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Lineage Switching from Acute Myeloid Leukemia associated with Systemic Mastocytosis to B-Acute Lymphoblastic Leukemia: A Diagnostic Dilemma

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Abstract

Relapse of acute leukemia is defined as the reappearance of more than 5% blasts in the bone marrow. In most instances, blast expresses the specific lineage (myeloid or lymphoid), similar to a diagnosis. However, it rarely converts to a different lineage, either myeloid shifting to lymphoid or vice versa, during relapse. Thus, it is labelled as switching lineage acute leukemia, after excluding the criteria for mixed phenotypic acute leukemia, which can be a challenge to diagnose. We describe a 24-year-old gentleman with a known case of acute myeloid leukemia associated with systemic mastocytosis (SM); eight months later, and after two complete cycles of chemotherapy, relapse occurred with a switched lineage to B-acute lymphoblastic leukemia. The laboratory investigation approaches and the challenges in the diagnosis are also discussed in this case report.

Keywords: Lineage-switching, B-acute lymphoblastic leukemia, acute myeloid leukemia, systemic mastocytosis

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INTRODUCTION

Acute leukemia is categorized as acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), and mixed phenotype acute leukemia (MPAL). AML is defined as a clonal proliferation of immature myeloid precursors or myeloblasts, with varying stages of myeloid differentiation. Based on the WHO's recent classification, ALL is derived from B- and T-lineage lymphoid precursors [1]. Systemic mastocytosis (SM) is a clonal neoplastic proliferation of mast cells (MC). SM associated with acute myeloid leukemia (SM-AML) is extremely rare.

The incidence of relapse AML is wide in range at 9–78% because of the heterogeneity of the treatment received across the world. The median relapse rate for studies with ≤ 24-month follow-up and > 24-month follow-up time has been reported as 32% and 42%, respectively [2]. Switch lineage acute leukemia occurs when acute leukemia transforms to a different lineage at relapse compared to the initial diagnosis. Lineage-switch ALs arise from a common pre-leukemic or leukemic clone and share a founder mutation, most often a rearrangement of mixed lineage leukemia (MLL) at 11q23. The most frequently reported are ALL switches to AML [3]. Lineage switching of B-ALL from AML is rarely reported. Therefore, to solve the diagnostic dilemma for our case, a

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thorough laboratory investigation and extensive literature search were performed, and we also considered other possible diagnoses in this patient.

Case Report

A 24-year-old male had been diagnosed with AML monocytic lineage for eight months previously. He initially presented with prolonged fever for 12 days, associated with loss of appetite and weight. His mother had a history of uterine carcinoma. Examination revealed dullness in Traube's space, with no hepatomegaly or lymphadenopathy. A full blood picture (FBP) at first diagnosis showed pancytopenia with the presence of 20% blast cells. Bone marrow aspiration (BMA) showed hypercellular marrow with 40% blast cells. Other lineages were markedly suppressed. Immunophenotyping (IPT) showed blast cells expressed dim-to-moderate CD45, moderate side scatter, CD34 (heterogenous), nTdT, HLA DR, dim CD117, CD13, CD33 (heterogenous), CD7, CD64, dim CD4, CD123, and 8.2% of subpopulation expressed MPO. It was negative for other B, T lymphoid markers, erythroid and megakaryocytic markers (Table 1). A trephine biopsy showed a heterogenous population of hematopoietic cells. There was an increase in immature cells in the intertrabecular spaces, and these cells were small to moderate in size, with a moderate amount of cytoplasm and prominent nucleoli. The cells were positive for CD117, MPO, TdT and CD34 with scattered positivity for CD20, PAX5, CD79a, CD3, CD68, and negative for CD19 (Figure 1). Also noted were many foci of granuloma-like lesions, composed of more than 15 small-to-medium sized cells, having oval to spindle nuclei and a moderate amount of cytoplasm. These clusters of cells surrounded a blood vessel and were immunoreactive to CD117 (strong), CD45, CD68 (highlighting the cytoplasmic granules), MPO (dim) and S100 (focal) but negative to CD1a, panCK, CD34, CD30 and toluidine blue. Also scattered singly within the marrow were cells of CD117+, S100+ and CD68+. Other cell lineages were reduced. The cytogenetic karyotyping was monosomy 18 and monosomy 22. The diagnosis was SM-AML.

The morphologic BMA assessment post-induction showed no response to treatment with the presence of 25% circulating blast cells. After eight months of chemotherapy, the patient presented with fever associated with generalized muscle pain and loss of appetite. The white cell count was $14.2\cancel{5}x10^3$/L, the hemoglobin was 11.7g/dL, and the platelet count was $16x10^9$/L with 80% circulating blast moderate-to-large in size; there was also moderate cytoplasm, no Aeur rods, and prominent nucleoli. Trephine imprints showed a homogenous population of blast cells, moderate to large in size, and positive for CD117, MPO, TdT and CD34 of immunohistochemistry stains, as shown in Figure 1. IPT of the blast cells expressed CD34, HLA-DR, TdT, CD117, CD38, CD25, with a heterogenous expression of CD19, CD79a, CD13, cylgM, cyCD22, and dim 20 with aberrant CD7. Trephine biopsy showed a homogenous population of blast cells, and the biopsy was also diffusely positive for CD34, CD117, TdT, PAX5, CD25, as shown in Figure 1. It was heterogenous for CD20 and CD79a with scattered positivity for MPO and CD3. A diagnosis of relapse with lineage switch from AML to B-ALL was thus made. Although the patient was then started on MEC (mitoxantrone, etoposide, and cytarabine), the bone marrow did not respond to treatment and the patient died after three months of relapse.

Table 1: Differences of immunophenotyping flow cytometry expression of blast cells during primary and relapse diagnosis.

Markers	Primary Diagnosis	Relapse Diagnosis
MPO	**+ A small population of blasts were positive**	**-**
CD79a	**-**	**+**
CD19	**-**	**+ (Heterogeneous)**
cyCD22	**-**	**+**
cyIgM	**-**	**+**
CD34	**+ (Heterogeneous)**	**+**
CD117	**+ (Dim)**	**+**
nTdT	**+**	**+**
HLA DR	**+**	**+**
CD13	**+**	**+**
CD33	**+ (Heterogeneous)**	**-**
CD7	**+**	**+**
CD4	**+ (Dim)**	**-**
CD123	**+**	**-**
CD64	**+**	**-**
CD38	**-**	**+**
CD20	**-**	**+ (Dim)**

+: positive, -: negative

DISCUSSION

A relapse with a lineage switch from AML to ALL is very uncommon, and only a few cases have been reported so far [3, 4]. The exact mechanisms for the switch lineage of acute leukemia remain unknown. However, the lineage commitment of hematopoietic progenitors appears to be multidirectional and reversible, depending on the specific signals provided [3]. Another theory is that the dysregulation of lineage-specific transcription factors may produce an aberrant bi-potential leukemic clone [5].

The majority of AML relapses occur within two years of initial treatment. In this case, the patient relapsed after eight months of chemotherapy and unfortunately passed away after three months of relapse. The duration to relapse is reported to be significantly shortened in patients with lineage switching and associated with a poor event-free survival [3, 4]. However, whether the clone of the lineage switching represents a recurrence of the original clone or the emergence of a new clone/subclone is still unknown [3].

The WHO recently established the diagnostic criteria that need to be fulfilled for MPAL. For myeloid lineage, MPO should be expressed by IPT, immunohistochemistry (IHC), or cytochemistry. For B-lineage, there should be strong CD19 with at least one of the following strongly expressed: CD79a, cytoplasmic CD22, or CD10; or weak CD19 with at least two of the following strongly expressed: CD79a, cytoplasmic CD22, or CD10. In the case of our patient, the IPT during relapse was only fulfilled for B-lineage and not for myeloid, according to the MPAL diagnostic criteria. Thus, MPAL was excluded in this case. In addition, the blast expressed a small amount of MPO at diagnosis and a loss of MPO expression, then gained CD79a, CD19, cyCD22, cyIgM, and CD20 at relapse.

Following this progress, the patient did not respond to treatment and died due to the complications of the disease, which may indicate a poor prognosis for switch lineage leukemia.

CONCLUSIONS

Thorough investigations, such as bone marrow aspiration, trephine biopsy, IPT flow cytometry, and immunohistochemical stain, should be performed following relapse of acute leukemia in order to exclude lineage switching, as sometimes morphology alone is of little help. This is important as the different disease entities have different prognostic factors and need different treatment modalities. Treating switch lineage acute leukemia thus remains challenging.

CONFLICTS OF INTEREST

The authors declare no conflict of interest for this case report.

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تحول النسب من سرطان الدم النخاعي الحاد المرتبط B بكثرة الخلايا البدينة الجهازية إلى سرطان الدم الليمفاوي الحاد: معضلة تشخيصية

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الملخص

يُعرَّف سرطان الدم الانتكاسي الحاد بأنه عودة ظهور أكثر من 5٪ انفجار في نخاع العظم. في معظم الحالات، عبر الانفجار عن النسب المحددة (النخاعي أو اللمفاوي) المشابهة للتشخيص. ومع ذلك، نادرًا ما يمكن تحويله إلى سلالة مختلفة إما أن يتحول النخاع الشوكي إلى اللمفويد أو العكس أثناء الانتكاس. وبالتالي، يتم تصنيفها على أنها تبديل ابيضاض الدم الحاد بعد استبعاد معايير ابيضاض الدم الحاد المختلط النمط الظاهري والذي يمكن أن يمثل تحديًا في التشخيص. وصفنا رجلًا يبلغ من العمر 24 عامًا مصابًا بحالة معروفة من سرطان الدم النخاعي الحاد (AML) المرتبط بكثرة الخلايا البدينة الجهازية ((SM، والذي حدث بعد 8 أشهر وبعد الانتهاء من دورتين من العلاج الكيميائي مع انتقال النسب إلى سرطان الدم الليمفاوي الدم الليمفاوي B الحاد (كرة). كما يناقش تقرير الحالة مناهج الفحص المختبري والتحديات في التشخيص.

الكلمات الدالة: تبديل النسب، سرطان الدم الليمفاوي B الحاد، اللوكيميا النخاعية الحادة، كثرة الخلايا البدينة الجهازية.