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Letter to the editor

Diagnostic dilemma in AML with MDS-related changes and blasts of mixed lineage: A case report

1. Introduction

The myelodysplastic syndromes (MDS) are a group of clonal hematopoietic stem cell diseases characterized by cytopenia, dysplasia in one or more of the major myeloid cell lines, and an increased risk of developing acute myeloid leukemia(AML). On the other hand, acute myeloid leukemia with myelodysplasia-related changes (AML-MRC) is a heterogeneous disorder defined by morphologic, genetic, or clinical features, and is regarded as a high-risk subgroup. AML-MRC is defined as a subtype with at least 20% blasts in peripheral blood or bone marrow: (1) arising from a previous MDS or mixed MDS/myeloproliferative neoplasm, (2) with complex cytogenetics(≥ 3 aberrations) or a single MDS-defining cytogenetic abnormality, and/or (3) with multilineage dysplasia. Besides, recent World Health Organization published that leukemia of mixed myeloid-lymphoid lineage with MDS related changes is classified primarily as AML-MRC with a secondary notation of a mixed phenotype, as opposed to a mixed phenotype acute leukemia [1]. However, only three AML-MRC cases with mixed lineage have been reported as such in the literature [2,3]. Here, we report the fourth case of AML-MRC with blasts of mixed lineage and discuss the cause of abnormal B lymphocytes.

2. Case report

The patient is an 86-year-old woman who was evaluated in hematology clinic for symptoms of progressive fatigue and dizziness for two months. A complete blood count obtained by her primary care physician showed pancytopenia (white blood cell count of $2.4 \times 10^3/\mu L$, absolute neutrophil count of $0.8 \times 10^3/\mu L$, hemoglobin of 6.2 g/dL with an MCV 104 fL, and a platelet count of $74 \times 10^3/\mu L$) in peripheral blood. She did not have any history of alcohol, tobacco or other substance use, and no history of exposure to chemotherapy or ionizing radiation. There wasn't any family history of primary hematologic disorders. On examination, the patient appeared well, without any signs of mucocutaneous bleeding or splenomegaly. Bone marrow aspirate revealed 8.5% blasts, but one month later showed 20.5% blasts with variable myeloblast and lymphoblast morphology (Fig. 1(A)) as well as extensive dyserythropoiesis and megaloblastic changes (Fig. 1(B–D)). The blasts of cell showed positive by myeloperoxidase stain, while the smaller showed negative (Fig. 1(E–F)). Flow cytometry analysis revealed two distinct blast populations: one subset expressed myeloid markers including CD117+, CD34+, CD33+, CD13+ (Fig. 2(A–D), and the other subset expressed a predominantly B-lineage phenotype including CD19part+, CD10dim, CD22+, CD79α+, CD34dim, TDT+ (Fig. 2(E–H)). Cytogenetic analysis by R-banding stain showed 5q deletionig[46, XX, del(5)(q13q33)] in 13 of the 20 metaphases. FISH also demonstrated this result. Targeted next-generation sequencing revealed mutations of TP53, DNMT3A, ALK and NOTCH2. Based on dysplasis, expression of B lineage antigens and abnormal karyotype in her bone marrow, the patients was diagnosed of AML-MRC with blasts of mixed B/myeloid lineage.

3. Discussion

AML-MRC, a distinct AML entity which account for 24% to 48% of all AML cases [4,5], is known to show a poor prognosis compared with de novo AML. Currently, the diagnosis of AML-MRC is based on a history of either MDS or MDS-related clinical features, such as dysplasia or cytogenetic abnormalities [6]. Although more than half of the patients present with de novo AML-MRC, it is unclear whether these patients are de novo AML or suffer from MDS that was clinically silent [7]. We couldn't find any explicit data indicating that the patient had a history of MDS, but the peripheral blood and BM smear findings were indicative of multilineage dysplasia. A diagnosis of AML-MRC can be established based on not only morphological analysis but also cytogenetic and molecular studies.

Most cases of AML-MRC were usually associated with adverse genetic abnormalities, particularly –5/del(5q), –7/del(7q), and/or complex karyotypes. Notably, in AML-MRC, 5q deletion is usually associated with a complex karyotype and harbor a poor outcome. Sequencing technology has revealed a number of molecular abnormalities involving a deletion of chromosome 5q and genes mutated include TP53, DNMT3A, ALK, and NOTCH2 in the patient. NOTCH2, another member of the NOTCH gene family, is preferential in mature B cells and is essential for marginal zone B-cell generation. Lee SY et al. [8] reported that 5 of 63 (approximately 8%) diffuse large B-cell lymphomas, a subtype of mature B-cell lymphomas, have NOTCH2 mutations, and Notch2 gain-of-function mutations in the pathogenesis of a subset of B-cell lymphomas. Study by Kiel MJ et al. [9] also suggested that NOTCH2 mutations play a role in the pathogenesis and progression of Splenic marginal zone lymphoma and are associated with a poor prognosis. Moreover, it has recently been demonstrated that NOTCH2 deleterious mutation was always found in ALL [10], and it is unclear whether abnormal B lymphocyte expression in blasts in the patient were associated with NOTCH2 mutation. In the meantime, we believed that the diagnosis of this case could be established by flow cytometry and immunohistochemistry, which was different from most of the similar case reports published so far.

But now, both patients with AML-MRC and thoses with a mixed phenotype acute leukemia have poor prognosis with refractoriness to conventional chemotherapy against AML, a more accurate and objective diagnostic approach for AML-MRC and blasts of mixed lineage is required.

4. Conclusion

In conclusion, AML-MRC with blasts of mixed B/myeloid lineage is rare but could be an important classification in the AML-MRC. The

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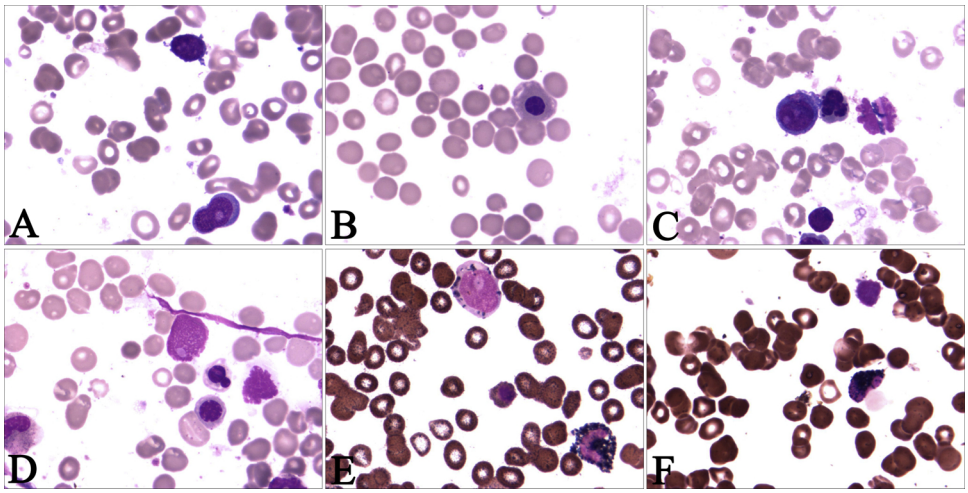

Fig. 1. Bone marrow smear. Bone marrow aspiration revealed a dual population of morphologically distinct blasts with myeloblast and lymphoblast (A) features and dyserythropoiesis characterized by megaloblastic (B), nuclear contour irregularities (C), and nuclear budding (D). The blast cells (E) were all positive for myeloperoxidase stain (MPO stain), while the smaller blast cells (F) negative.

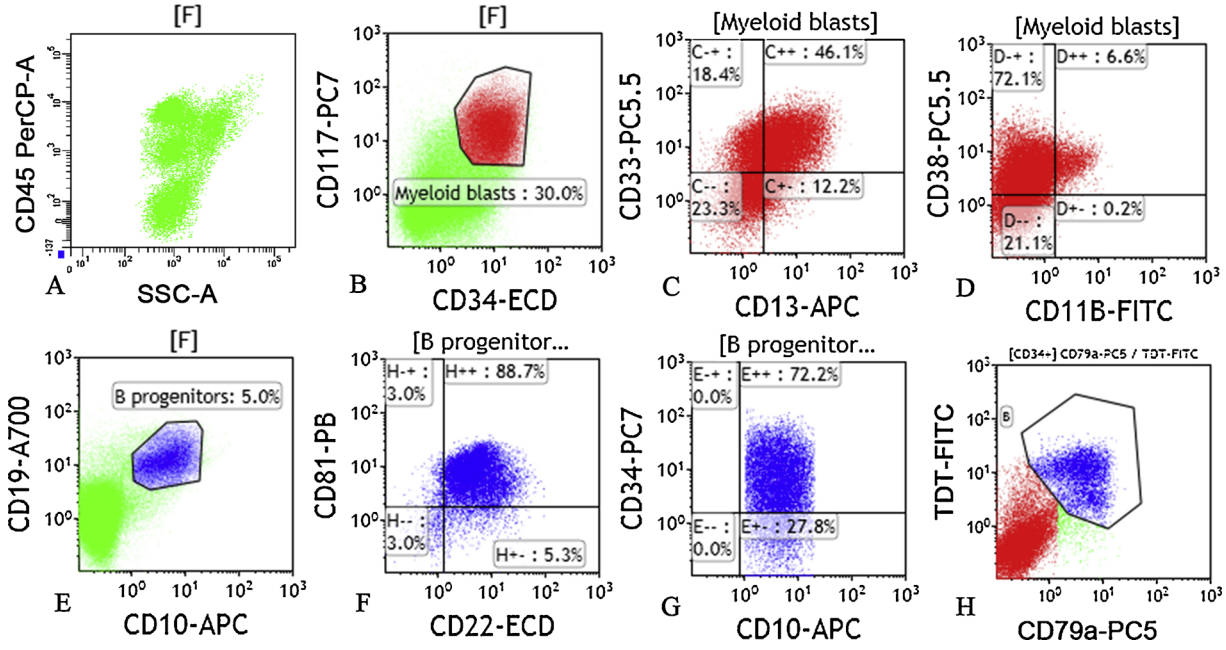

Fig. 2. AML-MRC with blasts of mixed B/myeloid lineage. Flow cytometry performed on the BMA demonstrates blasts of mixed B/myeloid lineage as evidenced by expression of CD117, CD33, CD13, CD38(A–D), CD19part, cCD79a, CD22, and TDT(E–H). The intensity of cCD79a expression in the blasts is equivalent to that seen in normal B lymphocytes.

diagnosis of AML-MRC was made and the mixed phenotype of blasts was noted. The final diagnosis in this infrequent cases reflected the settings of a new provisional entity for AML-MRC with blasts of mixed lineage in the current WHO classification.

Declaration of Competing Interest

The authors declare no conflict of interest.

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