Case # 110

Ph- Chronic Myeloproliferative Disorders

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Thrombosis and Myeloproliferative Neoplasms (MPNs)

- Thromboses and bleeding are common complications in the MPN, especially ET and PV
  - Thrombosis: 10 to 40% / bleeding: 5 to 20%
- CNS & CVS arterial thrombosis in PV
- Microcirculatory events in ET
- Abdominal venous thromboses
  - Incidence of ~10% in ET and PV patients
  - 10 to 50% of idiopathic cases have an underlying MPN
Thrombosis and MPNs

Because of the known risk of thrombosis in patients with MPN and the finding of MPN in patients presenting with unexplained thrombosis, JAK2-V617F analysis has provided an additional laboratory tool in evaluating patients who present with thrombotic complications.
Thrombosis Risk Factors

- Factor V Leiden mutation: 4.3% of population
- Prothrombin mutation: 1.7% of population
- Protein C, Protein S, or antithrombin deficiency
- Antiphospholipid syndrome
- Hyperhomocysteinemia, increased lipids
- Abdominal surgery, splenectomy, trauma, PNH, inflammatory diseases, oral contraceptives
- Age (over 60 y.o.) or history of thrombosis
- JAK2-V617F in <<1% of the general population at routine clinical laboratory detection levels
Case History

- 55 y.o. male, previously healthy
- Presented with cerebellar infarction
- No known cardiovascular risk factors
- No organomegaly
- No radiologic identifiable source of emboli
Laboratory Studies

- Hgb 14.8 g/dl
- WBC 4.6 x 10^9/L
- PLT 390 x 10^9/L

Differential:
- Neutrophils 57%
- Lymphocytes 23%
- Monocytes 16%
- Eosinophils 1%
- Basophils 1%
- Myelocytes 2%
Laboratory Studies

- Factor V Leiden (R506Q): Heterozygous
- Prothrombin 20210 G>A: No mutation
- Protein C, Protein S, antithrombin: Normal
- Cardiovascular risk factors: None
- Homocysteine: Normal
- Chromosomes: 46, XY[17], 45,X,-Y[3]
- JAK2-V617F: Present
JAK2-V617F Assay

Fluorescence (Fam/533)

Cycles

Patient

Positive Control
Diagnosis:
Early involvement by chronic myeloproliferative disorder, not otherwise classified, with associated JAK2-V617F
Follow-up

September 2007 – 15 mos. post-diagnosis

- Hgb 15.0 g/dl
- WBC 5.0 x 10^9/L
  - Differential – normal
- PLT 550 x 10^9/L  previous = 390 x 10^9/L
- Presumptive clinical diagnosis: ET vs. early PMF
- Started on hydroxyurea therapy
Additional Case

- 47 y.o. female
- Acute onset of mesenteric, portal, and splenic vein thromboses
- No liver disease / normal LFTs
- Normal coagulation studies
- No known cardiovascular risk factors
- No other thrombophilia risk factors
- No organomegaly
Additional Case

- Hgb 14.3 g/dl
- WBC 5.9 x 10^9/L
- PLT 263 x 10^9/L
- Differential:
  - Neutrophils 72%
  - Lymphocytes 25%
  - Monocytes 3%
- 46, XX[20]
- JAK2-V617F
  - Present
Additional Case

- One year follow-up:
  - No change in CBC
  - JAK2-V617F
    - Continued to be present
  - Bone marrow study performed
136 patients with documented arterial stroke and thrombophilia testing at Mayo

- Known MPNs were excluded

- One patient with JAK2-V617F (low burden)
  - Normal CBC, no splenomegaly, no BM study

**Conclusion:** Occult MPN are uncommon in cerebral arterial thrombosis

73 patients with portal vein occlusion
- 35.6% with JAK2-V617F

20 patients with Budd-Chiari syndrome
- 40% with JAK2-V617F

Conclusion: A high proportion of splanchnic, hepatic, and mesenteric vein thrombosis are associated with JAK2-V617F.

Primignani et al. Hepatol 2006; 44:1528-1534
Literature

- 99 patients with portal and/or mesenteric vein thrombosis
  - 17 (17%) with JAK2-V617F
  - 7 with MPN; 10 with no features of MPN
  - 3 of the 10 subsequently developed MPN

**Conclusion:** A proportion of JAK2-V617F cases associated with abdominal vein thromboses will evolve to overt MPN.

Splanchnic vein thromboses in two patients with JAK2 exon 12 mutation

**Conclusion:** The uncommon JAK2 mutations may also be associated with thrombotic events

**Literature**

- **Hepatic, Mesenteric, Cerebral Vein Thrombosis**

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<th>Known MPN (n= 19)</th>
<th>No MPN (n=120)</th>
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<td><strong>JAK2-V617F</strong></td>
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<td>Thrombophilia risk factors</td>
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**Conclusion:** Thrombophilia risk factors occur frequently in conjunction with **JAK2-V617F**

*De Stefano et al. J Thromb Haemostasis 2007; 5:708-714*
Conclusions

- Not all patients who harbor the JAK2-V617F present clinically with an overt MPN.

- The morphologic findings in cases with isolated JAK2-V617F may be quite subtle and may not always be sufficient for a MPN diagnosis.

- At least some patients with an isolated JAK2-V617F will evolve to a bonafide MPN.
Conclusions

- JAK2-V617F is an additional risk factor for developing either venous or arterial thromboses.

- Other associated risk factors for thrombophilia may occur simultaneously with a JAK2-V617F.

- JAK2 and bone marrow studies will increasingly be a routine part of an idiopathic thrombosis work-up.
Colleagues and Contributors

- Rebecca F. McClure
- William G. Morice
- Dong Chen
- Anamish Pardanani
- Ayalew Tefferi
- Molecular Hematopathology & Special Coagulation Laboratories
Thank you!
42 patients with catastrophic intra-abdominal thrombosis resulting in organ transplants

- 7 (17%) with JAK2-V617F
- 3 with PV or ET
- 4 with no clinical manifestations of MPN

**Conclusion:** JAK2-V617F, with or without known MPN, is a risk factor for catastrophic intra-abdominal thrombosis

*McMahon, et al. AJCP 2007; 127:736-743*
210 consecutive patients with **thrombophilia** work up at the Mayo Clinic
- Splanchnic vein thrombosis and known MPN cases excluded
- 13% with factor V Leiden mutations
- 5% prothrombin mutations

4 patients with **JAK2-V617F**
- No known MPN; normal counts; no splenomegaly
- Three with pulmonary embolisms (+ DVT)
- One with central retinal vein occlusion

**Conclusion:** **JAK2-V617F** is an additional risk factor for idiopathic, non-splanchnic vein thrombosis