

Case Report about Myelodysplastic Syndrome/Myeloproliferative Neoplasm with Ringed Sideroblasts and Thrombocytosis (Mds/MPN-Rs-T) and Review of Literature

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Abstract

Case Report

MDS/MPN-RS-T is a clinical-biological entity of haematological malignancies border between myelodysplastic syndromes (MDS) and myeloproliferative neoplasms (MPN), declared in 2016 by WHO as a separate entity of its own unlike old classifications. Its particularity lies in the association of an MDS with ringed sideroblasts (MDS-RS) with a MPN represented in this case by its similarity to an essential thrombocytemia (ET) because of thrombocytosis. Clinically, the association of splenomegaly with chronic "refractory" anemia guides the diagnosis. Cytology is a large-scale orientation tool. It sometimes targets some signs of peripheral dysgranulopoiesis with thrombocytosis and giant platelets. Bone marrow smear shows hyperlobed megakaryocytes (similar as those found in ET or primary myelofibrosis (PMF), sometimes cytoplasmic degranulation of the granular line and often many signs of dyserythropoiesis with more than 15% of ringed sideroblasts (RS) in Prussian blue staining. However, the molecular study retains its full scope to confirm the diagnosis by objectifying the mutation SF1B3 (spliceosome gene) generally found in MDS-RS, accompanied by the mutations found in negative BCR-ABL MPN (JAK2, CAL-R and MPL), thus explaining the hybrid nature of this rare myeloid entity. This genotype can be more complex when associated with other mutations characteristic of MDS (ASXL1, DNMT3A, SETBP1 or TET2) thus worsening the prognosis of patients. We report here a case of a 56-year-old patient followed for ET whose diagnosis was renewed in MDS / MPN-RS-T by cytology and molecular biology.

Keywords: MDS / MPN-RS-T, case report, WHO 2016, SF3B1, ringed sideroblasts, thrombocytosis.

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INTRODUCTION

Formerly called refractory sideroblastic anemia with thrombocytosis (RARS-T), new molecular advances have made it possible to better understand the pathophysiological mechanisms of this entity and to push research in the direction of targeted therapies. This is the reason why WHO has been able to redefine; in its 2016 classification of haematological malignancies; this entity in MDS / MPN-RS-T [1].

It is a border pathology between MDS and MPN with a better prognosis than MDS-RS but a little darker than ET [2]. The risk of blastic transformation is low. The median age is between 71 and 75 with a sex ratio close to 1[3].

OBSERVATION

A 56-year-old patient, with no particular pathological history and who is not taking any ongoing

drug treatment, shows splenomegaly with thrombocytosis exceeding 450 G / l on several hemograms spanning a period of 4 months. He was diagnosed in 2013 for ET based on positive "JAK2 V617F" mutation. Baseline hemogram values also showed mild normocytic aregenerative normochromic anemia at 10.9 g / dl and a normal white blood cell count. The patient was treated by hydroxyurea with partial improvement of his disease.

Our patient; lost to follow-up for 3 years; returns to hematology consultation where the course was marked by worsening of his anemia at 7.1 g / dl with a MGV at 101 fl, a persistent thrombocytosis at 635 G / l and a normal leukocyte count.

The blood smear had objectified the presence of many degranulated polynuclear neutrophils (PNN) with some signs of dyserythropoiesis and macroplatelets. This was against a conventional MPN,

which pushed explorations towards a bone marrow smear cytological study which showed many signs of dysmegakaryopoiesis (nuclear hyperlobulation with gigantism), dysgranulopoiesis (lack of chromatin condensation, karyochizes and cytoplasmic degranulation) and dyserythroipoiesis (irregularity of nuclear contours, interchromatin bridges, Jolly bodies and punctuation marks). Prussian blue staining was positive and showed more than 15% of RS. Blasts rate was 1%.

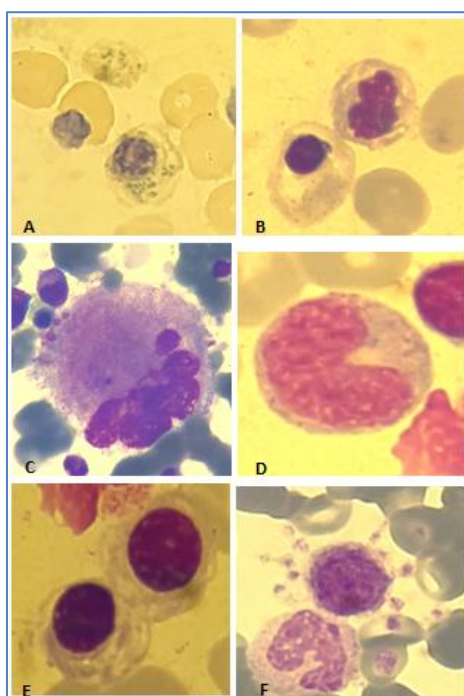
All other laboratory tests; including a cupremia; were normal.

The karyotype was normal in 30 mitoses studied.

NGS sequencing of a variety of genes had demonstrated the concomitant presence of two recurrent and deleterious mutations: JAK2 and SF3B1.

The diagnosis then shifted to a MDS / MPN-RS-T syndrome according to all biological criteria previously cited and to the 2016 WHO classification of haematological malignancies.

The patient was put on anagride for his thrombocytosis with aspirin, erythropoietin and blood transfusions for his anemia.



- A. Ringed sideroblasts.
- B. Dyserythroipoiesis (irregular nuclear contours, cytoplasmic basophil marks).
- C. ET like megakaryocyte.
- D. Dysgranulopoiesis (hypogranular metamyelocyte).
- E. Cytoplasmic deshemoglobinisation of erythroblasts.
- F. Giant platelet on peripheral blood smear

Fig-1 : Microscopic images of bone marrow and peripheral blood smears colored by MGG (×1000)

DISCUSSION

Through this observation, we report a rare case of a pathology reclassified in 2016 by the WHO as being an entity of its own, based on a better knowledge of its pathophysiological mechanisms in the hope of a targeted therapy already subject numerous clinical trials (spliceosome inhibitors) [4-7].

In our patient, being mistakenly considered as a MPN (ET), cytology contributed with great help to the suspicion of the diagnosis of MDS /MPN-RS-T and to the orientation of other biological assays for confirmation.

Detection dysgranulopoiesis signs in peripheral blood smear guided us to bone marrow and Prussian blue staining which showed 24% of ringed sideroblasts (RS). These are erythroid precursors containing iron-loaded mitochondria surrounding more than a third of nuclear circumference [8].

In this case, a survey carried out in our patient, despite of non-clonal conditions of RS, could guide the search of genetic anomalies of haematological malignancies associated with the RS phenotype.

Table-1: Causes of bone marrow ringed sideroblasts [8]

Clonal diseases
1. Myelodysplastic syndromes (MDS) + Refractory anemia with ringed sideroblasts (RARS) + Refractory cytopenia with multilineage dysplasia and ringed sideroblasts (RCMD-RS) + Refractory cytopenias with excess blasts-1/2 (RAEB-1/2) + Unclassifiable MDS (MDS-U) 2. Myeloproliferative neoplasms (MPN) + Essential thrombocythemia (ET) + Primary myelofibrosis (PMF) 3. MDS/MPN overlaps syndromes + MDS/MPN with ringed sideroblasts and thrombocytosis (MDS/MPN-RS-T) + Chronic myelomonocytic leukemia (CMML) + Unclassified MDS/MPN
Non-clonal conditions
1. Hereditary sideroblastic anemia + defect in heme synthesis XLSA (X linked sideroblastic anemia) – mutations in ALAS2 and SLC 25A38 + defect in Fe-S cluster biogenesis and protein synthesis XLSA/A (X-Linked sideroblastic anemia with ataxia)-mutations in ABCB7 and GLRX5 + defects in mitochondrial respiration MLASA (mitochondrial myopathy, lactic acidosis, and SA)-mutations in PUS1 and YARS2 PMPS (Pearson’s marrow-pancreas syndrome)-deletions, rearrangements, or duplications of mitochondrial DNA SIFD (congenital SA associated with B-cell immunodeficiency, periodic fevers, and developmental delay)-mutations in TRT1 NDUFB11-mutated sideroblastic anemia HSPA9-mutated sideroblastic anemia 2. Acquired conditions + Excess alcohol + Drug exposure (isoniazid, chloramphenicol, linezolid and penicillamine) + lead zinc toxicity + copper deficiency

The link between mutations in spliceosome genes and the RS phenotype has been observed in several studies since 2011 [9,10]. These genes are physiologically involved in the maturation processes of mRNAs by regulating the different key stages of splicing. These are SF3B1 (Splicing Factor 3 Binding partner 1), SRSF2 (Serine and arginine-Rich Splicing

Factor 2), U2AF1 (U2 small nuclear RNA Auxiliary Factor 1) and ZRSR2 (Zinc finger CCCH-type RNA binding motif and Serine / arginine Rich 2). Mutations within these genes, always heterogeneous, lead to the formation of aberrant transcripts having an impact on the pathophysiology depending on the cell type.

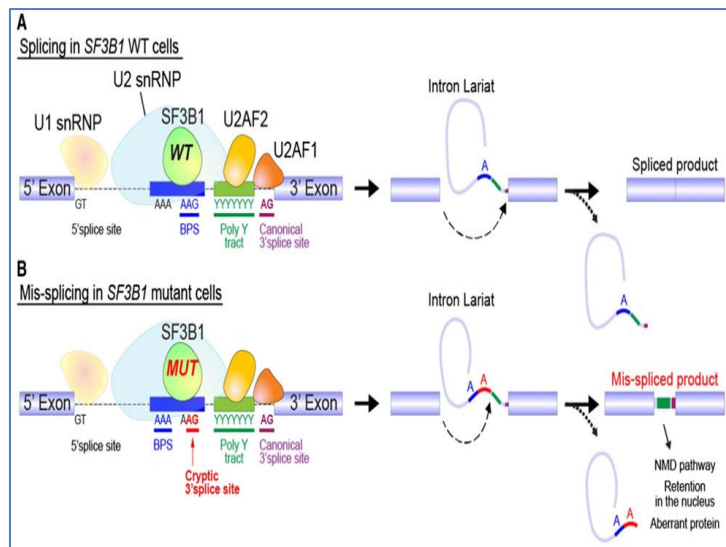


Fig-2: [8] Splicing catalysis, the spliceosome assembly pathway, and mechanisms of splice site selection in SF3B1 wild-type (WT) and mutant (MUT) cells.

A. Diagram of the 2 sequential transesterification reactions that represent the crucial catalytic steps in intron removal during splicing. An adenine nucleotide (termed the "invariant adenine") of the branch point sequence (BPS) initiates the first transesterification and generates a free 5' exon and intron-3' exon lariat. The 3' end hydroxyl of the free 5' exon then attacks the intron-3' exon junction. Completing the splice and releasing a lariat RNA intron.

A. Mechanisms of splice site selection in SF3B1 WT cells. An intron is defined via (i) the 5' splice site, (ii) the 3' splice site, (iii) the branch point sequence (BPS), and (iv) the polypyrimidine (poly-Y) tract. The definition of an intron depends on recognition of the 5' splice site and BPC by U1 and U2 small nuclear ribonucleoproteins (snRNPs), respectively. The earliest complex (complex E) is established by binding of (i) U1 snRNP to the 5' splice site, (ii) splicing factor 1 (SF1) to the BPS, (iii) U2AF2 (also known as U2AF65) to the polypyrimidine tract, and (iv) U2AF1 (also known as U2AF35) to the 3' SS. Formation of complex E in turn enhances the recruitment of U2 snRNP to BPS and leads to the formation complex A. SF3B1, a component of U2 snRNP, is involved in the binding to the BPS. Further assembly of other spliceosomal components, conformational rearrangements, and the two-step esterification reactions that mediate excision of the intron and ligation of the proximal and distal exon to synthesize mature mRNA follows these reactions.

B. potential mechanisms of splice site selection in SF3B1 mutant cells. Our current understanding suggests that aberrant splicing mediated by mutant SF3B1 utilizes a cryptic AG, and requires the canonical 3' splice site. Moreover, the cryptic AG requires the downstream canonical polypyrimidine tract to cause alternative splicing, and three adenosines upstream of the cryptic AG are part of the BPS for mutant SF3B1 but not for WT SF3B1.

The SF3B1 mutation has been shown to correlate with MDS-RS in more than 70% of cases and with MDS / MPN-RS-T in more than 80% of cases [11,12] with a positive predictive value for the RS phenotype comparable to 97.7% same as negative predictive value [13]. However, the exact link between the formations of RS in the event of an SF3B1 mutation has not yet been elucidated.

Association of SF3B1 mutation with JAK2 is present in 50% of patients with SMD / SMP-RS-T [14], although many other mutations encountered in negative BCR-ABL SMP may occur [15-19].

Regarding the prognosis of this entity, it has been shown to be more painless than the majority of MDS with RS phenotype [2], but few studies have been able to integrate the occurrence of the SF3B1 mutation

as being a factor involved in general patient survival or blastic transformation [20].

Treatment of MDS / MPN-RS-T anemia is similar to low-risk MDS based on blood transfusions. Other studies have demonstrated the effectiveness of lenalidomide in alleviating transfusion needs [21, 22]. In addition, ongoing clinical trials have used molecules such as luspatercept and are still in the design phase [23]. For the thrombotic risk linked to thrombocytosis and thrombopathies, it is advisable to use aspirin at a low dose of 100 mg / day [24]. Cytoreductive treatments; likely to exacerbate anemia; are only used in cases of high thrombotic risk [25].

CONCLUSION

The analysis of this case confirms the complexity of the diagnosis of this new entity "MDS / MPN-RS-T". It is based on cytological analysis and cytogenetic, molecular and phenotypic studies. Searching for mutations of SF3B1 and genes conventionally found in negative BCR-ABL1 MPN (JAK2, MPL, CALR) is necessary for diagnosis.

The association of these two types of mutations confirms the hybrid MDS / MPN nature of this new entity. Therapeutic approaches are largely inspired by those of MDS-RS and cytoreductive strategies of MPN. The advent of targeted therapies has made it possible to use JAK2 inhibitors in patients with proliferative symptoms but also spliceosome inhibitors. These are expected to appear in future clinical trials.

This study thus highlights the advantage of carrying out a molecular study in the diagnosis and monitoring of an MDS/MPN-RS-T, in order to detect the initiating mutations and possible anomalies acquired during the course of this disease; these can indeed impact the prognosis of the pathology but also the therapeutic management.

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