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Case Report

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Myeloid Sarcoma as a Manifestation of Lineage Switch from B-cell Acute Lymphoblastic Leukemia after Double Allogeneic Stem Cell Transplantation: A Case Report

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ABSTRACT

Phenotypic conversion between lymphoid and myeloid leukemic lineages is infrequent and generally associated with an unfavorable clinical prognosis. Most reported cases involve relapse of B-cell acute lymphoblastic leukemia (B-ALL) presenting as acute myeloid leukemia (AML). The development of extramedullary disease as myeloid sarcoma after lineage switch, particularly following sequential allogeneic hematopoietic stem cell transplantation (allo-HSCT), is exceedingly rare. A 36-year-old woman with Philadelphia chromosome-positive B-ALL achieved remission after chemotherapy and tyrosine kinase inhibitor-based therapy, but relapsed and underwent two consecutive allo-HSCTs from different donors. Eighteen months after the second transplantation, while in complete remission, she presented with localized knee pain. Imaging and histopathological evaluation confirmed myeloid sarcoma, and bone marrow analysis demonstrated AML, indicating a lineage switch. Treatment with local radiotherapy followed by venetoclax and azacitidine resulted in remission. This case highlights the importance of considering lineage switch in patients with atypical relapse patterns or isolated extramedullary lesions after allo-HSCT.

Keywords: Lineage switch, acute lymphoblastic leukemia, acute myeloid leukemia, myeloid sarcoma, allogeneic stem cell transplantation, extramedullary relapse

Introduction

Regulation of hematopoietic clones is fundamentally important for both normal and malignant hematopoiesis. Transitions between lymphoid and myeloid lineages in leukemia are rare and typically associated with poor clinical outcomes. Most lineage-switching cases involve a transition between acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML). In addition, leukemic lineage switching is more commonly observed in infants and young patients with epigenetic and transcriptional regulatory lysine methyltransferase 2A (*KMT2A*; formerly *MLL1*) gene rearrangements [1].

Granulocytic sarcoma is a localized tumor mass composed of immature cells of the granulocytic lineage. Synonyms used for this disease include myeloblastoma, myelosarcoma, chloroma, or extramedullary myeloid tumor [2]. Granulocytic sarcoma may appear in isolation or may occur during the course of AML, chronic myeloid leukemia, myelodysplastic syndromes, or myeloproliferative disorders [3]. Granulocytic sarcoma, a rare entity in leukemia, is most frequently reported in AML; it is much rarer in T-cell or B-cell ALL [4,5]. The most common locations include the skin, soft tissues, bone, periosteum, and lymph nodes [5,6]. In this case report, we present a patient who developed AML with myeloid sarcoma while in remission following treatment for ALL.

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Case Report

A 36-year-old woman with no comorbidities presented to the emergency department with diffuse muscle pain. A complete blood count revealed white blood cell 199.5×10^3/µL, neutrophils 100.74×10^3/µL, monocytes 51.81×10^3/µL, hemoglobin 10^9 g/dL, and platelets 407×10^3/µL. Due to symptomatic hyperleukocytosis, urgent leukapheresis was performed. Bone marrow examination showed 38% lymphoid blasts with a TdT^+, $CD34^+$, $HLA\text{-}DR^+$, $CD19^+$, $CD79a^+$ phenotype; pathology confirmed B-lymphoblastic leukemia/lymphoma (B-ALL/LBL), $CALLA^+$, World Health Organization 2017. Cytogenetic work-up at diagnosis demonstrated t(9;22)(q34;q11.2) *BCR-ABL1* positivity, while fluorescence *in situ* hybridization and polymerase chain reaction, corroborated the presence of the Philadelphia chromosome, and no additional abnormalities were identified. The patient received two cycles of Hype-cyclophosphamide, vincristine, adriamycin (doxorubicin), dexamethasone; however, a relapse occurred, and salvage therapy with dasatinib plus fludarabine, cytarabine, granulocyte colony-stimulating factor (FLAG) achieved a second remission. Cytogenetics at relapse again demonstrated *BCR-ABL1* positivity, supporting clonal continuity between the first and second leukemic episodes. She underwent allogeneic hematopoietic stem cell transplantation (allo-HSCT) from her HLA-matched sister, and early post-transplant chimerism studies showed >98% donor chimerism. In the 4th month, she developed a coronavirus disease-2019 infection, and a relapse of B-ALL was subsequently confirmed. A further remission was obtained with dasatinib plus FLAG followed by dasatinib, vincristine, and dexamethasone consolidation; eight months after the first transplant, she underwent a second allo-HSCT from a 9/10 TÜRKÖK donor. Post-transplant follow-up revealed steroid-responsive, grade II, cutaneous graft-versus-host disease (GVHD).

Eighteen months after the second transplant, the patient developed left knee pain; ultrasound demonstrated a 3-cm soft-tissue mass with tibial tuberosity erosion. Fine-needle aspiration showed a myeloid sarcoma that was immunohistochemically positive for HLA-DR, CD117, CD13, and focally for myeloperoxidase (MPO), and negative for TdT, CD20, and CD5. Bone marrow flow cytometry revealed 21.4% myeloid blasts expressing MPO, HLA-DR, CD34, CD13, CD33, and CD117. At the time AML was diagnosed, post-transplant chimerism analysis demonstrated 85% donor chimerism, consistent with mixed chimerism. Cytogenetic and molecular reassessment at this stage demonstrated continued *BCR-ABL1* positivity and a newly acquired trisomy 8 abnormality, which had not been present in the initial B-ALL sample. The persistence of *BCR-ABL1*, together with the emergence of trisomy 8, indicates clonal evolution of the original leukemic clone, supporting a lineage switch rather than a *de novo* or therapy-related AML. Intensive AML induction chemotherapy was not preferred because the patient had undergone two allo-HSCTs, had steroid-treated GVHD, had a reduced performance status, and had a high risk of treatment-related mortality. Therefore, treatment with azacitidine plus venetoclax was initiated as a more appropriate and better-tolerated option. The patient also received 39 Gy of local radiotherapy to the myeloid sarcoma site. She has completed three cycles of azacitidine and venetoclax and remains in remission at the most recent evaluation. Written informed consent was obtained from the patient for the publication of this case report and the use of all related clinical data and images.

Discussion

Approximately 50% of adult ALL cases relapse after the first remission [7]. Relapsed disease is most often characterized by preservation of the original immunophenotypic and cytogenetic features, with occasional acquisition of secondary abnormalities indicative of clonal evolution. However, transformation from ALL to AML is rare. *Lineage switching* is defined as the transition of leukemia diagnosed in one lineage (lymphoid/myeloid) to the other at relapse. This phenomenon is characterized by the loss of markers specific to one lineage and the acquisition of markers specific to another lineage. In most reported lineage-switch cases, patients with B-ALL/LBL relapse with AML [8].

The biological basis of lineage switching has not been fully elucidated, and multiple explanatory mechanisms have been proposed [9-11]. A proposed explanation for lineage switching involves a common progenitor cell capable of divergent differentiation, with selective therapeutic pressure enabling leukemic stem cells to adopt an alternative lineage fate. Additional hypotheses include dedifferentiation and transdifferentiation.

Fujisaki et al. [10] transplanted myeloid cells obtained from a case of T-ALL that exhibited lineage switching into severe combined immunodeficiency mice.

The differential leukemic phenotypes observed under cytokine-free versus Granulocyte-Macrophage Colony-Stimulating Factor-supplemented conditions indicate that leukemic stem cell differentiation is highly dependent on the microenvironment.

A case report by Kishore et al. [12] described a lineage-switching event similar to ours: a 10-year-old child diagnosed with ALL who—four years later during relapse—was found to have AML.

Another case report by Ruiz-Delgado et al. [13] presented a 60-year-old adult who experienced lineage switching from ALL to AML.

In a case series published by Zhou et al. [14], lineage switching from ALL to AML occurred in 28 patients, and from AML to ALL in 4 patients.

Lineage switching is extremely rare. This case represents a lineage-switching event in which a patient initially diagnosed with ALL later relapsed with AML.

Conclusion

This case illustrates an exceptionally rare example of lineage switching from B-ALL to AML accompanied by extramedullullary

myeloid sarcoma following sequential allogeneic stem cell transplantation. The occurrence of myeloid sarcoma as the initial manifestation of relapse underscores the biological complexity and plasticity of leukemic stem cells. Clinicians should maintain a high index of suspicion for lineage switch in patients with atypical relapse patterns, particularly in the presence of isolated extramedullary lesions. Comprehensive immunophenotypic and histopathological evaluation is essential for accurate diagnosis and timely initiation of appropriate therapy. Increased awareness of this phenomenon may facilitate earlier detection and improve clinical decision-making in similarly complex cases.

Ethics

Informed Consent: Written informed consent was obtained from the patient for the publication of this case report and the use of all related clinical data and images.

Footnotes

Authorship Contributions

Concept: R.Ş., Design: R.Ş., Data Collection or Processing: R.Ş., Analysis or Interpretation: S.K., Literature Search: R.Ş., Writing: R.Ş., S.K., K.E., Y.K.

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