

## Leukemic transformation in myelodysplastic syndrome: A case report with review of risk factors

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Received - 01 June 2019

Initial Review - 24 June 2019

Accepted - 09 August 2019

### ABSTRACT

Myelodysplastic syndromes are a group of clonal disorders affecting the hemopoietic stem cells and characterized by peripheral cytopenias with normocellular to hypercellular bone marrow and various morphological abnormalities in one or more hemopoietic cell lines. MDS carries a high risk of progression to acute myeloid leukemia especially in subtypes with increased myeloblasts. Here, we present the case of leukemic transformation in MDS in a 41-year-old male who presented with complaints of generalized weakness, loss of appetite for 2 months and fever on and off for 1 week. The patient was diagnosed as MDS-multilineage dysplasia after blood examination and bone marrow biopsy but the patient refused for further treatment.

**Keywords:** Acute myeloid leukemia, Leukemogenesis, Myelodysplastic syndrome.

Myelodysplastic syndromes (MDS) are a group of clonal disorders affecting the hemopoietic stem cells. They are characterized by cytopenia with normocellular to hypercellular bone marrow and various morphological abnormalities in hemopoietic cell lines. The condition carries a high risk of progression to acute myeloid leukemia (AML) especially in subtypes with increased myeloblasts. The incidence of the transformation of MDS to AML in India is about 0.5-2%, with a median time of 272 days [1]. Many factors have been evaluated for individual risk assessment in these patients. Various transforming mutations that affect hematopoietic stem cells can lead to different patterns of dysregulated signal transduction, bringing rise to phenotypic diversity [2].

### CASE REPORT

A 41-year-old male presented to our department with complaints of generalized weakness, loss of appetite for 2 months and fever on and off for 1 week. The patient's past, family and medical histories were non-significant. Physical examination revealed severe pallor with no organomegaly. The vitals were stable with a blood pressure of 110/80 mmHg and pulse rate of 68/min.

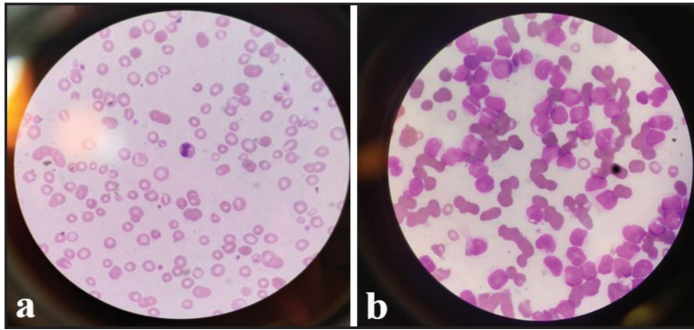
Complete blood count showed hemoglobin of 4.5 gm/dl, total leucocyte count (TLC) of 3560/mm<sup>3</sup> and platelet count of 70000/ul. Differential leucocyte count showed N-42%, L-52%, M-5%, E-1% where the percentage of blasts was <1% with a mild left shift. Hypolobated neutrophils were seen on peripheral blood film examination (Fig. 1). Bone marrow aspiration evaluation showed dysplastic features in >10% of the

erythroid cell (megaloblastic maturation, binucleation, nuclear budding), myeloid cells (hypolobation of neutrophils) and megakaryocytes (hypolobated and micromegakaryocytic form) (Fig. 2). Approximately, 7% of ring sideroblast were seen. Blast count was <5%. The patient was diagnosed as myelodysplastic syndrome-multilineage dysplasia.

The patient refused further evaluation and treatment. He came back to the hospital after one year with acute exacerbation of previous complaints. Complete blood count done at this time showed lower hemoglobin (2.6gm/dl) with higher leucocyte count (30340/mm<sup>3</sup>) and 33% blasts. Peripheral blood picture showed, in addition, hypolobated neutrophils and myeloid precursors with pseudo Chediak Higashi granules and cytoplasmic vacuolation. The patient again refused further evaluation and treatment except for blood transfusion. After 20 days of discharge, he returned with a TLC of 198670 cells/mm<sup>3</sup> and 76% blasts in the peripheral blood.

### DISCUSSION

Myelodysplastic syndrome (MDS) is a heterogeneous group of clonal stem cell disorder with variable disease course varying from indolent to rapid progression to AML. Andrew et al found a case to be transformed from MDS to AML with monocytic differentiation just within 1 month and the patient presented with the exacerbation of symptoms [3]. To assess the risk defining factors, it is important to understand the mechanism of disease progression which is not well established and is complex. Accumulation of cytogenetics and molecular aberrations, an



**Figure 1:** Peripheral blood film. Leishman stain:1000X. (a) hypolobated neutrophils and (b) blasts cells.

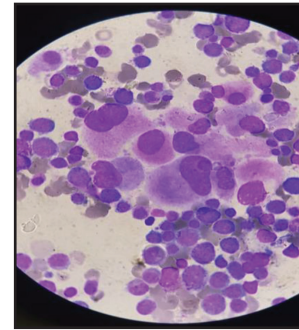
imbalance between apoptosis, a proliferation of hematopoietic cells, stromal defects and host response are some of the theories proposed for the leukemic transformation of MDS.

Class I mutation involved in signal transduction (kit, IDH 1, NPM1) affecting cellular survival and proliferation are implicated in MDS progression to AML [4] while Class II mutation (RUNX 1, Tet 2) affect cellular differentiation and have a significant role in MDS initiation. Some authors have observed a correlation between risk of transformation and karyotype complexity in patients with 5 q abnormality while the presence of abnormalities in chromosome 7 carried a high risk of disease progression independent of other chromosomal abnormalities [5,6].

Gene oncology analysis supports the proposition that apoptosis in early MDS leads to ineffective hematopoiesis while increased genomic instability due to DNA damage checkpoint disruption is seen in MDS with the transformation to AML. In a study, a high methylation profile of 10 selected genes was found to be an independent predictor of disease progression-free survival. A deranged immune response heralded by increased no of T-reg cell and decreased expression of the activity of natural killer cell receptors is seen in patients with high-risk MDS [7,8]. Morphological features related to AML transformation include >5% blasts in bone marrow smears, presence of abnormally localized immature precursors (ALIP) by immunohistochemistry (IHC), hypercellular bone marrow and significant fibrosis in bone marrow biopsies by reticulin stain. Abnormal immunophenotype which is associated with high-risk is aberrant express in lymphoid associated markers (CD4, CD7, CD56), overexpression of CD34, CD36, and Tdt.

## CONCLUSION

Many factors including percentage of blasts, infiltration patterns of blasts and complex karyotype have been associated with



**Figure 2:** Bone marrow aspiration:1000X: Hypolobated megakaryocytes and micromegakaryocytes.

greater risk of transformation. The present case did not have >1% blasts in peripheral blood or >5% blasts in bone marrow at the time of presentation but still progressed to AML. A multi-step leukemogenesis with an accumulation of cytogenetic and molecular aberrations during the course of the disease has been proposed in many studies.

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*Funding: None; Conflict of Interest: None Stated.*

**How to cite this article:** Singh P, Acharya S, Azad S, Thakur B, Kochhar M. Leukemic transformation in myelodysplastic syndrome: a case report with review of risk factors. *Indian J Case Reports.* 2019;5(4):386-387.

Doi: 10.32677/IJCR.2019.v05.i04.031