Focus on aggressive polycythemia vera

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Disclosure

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Introduction to polycythemia vera (PV)

• A clonal disorder involving a multipotent hematopoietic progenitor cell\(^1\)

• Characterized by the accumulation of phenotypically normal red blood cells, white blood cells, and platelets, alone or in combination, in the absence of a definable stimulus\(^1\)


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There is an aggressive subtype of PV

- One study found a subset of patients with PV with a much lower median survival rate, estimated at 5.8 years\(^1\)
- This is consistent with the median survival in primary myelofibrosis\(^2\)

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Overall Survival in PV by Investigational Risk Stratification System\(^1\)

Risk-stratified survival that considers karyotype in 631 patients with PV.

PV, polycythemia vera.

No guidelines exist for identifying PV with an aggressive course

- Patients with PV who are aged <60 years and have no history of thrombosis are generally considered “low risk”\(^1\)
- This stratification is designed to estimate the likelihood of thrombotic complications in PV, but not survival\(^1\)
- The phenotypic variability of PV provides some clues to outcomes\(^2\)
- In addition, a study using gene expression profiling of CD34+ hematopoietic stem cells was able to accurately identify a subset of patients with aggressive PV\(^3\)


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The phenotypic variability of PV

- PV may present as erythrocytosis, leukocytosis, or thrombocytosis, alone or in combination

<table>
<thead>
<tr>
<th>Presenting Blood Counts at Time of Diagnosis of PV</th>
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<tbody>
<tr>
<td>Isolated erythrocytosis</td>
</tr>
<tr>
<td>Isolated leukocytosis</td>
</tr>
<tr>
<td>Isolated thrombocytosis</td>
</tr>
<tr>
<td>Erythrocytosis and thrombocytosis</td>
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<tr>
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</tr>
</tbody>
</table>

PV, polycythemia vera.


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Isolated erythrocytosis in PV

- In our practice, isolated erythrocytosis is seen in fewer than 20% of cases of PV\textsuperscript{1,2}
- Excess red blood cell production is readily controlled by periodic phlebotomy, which immediately\textsuperscript{3,4}:
  - reduces erythrocyte mass
  - lowers blood viscosity

**Threshold for Erythrocytosis\textsuperscript{5}**

- Females: >16.5 g/dL
- Males: >18.5 g/dL

**References:**

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Leukocytosis in PV

- While uncommon, isolated leukocytosis can be the presenting manifestation of PV\(^1\).
- In the author’s experience, a minor degree of leukocytosis has no clinical significance and requires no therapy in asymptomatic patients with uric acid >9 mg/dL\(^2\).
- Progressive leukocytosis is a harbinger of extramedullary hematopoiesis or disease acceleration and can thus serve as a guide to disease control.


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Isolated thrombocytosis in PV

- Occurs in 7% to 20% of patients with PV (particularly women)\(^1,2\)
- PV should be considered in the differential diagnosis of isolated thrombocytosis\(^3\)
- Thrombocytosis in PV is associated with transient microvascular blockage manifested by erythromelalgia\(^4,5\) or a constellation of neurologic symptoms that include intractable migraine\(^6\)
  - These can be reversed or prevented by aspirin-induced platelet inactivation or a reduction in the platelet count\(^7,8\)

References:

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Erythrocytosis, leukocytosis, and thrombocytosis in PV

• Approximately 40% of patients with PV present with hyperproliferation of all 3 cell lines\(^1\)
  – This form of the disease is generally more aggressive and frequently associated with splenomegaly and constitutional symptoms\(^2\)


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The genetics of high-risk patients

- A study suggests that gene expression profiling may make it possible to identify the subset of patients with aggressive PV\(^1\)
  - These patients might benefit from early intervention before myelofibrosis or marrow failure ensues

- Most previous gene expression studies were performed with granulocytes and provided some diagnostic but no prognostic information

- The new study analyzed gene expression in CD34+ peripheral-blood hematopoietic stem cells using oligonucleotide microarray technology after correcting for potential confounding by sex\(^1\)


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Men with PV had twice as many upregulated or downregulated genes as women with PV, but there was a core of 102 genes that were consistently dysregulated in the disease process. 

55 of these 102 genes are also dysregulated in chronic myelogenous leukemia.

PV, polycythemia vera.


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Prediction of aggressive vs indolent PV

• These 102 core genes were used to identify a subset of patients with increased thrombotic events, increased transformation to acute leukemia, and decreased survival\(^1,2\)

• The number of genes required for distinguishing indolent from aggressive PV could be reduced to 10\(^1,2\)


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Conclusions

• The course of PV may span decades, but a subset of patients has aggressive disease with outcomes comparable to those of myelofibrosis\(^1\)\(^,\)\(^2\)

• No guidelines exist to identify PV that is aggressive with respect to splenomegaly, leukemic or fibrotic transformation, or survival

• In some cases, the type(s) of cell(s) overexpressed may provide some clues to outcomes\(^3\)

• A study using gene expression profiling of CD34+ hematopoietic stem cells was able to accurately identify the subset of patients with increased thrombotic events, increased transformation to acute leukemia, and decreased survival\(^4\)