Case Report

Acute Myeloid Leukemia Transformed from Aplastic Anemia following Anti-thymocyte Globulin Therapy: A Case Report with Clinicopathologic and Molecular Findings

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Abstract: Aplastic Anemia (AA) incidence is threefold higher in Asia compared to the western world. It is associated with pancytopenia that is induced by impaired bone marrow function. Cytopenias of at least two lineages are required for the diagnosis. Symptoms include pallor, weakness, fever, frequent infections, bruises, petechiae, and mucosal bleeding. Bone Marrow Transplant (BMT) and immunosuppressive therapy are the treatment options. Patients with Severe Aplastic Anemia (SAA) are susceptible to developing malignancies like acute myeloid leukemia (AML) or Myelodysplastic Syndrome (MDS). In this report, we present a case of SAA who transformed to AML/MDS. 5 years of post- Anti-Thymocyte Globulin (ATG), she acquired monosomy 7, RUNX1 & SETBP1 gene mutations. RUNX1 and SETBP1 mutations are correlated with poor overall survival and are predicted to have a lack of response from hypo-methylating agents. As the aspect of somatic mutation is complex and still not fully understood, it should be cautiously analyzed along with morphologic and cytogenetic results.

Keywords: Bone marrow transplant, Immunosuppressive therapy, Acute myeloid leukemia, RUNX1, SETBP1, Anti-Thymocyte Globulin.

INTRODUCTION

Aplastic Anemia (AA) incidence is variable worldwide with 2-3 times higher in Asia compared to western countries. The reason for this difference is not known [1]. Aplastic anemia can be either inherited or acquired, associated with pancytopenia that is caused by impaired function of bone marrow [2]. Cytopenias of at least two lineages are required for the diagnosis. The hypocellular bone marrow could be life-threatening with a high rate of mortality if remains untreated [3]. The disorder could occur at any age and in either gender. Symptoms include pallor, weakness, fever, frequent infections, bruises, petechiae, and mucosal bleeding [4]. In diagnosed patients, Bone Marrow Transplant (BMT) is considered a first-line treatment option but the outcome is mainly depending on the age. Patients under the age of 40 have a survival rate of up to 94% [5]. The older patients or who are ineligible for BMT, Immunosuppressive Therapy (IST) with Anti-thymocyte Globulin (ATG) and Cyclosporine A (CsA) can be used as primary therapy. Recent studies showed a 63-65% response rate of ATG with favorable survival outcomes [1]. It has already been identified that patients with severe Aplastic Anemia (SAA) are prone to develop malignancies like Acute Myeloid Leukemia (AML) or Myelodysplastic Syndrome (MDS). It is about a 15-20% rate of incidence of secondary AML/MDS in aplastic anemia patients at ten years [6].

Here we report a case of a patient of aplastic anemia post-ATG transformed into AML having both RUNX1 and SETBP1 somatic mutations concurrently along with the monosomy 7. To our best knowledge this would be the unique case report of this kind.

CASE REPORT

In 2017, a 43-years old female presented with complaints of shortness of breath, chest pain, orthopnea, and fever for 4 days, and per vaginal bleeding for 3 days. Her appetite and sleep were disturbed. Complete blood count findings were: Hemoglobin 3.2g/L, Total leukocyte count (TLC) $2.6x10^9$/L, platelets $01x10^9$/L. Liver and renal profile, uric acid, Lactate dehydrogenase, Coagulation profile, Malaria parasite test, and ultrasound Abdomen were within normal range. Systemic examination was unremarkable. On basis of the above findings, her bone marrow biopsy was performed which was markedly hypocellular with a cellularity of 5% and no evidence of fibrosis or infiltration. Diagnosis of severe aplastic anemia was made. Karyotype revealed normal female karyotype. Packed red blood cells and platelets were transfused on and off. As the patient was not eligible for BMT due to being aged >40 years, IST was given with Rabbit Anti-Thymocyte Globulin (rATG). The patient's counts gradually recovered to normal after 6 months of ATG. She remained

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well till March 2022, after which she presented with complaints of weight loss and abdominal pain. CBC showed TLC 8.96 x10^9/Lwith 6% blasts and >50% of abnormal monocytes. Patient bone marrow biopsy & karyotyping were performed revealing transformation to AML/MDS. Her karyotyping showed Monosomy 7 shown in the Fig. (**1**).

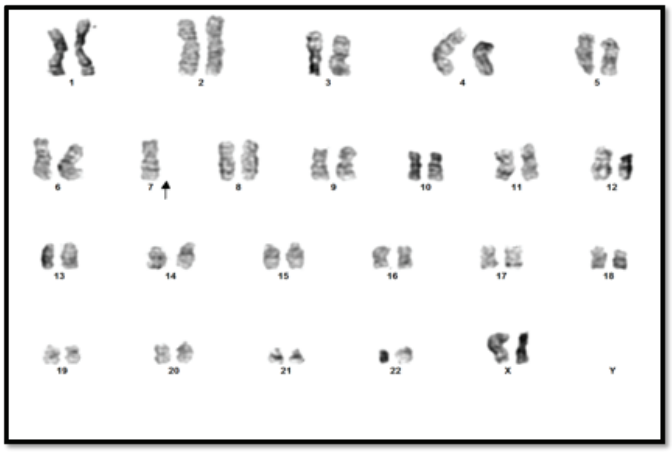

Fig. (1). Karyotype of the patient showing Monosomy 7.

Next generation sequencing was done for AML/MDS panel including the following genes:
ASXL1, CALR, CEBPA, SETBP1, CSF3R, DNMT3, EZH1, HRAS, MLL-PTD, MPL, MYD88, NPM1, PDGFRB, PHF6, RUNX1, TET2, TP53, U2AF1, WT1, ZRSR2.
Genes in which the patient had mutations are discussed in Table **1**.

Table 1. The Mutations Identified in Next Generation Sequencing AML/MDS Panel.

Gene	Mutation	VAF	Clinical significance
RUNX1	c.316T>A, p.Trp 106Arg (W106R)	38%	Pathogenic
SETBP1	c.2614G>A, p.Gly 872Arg (G872R)	35%	Likely pathogenic

The recent aspirate smear shows the following in the Fig. **(2).**

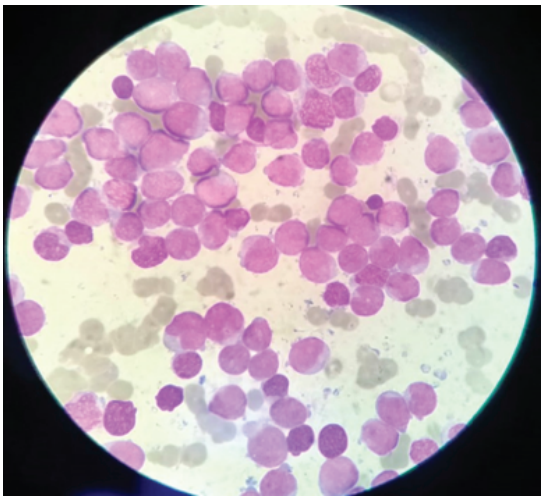

Fig. (2). Bone Marrow Aspirate Smear Image of Patient Showing Blast Cells and Abnormal Monocytes.

DISCUSSION

In this report, we presented a case of SAA that transformed into AML/MDS. 5-years of post-ATG, she acquired monosomy 7, RUNX1 & SETBP1 gene mutations. Clonal evolution is one of the most concerning complications of AA treated with IST [7]. Patel et al. reported that in a large cohort, approximately 10% of SAA patients treated with IST developed clonal evolution [8]. Therefore, patients with severe AA require profound and prolonged surveillance with marrow morphology and cytogenetics. Progression towards secondary myeloid neoplasm or identification of monosomy-7 should bringon clinicians to go for BMT for eligible patients [9].

Monosomy 7 is the most specific aberration identified in 20-60% of patients with AA who evolved to MDS [10]. In such patients, monosomy 7 is usually present either isolated or in conjunction with other somatic mutations, most frequently RUNX1 and ASXL1 gene, unlike primary MDS where monosomy-7 is identified with TP53 and complex karyotype [10]. Patient prognosis linked to gene mutation. The number of gene mutations is associated with overall survival, and advanced disease is associated with higher mutational burdens in MDS. Studies found that RUNX1 and SETBP1 mutations correlated with poor overall survival [11]. According to a review study, RUNX1 mutation usually develops in the later stage of MDS, so it may be more likely to be the mutation needed for transformation to AML [12]. SETBP1 mutations coinciding with cytogenetic abnormality correlated with shortened survival. SETBP1 mutations are acquired at the time of leukemic evolution very frequently with the concurrence of an increased number of blasts which suggests

that it may play an important role in disease progression [13]. In recent research, it has found that patients of MDS/MPN with RUNX1 and SETBP1 gene mutations are predicted to lack the response from hypo-methylating agents which suggests that genetic screening can identify patients with HMA refractory phenotype [14]. Once the patient become refractory to HMA, their outcome is poor and very limited treatment options are left. Supportive care may only be decided for the management of these kinds of patients [15].

As the aspects of somatic mutations are complex and still not fully understood, they should be cautiously analyzed by the clinician along with morphologic and cytogenetic data before planning the treatment.

CONFLICT OF INTEREST

Declared none.

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