

A rare case of mixed phenotype acute leukemia: Acute myeloid leukemia to early T-cell precursor acute lymphoblastic leukemia transformation

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ABSTRACT

Mixed phenotype acute leukemia (MPAL) is comprised of both lymphoid and myeloid markers or blasts in a cell single population. Diagnostic criteria rely on classifications provided by identifying these lineages using cytogenetic markers taken throughout the disease course. We describe an interesting presentation of a patient who had first presented with acute myeloid leukemia (AML) which later transformed into early precursor T-cell acute lymphoblastic leukemia (ETP-ALL). Cytogenetics were taken throughout the course of the cancer and confirmed the presence of a CD34 precursor cell marker. This transformation and the cytogenetic markers indicated a pluripotent progenitor cell origin confirming the diagnosis of MPAL. This case highlights a pluripotent progenitor origin with initial presentation as AML (myeloid clone) and later as ALL after an initial partial response to AML therapy due to clonal evolution.

Keywords: Mixed phenotype acute leukemia; ETP-ALL; AML; MPAL

INTRODUCTION

Mixed phenotype acute leukemia (MPAL) is comprised of both lymphoid and myeloid markers or blasts in a single population. The diagnosis requires identifying markers that suggest a precursor progenitor cell, which could develop into either of these hematopoietic lineages. The most recent classification system for determining MPAL is from the World Health Organization (WHO) in 2008 and was updated in 2016. This system indicates that the detection of myeloperoxidase when the blasts also meet criteria for B- or T-cell lineage meets the criteria for MPAL diagnosis. The European Group for Immunological Classification of Leukemias system is another way to diagnose MPAL but is much older and was proposed in 1995. Mixed phenotype acute leukemia accounts for only

2% of all acute leukemias using these systems and is extremely rare. Outcomes for this leukemia are poor due to complex karyotypes and lack of an appropriate effective treatment strategy.¹

CASE

A 57-year-old female patient presented in April 2020 complaining of generalized weakness and easy bruising without lymphadenopathy or hepatosplenomegaly. Labs showed pancytopenia with a hemoglobin 7 gm/dl and platelets 3,000/ μ L. Bone marrow biopsy showed hypercellular marrow with 60% CD 34+ myeloblasts confirming acute myelogenous leukemia (AML). Cytogenetics showed abnormalities in chromosomes 17 and 20. Isocitrate dehydrogenase (IDH1), KIT, and Fms-like Tyrosine kinase (FLT3) mutations for AML were negative. Markers were positive for CD8, CD5, and CD4; CD1a antigens were not tested. The patient was treated with chemotherapy for AML with daunorubicin and cytarabine; the bone marrow after 4 weeks treatment showed 4.8% CD 34+ myeloblasts.

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After this initial chemotherapy, the patient left treatment against medical advice and was lost to follow up until she presented again with an acute exacerbation of symptoms.

The patient presented 8 weeks later in June 2020 with shortness of breath, fatigue, and severe thrombocytopenia. Cytogenetics were repeated and were consistent with an AML diagnosis with markers positive for the CD64 antigen. Less than 1 week later, restaging bone marrow biopsy showed 85% blasts CD34+, and cytogenetics now identified early T-cell precursor acute lymphoblastic leukemia (ETP-ALL) and pluripotent cells. The cerebrospinal fluid contained atypical mononuclear ALL cells with some immature-appearing features (high N:C ratios and fine chromatin). At this time CD1a and CD8 were both negative, CD4+ and CD5 were weakly positive (3%), and stem cell markers CD 34 and cCD3 were also positive. This new profile fit the cytogenetic profile of ETP-ALL. The patient was treated with Hyper CVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone) with venetoclax; treatment was complicated by persistent neutropenia with *E. coli* sepsis, and the patient died.

DISCUSSION

This case highlights a pluripotent progenitor origin for MPAL. After the therapy of AML, the cytogenetic reports indicated ETP-ALL and the change from a myeloid to lymphoid lineage indicated a MPAL diagnosis. The 2016 WHO criteria focus on identifying cytogenetic markers that require the presence of the different hematopoietic lineages: B, T, and myeloid. The patient had the presence of CD64 confirming a myeloid lineage and cCD3 representing the T lineage. CD19 was not present, which is needed for the criterion of presence of B lineage.¹ Further, the presence of the CD34 marker suggests that this cancer was an MPAL since this is the genetic marker for the hematopoietic stem cell precursor before differentiation into myeloid or lymphoid lineages and could explain the transformation from AML to ETP-ALL after the AML had been treated.

Early T-cell precursor acute lymphoblastic leukemias are characterized by a very early differentiation

arrest and show unique genetic features that overlap both with T-cell-ALL and AML.² Genetic mutations associated with the two cancers have a similar prevalence.³ Mutations common in AML like *FLT3* and *IDH1/IDH2* have been described in ETP-ALL. In AML these genetic markers can be used to determine a prognosis. For instance, the *KIT* mutation indicates an adverse prognosis but can be targeted with tyrosine kinase inhibitors like dasatinib in AML.⁴ Currently AML testing also focuses on mutations of *FLT3*, Nucleophosmin 1, CCAAT enhanced binding protein to determine a prognosis.⁵ *FLT3* is a receptor tyrosine kinase involved in hematopoiesis, and an adverse prognosis in AML is correlated with higher allelic ratios.⁴

DNMT3A mutations can be detected in both AML and ETP-ALL. This enzyme is involved in epigenetic regulation of genome methylation and is detected in about 20% of AML patients and is associated with a poor prognosis in AML.^{4,5} The genetic markers that are used to identify ETP-ALL are typically CD1a-, CD8-, CD5weak+ and positive for one or more stem cell (like CD34) or myeloid antigens.⁶ These leukemias also have a lower incidence of *NOTCH1* mutations and often the presence of *FLT3* and DNA Methyltransferase 3A(*DNMT3A*) mutations.³ Additional cytogenetic markers identified in our patient were monosomy 5, trisomy 8, and a deletion of the 20q chromosome; this combination represents a complex karyotype which indicates a poor outcome. Deletions of the long arm of chromosome 20 have been seen in both myeloid and lymphoid disease and suggest a pluripotent stem cell origin.⁷

Early T-cell precursor acute lymphoblastic leukemia has a high proportion of remission failure of about 72% and has increased genomic instability.² Mutations in DNA mismatch repair *MLH3* and *MSH5* have occurred in several cases.² The absence of biallelic *TCRG* deletion as a poor prognostic marker is being studied.² Hematopoietic stem cell transplantation after first remission should be considered. Addition of nelarabine to Hyper CVAD therapy alone did not improve overall survival.^{3,5}

New therapies in development include Hyper CVAD with venetoclax, which is still in a phase Ib trial. Initial results are promising and show that using venetoclax, which is a *BCL2* inhibitor, added to the

standard chemotherapy regimen is well tolerated and effective. A recent trial indicated that 64% of patients achieved a complete response or a complete response with incomplete count recovery.⁸ Other therapies which focus on inhibiting specific gene proteins, such as FLT3, IDH, DNMT3A, and NOTCH1, are also available or in development. For instance, Midostaurin and Gilteritinib block FLT3 proteins and can be combined with other chemotherapeutic drugs for a more effective treatment of AML.

Consent: The patient provided consent for this submission.

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