Question 45
A 62 year old man with a history of controlled hypertension presents with worsening lethargy over several months and more recently, weight loss, night sweats and easy bruising. Examination reveals anaemia, bruising from firm splenomegaly 12cm below the left costal margin; no lymphadenopathy is evident.

Full blood examination reveals:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Result</th>
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</thead>
<tbody>
<tr>
<td>Hb</td>
<td>81 g/L (135-170)</td>
</tr>
<tr>
<td>MCV</td>
<td>100 fL (80-95)</td>
</tr>
<tr>
<td>White cell count</td>
<td>3.4 x 10^9 (3.5 -9.5)</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>1.0 x 10^9/L (1.5 -6.0)</td>
</tr>
<tr>
<td>Bands</td>
<td>0.5 x 10^9/L</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>0.3 x 10^9/L</td>
</tr>
<tr>
<td>Myelocytes</td>
<td>1.20 x 10^9/L (0.70 – 1.35)</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>0.1 x 10^9/L (0-0.4)</td>
</tr>
<tr>
<td>Monocytes</td>
<td>0.2 x 10^9/L (0.2 -0.6)</td>
</tr>
<tr>
<td>Basophils</td>
<td>0.10 x 10^9/L (0 -0.15)</td>
</tr>
<tr>
<td>Basophils</td>
<td>2 nucleated red cells/ 100 leucocytes</td>
</tr>
<tr>
<td>Platelet count</td>
<td>75 x 10^9/ L (150- 450)</td>
</tr>
</tbody>
</table>

The blood film is shown below:

Coagulation screen normal
Routine biochemistry is unremarkable except for:

<table>
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<tr>
<td>Lactate dehydrogenase (LDH)</td>
<td>525 U/L (&lt;250)</td>
</tr>
<tr>
<td>Uric acid</td>
<td>0.62 mmol/ L (0.15 – 0.50)</td>
</tr>
</tbody>
</table>

The most likely diagnosis is:
A. Metastatic carcinoma
B. Megaloblastosis
C. Primary myelofibrosis
D. Systemic lupus erythematosus
E. Chronic myeloid leukaemia

Answer:
This presentation and blood film findings can be that of any myeloproliferative disease, but not:
A. Metastatic cancer should not cause these blood film abnormalities
B. Megaloblastosis refers to impaired DNA synthesis, mainly due to B12/ folate deficiency or drugs that impair DNA metabolism (eg purine antagonists, HAART). Usually MCV >100 fL, there should be hypersegmented n° on blood film and there should not be splenomegaly.
D. SLE more common in women, and this is the wrong age group. Nothing in history to suggest a connective tissue disorder.

Either C or E, however in CML there should be ↑↑ white cell count and normal platelet count at diagnosis.

Tear drop RBC = Membrane damage from collagen fibres
Nucleated RBC = Premature release of erythroid precursors
No blasts

Myeloproliferative diseases
- Clonal expansion of multipotent haematopoietic stem cell -> overexpansion of one or more formed elements of blood
  o Polycythaemia rubra vera (PRV)
  o Essential thrombocytosis (ET)
  o Chronic myeloid leukaemia (CML)
  o Chronic idiopathic myelofibrosis
- May transform into acute leukaemia either naturally or as a result of treatment
- Phenotypically similar and large overlap
- However, CML genotypically distinct as it is associated with specific translocation t(9;22) -> unique fusion protein bcr-abl and unique response to imatinib (Gleevec, which induces apoptosis in cells expressing bcr-abl)
- Systemic mastocytosis very phenotypically similar to CML, but has own category due to distinct clinical syndromes which characterise mast cell proliferation

Chronic idiopathic myelofibrosis
- Also known as agnogenic myeloid metaplasia, myelofibrosis with myeloid metaplasia
- Clonal expansion of multipotent haematopoietic stem cell of unknown aetiology characterised by:
  o Marrow fibrosis (note that the responsible fibroblasts are NOT clonal; BMAT difficult due to fibrosis but if done: hypercellular marrow with trilineage hyperplasia especially ↑ megakaryocytes which are otherwise normal)
  o Myeloid metaplasia
  o Extramedullary haematopoiesis
  o Splenomegaly (which may be massive)
  o May be associated with autoimmunity: immune complexes, ANA, RhF or positive Coombs (this is not present in the other myeloproliferative disorders)
- Degree of myelofibrosis and degree of extramedullary haematopoiesis in not related
- Fibrosis is due to overproduction of transforming growth factor β and thrombopoietin
- Clinical features and diagnosis:
  - No specific symptoms and signs early on
  - Usually asymptomatic and detected by splenomegaly +/- mild hepatomegaly (OR) routine bloods
  - Extramedullary haematopoiesis may cause portal HT (varices, ascites), pulmonary HT, intracranial HT, pericardial tamponade, spinal cord compression, skin nodules
  - Anaemia usually mild initially
  - Splenomegaly may be massive -> hypersplenism, infarction with fever and pain, early satiety
  - X rays may reveal osteosclerosis
  - Hyperuricaemia and secondary gout (↑ turnover of cells)

- Do cytogenetics to exclude CML and for prognostic purposes
  - **Complex karyotype abnormalities → poor prognosis**
  - Associated very ↑ CD 34+ cells in flow cytometry

- Progression:
  - Median survival 5 years (1-15 years)
    - Poor prognostic features include degree of marrow failure, ↑ age, complex cytogenetics
  - Progressive marrow failure, transfusion dependence and ↑ organomegaly with its complications
  - Prone to deep infections especially lungs
  - Can evolve from chronic -> accelerated phase
  - 10% develop acute leukaemia (does not respond to treatment)

- No specific treatment:
  - Erythropoietin worsens splenomegaly
  - If hypersplenism -> splenectomy (but for unknown reasons ↑ risk of acute leukaemia)
  - Allopurinol for hyperuricaemia and gout
  - Hydroxyurea may control organomegaly
  - Can also try IFNα, steroids +/- thalidomide
  - Consider allogenic stem cell transplant in younger