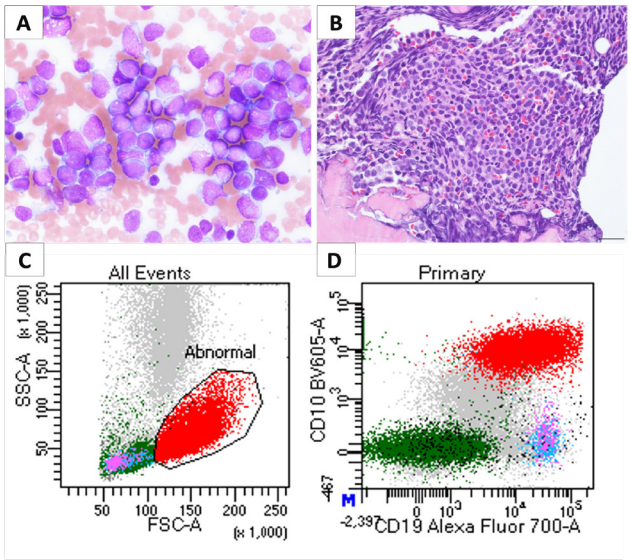


Figure 1. A) Bone marrow aspirate demonstrating medium-sized blasts with high nuclear to cytoplasmic ratio, fine dispersed chromatin and occasional prominent nucleoli (40×). B) Bone marrow core biopsy demonstrating hypercellularity with sheets of blasts (20×). C) Peripheral blood flow cytometry showing abnormal population of B lymphoblasts (25% of cells). D) Peripheral blood flow cytometry showing CD19 and CD10 positivity for B lymphoblasts.

CD33 (subset dim), and CD45 (dim), and lack of CD34. The patient was then trialled on a second-line treatment with blinatumomab. During his hospitalisation for his first cycle of blinatumomab, he experienced two episodes of grade 2 cytokine release syndrome. Both episodes were managed successfully with systemic corticosteroids. The patient and the family requested that the treatment be changed as he was concerned about the side effects. The therapy was eventually discontinued after discharge and he was offered treatment with InO, which he started five days after day eight of cycle one of blinatumomab. He completed three cycles with good tolerance to the treatment. Over the next few months, repeat bone marrow evaluations demonstrated continued residual involvement by B-ALL. However, the immunophenotype of the tumour cells had been evolving, with blasts positive for CD19, CD22, CD10, CD33 (dim) and CD45 (dim), negative for CD13, and with a notable loss of the previously expressed CD34 and CD20.

Twelve months after the initial diagnosis, a bone marrow biopsy revealed residual disease with hypocellular marrow and increased reticulin fibrosis (MF 2-3). It was decided to continue the patient on InO due to improvement in the blast counts.

Fifteen months after the initial presentation, the patient was hospitalised due to progressive elevation of liver enzymes, which was suspected to be related to InO therapy; at that moment, the patient had finished his fourth cycle. On admission, he met sepsis criteria suspected to be secondary to an intra-abdominal source. The patient was started on broad-spectrum antibiotics with piperacillin/tazobactam.

A peripheral smear review and flow cytometric analysis demonstrated increased blast equivalents (26%), suspicious for a high-grade myelomonocytic neoplasm. Flow cytometry demonstrated the vast majority of the abnormal myelomonocytic population to be positive for CD36, CD64, CD15, CD45 (dim) and HLA-DR, and negative for CD14 and CD13, consistent with acute monocytic leukaemia (AML-5). In addition, a minute population of B lymphoblasts was also identified at 0.3% of total events. The small population of B lymphoblasts were positive for CD22, CD10, CD33 (dim), CD45 (dim), negative for CD34 and CD13, and a notable loss of CD19, possibly due to blinatumomab therapy.

Subsequent bone marrow evaluation confirmed the presence of a newly diagnosed AML *(Fig. 2 and Fig. 3)*, with 70% monoblastic and monocytic-appearing blasts on touch preparation evaluation, with no morphologic evidence of residual B-ALL. Concurrent FISH analysis demonstrated an additional copy of KMT2A in 23.5% of the nuclei examined. Concurrent karyotype analysis demonstrated an abnormal complex chromosomal complement including 59–61,XY,+X,+Y,+1,del(1)(q12),dup(1)(q24q44),+5,del(5)(q15q33),+6,add(6)(q21),add(6)(q21),del(6)(p22),+8,+10,add(10)(q26),+11,add(11)(p10),+14,+18,-18,add(18)(q21),+19,+21,+21,add(21)(p10),+1–4mar[cp15].

The patient's previous karyotype provides the basis for this current karyotype with gains of multiple chromosomes (1, 6, 8, 10, 11, 14, 18, 19 and 21). There were now numerous additional structural abnormalities, including a deletion of the long arm of chromosome 5, which is usually associated with myeloid disorders, including AML. Lastly, next generation sequencing demonstrated a TP53 mutation (p.C238_S240del) at 60.2% variant allele frequency. This mutational location is in the DNA-binding domain of the TP53 gene and is therefore likely to be a functionally deleterious mutation. Myeloid neoplasm post cytotoxic therapy was not contemplated based on latency period. See *Table 1* for details regarding clonal evolution.

Unfortunately, the patient developed worsening acute liver failure requiring a transfusion of cryoprecipitates. He then had a cardiorespiratory arrest and expired after unsuccessful resuscitative efforts.

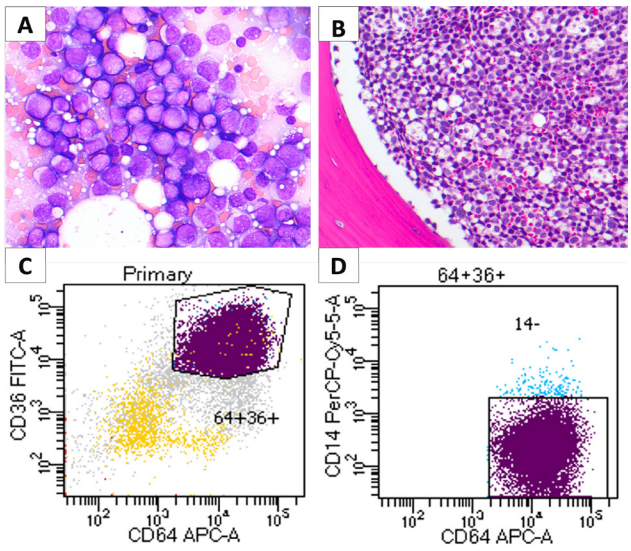


Figure 2. A) Bone marrow aspirate demonstrating large-sized blasts with high nuclear to cytoplasmic ratio, prominent nucleoli and azurophilic intra-cytoplasmic granules (40×). B) Bone marrow core biopsy demonstrating hypercellularity with sheets of blasts (20×). C) Peripheral blood flow cytometry showing an abnormal population of monocytes which express CD64 and CD36 (59% of cells). D) Peripheral blood flow cytometry showing an abnormal loss of CD14 in the monocyte population.

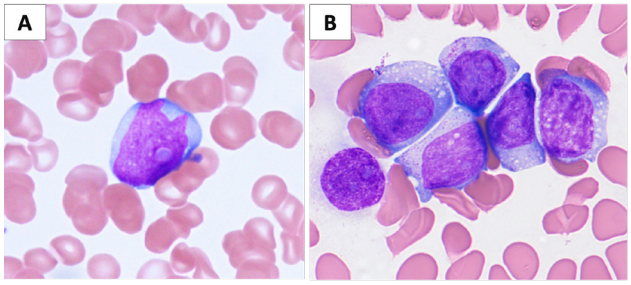


Figure 3. A) Peripheral blood smear at the time of original diagnosis of B-ALL demonstrating a medium to large-sized B-lymphoblast with high nuclear to chromatin ratio, irregular nuclear contours and prominent nucleoli (40×). B) Peripheral blood smear at the time of diagnosis of AML demonstrating multiple large-sized blasts with moderate amounts of pale blue cytoplasm, prominent nucleoli, small azurophilic intra-cytoplasmic granules and vacuolated cytoplasm (40×).

Time from diagnosis (months)	Clonal characteristics of the acute leukaemia based on testing
0 months	Flow cytometry: blast positivity for CD19, CD10, CD22, TdT, CD45 (dim), CD79A, CD20 (spectrum), CD34 (subset) and negativity for myeloperoxidase and T-cell associated antigens.
	FISH analysis: extra copy of the KMT2A gene region, with no rearrangement.
	Karyotypic analysis: abnormal karyotype including 58–61,XX,i(Y)(q10),+1,+1,+6,+6,+8,+10,+11,+14,+18,+19,+19,+21,+21, +mar[cp20].
EWALL protocol (induction) **EWALL protocol (consolidation)**	
6 months	Negative MRD per flow cytometric analysis on bone marrow biopsy.
Maintenance therapy (6-MP + vincristine – 3 cycles)	
9 months	Flow cytometry: blasts comprising 16% of analysed events and expressing CD19, CD10, CD20 (variable), CD22, CD33 (subset dim), CD45 (dim), and lack of CD34.
Blinatumomab (1 cycle) **InO (3 cycles)**	
12 months	Flow cytometry: blast positivity for CD19, CD22, CD10, CD33 (dim), and CD45 (dim), negative for CD13; and with a notable loss of the previously expressed CD34 and CD20.
InO (4th cycle)	
15 months	Flow cytometry: Abnormal myelomonocytic population positive for CD36, CD64, CD15, CD45 (dim) and HLA-DR, and negative for CD14 and CD13. An abnormal small population of B lymphoblasts were positive for CD22, CD10, CD33 (dim), CD45 (dim), negative for CD34 and CD13, and a notable loss of CD19.
	FISH analysis: This demonstrated an additional copy of KMT2A in 23.5% of the nuclei examined.
	NGS: TP53 mutation (p.C238_S240del) at 60.2% variant allele frequency.
	Karyotypic analysis: abnormal complex chromosomal complement including 59–61,XY,+X,+Y,+1,del(1)(q12),dup(1)(q24q44),+5,del(5)(q15q33), +6,add(6)(q21),add(6)(q21),del(6)(p22),+8,+10, add(10)(q26),+11,add(11)(p10),+14,+18,-18, add(18)(q21),+19,+21,+21,add(21)(p10),+1-4mar[cp15]. Deletion of the long arm of chromosome 5.

Abbreviations: 6-MP, 6-mercaptopurine; EWALL, European working group on adult ALL protocol, low intensity cytotoxic chemotherapy for B-ALL; InO, inotuzumab ozogamicin; MRD, measurable residual disease; NGS, next generation sequencing.

Table 1. Chronologic description of the patient's B-ALL clonal evolution.

DISCUSSION

Lineage switch in acute leukaemia is a rare and unique phenomenon that can occur in adult patients and is associated with very poor outcomes[3,5]. This event is characterised by the transformation of acute lymphoid leukaemia to acute myeloid leukaemia or vice versa. The mechanisms behind lineage switch in B-ALL remain unclear, although several hypotheses have been proposed to explain this phenomenon. The KMT2A rearrangement has been documented as a chromosomal abnormality present in B-ALL patients with the potential for lineage switch[6,7]. This is a rare complication of B-cell directed therapy with a poor outcome, highlighting an urgent need for additional research to understand the potential mechanism and future targets for novel therapies. We present a case of a 79-year-old male who underwent a lineage switch following therapy with B-cell targeted therapy.

Leukaemia that switch their lineage of origin during therapy or show poorly differentiated or undifferentiated features have been noted in experimental studies to have an early common progenitor that can differentiate along both the lymphoid and myeloid lineages[8]. Some hypotheses propose that chemotherapy might suppress or eradicate the leukemic clone apparent at diagnosis, allowing for the expansion of a subclone with a different immunophenotype[7]. A lineage switch may represent either the emergence of a new leukemic clone with high plasticity attributes, or a relapse of the original clone with heterogeneity at the morphological level[8].

Interestingly, previously published cases documenting this phenomenon have often been in cases with KMT2A rearrangements and increasingly in patients who received CD19-directed therapies such as blinatumomab[9]. Despite this well-documented association and BCR-ABL1, additional data on genetic and molecular basis remains scant[10]. While there is not a rearrangement of KMT2A in this case, the

patient did have an extra copy of KMT2A, and he received blinatumomab and InO therapy. To this date, only one additional case has been published documenting lineage switch in patients with mixed lineage leukaemia gene amplification[11].

InO is an anti-CD22 monoclonal antibody-drug conjugate that is used for patients with relapsed/refractory B-ALL. Some studies suggest better outcomes with sequential therapy using both blinatumomab and InO for the treatment of relapsed/refractory B-ALL[12]. The effects of increasing the risk of lineage switch while using these immunotherapies sequentially remain unclear. However, there are known case reports of this event, occurring after sequential therapy[5]. In our patient, InO was started as a salvage therapy as he did not tolerate blinatumomab; he received both immunotherapies sequentially.

It is possible that the selection pressure of multiple rounds of B-ALL-directed chemotherapy and targeted agents eradicated the bulk of the patient's initial leukemic burden. However, precursor leukemic cells harbouring the extra KMT2A gene could theoretically possess lineage plasticity[13]. Another possible consideration in this case is morphologic remission of the original B-ALL with the development of a new therapy-related AML. While evidence of a TP53 mutation was not evaluated at the time of the original diagnosis of acute lymphoblastic leukaemia, its presence could indicate a de novo therapy-related AML. However, this possibility is less likely based on the timeline and that both the initial B-ALL and later AML were clonally related. Mutations of TP53 are generally associated with aggressive, malignant neoplasms, which could favour plasticity and ultimately lineage switch[14]. Although TP53 mutations have been described as the most frequent mutations in lineage switch patients in some cohorts, their frequency does not appear to exceed that of the general leukaemia of the same lineage, casting doubt regarding the relative importance of TP53 for lineage switch[14]. More research is needed to describe the complete genetic landscape and pathophysiological mechanisms driving lineage switch.

In our case, CD19 expression was lost after receiving treatment with directed therapy. Although less frequent than in CAR T-cell therapy, CD19 antigen loss after anti-CD19 directed treatment may arise through various mechanisms. These include splice variants, mutations that produce truncated or misfolded CD19, and expansion of CD19-negative subclones. Notably, few of these molecular alterations are detected in baseline samples, suggesting that CD19 loss may emerge de novo under selective therapeutic pressure[15]. In this context, sequential administration of blinatumomab and InO may exert dual antigenic pressure on leukemic cells, potentially driving antigen loss or lineage switch. Although direct evidence remains limited, growing reports document CD19 or CD22 downregulation following targeted therapies, suggesting that serial exposure to both agents may contribute to clonal escape and phenotypic evolution[15]. Further longitudinal analyses are needed to clarify whether dual-antigen pressure indeed promotes lineage switching.

CONCLUSION

Lineage switch in acute leukaemia is a unique phenomenon that are increasingly described since the introduction of targeted immunotherapies. Our case demonstrates a lineage switch from B-ALL to AML in a patient with an extra copy of KMT2A following therapy with blinatumomab and InO. The sequential use of targeted immunotherapies in the relapse setting raises concerns regarding potential risks for lineage switch. Education and close monitoring are critical to identification of this rare complication.

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