

## Leukaemia Section

### Short Communication

# Myelodysplastic/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T)

Matthew Koo, Robert S. Ohgami

Department of Pathology, Stanford University, Stanford, CA, USA;  
ROhgami@stanfordhealthcare.org

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## Abstract

Review on Myelodysplastic/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis

### Keywords

Myelodysplastic syndrome; myeloproliferative syndrome; ring sideroblasts; thrombocytosis

## Clinics and pathology

### Disease

Myelodysplastic/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T), formerly a provisional diagnosis of refractory anemia with ring sideroblasts associated with marked thrombocytosis (RARS-T) under the MDS/MPN unclassifiable group, has been recognized as a full entity in the 2016 WHO classification (Arber et al., 2016). It is characterized by thrombocytosis of  $\geq 450 \times 10^9/L$ , refractory anemia, dyserythropoiesis with excess ring sideroblasts ( $\geq 15\%$  of erythroid precursors, irrespective of SF3B1 mutational status), and megakaryocytes morphologically resembling that which may be seen in primary myelofibrosis (PMF) or essential thrombocythemia (ET).

### Phenotype/cell stem origin

The etiopathogenesis of MDS/MPN-RS-T is heterogeneous (Gurevich et al., 2011). Ring

sideroblasts be a manifestation of abnormal erythropoiesis with mitochondrial iron overload (Patnaik et al., 2015).

### Epidemiology

MDS/MPN-RS-T is a rare disorder accounting for  $< 1\%$  of all cases of MDS (Orazi et al. 2008).

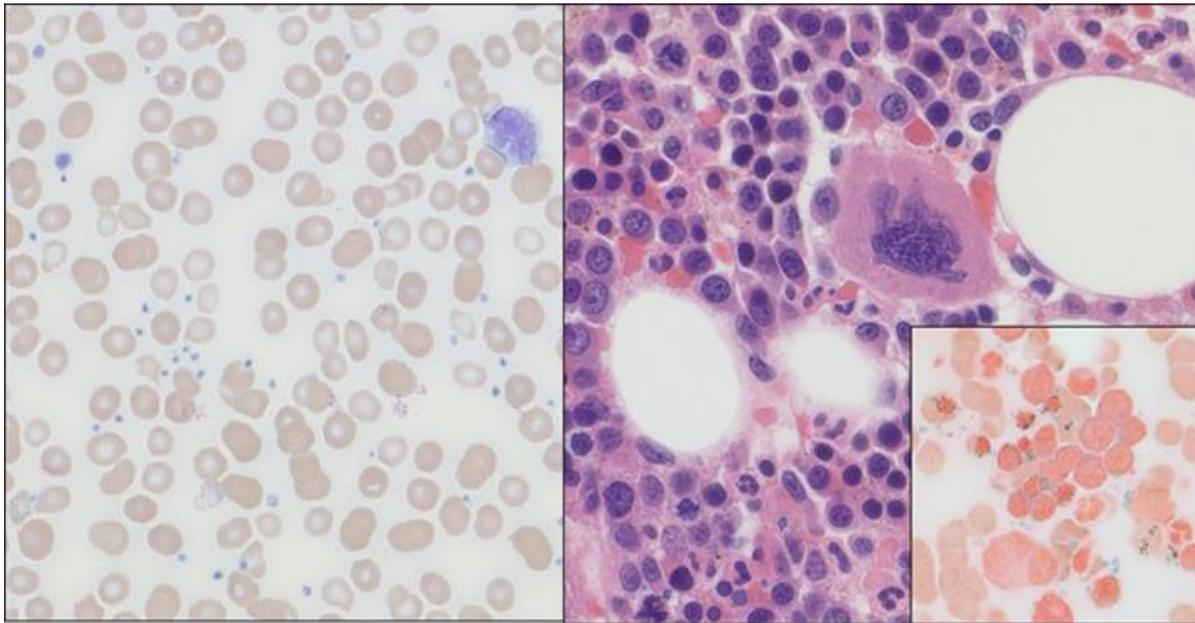
In one study of 18 patients, M:F ratio was 1.25:1 and age range was 40-83 years with a median of 66 years (Gurevich et al., 2011).

### Clinics

The Gurevich et al. study also found presenting signs and symptoms of fatigue (5/18), "heavy"/abnormal menstrual bleeding (2/18), nosebleed (2/18), upper respiratory tract infection/flu-like symptoms (2/18), weight loss (1/18), and chest pain (1/18). 5/18 patients reported no significant symptoms and presented with incidental anemia and/or thrombocytopenia. Splenomegaly was palpable in 2/18 patients; the remainder of the patients (16/18) had an unremarkable physical examination.

Platelet count ranged from  $515-1100 \times 10^9/L$  with a median of  $645 \times 10^9/L$ . Hemoglobin ranged from 7.2-12.6 g/dL with a median of 10.2 g/dL. Leukocyte count was normal in 14/18 patients and slightly below reference range in 1/18 patients.

The remaining 3/18 patients showed a mildly elevated leukocyte count that ranged from  $12.9-16.3 \times 10^9/L$  (Gurevich et al., 2011).



**Figure:** Image showing a peripheral blood smear in the left panel with thrombocytosis. A bone marrow biopsy is shown on the right with an atypical megakaryocyte and numerous ring sideroblasts (right inset).

## Pathology

Peripheral blood findings include thrombocytosis with megathrombocytes, macrocytic or normocytic normochromic anemia with anisopoikilocytosis, and myeloid left shift with mild dysplastic features. Bone marrow aspirate smear findings include increased megakaryocytes, myeloid left shift with mild dysplastic features (including hypogranulation and abnormal nuclear lobation) and <5% blasts, relative erythroid preponderance with dysplastic features (including nuclear-cytoplasmic dyssynchrony, megaloblastic changes, binucleated erythrocytes, karyorrhexis, and nuclear budding) and increased ring sideroblasts ( $\geq 15\%$ ).

Bone marrow core biopsy and clot section findings include a hypercellular marrow with megakaryocyte hyperplasia and increased clustering with dysplastic cytomorphology (including abnormally large, hyperchromatic, hypolobated, and micromegakaryocytic forms) (Gurevich et al., 2011).

## Treatment

Management is typically individualized to address the anemia (erythropoiesis stimulating agents and/or transfusion) and the thrombotic risk (aspirin).

The value of cytoreductive therapy (hydroxyurea, lenalidomide, IFN- $\gamma$ , busulfan, anagrelide) is uncertain and may exacerbate the baseline anemia.

## Prognosis

Using either the IPSS for MDS or the revised IPSS,

most patients with MDS/MPN-RS-T fall into a low risk group.

Overall prognosis is intermediate between that of ET and myelodysplastic syndrome with ring sideroblasts (MDS-RS) (Patnaik et al. 2015). Compared to patients with ET, patients with MDS/MPN-RS-T have been found to have a shorter overall and leukemia-free survival but a lower risk of thrombosis. Compared to patients with MDS-RS, patients with MDS/MPN-RS-T have been found to have better survival but a higher risk of thrombosis (Broseus et al., 2012).

## Genetics

### Note

Somatic mutations in several genes are seen in MDS/MPN-RS-T. Notably mutations in JAK2 are frequent, seen in 30-70% of cases.

Most cases harbor a specific JAK2 point mutation: JAK2V617F.

Mutations in SF3B1 are also common (70-95% of cases) and associated with the morphologic finding of ring sideroblasts.

MPL and CALR mutations are rare (<5% of cases).

## Cytogenetics

### Cytogenetics morphological

No clonal cytogenetic abnormality is detected in about 80% of patients (Patnaik et al., 2015). Recurrent cytogenetic abnormalities have not been described to date.

## Genes involved and proteins

### **MPL (MPL proto-oncogene, thrombopoietin receptor)**

**Location** 1p34.2

#### **Protein**

MPL encodes for CD110, also known as thrombopoietin receptor, which plays a critical role in thrombopoiesis. Thrombopoietin (THPO)-CD110 binding leads to receptor dimerization and downstream signaling. Mutations leading to constitutive activation of CD110 have been linked to overproduction of abnormal megakaryocytes (Tefferi et al., 2014).

### **SF3B1 (splicing factor 3b subunit 1)**

**Location** 2q33.1

#### **Protein**

SF3B1 encodes for subunit one of the splicing factor 3b protein complex. Splicing factor 3b, splicing factor 3a, and a 12S RNA unit combine to form the U2 small nuclear riboproteins complex (U2 snRNP). The splicing factor 3a/3b complex may function as an anchor region for U2 snRNP to bind pre-mRNA.

### **JAK2 (janus kinase 2)**

**Location** 9p24.1

#### **Protein**

JAK2 encodes for the predominant kinase of erythropoietin receptor signaling. JAK2<sup>V617F</sup> mutations lead to constitutive activation of and downstream signalling by this kinase, which allows hematopoietic cells to grow in a cytokine-independent manner.

### **CALR (calreticulin)**

**Location** 19p13.13

#### **Protein**

CALR encodes for calreticulin, which has many functions including calcium homeostasis, protein folding, cell proliferation, and apoptosis. CALR mutations may be found in patients with JAK2-negative/MPL-negative ET and PMF.

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