Received: 16 November 2021 | Revised: 25 November 2022 | Accepted: 5 May 2023

DOI: 10.1002/ccr3.7409

CASE REPORT

Clinical Case Reports Open Access WILEY

# A case of MDS/MPN overlap syndrome with ring sideroblasts and thrombocytosis: Tackling the quandary of thrombosis versus hemorrhage

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**Key Clinical Message**

No formal treatment guidelines for MDS/MPN-RS-T exist. With salient features such as anemia and thrombocytosis, management is individualized and aims to address anemia, thrombosis, and in some cases acquired von Willebrand's disease.

**Abstract**

Myelodysplastic/myeloproliferative overlap syndrome with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T) is a rare myeloid neoplasm showing myelodysplastic and myeloproliferative features. With extremely raised platelets, possibility of acquired von Willebrand and risk of hemorrhage is increased. With this quandary in mind, a descriptive case and a brief discussion of available treatments ensues.

**KEYWORDS**

myelodysplastic/myeloproliferative overlap disorders, ring sideroblasts, splicing factor 3b subunit 1

## 1 | INTRODUCTION

Rare, indolent, and likely due to stepwise accumulation of molecular mutations, MDS/MPN overlap syndrome with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T) is a myeloid neoplasm associated with dysplasia and cytopenias as well as myeloproliferation and cytoses.[1] Therefore, in this entity, driver mutations of *JAK2 V617F* but also *CALR* and *MPL W515* have been attributed to the proliferative features, whereas the presence of ring sideroblasts, dyserythropoiesis, and cytopenias are attributable to *SF3B1 (K700E)* or other similar mutations.[2] Previously being a provisional entity in the 2008 iteration of WHO, this disorder is now fully characterized requiring persistent thrombocytosis ($>450\times0^9$/L), anemia with erythroid/multilineage dysplasia, ≥15% ring sideroblasts, <1% blasts in the peripheral blood, and <5% blasts in the bone marrow. Other diagnostic requirements include the presence of *SF3B1* mutation and lack of reactive causes of ring sideroblasts, diagnosis of other myeloproliferative or myelodysplastic entities and absence of certain gene rearrangements diagnostic of other myeloid neoplasms (i.e., *BCR-ABl1*, *PDGFRA*, *PDGFRB*, *FGFR1*, *PCM1-JAK2*, *t(3;3)(q21q26)*, *inv* (3)*(q21q26)*, *or del (5q) (MDS with thrombocytosis)*).[1] A descriptive case of an elderly patient with MDS/

MPN-RS-T presenting with critical thrombocytosis with incident hematomas follows.

## 2 | CASE PRESENTATION

A 90-year-old man was admitted to our hospital with symptomatic microcytic anemia and a swollen left leg. His pertinent past medical history included atrial fibrillation for which he was anticoagulated with rivaroxaban. His hemoglobin on arrival was 63 g/L with an MCV of 70 fL showing biochemical evidence of iron deficiency. At the same time, his complete blood count (CBC) was notable for marked thrombocytosis ($2114\times10^9$/L) and neutrophil predominant leukocytosis ($16.3\times10^9$/L). Circulating blasts were not flagged. An ultrasound of his lower limbs demonstrated two hematomas within the left calf measuring $10.7\times4.9\times1.7$ cm and $12.5\times6.0\times3.0$ cm, respectively, (Figure 1, panel A, posterior and medial complex fluid collection (yellow arrows) consistent with a hematoma is seen). As well, imaging evidence of chronic deep vein thromboses in the right and left popliteal veins was present (Figure 1, panel B, right popliteal vein (red arrow) demonstrating circumferential thickening (yellow arrows) consistent with thrombus formation is shown). Upper and lower endoscopic assessment demonstrated no evidence of bleeding and testing for acquired von Willebrand disease was within normal limits. Specifically, von Willebrand indices were normal (antigen at 1.26 IU/ML (range 0.5–1.7), ristocetin cofactor activity at 0.5 IU/mL (range 0.5–1.5) and factor VIII at 1.48 IU/mL (range 0.5–1.5). Multimers analysis is not done at our institution. In view of normal values bleeding due to vWD was excluded. Given his anemia and hematomas, his anticoagulation was held. He was subsequently treated with packed red cell transfusion and IV iron sucrose infusion. In lieu of the degree of thrombocytosis which was not in keeping with hemorrhage or iron deficiency, in addition to dysplastic features (e.g., giant pale platelets) on peripheral blood film review, a bone marrow biopsy was requested and performed. The aspirate showed morphologic evidence of dyserythropoiesis such as normoblasts with irregular nuclear contours, multinucleated precursors, and presence of ring sideroblasts (Figure 1, panels C,D and I ×50 magnification; please see black arrows). Presence of hypogranular/pelgeroid granulocytes and frank micromegakaryocytes provided evidence of multilineage dysplasia (Figure 1, Panels C–E). Extremely large multinucleated megakaryocytes (so called "staghorn" type) that exhibited loose cellular association in aggregates were some myeloproliferative features as identified by trephine hematoxylin and eosin (H&E). Cluster of differentiation 61, part of the antigenic glycoprotein IIb/IIIa complex, is expressed on platelets and megakaryocytes, and underlines the number and morphology of the megakaryocytes confirming the H&E results (CD61; Figure 1, panels F–H ×50 magnification). Further ancillary testing demonstrated a normal male karyotype as well as mutations in genes additional sex combs-like 1 (*ASXL1*), DNA methyltransferase 3 alpha (*DNMT3A*), Splicing factor 3B subunit 1 (*SF3B1*), and Janus kinase 2 (*JAK2*) facilitating the diagnosis of MDS/MPN-RS-T. Upon radiographic stabilization of his hematoma, anticoagulation was reinitiated. At discharge the patient was treated with 500 mg P.O. daily hydroxyurea resulting in reduction in his platelet count to $686\times10^9$/L 2 weeks post his admission. He remains stable in the community on this same dose of hydroxyurea.

## 3 | DISCUSSION

### 3.1 | Molecular basis of MDS/MPN overlap syndrome

Previously known as refractory sideroblastic anemia with thrombocytosis (RARS-T), MDS/MPN-RS-T manifests with clinicopathological features of refractory anemia with ring sideroblasts and essential thrombocythemia (ET). This predictably translates into prognosis that is better than that seen in patients with MDS but worse than in those with ET. For instance, this entity has a better overall survival and a lower rate of leukemic transformation as compared to MDS-RS-SLD, both of which are worse as compared to ET.[3] Now fully characterized in the newest WHO (World health organization classification of tumor of hematopoietic and lymphoid Tissues), the molecular basis for the dual nature of this entity has been elucidated and includes mutation of driver genes that result in myeloproliferation as well as myelodysplasia. The decreasing rank order of such mutations include *SF3B1*, *JAK2*, *ASXL1*, *DNMT3A*, and *SETB1*. Up to 50% of the affected patients harbor the first two mutations simultaneously.[4,5] Specifically, *SF3B1*, which resides in the spliceosome complex, is mutated in approximately 80% of these patients and results in abnormal splicing of the mitochondrial iron transporter solute carrier family 25 member 37 *SLC25A37*.[6] Consequentially, ring sideroblasts and ineffective erythropoiesis are seen and translate clinically to anemia. Found in myeloproliferative neoplasms among others, Janus kinase 2 mutation is seen up to 60% of MDS/MPN-RS-T patients. The wild-type protein is a nonreceptor tyrosine kinase mediating a proliferative response to erythropoietin, thrombopoietin, and granulocyte colony stimulating factor (GCSF) by acting on their appropriate receptors. The downstream effectors include the

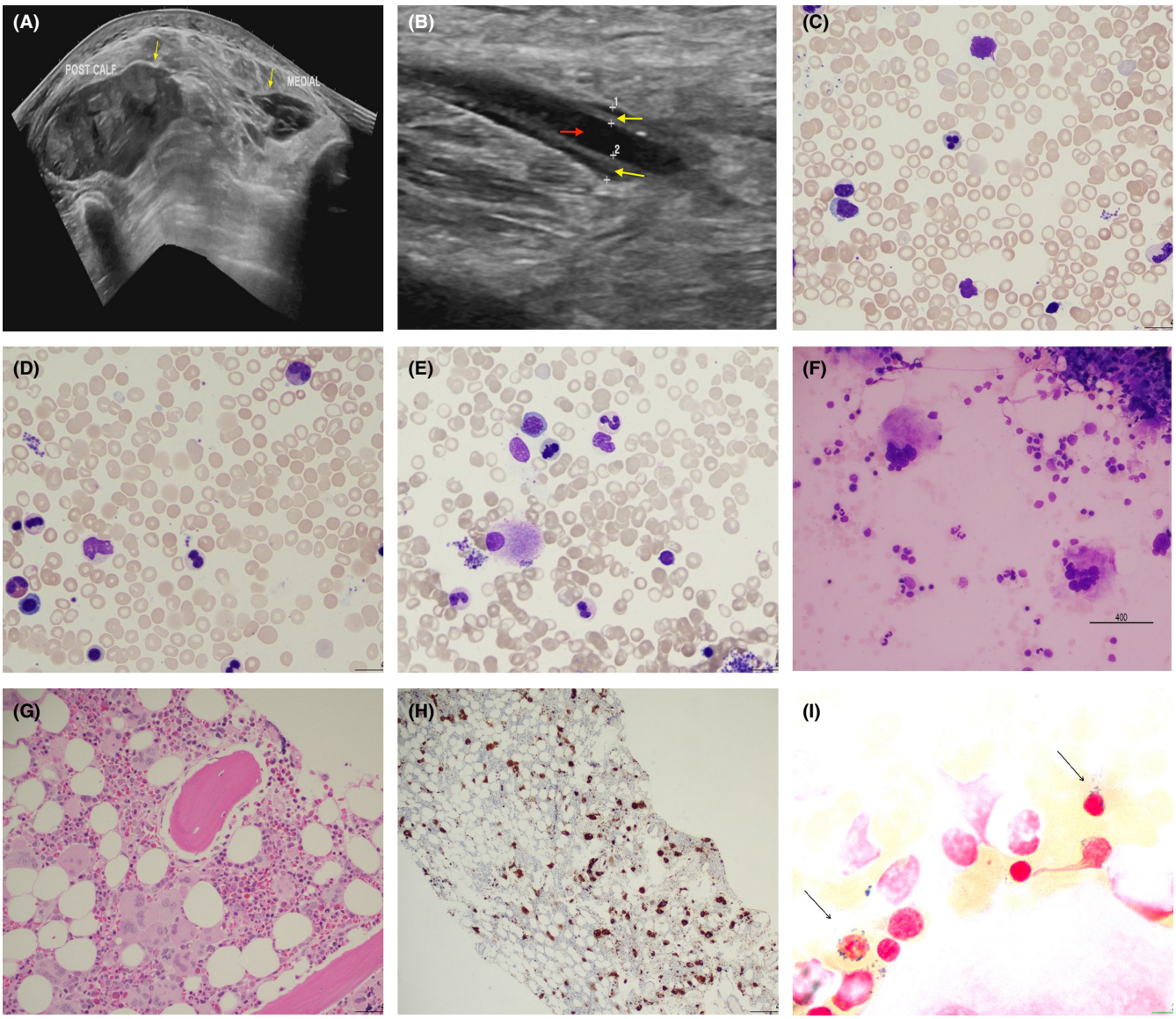


**FIGURE 1** Morphological features of myelodysplasia and myeloproliferation are evident. Ultrasound images of the left calf demonstrating a posterior and medial complex fluid collection (yellow arrows) consistent with a hematoma is shown (panel A). Ultrasound image of the right popliteal vein (red arrow) demonstrating circumferential thickening (yellow arrows) consistent with thrombus possibly of chronic etiology (panel B). Evidence of dyshematopoiesis is shown (panels C–E ×50 magnification). Accordingly, normoblasts with irregular nuclear contours, pelgeroid neutrophils, and small hypolobated megakaryocytes are seen. Features of a myeloproliferative neoplasm includes presence of large megakaryocytes with so called "staghorn nuclei" (panel F ×50 magnification) showing loose cellular aggregates (trephine H&E, ×20, and CD61 ×10 magnification). Two ring sideroblasts are shown (panel I, Perl's Prussian blue stain for iron ×100 magnification).

mitogen activated protein and phosphoinositide 3 kinases (MAPK and PI3K, respectively) as well as the signal transducer and activator of transcription (STAT) pathways.[7,8] Unregulated, factor independent constitutive activation of these pathways is the basis of the myeloproliferation seen in these neoplasms. Alternatively, and in place of *JAK2*, a frameshift mutation of the calreticulin molecule (*CALR*) can cause deletion of a KDEL (lysine, aspartate, glutamate and leucine) sequence found on the wild-type protein. The resultant mutant binds to the N-glycosylated extracellular domain of the thrombopoietin receptor similarly causing the mitogen independent and persistent activation of the STAT5, MAP, and PI3/AKT pathways.[9,10] A mutation in myeloproliferative leukemia protein (*MPL*; alternatively known as CD110 or thrombopoietin receptor) itself can cause a similar outcome.[11,12] The extent of gene expression is tightly regulated and aberrancy in molecular mechanisms that achieve these mechanisms can cause genetic dysregulation and oncogenesis. Some of these mechanisms include methylation, acetylation, or

phosphorylation of DNA packaging histones that organize the chromatin into nucleosomes. Polycomb repressive complex 2 (PRC2) encoded by enhancer of zeste homologue2 (*EZH2*) is the catalytic domain of the histone H3 lysine 27 methyltransferase. Additional of sex combs-like (*ASXL1*) is a related protein that recruits PRC2 complex resulting in histone modification. Its loss of function by mutation results in loss of polycomb repression and myeloid transformation. DNA methyl transferase 3A (*DNMT3A*) adds a methyl group to 5′cytosine in CpG causing global gene silencing via formation of 5-methylcytosine. Ten-eleven translocation 2 (*TET2*) causes the demethylation of DNA by converting the resultant 5-methyl cytosine via hydroxylation. Isocitrate dehydrogenase 1/2 (*IDH1/2*) provide the α-ketoglutarate required for this reaction. Mutations in any of these actors can functionally decrease the resultant DNA methylation and gene silencing triggering myeloproliferation.[13–15]

## 3.2 | Anemia, thrombosis, and adaptive therapy

In this neoplasm, the risk of thrombosis is similar to ET where overall survival is impacted by presence of *SF3B1* but not *JAK2* mutations and/or prior history of thrombosis.[16] The mechanism of increased thrombotic predisposition is not clear and requires further studies. However, similar to ET a relative loss of endothelium derived relaxing factor (EDRF or nitric oxide) by platelet uptake may be involved. The result is vasomotor symptoms such as migraines, palpitation, and erythromelalgia along with vascular stasis with arterial and venous thrombosis.[17,18] At an extremely high platelet counts ($>1000\times10^9$/L) a therapeutic quandary may exist where some patients can develop an acquired von Willebrand's disease and hemorrhage. This is presumably also due to abnormal platelet uptake and factor destruction. In absence of a high platelet count and increased risk of bleeding, low dose aspirin may be beneficial in treating arterial thromboses along with a significant decrease in vasomotor symptoms. In the setting of a contraindication to aspirin, other antiplatelet agents (clopidogrel, prasugrel, and ticagrelor etc.) work similarly.[19–21] Proper evaluation for acquired von Willebrand' s includes measuring von Willebrand antigen, ristocetin cofactor activity, and multimers analysis.[22] With concomitant anemia the use of cytoreductive therapy is nuanced and may exacerbate the existing anemia. Consequently, its use must be justified against a significant increase in risk of thrombosis. Specifically, if cytoreductive therapy is indicated, hydroxyurea or second line agents such as, lenalidomide, interferon alpha, or busulfan have been used and are effective against acquired von Willebrand with improvement in bleeding symptoms.[23,24] The management of anemia is similar to treatment of lower risk MDS and includes transfusion support and the use of erythropoietin stimulating agents (ESA).[25,26] In normal erythropoiesis, the binding of TFG beta superfamily ligand to activin receptor type IIB causes phosphorylation of downstream small mothers against decapentaplegic (SMAD) 2/3 with overall inhibition of erythroid maturation and cellular regeneration. Luspatercept is a recently FDA approved fusion protein partly made up of modified extracellular domain of activin receptor type IIB and human IgG1 Fc domain. This molecule can effectively trap the transforming growth factor (TGF) beta superfamily ligand making it unavailable for signal transduction. The end effect is promotion of erythroid maturation and effective erythropoiesis.[27] Reserved for refractory or progressive cases, and confounded by graft-versus-host disease and nonrelapse mortality, allogeneic stem cell transplantation is the only curative therapy.[28]

## AUTHOR CONTRIBUTIONS

**Hannah Cherniawsky:** Conceptualization; writing – original draft; writing – review and editing. **Habib Moshref Razavi:** Conceptualization; resources; supervision; writing – original draft; writing – review and editing.

## FUNDING INFORMATION

There is no funding associated with submission.

## DATA AVAILABILITY STATEMENT

No data were used in the current study.

## CONSENT

Authors confirm that patient consent has been signed and collected in accordance with the journal's patient consent policy.

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**How to cite this article:** Cherniawsky H, Razavi HM. A case of MDS/MPN overlap syndrome with ring sideroblasts and thrombocytosis: Tackling the quandary of thrombosis versus hemorrhage. *Clin Case Rep*. 2023;11:e7409. doi:10.1002/ccr3.7409