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Is Myeloproliferative Neoplasm with Splanchnic Vein Thrombosis a Distinct Clinical Entity?

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CLINICAL HISTORY

A 29 year-old previously healthy female presented with sub-acute symptoms of weight loss, right upper quadrant pain and nausea.

CBC results: WBC-11.7, Hb- 12.5, Platelet- 286, MCV- 90, MCV- 26.8, RDW- 18%.

Imaging: Ultrasound and MRI of the abdomen were suggestive of Budd-Chiari syndrome that was supported by a liver biopsy showing features of hepatic outflow obstruction(Figure 1). There was no clinical or radiological evidence of splenomegaly. The hypercoagulable work-up was negative. An underlying Myeloproliferative Neoplasm (MPN) was suspected.

BONE MARROW FINDINGS

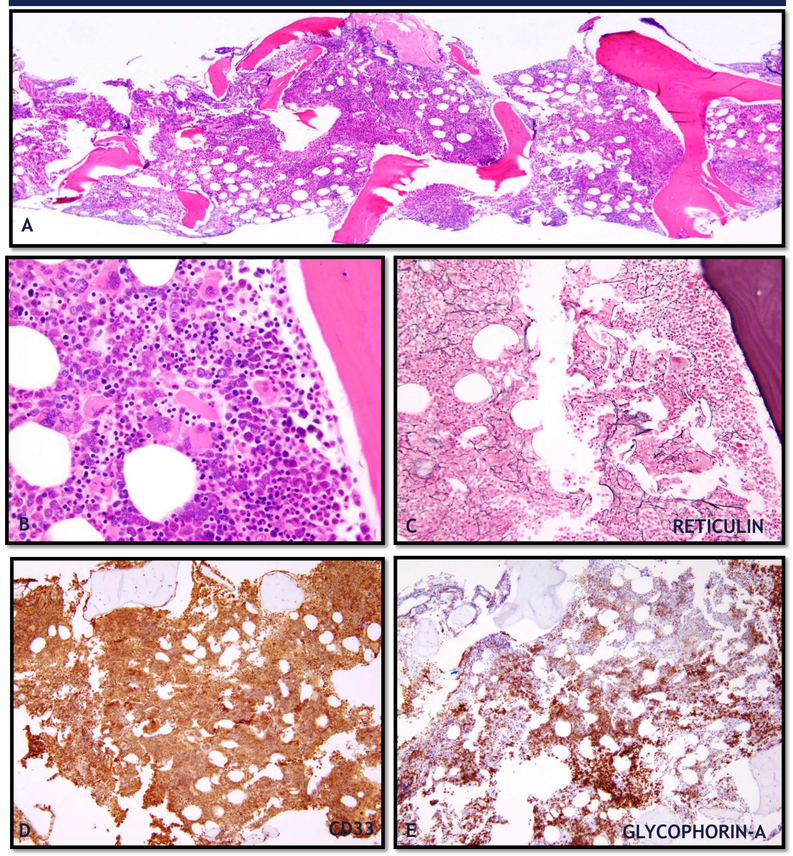


Figure 2. A) Bone marrow core biopsy showing 75% cellularity, 20x **B)** Clustering of megakaryocytes, 200x **C)** Diffuse increased reticulin fibrosis, 100x **D)** Myeloid cells highlighted with immunostain CD33, 100x **E)** Glycophorin-A immunostain showing mild increase in erythroid lineage (decreased M: E ratio).

IMAGING

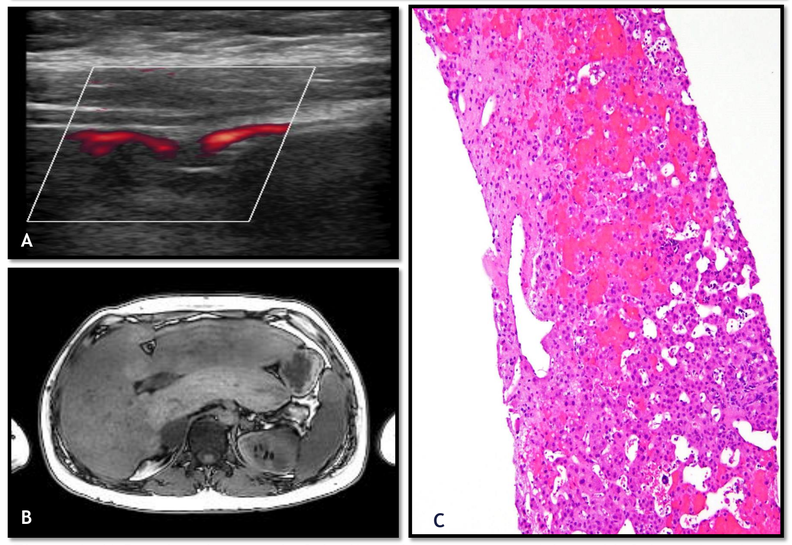


Figure 1. A) Doppler ultrasound of the liver showing patent right and left hepatic veins, with middle hepatic vein outflow obstruction **B)** Liver, MRI showing hepatomegaly (caudate lobe), peripheral fibrosis and edema consistent with subacute Budd-Chiari syndrome **C)** Histology of the liver consistent with outflow obstruction

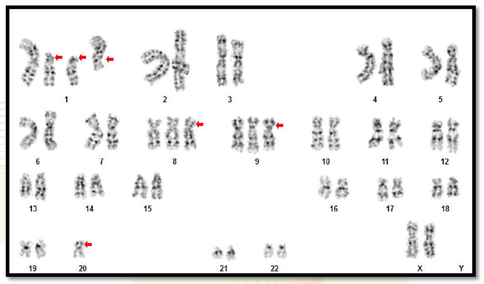
FINAL DIAGNOSIS: MYELOPROLIFERATIVE NEOPLASM, POLYCYTHEMIA VERA, CO-EXISTING WITH IRON DEFICIENCY, JAK2+ (ASSOCIATED WITH SPLANCHNIC VEIN THROMBOSIS)

- Normocellular bone marrow with reduced myeloid to erythroid ratio (1:1)
- Erythroid lineage with left shifted maturation.
- Abnormal proliferation and clustering of megakaryocytes
- The background showed mild diffuse reticulin fibrosis.

(See Figure 2)

CYTOGENETICS

Complex karyotype, bone marrow: **46,XX,+1,del(1)(p13), del(1)(q25),-20 [11] / 49,idem,+del(1)(p13), +8,+9[9]**



FOLLOW-UP LABORATORY STUDIES

- Erythropoietin level- 13.5 mIU/ml (normal)
- LDH level- 213 IU/L (normal)
- Iron studies: Serum iron- 39 mcg/dL (low), Iron saturation- 8% (low), Iron binding capacity 494 mcg/dL (high), Serum ferritin 14 ng/mL (low)
- Molecular testing (Real time quantitative PCR, peripheral blood sample): Positive for *JAK-2* V617F mutation; Negative for *BCR/ABL1*

DISCUSSION

MPNs comprise of two categories- BCR-ABL1 positive MPN or chronic myeloid leukemia and BCR-ABL1 negative MPNs that include polycythemia vera, essential thrombocythemia , and primary myelofibrosis.

Ten percent of the patients who present with splanchnic vein thrombosis (SVT) have an underlying occult or overt MPN. These patient histories are often complicated by iron deficiency due to thrombosis and bleeding, which may result in normal hemoglobin and/or platelet levels. The hypercoagulable state of polycythemia vera is likely a direct result of the JAK2 mutation. As a consequence of mutated *JAK2* function, there is a generalized hypersensitivity to cytokines, with over-expression of pro-coagulant factors and adhesion molecules at the vascular wall. Of note, *JAK2* exon 12 and *MPL*515 mutations are extremely rare in SVT.

A recent meta-analysis has suggested that patients with MPNs associated with thrombosis in hepatic veins, and/or portal veins are possibly a distinct clinical category than patients with MPNs without thrombotic complications (*Leukemia research* 2015;(39):525-529). The clinico-pathologic features of the former group have been recently characterized and include younger age at presentation, female predominance and normal peripheral cell counts as seen in our patient. As these patients often present with normal hemoglobin and/or platelet count due to bleeding/thrombosis and iron deficiency, a JAK2 analysis and bone marrow biopsy evaluation should always be considered a key component of the diagnostic algorithm. Even these studies are sometimes not enough to distinguish between various MPN entities and a comprehensive approach is necessary for reaching a diagnosis.