CASE REPORT

A Rare Case of Plasma Cell Myeloma, Myelodysplastic Neoplasm with Low Blast and SF3B1 Mutation and Dyserythropoiesis with Ring Sideroblasts

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Abstract

Myelodysplastic syndromes (MDS) are heterogeneous hematological neoplasms which lead to dysplasia, cytopenia and hematopoiesis. They have a risk of transforming into Acute Myeloid Leukemia (AML) in some cases. Genetic markers that are determined by cytogenetics, SNP-A karyotyping and molecular mutations have evolved to define conditions of pathogenesis and risk evaluation for the development of AML. Among the concerned are the mutations of the spliceosome (SF3B1, SRSF2, ZRSR2 and U2AF1) epigenetic mutations (DNMT3A, EZH2) and also mutations in transcription factors (RUNX1) and tyrosine kinases (N-RAS, K-RAS). Here, we report a case of an 80-year-old female patient presented for the evaluation of myeloma. A morphology report shows changes that suggest multiple myeloma. Lab data shows anemia, elevated creatinine and calcium; CBC revealed mild neutrophilic leukocytosis and microcytic anemia. Bone marrow demonstrated approximately 50-60% involvement by a plasma cell infiltrate; there was mild dysgranulopoiesis and dyserythropoiesis which are suggestive of plasma cell myeloma. Frequent mutations in MDS and overlap syndromes were discovered due to advances in genomic studies. The differential diagnosis of MDS is challenging because they overlap the disorders sharing features of other illnesses. It is expected that more research on MDS and overlapping disorders will highlight the roles of mutations as "therapeutic targets" and "prognostic indicators".

Keywords: *Myelodysplastic syndrome, SF3B1, molecular mutations, dyserythropoiesis, plasma cell myeloma.*

INTRODUCTION

MDS are a class of diverse clonal hematological tumours illustrated by futile hematopoiesis, exhibiting morphologic dysplasia of hematopoietic cells and peripheral cytopenias [1]. There are numerous benign or cancerous situations showing morphological characteristics identical to MDS and MDS overlap disorders, frequently making it challenging to correct diagnoses of cases [2]. Such MDS overlap disorders comprise myelodysplastic / myeloproliferative neoplasms (MDS/MPNs) with Both MDS and MPN characteristics and hypoplastic MDS (hMDS) with aplastic anemia (AA) features [3]. Furthermore, MDS overlap disorders may involve secondary AML developing from MDS, and some probable pre-MDS situations displaying cytopenia or somatic mutations but not as per MDS diagnostic criteria [4, 5].

The World Health Organization (WHO) classification states Plasmablastic Lymphoma (PBL) is an aggressive B-cell NHL (non-Hodgkin lymphoma) characterized by diffused proliferation of large cancerous cells, similar to B immunoblasts in which all neoplastic cells have the immune-phenotype of plasma cells [6]. Many case reports and small series have been related to both immune-deficient and immunocompetent cases and implying different anatomic locations [7]. However, PBL is still a rare illness which is challenging owing to difficulty in diagnosis due to its likenesses with multiple myeloma (MM) and has no standard of care with poor prognosis [8]. Refractory anemia with ring sideroblasts related to evident thrombocytosis (RARS-T) has now been recognized distinctly in the amended WHO 2016 classification. In the WHO 2008 classification, it was provisionally in the myelodysplastic syndromes/ myeloproliferative neoplasms (MDS/MPN) unclassifiable class [6, 9].

Different plasma cell dyscrasias with diverse kinds of myeloid tumours usually coexist in cases receiving chemotherapy with alkylating agents in the long-term, preceding leukemia development. There have been reports of rare cases of concurrent coexistence of these two cancers which were not linked with prior treatment [10] although the coexistence of PBL with myeloid tumours has not been generally reported [8]. As far as we know, we are reporting a rare case of plasma cell myeloma, myelodysplastic neoplasm with low blast and SF3B1 mutation and dyserythropoiesis with ring sideroblasts.

CASE REPORT

Clinical Presentation

An 82-year-old female was presented for the evaluation of myeloma to the hematology department in July 2023. Images of the morphology report showed changes that were suggestive of multiple myeloma. Initial lab data showed anemia, elevated creatinine and calcium. The current available CBC revealed mild neutrophilic

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leukocytosis and microcytic anemia. Bone marrow demonstrated approximately 50-60% involvement by a plasma cell infiltrate. No amyloid was seen with Congo red staining. The bone marrow demonstrated mild dysgranulopoiesis and dyserythropoiesis. Iron staining showed increased iron stores and few ring sideroblasts. No increase in blasts was seen. Concurrent flow cytometric analysis revealed 10.4% lambda-restricted, clonal plasma cells with aberrant CD56 expression. Overall, the findings were consistent with plasma cell myeloma. The findings of mild dyspoiesis and few ring sideroblasts along with the presence of anemia were of concern for a low-grade MDS; as such MDS - Fluorescence *in-situ* Hybridization (FISH) study and core myeloid panel molecular testing by NGS were ordered whereas Cytogenetics and myeloma FISH study were also performed.

Laboratory Findings

Core Biopsy and Iron Staining

The core biopsy was small and crushed (limited for evaluation). Numerous marrow particles were seen on the clot sections (adequate for evaluation). The bone marrow was hypercellular for the age of the patient (~50% cellular), secondary to an extensive plasma cell infiltrate. There was residual trilineage hematopoiesis (~40-50%).

Blasts were not augmented. Megakaryocytes were appropriate and typical morphologically. The M:E ratio was 1.94, which is normal. Lymphoid aggregates were not seen. Granulomas or metastasis were not detected on H&E staining. An iron stain was tested on an aspirate smear, which showed increased iron stores. Few ring sideroblasts were noticed. CD138 performed on the core and clot section demonstrated a fairly extensive plasma cell infiltrate ~ 50 – 60% marrow involvement **(Fig. 1).**

Molecular Profiling

Comprehensive molecular profiling was carried out which used next-generation sequencing (NGS). Sanger Sequencing and fragment length analysis testing were done to identify molecular abnormalities (including SNVs, INDELS and CNVs) in 284 genes involved in hematologic tumours, comprising leukemia, lymphoma and MDS. Clinical relevance and effects of noticed oddities wherever possible are explained as follows.

Spotted Genomic Alterations and Karyotyping Result

There was a normal female chromosome complement with no clonal abnormality detected at the available resolution (**Fig. 2**).

SF3B1	KRAS (G12A)	SAMD9L	TSC2	No detectable autosomal Chromosomal structural gain or loss.

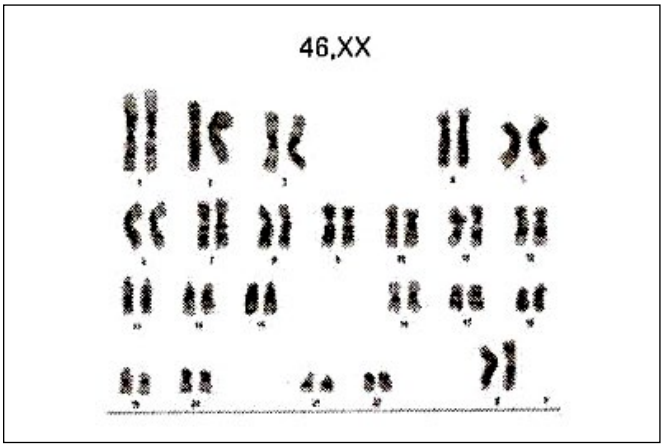

Fig. (2): Karyotyping result – No clonal abnormality was detected, showing a normal female chromosome.

Heterogeneity

There was a dominant abnormal clone with SF3B1 mutation. The KRAS, SAMD9L and TSC2 mutations were detected in subclones.

Diagnostic Suggestions

SF3B1, KRAS, SAMD9L, TSC2	The outcomes were coherent with myelodysplastic syndrome with ring sideroblasts (MDS-RS/ MOS-SF3B1).

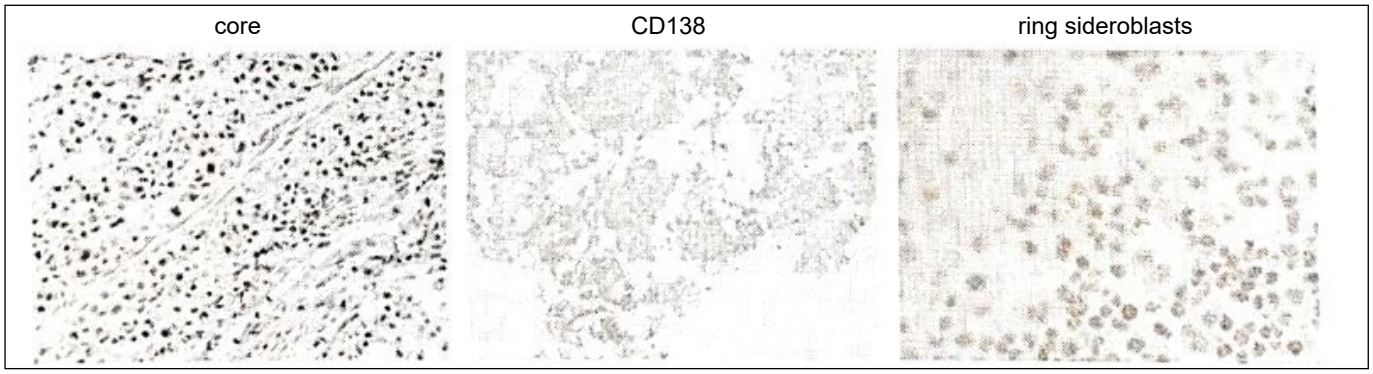

Fig. (1): Core and clot section for CD 138.

Therapeutic Suggestions

SF3B1	Spliceosome modifiers
KRAS	MEK inhibitors
TSC2	mTOR inhibitors

FISH Analysis

The FISH analysis was found to be consistent with trisomy of chromosomes 3, 5, 9, and 1 suggesting hyperdiploidy. Hyperdiploidy had been reported as a standard risk of genetic abnormality in multiple myeloma. There was no evidence of gain or amplification of 1q21 or deletion of 5q, 7q, 13q, 17p, 20q, or trisomy 8. This evaluation also asserted the presence of KMT2A (MLL), IGH/CCND1, or IGH/FGFR3 rearrangements as well as a numerical abnormality of chromosomes 1, 13, or 17 (**Figs. 3-6).** Association with other investigational outcomes was proposed. Multiple Myeloma FISH analysis was performed employing the automated Plasma Cell Enrichment (PCE) process method on the available specimen; 100 interphase nuclei were examined for each probe. The MDS FISH panel was performed manually on the available tissue specimen; 200 interphase nuclei were assessed for each probe. As per the clinical indication of microcytic anemia, leukocytosis, metastatic disease and myeloma, 9 multiplex probe sets, 3 single probes, and an internal probe (IGH) were hybridized to diagnose the illness accurately, assess the prognostic aspects, and classify the illness according to abnormal results. No clonal abnormality was detected but this testing does not imply any submicroscopic oddities or that in the non-dividing cells.

DISCUSSION

A *de novo* MDS is the one with ring sideroblasts and thrombocytosis (MDS with RS-T) which is indicated by the concurrent existence of dyserythropoiesis, 15% ring sideroblasts, and more than 450 × 109 /L of platelet count; the peripheral blood (PB) blasts and bone marrow (BM) blasts ought to be less than 1% and 5% respectively [11]. In the former iteration of the WHO classification, this provisional entity was denoted as "refractory anemia with ring sideroblasts related to marked thrombocytosis", but now it is a separate MDS type; recurrent SF3B1 mutations in this illness have aided its identification as a separate subtype. There is an increased number of rings sideroblasts reported at initial diagnosis in general. Due to therapy or disease progression, other recognized MPNs may exhibit augmented ring sideroblasts but such cases are not categorized as MDS/MPN RS-T [12].

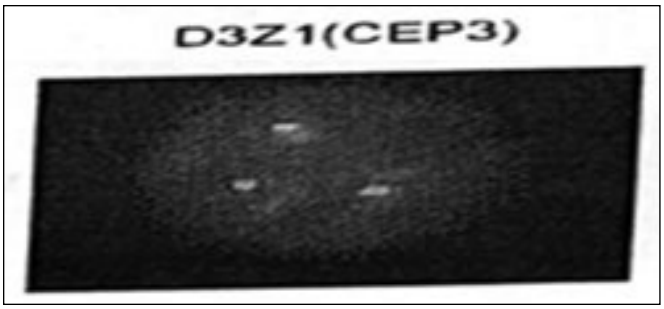

Fig. (3): Trisomy 3 (D3Z1) in 71% of the cells analyzed.

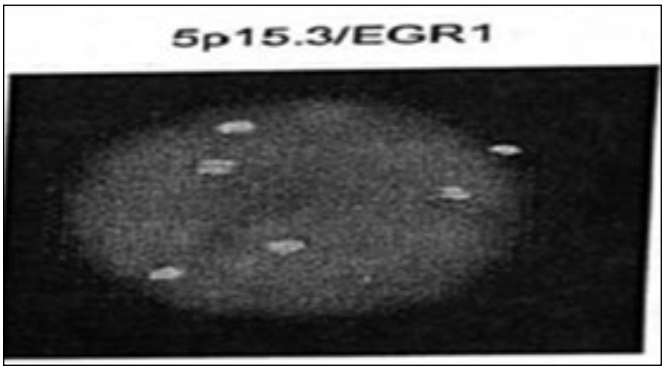

Fig. (4): One extra copy of 5p/EGR1 in 30% of the cells analyzed.

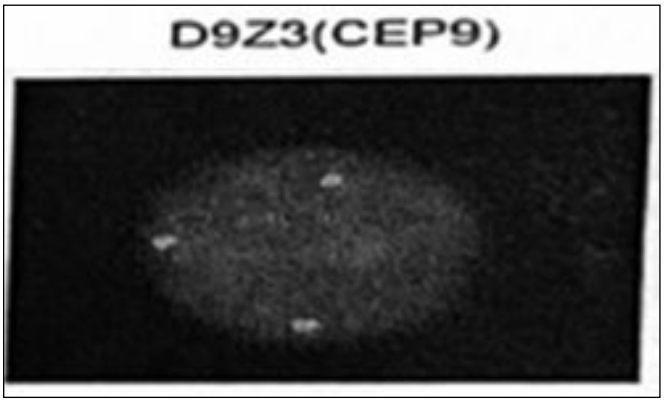

Fig. (5): Trisomy 9 (D9Z3) in 45% of the cells analyzed.

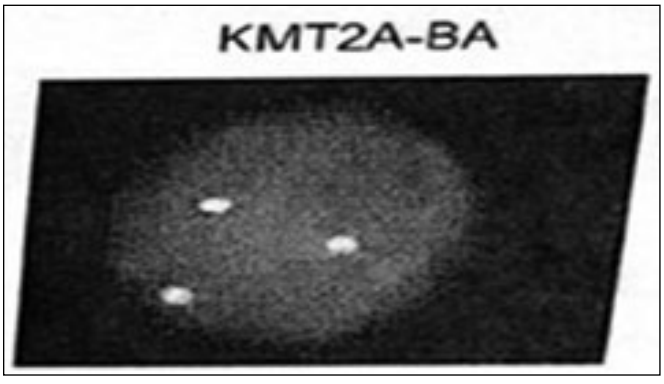

Fig. (6): One extra copy of KMT2A in 12% of the cells analyzed.

The signs and symptoms of MDS/MPN RS-T overlap with other Philadelphia-negative MPNs inclusive of essential thrombocythemia (ET) with the general occurrence of Splenomegaly (40%) and also hepatomegaly [13]. The presence of anemia is invariable and it is often macrocytic; it is helpful to distinguish

MDS/MPN RS-T from ET. The cytopenias are typically of minor degree in comparison to MDS-RS cases. Platelet anisocytosis is seen on microscopic examination of the PB involving augmented forms having irregular shapes and hypogranulation. Mild leukocytosis may be observed rarely but the leukocyte count and distribution are in normal limits typically [14].

Megaloblastoid and dysplastic erythroid hyperplasia and augmented ring sideroblasts (15%) are often seen in BM. Due to unusual perinuclear mitochondrial deposits of iron, RSs are formed. These are characterized by the existence of a minimum of 5 siderotic granules encompassing a minimum of 1/3rd of the nuclear circumference. Multilineage dysplasia may exist but is not a requirement for diagnoses. Typically, the megakaryocytes are augmented, and they look like the ones detected in other MPNs (Philadelphia-negative). Risen reticulin fibrosis may be observed in a sub-group of cases. About 10% of patients exhibit an unusual karyotype and w80% have confirmed clonality through mutation testing [11]. Myeloid neoplasms meeting conditions for MDS with isolated del(5q) and those embracing t(3;3) (q21.3;q26.2), inv(3) (q21.3q26.2) are eliminated from this group as per the definition, along with the cases having BCR-ABL1 fusion. A part of the RNA splicing machinery is SF3B1, which is the most frequent somatic mutation (>80%) seen in MDS/ MPN with RS-T. The most common variant is SF3B1 K700E (w50%) but codons 622, 625, 666, and 666 are also hot spot zones [15, 16]; SF3B1 mutations are frequently linked with JAK2 V617F (w30%–50%) and lesser with MPL or CALR mutations. There have been rare reports of concurrent JAK2 and MPL mutations but they seem to exist in exclusive clones jointly [17]. JAK2 and MPL mutations may be developed during the illness and are generally related to enhanced platelet counts. Other recurrent mutations have connection in the spliceosome machinery: SRSF2 (w7%), U2AF1 (w5%), ZRSR2 (w3%); in signaling pathways: SETBP1 (w13%), CBL(w4%); epigenetic modulators: ASXL1 (w15– 30%), TET2 (w10–25%), EZH2 (w7%), DNMT3A (w15%), IDH2 (w4%); and transcription regulators: ETV6 (w3%), RUNX1 (w1) [18, 19]. The median OS for MDS/ MPN RS-T cases is reported from 76 to 128 months, which is notably shorter in comparison to the OS of cases with ET but longer than MDS-RS cases [20]. According to the amended International Prognostic Scoring System (R-IPSS), most cases lie in the lower-risk category [21]. In this illness, the existence of SF3B1 mutation is a distinct predictor of prolonged OS (6.9 years in mutated patients *versus* 3.3 years in wild-type patients); JAK2 mutations too predict a more sluggish clinical sequence and favourable consequences [22]. On the contrary, anemia and an unusual karyotype, SETBP1 and ASXL1 mutations are linked with lesser survival [23]. ET (essential thrombocytopenia) is the chief differential diagnosis of MDS/MPN RST. Dissimilar to MDS/ MPN-RS-T, ET cases usually show characteristically normal BM cellularity, and no anemia or morphological dysplasia in the erythroid or granulocytic series. Other non-neoplastic presentations related to augmented ring sideroblasts should be distinguished from MDS/MPN RS-T. These comprise too much alcohol intake, lead poisoning, copper and pyridoxine deficiency, isoniazid treatment, and congenital sideroblastic anemia [24].

CONCLUSION

To conclude, this case is significant for the coexistence of Plasma cell myeloma with myelodysplastic syndrome and ring sideroblasts. Mutations in SF3B1 and low-level mutations in KRAS, SAMD9L, and TSC2 genes were detected. These findings are consistent with myelodysplastic syndrome with ring sideroblasts and patients with ring sideroblasts/SF3B1 (MDS-RS/MDS-SF3B1) mutation may respond to the FDA-approved drug Luspatercept. MDS/MPN have the features of both MDS and MPN. Their molecular characteristics do not display any isolating form, rather they demonstrate numerous varieties within the group. Remarkably, MDS/MPN-RS-T is observed as a true hybrid neoplasm in terms of both clinicopathological and molecular features. The NGS technology led to the discovery of common MDS mutations and overlapping syndromes. The diagnosis of these complications is dependent on the clinical, morphological and laboratory outcomes along with genomic interpretation. These mutations may likely be utilized as a source of therapeutic targets and prognostic biomarkers if there is a revised classification of MDS and overlapping syndrome.

CONSENT FOR PUBLICATION

Written informed consent was taken from the patient.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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AUTHORS' CONTRIBUTION

All authors contributed equally to the writing of the manuscript.

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