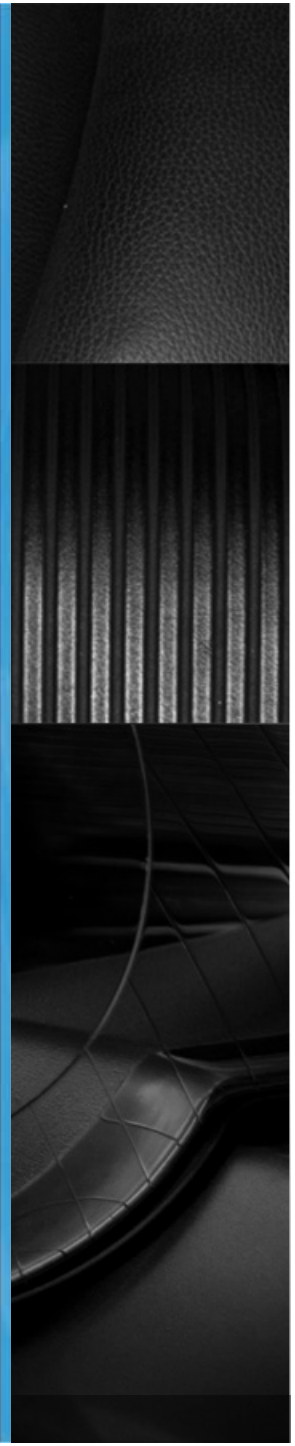
Myeloproliferative disorders (MPD)



- A 63 year-old man is evaluated for increased lethargy.
- He does not smoke cigarettes and takes no medications.
- On physical examination, vital sign are normal,
- Arterial oxygen saturation is 99% on ambient air.

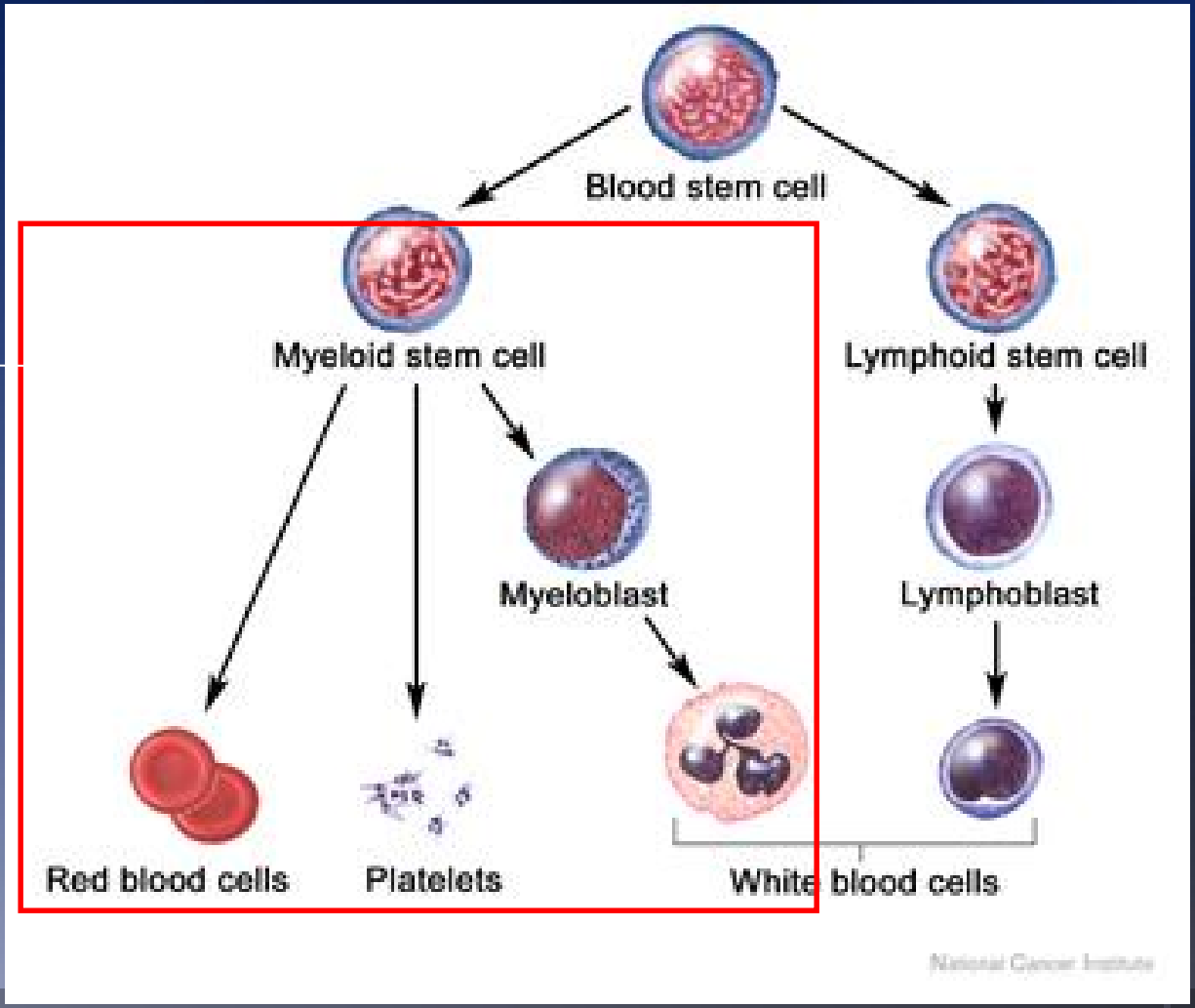
  Cardiopulmonary examination is normal.
- The abdomen is soft, and there is no hepatosplenomegaly.

- Hemoglobin 20.2 g/dL
- Platelet count 500,000/μL
- Leukocyte count 11200/μL

§ The MPD are a group of clonal stem cell disorders characterized by aberrant regulation of proliferation that results in *excess production of myeloid* elements (red blood cells, platelets, or certain white blood cells) in the bone marrow , which results in marked splenomegaly and leukocytosis.

Hematopoietic Progenitors and MPNs

Genetic Mutation



Classification

- Chronic myeloid leukemia (CML)
- Polycythemia vera (PV)
- Essential thrombocythemia (ET)
- Primary myelofibrosis (PMF)

Epidemiology

- The peak incidence of PV is age 50-70 years.
- There is slight male preponderance.

Polycythemia Vera

- PV is a clonal, chronic, progressive MPD often of insidious onset, characterized by an *absolute increase in red cell mass* and also usually by *leukocytosis, thrombocytosis, and splenomegaly*.

Etiology

- The etiology of PV is unknown, but familial occurrence in 6% of patients.
- *JAK-2* (mutation in the gene on chromosome 9) has been found in 97% of PV appears to have a central role in the pathogenesis of PV.

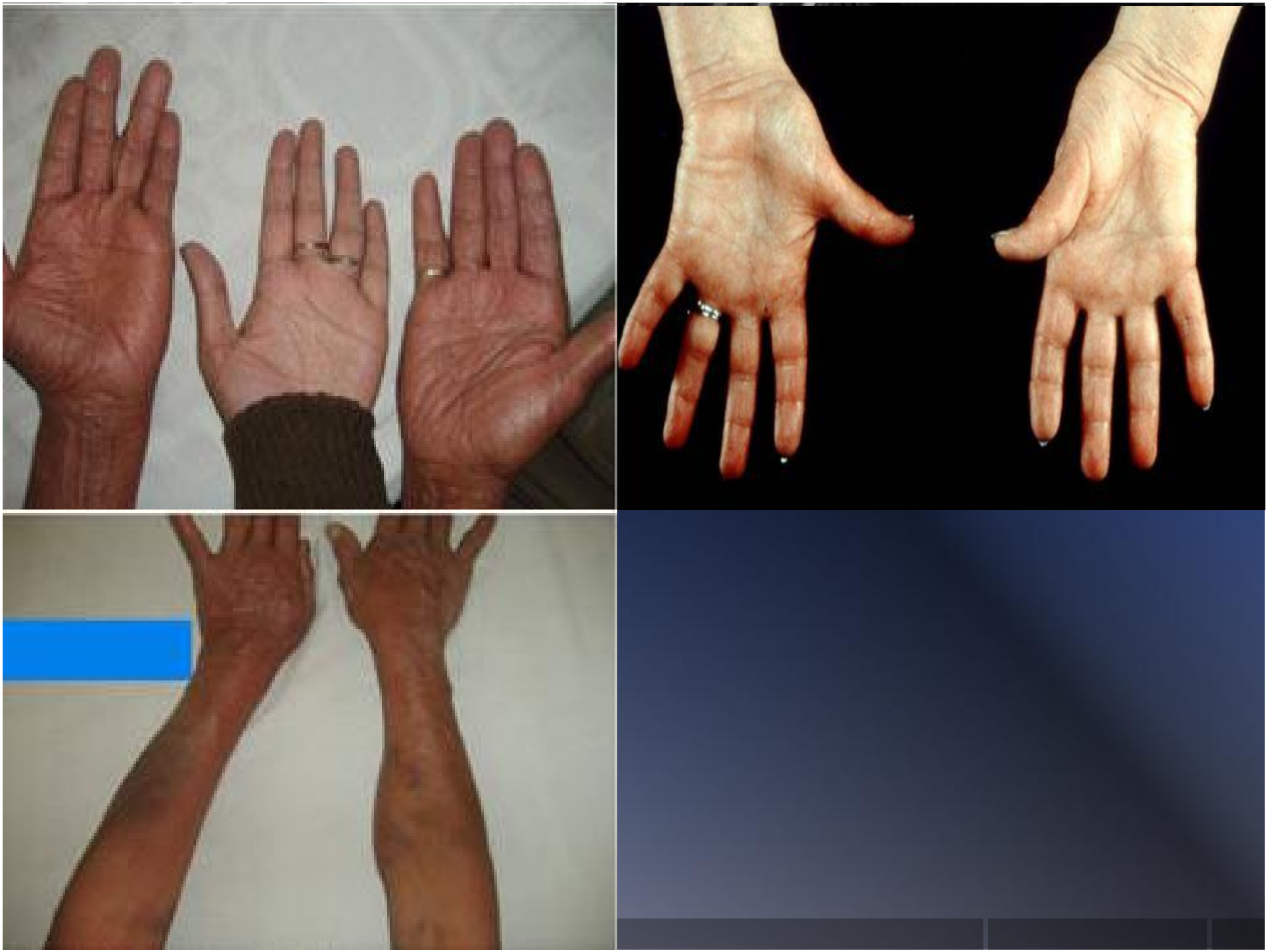
Clinical presentation

- Some patients with PV are *discovered incidentally* when an elevated hematocrit is noted on a CBC obtained for some other reason.

- *Plethora*
- *Symptoms of hypervisocity*: Headaches, blurry vision, altered hearing, shortness of breath, and malaise
- *Pruritus*: especially following vigorous rubbing of the skin after a warm bath or shower.

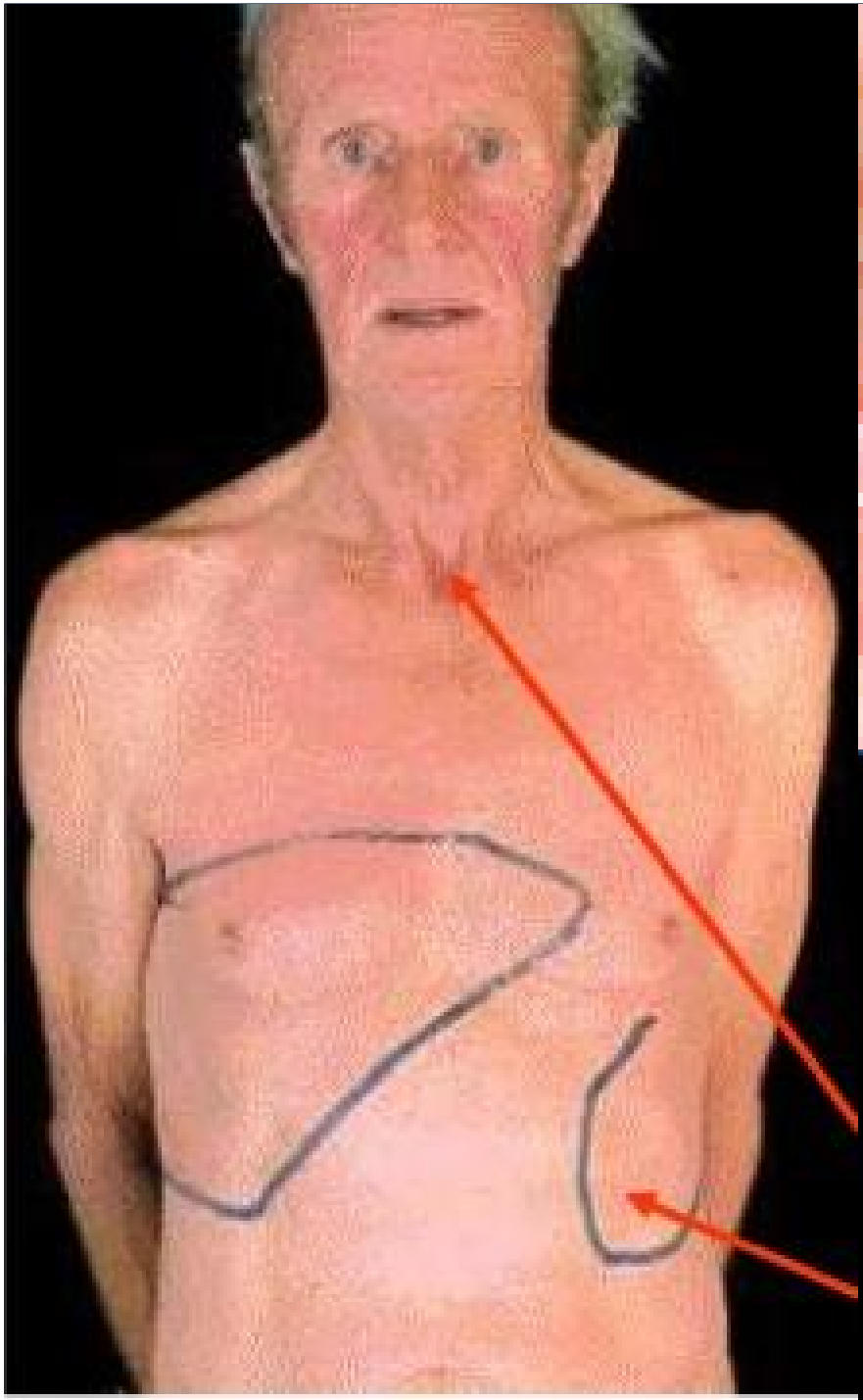
- Thrombosis: venous and arterial thrombosis are common in PV.
  - Venous thrombosis can occur in unusual sites.
  - A prior major thrombotic complication (eg, CVA, MI, amaurosis fugax, pulmonary embolus).
- Bleeding, especially gastrointestinal, is seen in PV.

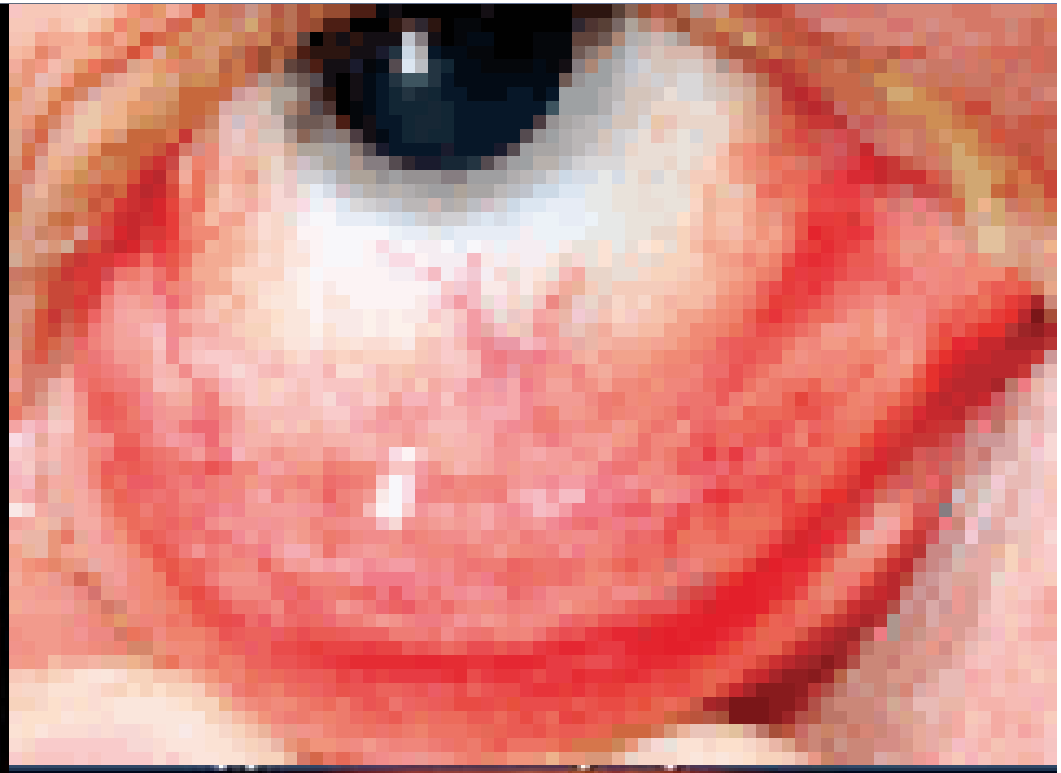
- *GI symptoms*: gastroduodenal erosions and ulcer.
- *Erythromelalgia*: burning pain in the feet or hands accompanied by erythema, pallor, or cyanosis, in the presence of palpable pulses.
- *Acute gouty arthritis*.

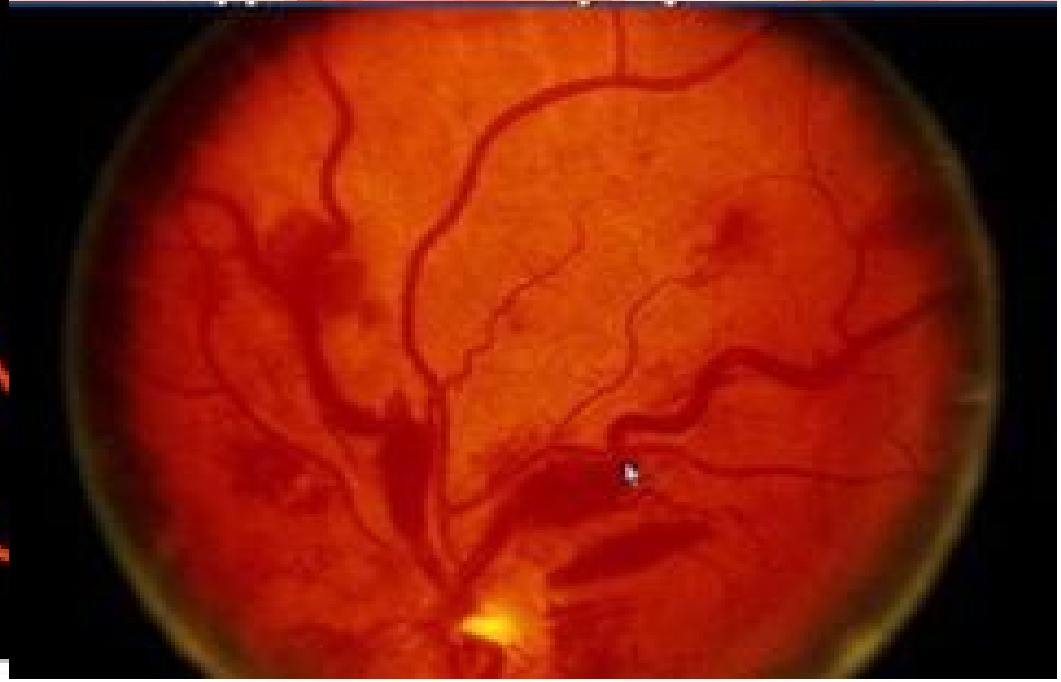


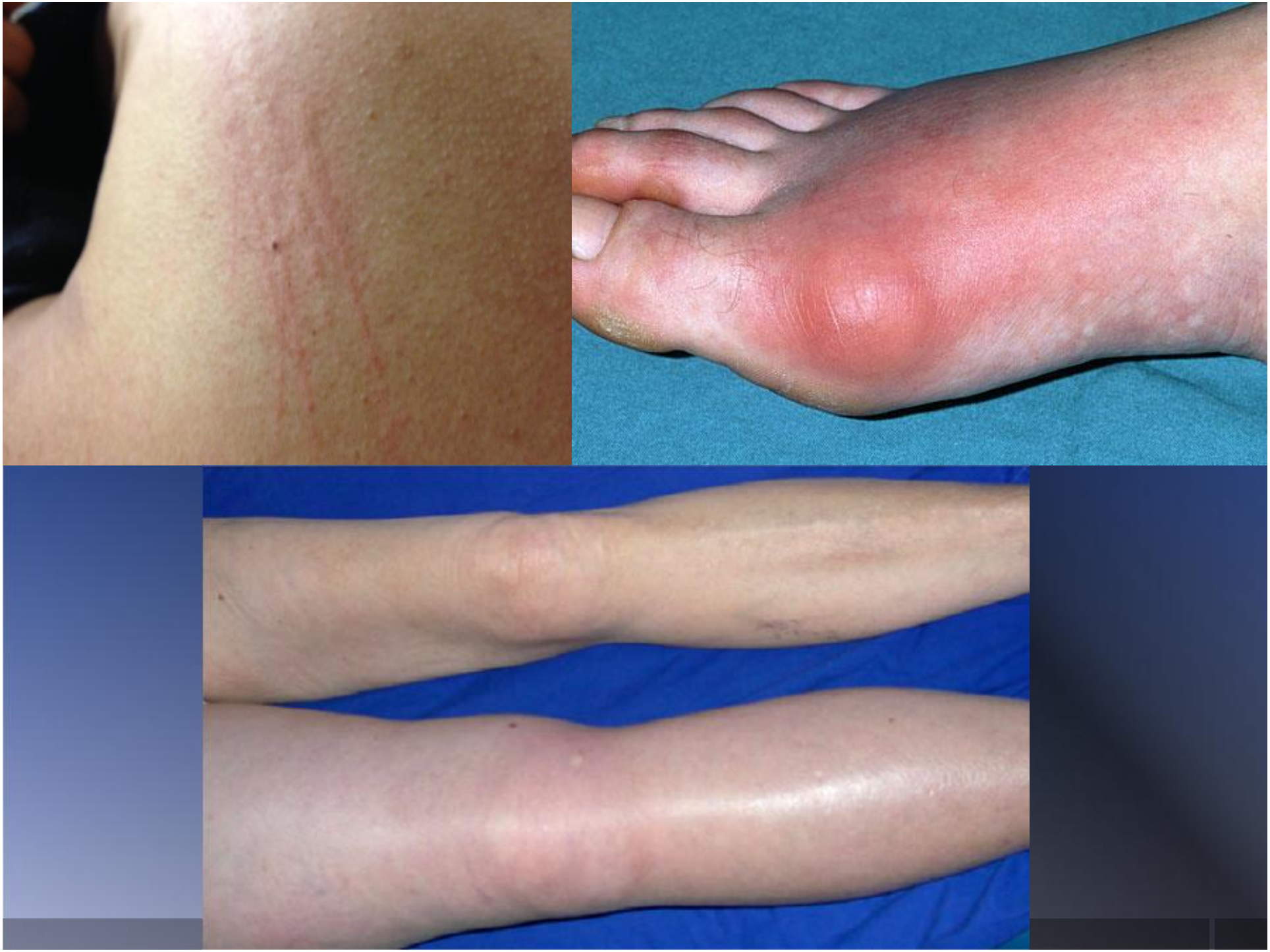
Physical examination

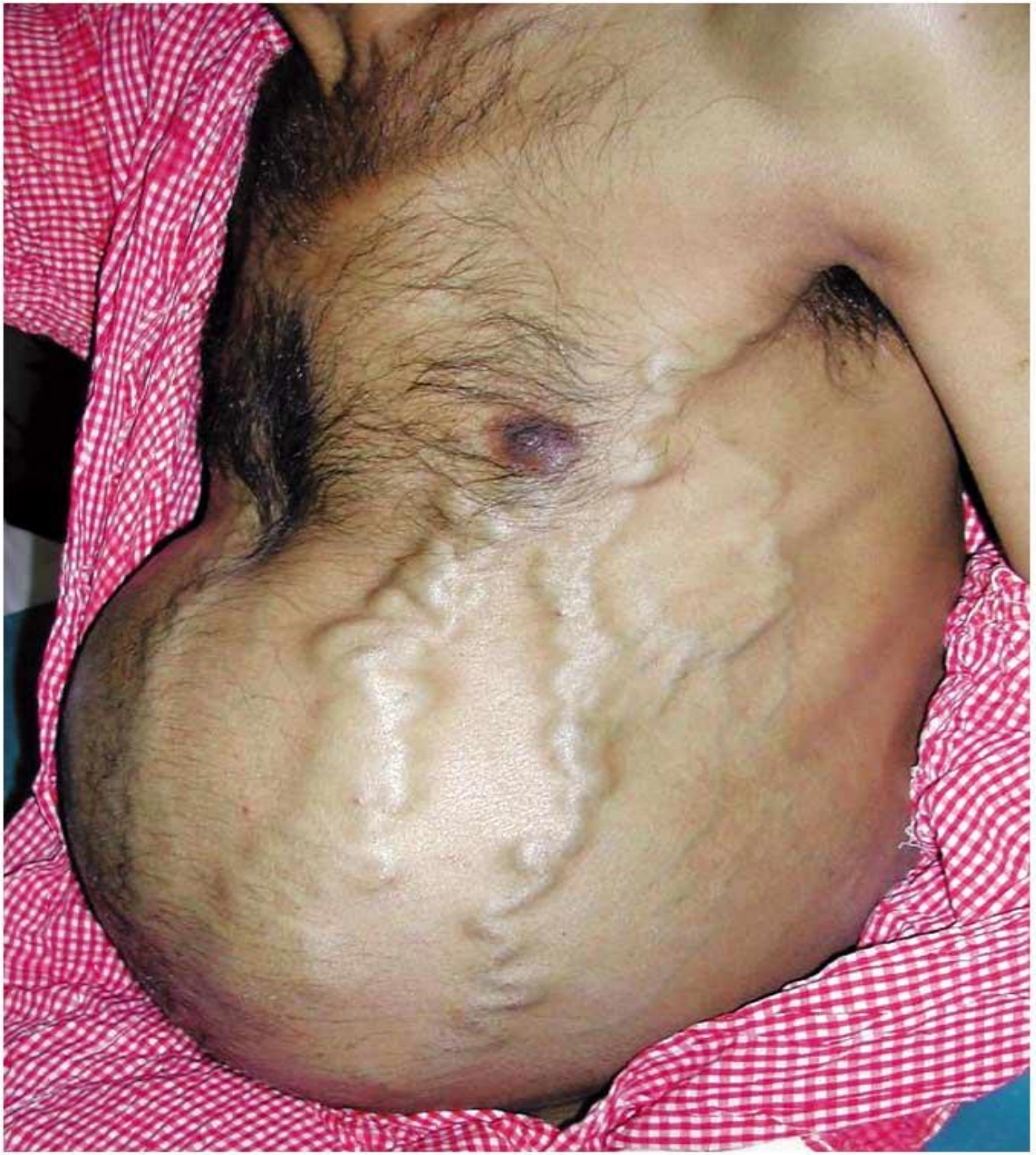
- The major abnormal findings on physical examination include *splenomegaly, facial plethora, and hepatomegaly*.
- Other physical findings:
  - Injection of the optic fundus
  - Excoriation of the skin
  - Stigmata of a prior arterial or venous thrombotic event
  - Gouty arthritis and tophi.











Laboratory finding

- Laboratory findings in PV include an elevated hemoglobin and red blood cell mass, increase platelet count, and a WBC count.
- Bone marrow cellularity was increased.
- A low serum erythropoietin level is highly suggestive of PV.
- Increase uric acid and LDH.

WHO criteria for polycythemia vera

Major criteria

- Hemoglobin >18.5 g/dL in men, 16.5 g/dL in women
- Presence of JAK2 mutation

Minor criteria

- Bone marrow biopsy showing hypercellularity
- Serum erythropoietin level below the reference range for normal
- Endogenous erythroid colony formation in vitro.

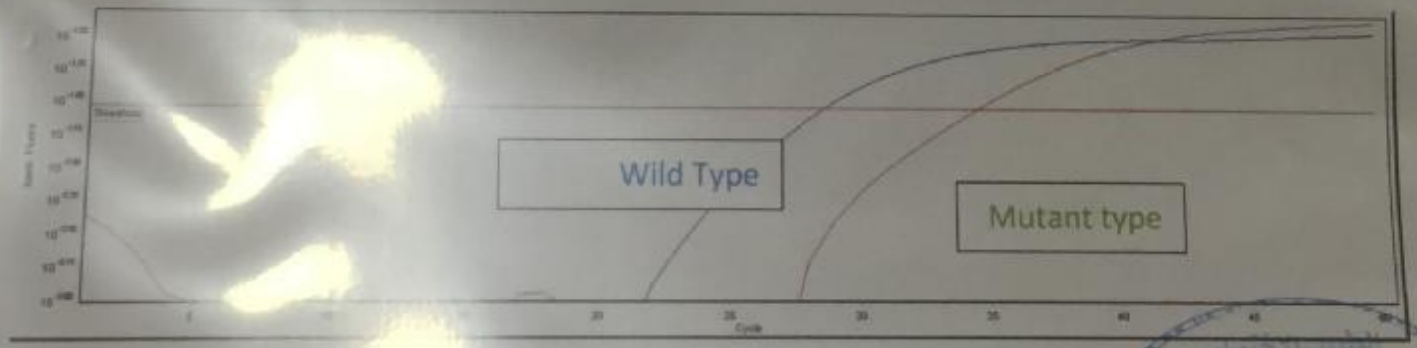
Diagnosis requires the presence of both major criteria and 1 minor criterion or the presence of the first major criterion together with 2 minor criteria

Which of the following is the most appropriate next diagnostic test?

1. Ultrasound of the abdomen
2. Echocardiogram
3. *JAK2* mutation analysis
4. Erythrocyte mass study

TEST RESULT AND VIRAL LOAD

TEST PERFORMED	RESULT	NOTE
Jak 2 mutation (V617F/G1849T)	Positive	Test for both mutant and wild type done and reveal positive for mutant type
ΔΔ ct	4.57	

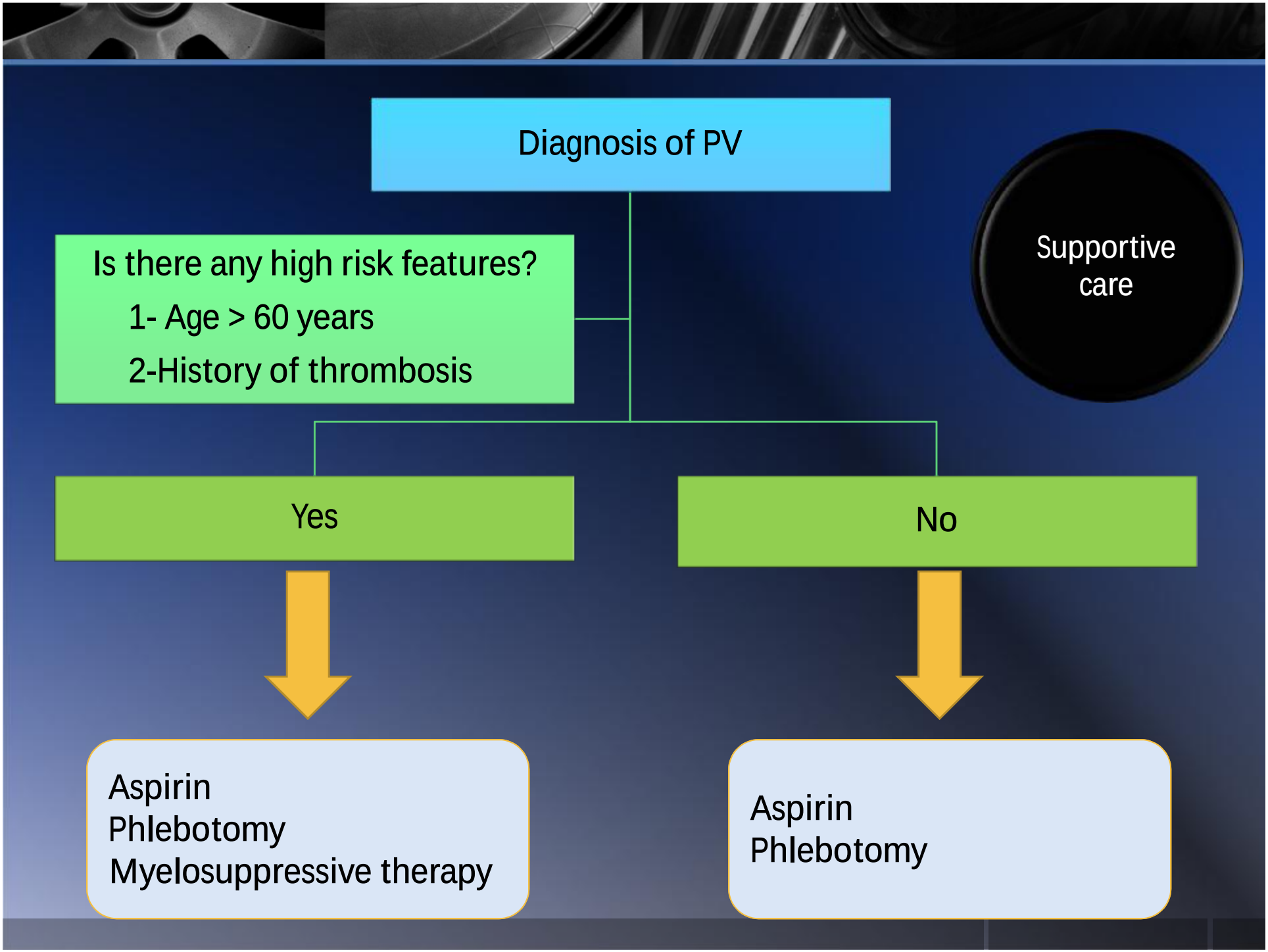


ΔΔct is correlated with quantity of mutant type, but cannot be consider as a titer

The test done by ipsogen RG RT-PCR Kit on Rotor-Gene Instruments from Qiagen GmbH Germany

Absence of Jak2 (V617F/G1849T) mutation dose not exclude the presence of other Jak 2 mutation.

The test can report false negative results in case of additional mutations located in nucleotides 88504 to 88622



Treatment

- Hematocrit control :
  - 500 ml of blood are removed every 5-7 days until reaching our aim.
  - Optimal control: hematocrit below 45% in men and 42% in women.
- Aspirin (75 to 100 mg/day) be given to all patients .

§ *Patients at high risk for thrombosis (ie, age >60, prior thrombosis):* we recommend adding myelosuppressive agent:

- ü Hydroxyurea.
- ü Radioactive phosphorus in elderly
- ü Interferon alpha in pregnant women.

Supportive care

- Pruritus: antihistamines, H2-receptor blockers, and myelosuppressive drugs.
- Hyperuricemia and acute gout treatment.
- Erythromelalgia: low-dose aspirin or with myelosuppression.
- Treatment of Bleeding.

Prognosis

- The median survival of untreated symptomatic patients with PV is 6-18 months, whereas survival of treated patients is 10 years or more.
- The main causes of death include:
  - Thrombosis and/ or Hemorrhage
  - Hematologic malignancies (ie, AML or MDS),
  - Non-hematologic malignancies
  - Myelofibrosis

- After 3 years the patient presented with history of progressive pallor. His CBC show: hemoglobin= 5 gm/dL, platelets counts= 100000 cells/cmm, WBC count= 25000 cells/cmm,
- What are further investigations you will recommend?
- Blood film show myeloblast cells=10000 cells/ cmm.
- Outline the lines of treatment of this patient?