Myeloproliferative Disorders in the Elderly: Clinical Presentation and Role of Bone Marrow Examination

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Chronic Myeloproliferative Disorders (MPD)

- Bcr-Abl Negative
  - Polycythemia Vera (PV)
  - Essential Thrombocytosis (ET)
  - Agnogenic Myeloid Metaplasia/Idiopathic Myelofibrosis

- Bcr-Abl Positive
  - Chronic Myeloid Leukemia
Introduction

- Older patients with high blood cell counts more likely to be referred for further evaluation, including Bone Marrow (BM) biopsy.
- Median age of diagnosis of MPD is 60 years with 25-50% patients over 60 years of age.
- Histopathological data not mandatory for diagnosis of MPD.
- BM Biopsy is not without complications, especially in elderly.
Complications from BM Biopsy

- Bain et al: 26 adverse events among 54,890 BM biopsies
- Hemorrhage in 14 patients: six needing blood transfusion and one death
- Risk factors for hemorrhage were:
  - diagnosis of MPD
  - aspirin therapy or both
  - warfarin therapy
  - disseminated intravascular coagulation
  - obesity
BM Biopsy in the Elderly

- Higher co-morbidities
- Aging hematopoietic system
- Increased qualitative platelet defects and/or coagulopathy → increased bleeding
Objectives

- **Primary objective:**
  Determine by retrospective review, what percentage of elderly patients referred to the Hematology-Oncology clinic at the Durham Veterans Affairs Medical Center with a suspicion of MPD, who subsequently undergo BM biopsy actually have an underlying disorder like CML, PV, ET, or MF

- **Secondary objectives:**
  1. Determine clinical characteristics of these elderly patients and compare them to their younger counterparts
  2. Determine if complications occurred as a result of BM biopsy i.e. infection, bleeding, or hematoma
Eligibility Criteria

All patients referred to the Hematology-Oncology clinic at the Durham Veterans Affairs Medical Center between July 1, 2000 to June 9, 2005 specifically to rule out a MPD. These included:

- Leukocytosis particularly neutrophilia i.e. White Blood Cell Count $> 12 \times 10^9$/L and neutrophils $> 7.5 \times 10^9$/L
- Polycythemia i.e. Hematocrit $> 42\%$ in females and $> 47\%$ in males
- Thrombocytosis i.e. platelet count $> 500 \times 10^9$/L
Results

- N=141 patients referred for leukocytosis, polycythemia, and/or thrombocytosis
- N=76 (54%) < 60 years and n=65 (46%) were ≥ 60 years
- Older patients with more co-morbidities: 39/65 (60%) older patients with ≥ 2 co-morbid conditions vs. 24/76 (31.5%) in younger patients ($p=0.0068$)
- Most common co-morbid conditions: Hypertension and Type 2 DM
### Clinical and Demographic Features

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Age &lt;60 years</th>
<th>Age ≥ 60 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total n=141</td>
<td>76</td>
<td>65</td>
</tr>
<tr>
<td>Fatigue</td>
<td>12</td>
<td>16</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>≥ 2 co-morbid conditions</td>
<td>24/76</td>
<td>39/65</td>
</tr>
<tr>
<td>Aspirin use</td>
<td>20</td>
<td>26</td>
</tr>
<tr>
<td>Smoking/ Tobacco use</td>
<td>74</td>
<td>60</td>
</tr>
<tr>
<td>Thrombo-embolic complications</td>
<td>8</td>
<td>4</td>
</tr>
</tbody>
</table>
BM Biopsy

- In all 66/141 (47%) patients underwent a BM aspiration and biopsy

- 53% had no BM examination: combination of patient and physician factors for refusal

- Of the 66 who underwent BM biopsy 25 (38%) patients < 60 years, 41 (62%) patients ≥ 60 years; p=0.0003
## Results of BM Biopsy

<table>
<thead>
<tr>
<th>Total patients n=141</th>
<th>&lt;60 years n=76 (54%)</th>
<th>≥ 60 years n=65 (46%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BM biopsy n=66</td>
<td>25 (38%)</td>
<td>41 (62%)</td>
<td>0.0003</td>
</tr>
<tr>
<td>Chromosomal analysis n=46</td>
<td>16 (35%)</td>
<td>30 (65%)</td>
<td>0.0067</td>
</tr>
<tr>
<td>CML n=15</td>
<td>6</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>ET n=25</td>
<td>6</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>PV n=20</td>
<td>11</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Any complication after BM biopsy</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>
Yield from BM Biopsy

- Patients ≥ 60 years n=41, 37 (90%) patients in all diagnosed with CML (majority bcr- abl +), PV or ET

- Patients <60 years n=25, 23 patients (92%) in all diagnosed with CML (all bcr- abl +), PV or ET

- No increased risk of infection, bleeding or hemorrhage in either group
Other Diagnosis

Includes patients without BM biopsy (n=75) and 6 patients who underwent a BM biopsy

- Leukocytosis of unknown origin n=25
- Reactive Leukocytosis (drugs, smoking, inflammations) n=13
- Secondary Erythrocytosis (based on smoking history, oxygen saturation, sleep apnea) n=20
- Secondary Thrombocytosis (infection, inflammation, iron deficiency anemia) n=8
- Unknown causes n=15
Limitations

- 53% patients did not have BM biopsy: may have been able to diagnose a higher number of MPDs
- No complications from BM biopsy? due to selection of specific patients
- No data on JAK2 V617F mutation
- Retrospective review of predominantly male patients
Conclusions

- Older patients referred for MPD work-up have more co-morbid conditions
- No differences in clinical features and thrombo-embolic disease
- Older patients with suspected MPD undergo more BM examinations
- In patients with presumed MPD, a BM biopsy is of high yield in diagnosis of MPD
- No increase in risk of complications from BM examination
BM Biopsy for Diagnosis of PV

- Marrow histology is not part of PVSG diagnostic criteria
- BM histology is part of minor criterion in the WHO classification
- Inter-observer variation in quantifying erythroid and megakaryocytic proliferation

THUS: Role of BM biopsy in the evaluation of PV remains controversial!
BM Biopsy for Diagnosis of ET

- BM histology is part of PVSG diagnostic criteria and WHO criteria
- Need to rule out CML, MF, MDS, and show stainable iron i.e. no Fe deficiency
- ET can be divided into histologically distinct subgroups (true ET, prefibrotic MF, and early overt MF) with different prognosis
- Interobserver variation in assessing megakaryocyte morphology
- THUS: Role of BM biopsy in the evaluation of ET remains controversial!
Conclusions

Notably in our retrospective study:

- No diagnosis of MPD was made without BM biopsy.
- In patients (young and old) with presumed MPD, a BM biopsy was of high yield in making a diagnosis of MPD.
- In JAK2 era: algorithms for diagnosis suggest confirming diagnosis of MPD with a BM biopsy even if peripheral blood PCR for JAK2 V617F mutation is positive.
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