QUESTION 51

A 48-year-old previously well man, currently smoking 10 to 20 cigarettes/day, presents with the progressive onset over several months of lethargy and headache. He takes no medications.

Examination reveals him to be plethoric and hypertensive with no other significant findings.

Full blood examination shows:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemoglobin</td>
<td>216 g/L [135-170]</td>
</tr>
<tr>
<td>Mean corpuscular volume (MCV)</td>
<td>76 fL [80-95]</td>
</tr>
<tr>
<td>White cell count</td>
<td>13.3 x 10^9/L [3.5-9.5]</td>
</tr>
<tr>
<td>Differential:</td>
<td></td>
</tr>
<tr>
<td>Neutrophils</td>
<td>10.2 x 10^9/L [1.5-6.0]</td>
</tr>
<tr>
<td>Bands</td>
<td>1.5 x 10^9/L</td>
</tr>
<tr>
<td>Myelocytes</td>
<td>0.2 x 10^9/L</td>
</tr>
<tr>
<td>Monocytes</td>
<td>0.3 x 10^9/L [0.2-0.6]</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>0.8 x 10^9/L [0-0.4]</td>
</tr>
<tr>
<td>Basophils</td>
<td>0.30 x 10^9/L [0-0.15]</td>
</tr>
<tr>
<td>Platelet count</td>
<td>474 x 10^9/L [150-400]</td>
</tr>
</tbody>
</table>

Which one of the following would most strongly support a diagnosis of polycythaemia vera?

A. Raised serum vitamin B\textsubscript{12} level.
B. Elevated total red cell mass.
C. Normal marrow karyotype.
D. Elevated serum uric acid level.
E. Lowered serum erythropoietin level.

Polycythemia vera (PV) is one of the chronic myeloproliferative disorders, which are collectively characterized by clonal proliferation of myeloid cells with variable morphologic maturity and hematopoietic efficiency. PV is distinguished clinically from the other myeloproliferative disorders by the presence of an elevated red blood cell mass (RCM). However, an increased RCM alone is insufficient to establish the diagnosis, since this finding is also observed in a variety of conditions associated with chronic hypoxia and, rarely, with tumors that secrete erythropoietin.

**Diagnostic Criteria for PCV**

**Increased red blood cell mass —**

- RCM, normalized to body surface area, should be considered elevated if it is more than 25 percent above the mean expected value.
- The majority of female patients with a hemoglobin concentration >16.5 g/dL (or hematocrit [HCT] above 50 percent) and all male patients with a hemoglobin concentration >18.5 g/dL (or HCT above 56 percent) have an increased RCM.

**Palpable splenomegaly —**

- Since splenomegaly may not always be detectable by physical examination, other diagnostic criteria accept the finding of a nonpalpable spleen that is enlarged on an imaging test as a minor or secondary criterion.

**Thrombocytosis and leukocytosis —**

- An absolute neutrophil count >10,000/microL.

**Leukocyte alkaline phosphatase and serum B12 studies —**

- Although an elevated LAP score is reasonably sensitive for PV (approximately 70 percent), it is not specific.
- B12 studies are neither sensitive nor specific.
As a result, the LAP score and B12 studies are not included as major or minor criteria in any of the newer published algorithms.

False positive results —
- secondary causes of an elevated RCM are much more common than PV
- It has been estimated that the practicing hematologist sees 10 cases of relative or secondary polycythemia for every new patient with PV
- Application of the PVSG criteria may lead to false positive results in patients with cirrhosis who smoke heavily. Cirrhosis may be associated with splenomegaly, while concomitant smoking may lead to an elevated RCM due to high levels of carbon monoxide and/or the development of chronic obstructive pulmonary disease. Similarly, since splenomegaly, leukocytosis, and thrombocytosis are common to all of the chronic myeloproliferative diseases, a patient with chronic myelogenous leukemia, essential thrombocythemia, or agnogenic myeloid metaplasia (AMM) who has an elevated hematocrit for another reason (eg, hypoxia, smoking) may be falsely diagnosed as having PV. This is an important distinction clinically because each of these disorders is treated in a different manner.

False negative results —
- false negative results occur in approximately 10 percent of patients
- Calculation of the red blood cell mass may be falsely low in patients who are obese.
- Patients with PV who have had significant recent gastrointestinal blood loss (“bled down” polycythemia) may present with a normal hematocrit. Such patients may be incorrectly diagnosed as having iron deficiency or essential thrombocythemia since their high platelet counts, low red blood cell indices, and low serum ferritin concentrations may be the most striking features.
- Patients who have PV and are also hypoxic for unrelated reasons (eg, coexisting chronic lung disease) will not fulfill the PVSG criteria.
- An increased red cell mass may not be apparent in patients with early PV, less severe disease, or an elevated plasma volume.
- Patients with severe complications related to PV (eg, Budd-Chiari syndrome) but without classical features of the disease may not fulfill the classic PVSG criteria.

Bone marrow aspiration and biopsy —
- An increased number of megakaryocytes in a moderately to markedly hypercellular marrow has been considered one of the diagnostic hallmarks of PV

Clonal markers —
- deletion of the long arm of chromosome 20, trisomy for chromosomes 8 or 9, or loss of heterozygosity on the short arm of chromosome 9 are found in up to 30 percent of previously untreated patients with PV
- chromosome 9p24 houses the JAK2 gene, which carries a somatic point mutation in the vast majority of patients with PV

Serum erythropoietin —
- low serum erythropoietin (EPO) concentrations

The question is asking for a differentiating factor between primary PCV and polycythaemia from other causes eg hypoxia.

A. Raised serum vitamin B₁₂ level.
Could be raised in either

B. Elevated total red cell mass.
Needs to be relative to mass and clinical circumstance, not a useful measure and not a good distinguishing factor

C. Normal marrow karyotype.
Could be normal in either

D. Elevated serum uric acid level.
Not related

E. Lowered serum erythropoietin level.
In acquired polycytheamia eg hypoxia, erythropoietin will be high as renal cells responding to hypoxia but low in PCV