

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

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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 discussion of available treatments ensues

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Abstract (50 words) :

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.

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 cytoses¹. 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 chiefly associated with *SF3B1 (K700E)* or other similar mutations². Previously being a provisional entity in the 2008 iteration of WHO, this disorder is now fully characterized requiring persistent thrombocytosis ($> 450 \times 10^9/L$), anemia with erythroid /multilineage dysplasia, $\geq 15\%$ 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. Here we describe a case of an elderly patient with hematomas, and critical thrombocytosis (initially suspect for acquired von Willebrand disease) who was diagnosed with MDS/MPN-RS-T.

Case presentation.

A 90-year old gentleman 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 ($2114 \times 10^9/L$) and neutrophil predominant leukocytosis ($16.3 \times 10^9/L$). Circulating blasts were not flagged. An ultrasound of his lower limbs demonstrated two hematomas within the left calf measuring $10.7 \times 4.9 \times 1.7$ cm and $12.5 \times 6.0 \times 3.0$ cm respectively (Figure, 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, 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. 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 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, panels C-D and I x 50 magnification; please see black arrows). Presence of hypogranular/pelgeroid granulocytes and frank micromegakaryocytes provided evidence of multilineage dysplasia (Figure, 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) and cluster of differentiation 61 (CD61; figure, panels F-H x 50 magnification). Further ancillary testing demonstrated a normal male karyotype as well as mutations in genes *ASXL1*, *DNMT3A*, *SF3B1* and *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 $686 \times 10^9/L$ two weeks post his admission. He remains stable in the community on this same dose of hydroxyurea.

Discussion .

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 compared to ET³.

Now fully characterized in the newest WHO, 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 splicing factor 3 binding partner 1 (*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 *SLC25A37*.⁶ Consequently, 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 non-receptor tyrosine kinase mediating a proliferative response to erythropoietin, thrombopoietin and granulocyte colony stimulating factor (G-CSF) by acting on their appropriate receptors. The downstream effectors include the mitogen activated protein and phosphoinositide 3 kinases (MAPK, 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 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. One such mechanism includes 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 myeloproliferation¹³⁻¹⁵.

Anemia, thrombosis and adaptive therapy

In this entity, 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 thrombosis¹⁶. 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, erythromelalgia along with vascular stasis with arterial and venous thrombosis^{17,18}. At an extremely high platelet counts ($>1000 \times 10^9/L$) 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, ticagrelor etc.) work similarly¹⁹⁻²¹. Proper evaluation for acquired von Willebrand's includes measuring von Willebrand antigen, ristocetin cofactor activity and multimers analysis²². 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 TGF beta superfamily ligand to activin receptor type IIB causes phosphorylation of downstream 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 TGF beta superfamily ligand making it unavailable for signal transduction. The end effect is promotion of erythroid maturation and effective erythropoiesis²⁷. Reserved for refractory or progressive cases, and confounded by graft versus host disease and non-relapse mortality, allogeneic stem cell transplantation is the only curative therapy²⁸.

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

Data Availability

No data were used in the current study

Conflicts of interest

None

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Consent statement

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

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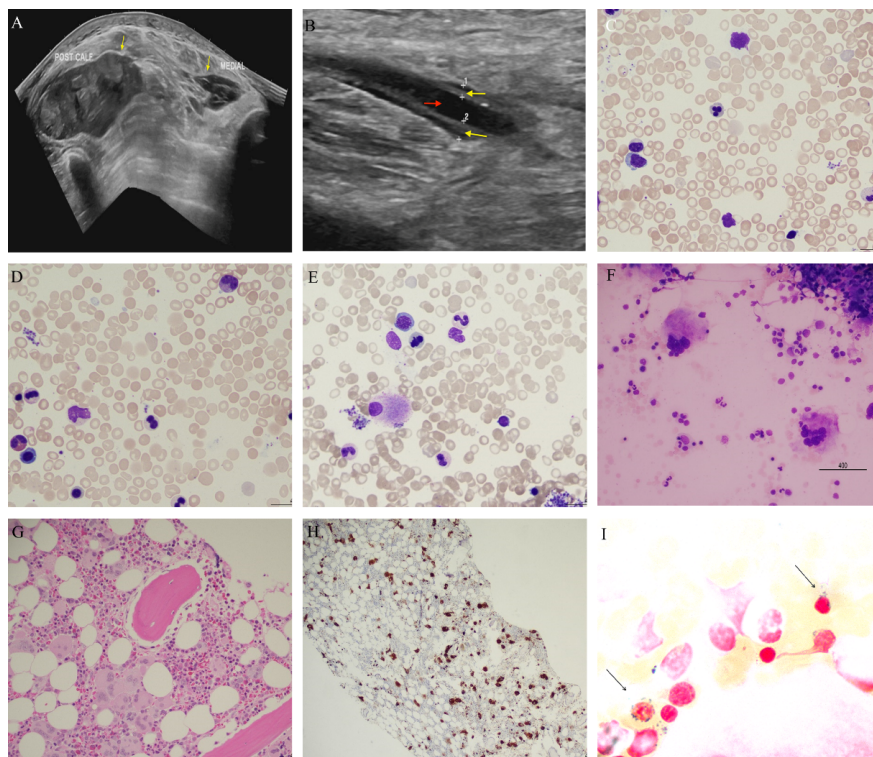


Figure.

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 x50 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 X 50 magnification) showing loose cellular aggregates (trephine H&E, X20 and CD61 X10 magnification). Two ring sideroblasts are shown (panel I, Perl’s Prussian blue stain for iron X 100 magnification).

