COEXISTENCE OF β-THALASSEMVIA AND POLYCYTHEMIA VERA: A CHICKEN-AND-EGG DEBATE?

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Presentation at emergency room

- 60-year-old female
- Egyptian origin
- Absent medical history

**Complaints**
- Deteriorating general condition since two weeks
- Sore throat
- Mild dyspnea on exertion
- Vertigo

**Clinical examination**
- No raised temperature
- Normal blood pressure
- Normal heart rate
- Normal oxygen saturation
- Pure breath sounds
- Painful palpation of the right hypochondrium
<table>
<thead>
<tr>
<th>Laboratory test</th>
<th>Normal values</th>
<th>Units</th>
<th>Test result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythrocyte count</td>
<td>3.75-5.11</td>
<td>x10^{12}/L</td>
<td>10.53</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>35.5-46.5</td>
<td>%</td>
<td>58.6</td>
</tr>
<tr>
<td>Total hemoglobin</td>
<td>11.8-15.5</td>
<td>g/dL</td>
<td>19.8</td>
</tr>
<tr>
<td>MCV</td>
<td>84.0-98.3</td>
<td>fL</td>
<td>55.7</td>
</tr>
<tr>
<td>MCH</td>
<td>27.6-32.9</td>
<td>pg</td>
<td>18.8</td>
</tr>
<tr>
<td>White blood cell count</td>
<td>4.2-9.8</td>
<td>x10^{9}/L</td>
<td>11.2</td>
</tr>
<tr>
<td>Platelet count</td>
<td>162-351</td>
<td>x10^{9}/L</td>
<td>650</td>
</tr>
<tr>
<td>LDH</td>
<td>240-480</td>
<td>U/L</td>
<td>606</td>
</tr>
<tr>
<td>C-reactive protein</td>
<td>0.0-7.0</td>
<td>mg/L</td>
<td>2.48</td>
</tr>
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</table>
CASE PRESENTATION

Presentation at emergency room

Further exploration

- Chest radiograph (or chest X-ray)
  - Normal heart
  - No bleeds
- X-ray CT of the head
  - No bleeds
  - No masses
- Abdominal ultrasonography (ultrasound) and X-ray CT
  - Strikingly enlarged spleen of 140 mm

Exclusion of secondary causes of erythrocytosis

- no smoking
- no hypoxia
- absence of cardiac, pulmonary and renal disease
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• Repetitive attempts for bone marrow puncture failed due to thickened fat tissue surrounding the cristae, hence bone marrow examination could not be performed.

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<td>U/L</td>
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• The presence of JAK2 V617F mutation was confirmed
Work up

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WHO criteria for the diagnosis of polycythemia vera (PV) fulfilled
### Work up

#### Unexplained microcytosis

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<th>Units</th>
<th>Test result</th>
</tr>
</thead>
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<tr>
<td>Ferritin</td>
<td>13.0-150</td>
<td>µg/L</td>
<td>24.6</td>
</tr>
<tr>
<td>Serum iron</td>
<td>50-150</td>
<td>µg/dL</td>
<td>61</td>
</tr>
<tr>
<td>Transferrin</td>
<td>200-360</td>
<td>mg/dL</td>
<td>272</td>
</tr>
<tr>
<td>HbA2 (chromatography)</td>
<td>2-3</td>
<td>%</td>
<td>4.1</td>
</tr>
<tr>
<td>HbF (chromatography)</td>
<td>0.2-1.0</td>
<td>%</td>
<td>2.7</td>
</tr>
<tr>
<td>Hb electrophoresis</td>
<td>Normal pattern</td>
<td>/</td>
<td>Elevated HbA2 and HbF</td>
</tr>
<tr>
<td>Hb mutation analysis</td>
<td>No mutation</td>
<td>/</td>
<td>c.[93-21G&gt;A] mutation, heterozygous state (beta+)</td>
</tr>
</tbody>
</table>
Treatment

Start treatment

- Hydroxyurea 2X500mg daily
- Aspirin 80mg/day
- Folic acid 4mg/day

- Until platelet count < 600 000 and hematocrit < 42% are achieved
- Because no symptoms of hyperviscocity were present at further evaluation phlebotomy was not added to the initial treatment.
After two weeks treatment

- Leukocytosis and thrombocytosis partially corrected
- Hematocrit level showed no response (66.7%)
- Increase of bilateral malleolar edema.

- Hydroxyurea 2X500mg daily
- Aspirin 80mg/day
- Folic acid 4mg/day
- Phlebotomy (weekly)
Although the first phlebotomy showed a steep decline in hematocrit, phlebotomy was discontinued due to associated vertigo and fatigue.

Reevaluation after ten weeks of treatment still showed a hematocrit of 57.8% with mild leukocytosis and thrombocytosis. The daily dose of hydroxyurea was subsequently increased to 3X500mg/day.
After 6 months treatment

- Hydroxyurea 3X500mg daily
- Aspirin 80mg/day
- Folic acid 4mg/day

- Patient still has headache and vertigo
- Patient undermedicates: only 1X500mg daily
## Overview of cases reported in literature

<table>
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<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>60</td>
<td>75</td>
<td>71</td>
<td>68</td>
<td>48</td>
</tr>
<tr>
<td>Gender</td>
<td>Female</td>
<td>Female</td>
<td>Female</td>
<td>Female</td>
<td>Female</td>
</tr>
<tr>
<td>Thalassemic disorder</td>
<td>β-thalassemia minor</td>
<td>β-thalassemia minor</td>
<td>β-thalassemia minor</td>
<td>β-thalassemia minor</td>
<td>Sickle cell β-thalassemia minor</td>
</tr>
<tr>
<td>Mean Corpuscular Volume (fL)</td>
<td>55,7</td>
<td>59,2</td>
<td>65</td>
<td>N/A (microcytosis)</td>
<td>70</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>58,6</td>
<td>51,8</td>
<td>48,1</td>
<td>59</td>
<td>42</td>
</tr>
<tr>
<td>Total hemoglobin (g/dL)</td>
<td>19,8</td>
<td>15,4</td>
<td>15,6</td>
<td>15,5</td>
<td>14,4</td>
</tr>
<tr>
<td>Hemoglobin A2 (%)</td>
<td>4,1</td>
<td>4,3</td>
<td>5,5</td>
<td>4,7</td>
<td>4,9</td>
</tr>
<tr>
<td>Hemoglobin mutation analysis (*)</td>
<td>c.[93-21G&gt;A] mutation, heterozygous state (beta+)</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N.A</td>
</tr>
<tr>
<td>Erythropoietin</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>JAK2 V617F mutation</td>
<td>Yes</td>
<td>Yes</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

N/A Not available, (*) PCR amplification + direct sequencing HBB gene
Association?

- The prevalence of PV is about 30 cases per 100 000 individuals.
- About 10 in 30 000 annual births worldwide is affected by beta-thalassemia.

- Coincidental association, hence limited number of reported cases plausible.

- However, disease association may be underdiagnosed; both pathologies are essentially different with possible antagonizing hematological effects, one masking the effect of the other.
Discussion

Hypothesis

Hereditary hemolytic anemia = a lifetime of increased demand for differentiated hematopoietic cells

- Requires corresponding increase in cell divisions at the stem cell level,

- A greater number of stem cell divisions in patients with beta-thalassemia trait could therefore contribute to a greater risk for new somatic mutations, including the Jak2 V617F mutation.
In conclusion, we suggest that the prevalence of JAK2V617F mutations in beta-thalassemia trait individuals –generally considered asymptomatic–, and vice versa, the prevalence of hemoglobinopathy in PV patients, should be the subject of further investigation to explore disease association.
Thanks for your attention