A benign course of MDS with del 7q and ASXL1 mutation

Abstract
Myelodysplastic syndromes (MDS) are heterogeneous group of clonal hematologic malignancies characterized by impaired hematopoietic differentiation. The aim of study was to identify mutations in the genes like ASXL1, EZH2, UTX, DNMT3A, IDH1/IDH2, and TET2 that can be used in disease prognosis and as well in deciding therapeutic options. Here we report a case of a 57 year old man who was diagnosed as MDS and sub categorized as refractory cytopenia with multilineage dysplasia (RCMD) on the basis of morphologic and cytogenetic analyses (46, XY, del (7q) (15). DNA was extracted with Qiagen extraction kit.

Introduction
Myelodysplastic syndromes (MDS) are group of heterogeneous clonal stem cell disorders characterized by cytopenias, ineffective hematopoiesis and tendency to evolve into acute myeloid leukemia.\(^1\)\(^2\) Decade of research on the molecular pathogenesis of MDS have identified disease causing alleles in patients but still their pathological contributions are not completely understood. The prognostic impact on the clinical course of the disease for these genetic aberrations is still under clinical investigations. Recent whole genome and targeted gene studies have found novel somatic mutations that improve our understanding of molecular basis of disease, among which additional mutations are present in ASXL1 gene. In addition, a missense variant that is c. 5162 T>G, p. L1721W of TET2 gene was also identified. Mutations in ASXL1 gene are commonly found in advanced stages of MDS and are associated with poor prognosis and overall inferior survival. However our study finds a better overall survival in this patient with good prognosis as he is maintaining stable counts with no history of recurrent infections or fever or any bleeding manifestation which is in contrast to previous reported cases. Peripheral smear reviewed on monthly follow ups do not reveal blast cells. Hence mutation screening of large number of patients is required to understand the underlying mechanisms in the pathogenesis of disease.

Keywords: genome screening, ASXL1 mutation, del7q

Abbreviations: MDS, myelodysplastic syndromes; RCMD, refractory cytopenia with multilineage dysplasia; AML, acute myeloid leukemia; SNVs, single nucleotide variants

Case presentation
A 57 year old man was referred to our institute with history of fever on and off, generalized weakness and pallor for 06 months. Complete blood counts were done which showed Hb of 6.6 g/dl, WBC count of 2.1x10^-9/L with ANC (absolute neutrophil count) of 0.2 x10^-3/L, platelet count of 13x10^-9/L with MCV 99 fl, MCH 31 pg MCHC 31, Neut-x 344 and Neut y 732. Review of peripheral smear revealed pancytopenia and dysplastic neutrophils. Bone Marrow Biopsy showed hypercellular marrow exhibiting erythroid hyperplasia and dyserythropoietic features like nuclear cytoplasmic asynchrony, inter cytoplasmic bridging along with dysplastic neutrophils. Blast cells were less than 05% (500 cell differential). Iron grade was 4+. Patient was given Vitamin B12 and folic acid along with PRBCs transfusion. He also received GCSF for 5 days. Deletion 7q was identified in 15 metaphases on bone marrow cytogenetics analysis (Figure 1). His IPSS score at the time of diagnosis was 1.5 (cytopenias=3, Blast cells=<5%). Based on the morphologic and cytogenetic findings, the patient was diagnosed as MDS and subcategorized as Refractory Cytopenia with Multi lineage Dysplasia (RCMD).

DNA was extracted from the blood sample of MDS patient from (National Institute of Blood Diseases (NIBD) OPD using QIAamp DNA Blood Mini Kit (Qiagen) following the manufacturer’s instructions. This case report was approved by the Institutional Review Board (ERC/ IRB) with and conform to the tenets of the Declaration of Helsinki. Written informed consent was obtained from patient. Next generation sequencing was performed by using TruSight custom amplicons kit containing all the reagents necessary for amplification, amplitcromer enrichment and indexing of samples (Illumina, USA). Libraries were generated with the highly multiplexed oligonucleotides probes, pooled and loaded into the MiSeq (Illumina®, Experience Genetic Energy™) system for automated sequencing and data analysis. Each procedure was done according to the manufacturer’s instructions. Data...
Mutations in ASXL1 gene are detected in 11-22% of MDS and are generally associated with aggressive diseases and poor outcome.\textsuperscript{1,3} We found p.Q1039Ter mutation in exon 13 of ASXL1 in our patient. Wang et al.\textsuperscript{8} also reported this stop gained mutation in 47 year old Chinese patient of RCMD with poor karyotype. They suggested that a mutated ASXL1 might confer a growth advantage to immature hematopoietic cells.\textsuperscript{8}

Mutations in ASXL1 are associated with poor prognosis across the spectrum of malignant myeloid diseases. Regardless of cytogenetics (7q del) and molecular (ASXL1) alteration in this patient, both having been associated with aggressive course and bad prognosis this is an unusual case with stable course of disease and better overall survival. This is contrary to what has been reported previously\textsuperscript{1,6,9} which might be due to heterogeneity of our Pakistani population with diverse genetic background of patient. However, genetic screening of large cohort of patients is required to understand the underlying mechanisms in disease pathogenesis and resultant clinical outcome.

**Conflict of interest**

The authors declare that they have no competing interests.

**References**

1. Thol F, Friesen I, Damm F, et al. Prognostic Significance of ASXL1 Mutations in Patients with Myelodysplastic Syndromes. *J Clin Oncol*. 2011;29:2499–2506.

2. Gelsi-Boyer V, Trouplin V, Adéfrière J, et al. Mutations of polycomb-associated gene ASXL1 in myelodysplastic syndromes and chronic myelomonocytic leukaemia. *Br J Haematol*. 2009;145(6):788–800.

3. Chen TC, Hou HA, Chou WC, et al. Dynamics of ASXL1 mutation and other associated genetic alterations during disease progression in patients with primary myelodysplastic syndrome. *Blood Cancer J*. 2014;4(4):e177.

4. Boulward J, Perry J, Pellagatti A, et al. Frequent mutation of the polycomb-associated gene ASXL1 in the myelodysplastic syndromes and acute myeloid leukaemia. *Leukemia*. 2010;24(5):1062–5.

5. Gelsi-Boyer V, Brecqueville M, Devillier R, et al. Mutations in ASXL1 are associated with poor prognosis across the spectrum of malignant myeloid diseases. *J Hematol Oncol*. 2012;5:12.

6. Bejar R, Stevenson K, Abdel-Wahab O, et al. Clinical effect of point mutations in myelodysplasicyndromes. *N Engl J Med*. 2011; 364(26):2496–2506.

7. Kraus TF, Greiner A, Steinmaver M, et al. Genetic Characterization of Ten-Eleven-Translocation Methylcytosine Dioxygenase Alterations in Human Glioma. *J Cancer*. 2015;6(9):832–842.

8. Wang J, Ai X, Gale RP, et al. TET2, ASXL1 and EZH2 mutations in Chinese with myelodysplastic syndromes. *Leuk Res*. 2013;37(3):305–311.

9. Devillier R, Mansat-De Mas V, Gelsi-Boyer V, et al. Role of ASXL1 and TP53 mutations in the molecular classification and prognosis of acute myeloid leukemias with myelodysplasia-related changes. *Oncotarget*. 2015;6(10):8388–8396.

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