Myeloprolifrative disorders

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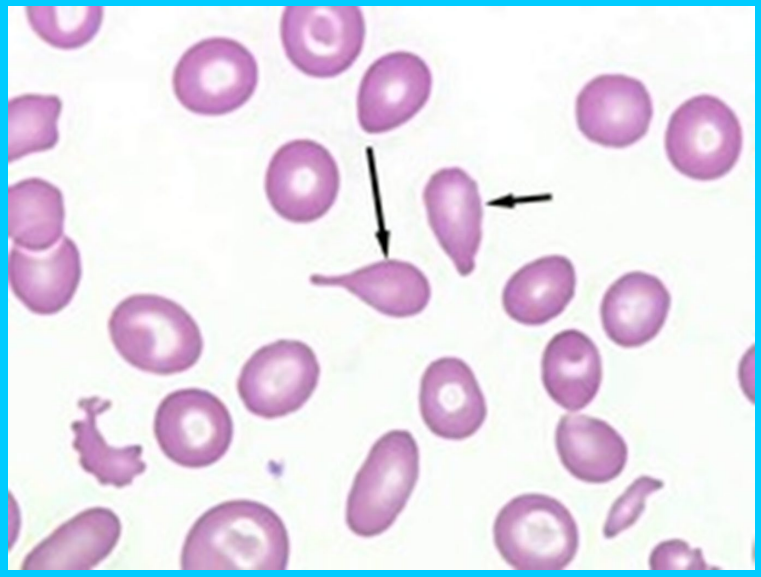
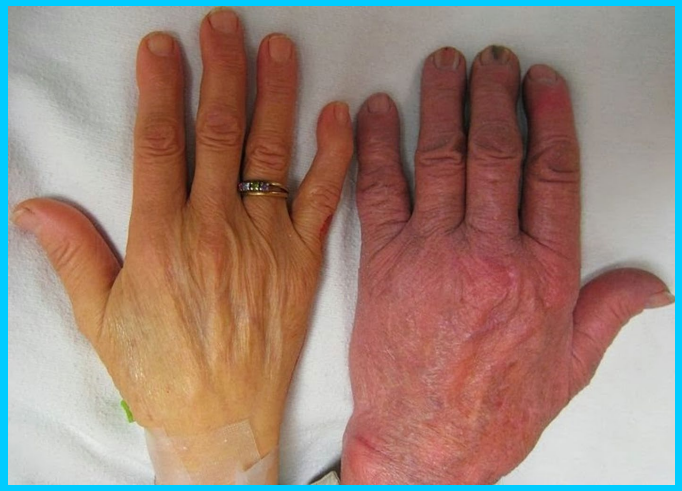




Myeloprolifrative Disorders

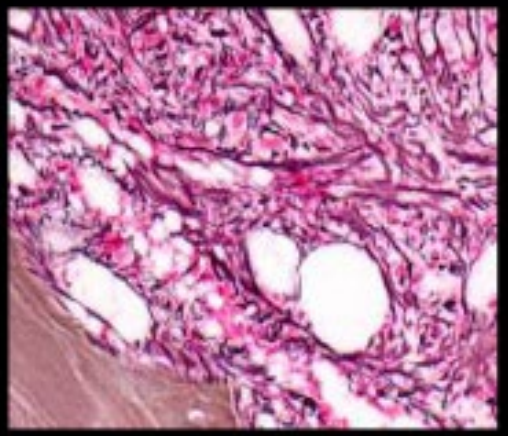
Make up of group of chronic conditions
Characterized by clonal proliferation of
Marrow erythroid precursors(PRV)
Megakareocytes(primary thrombocythaemia
And myelofibrosis)or myeloid cells(CML)

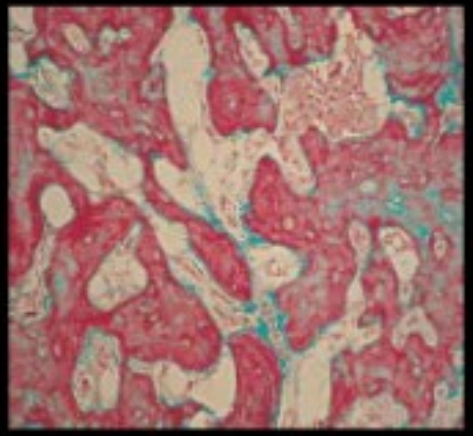
Although the majority of patients are classifiable as having one of these disorders, some have overlapping features and there is often progression from one to another, e.g. PRV to myelofibrosis.

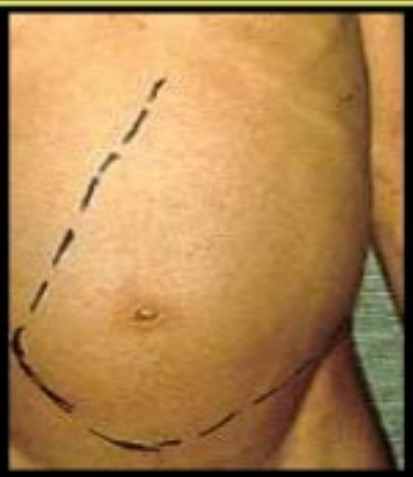
A mutation in the gene on chromosome 9 encoding the signal transduction molecule JAK-2 (JAK-2 V617F) has been found in more than 90% of PRV cases and 50% of those with essential thrombocythaemia and myelofibrosis; less frequently, mutations may be identified in exon 12 of JAK-2. Mutations in the calreticulin gene (CALR), which produces a chaperone protein that protects proteins moving from the endoplasmic reticulin to the cytoplasm, have been found in a further 25% of patients with essential thrombocythaemia.

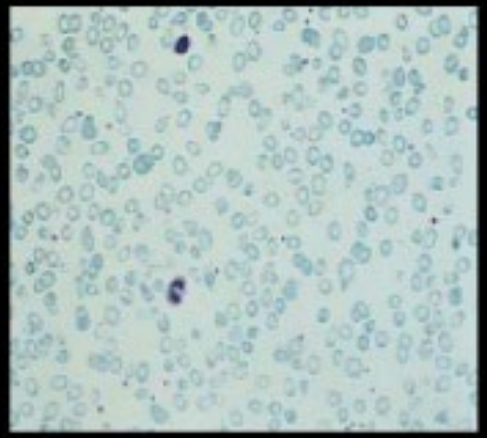
Less commonly, mutations can be detected in the thrombopoietin receptor gene MPL

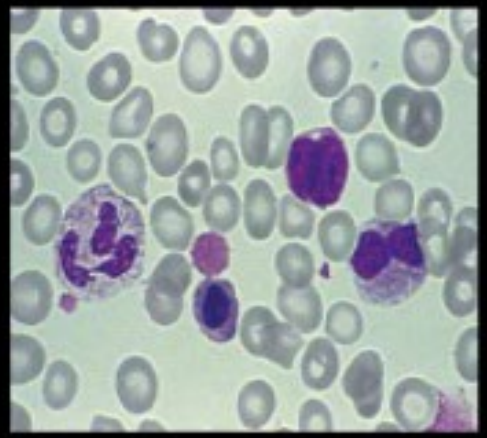
Myelofibrosis











Myelofibrosis

In myelofibrosis, the marrow is initially hypercellular, with an excess of abnormal megakaryocytes that release growth factors, such as platelet-derived growth factor, to the marrow microenvironment, resulting in a reactive proliferation of fibroblasts. As the disease progresses, the marrow becomes fibrosed.

Most patients present over the age of 50 years, with lassitude, weight loss and night sweats. The spleen can be massively enlarged due to extramedullary haematopoiesis (blood cell formation outside the bone marrow), and painful splenic infarcts may occur.

Myelofibrosis:

Characterized by

1-bone marrow fibrosis ,

2-extra-medullary Haematopoiesis(blood cell formation outside the bone Marrow) and

3-leucoerythroblastic blood picture.

Clinical features:

-about 20%f patients are asymptomatic.

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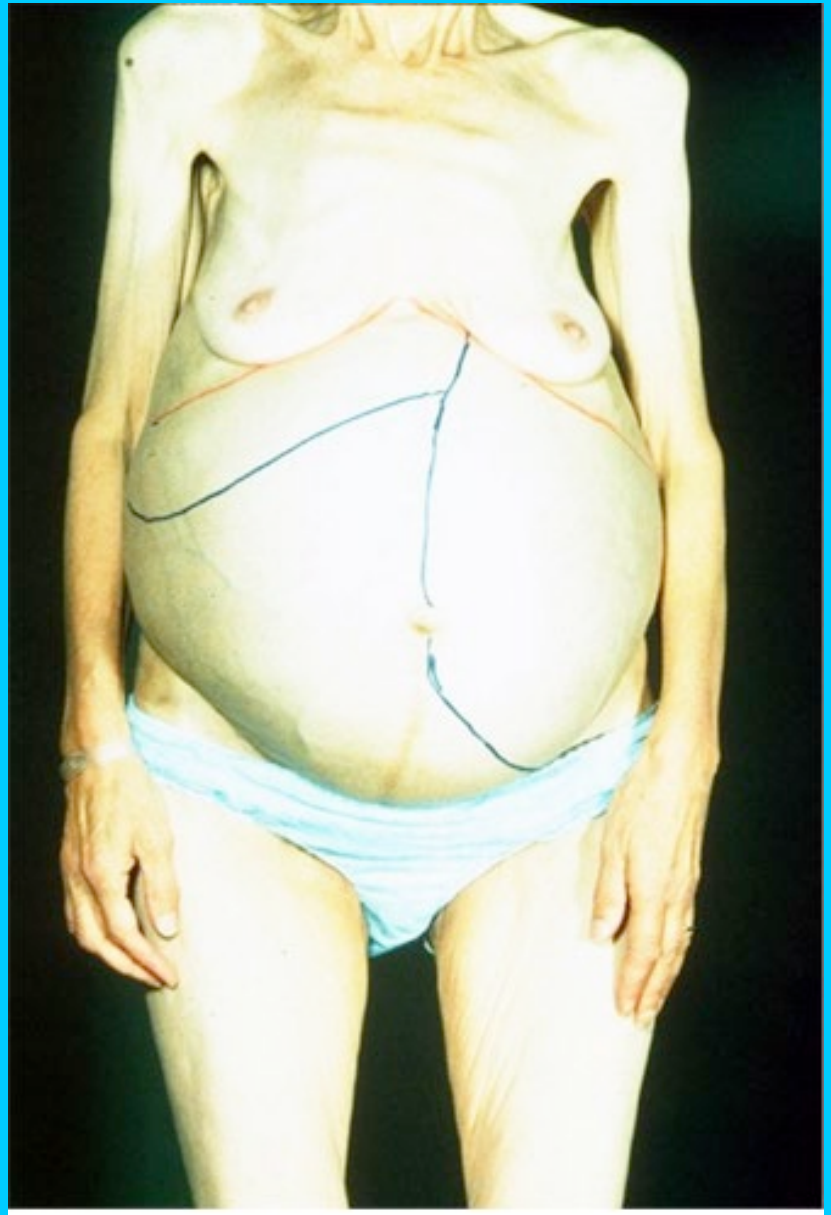
night sweats, lassitude, and weight loss are common presenting complaints

2-splenomegaly:spleen can be massively enlarged due to Extramedullary haematopoiesis (blood cell formation outside the bone marrow), and painful splenic infarcts may occur

symptoms are:
-left upper quadrant discomfort.
-diarrhoea from splenic compression of the intestine.
-early satiety from pressure on the stomach.



Characteristic body habitus of a patient with myelofibrosis exhibiting signs of cachexia and muscle wasting, hepatosplenomegaly with a protuberant abdomen.

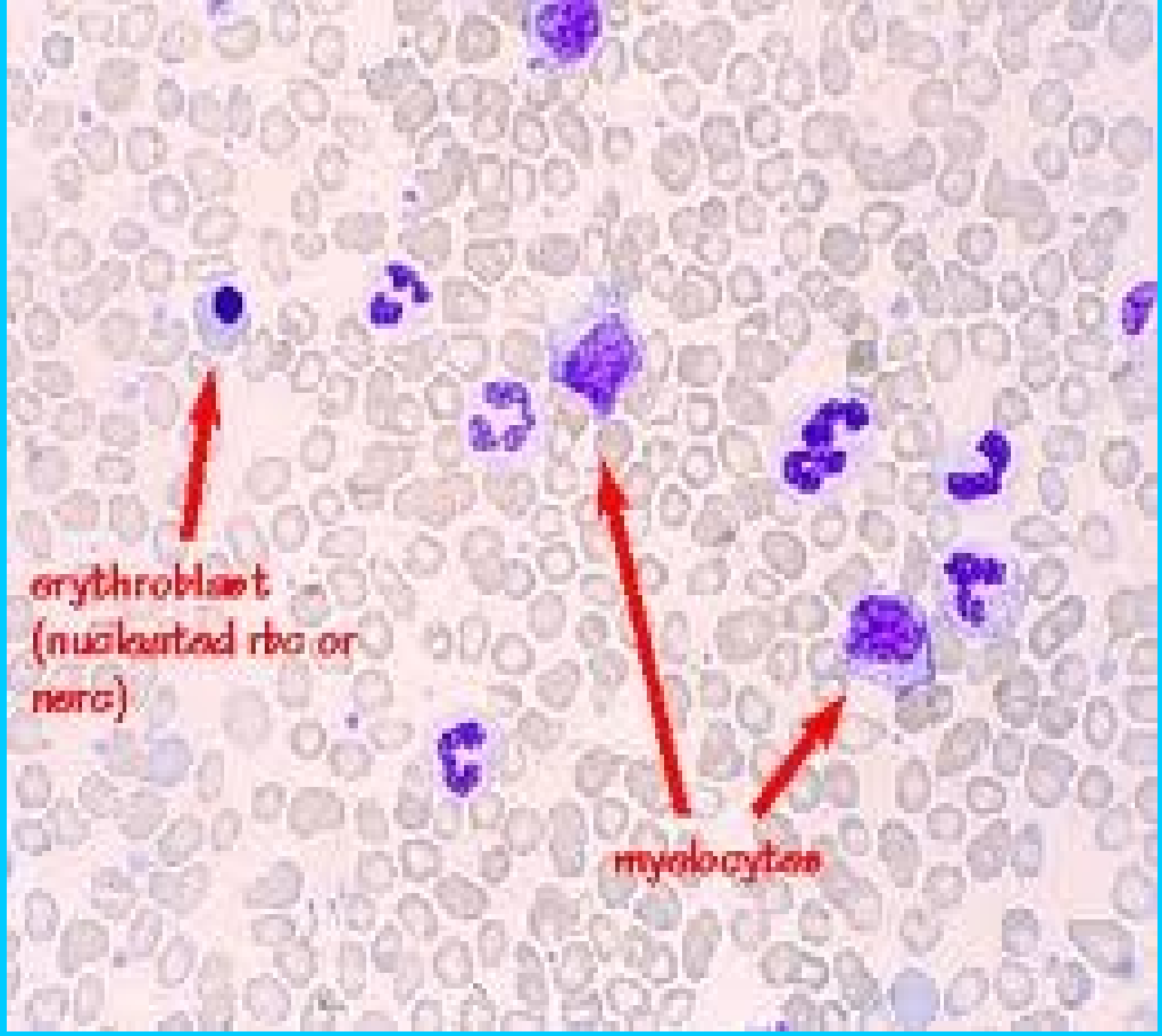
3-hypermetabolism from red cells turn over, symptoms are:
-weight loss, night sweat and fever.
-problems related to hyperuricaemia include gout or urinary tract obstruction from urate ston.

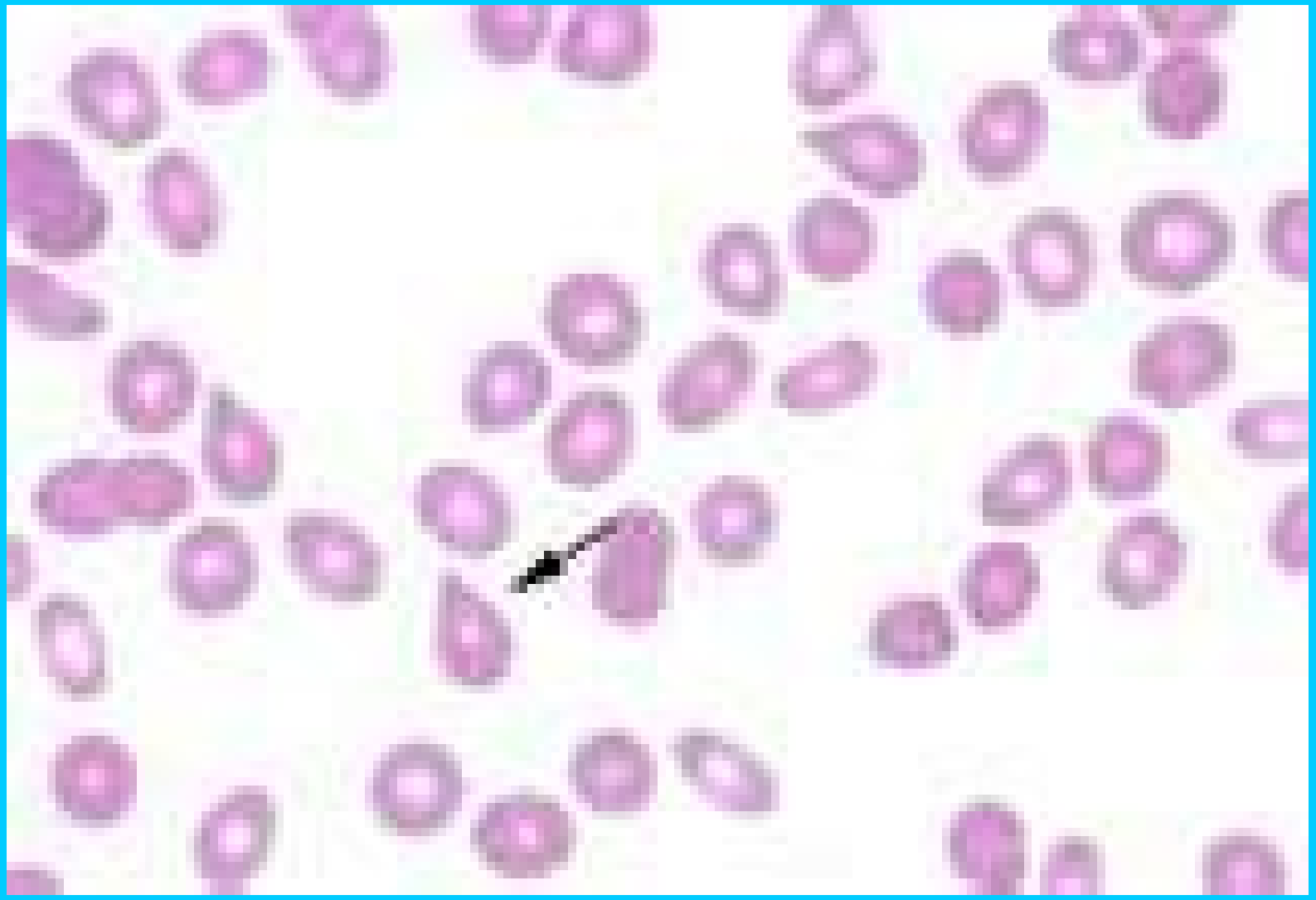
The characteristic blood picture is leucoerythroblastic anaemia, with circulating immature red blood cells (increased reticulocytes and nucleated red blood cells) and granulocyte precursors (myelocytes).

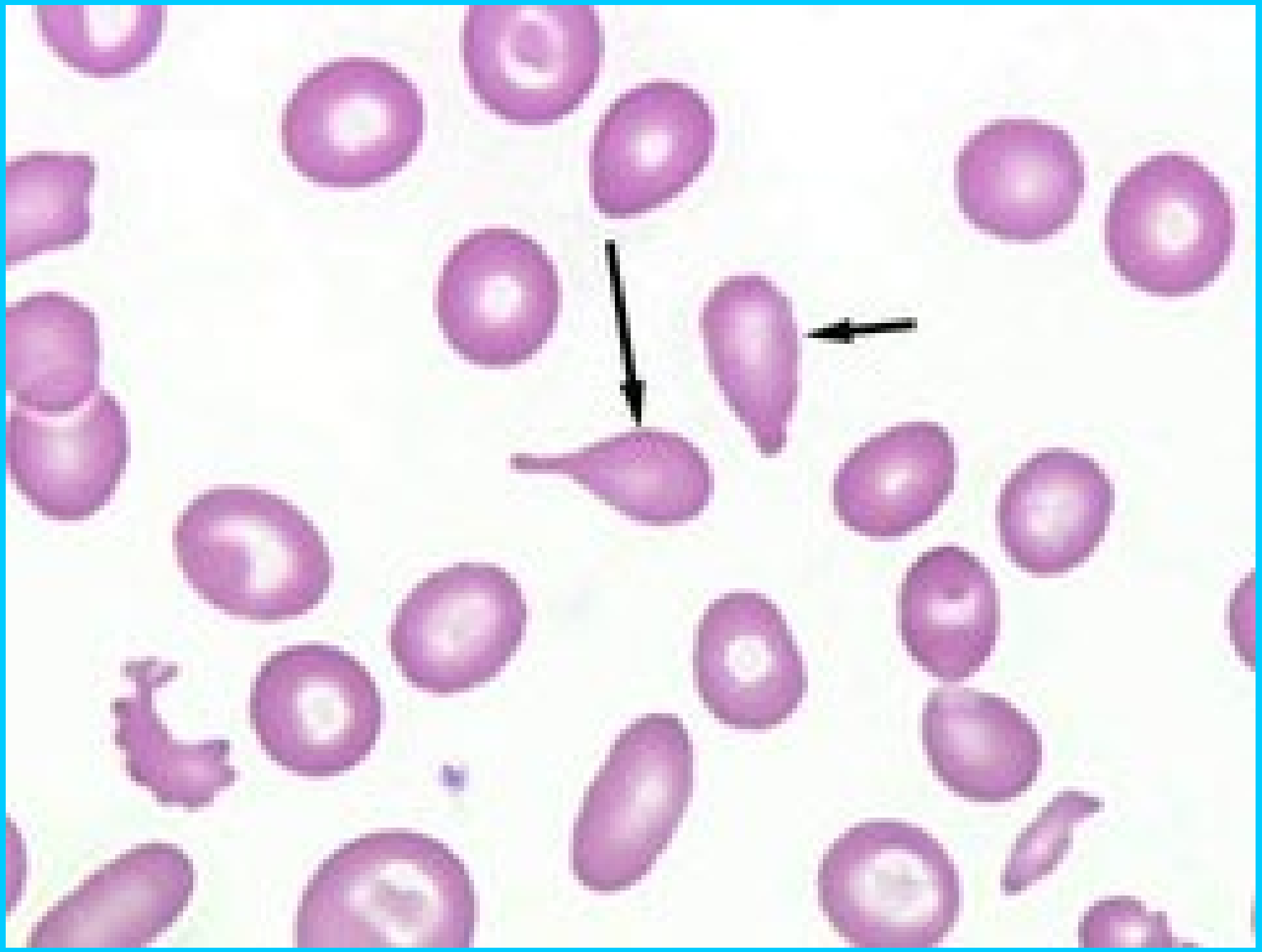
The red cells are shaped like teardrops (teardrop poikilocytes), and giant platelets may be seen in the blood.

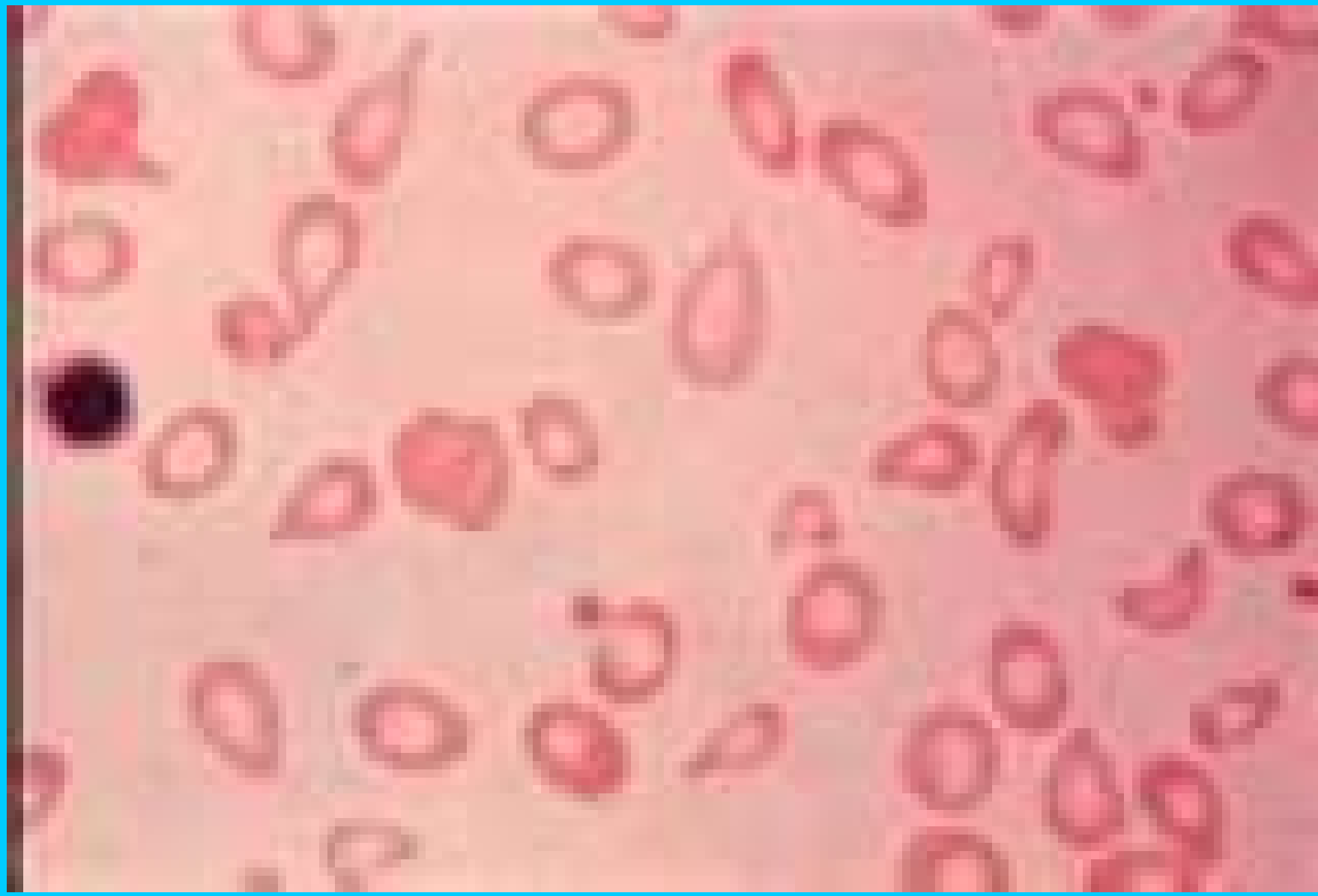
The white count varies from low to moderately high and the platelet count may be high, normal or low. Urate levels may be high due to increased cell breakdown, and folate deficiency is common. The marrow is often difficult to aspirate and a trephine biopsy shows an excess of megakaryocytes, increased reticulin and fibrous tissue replacement.

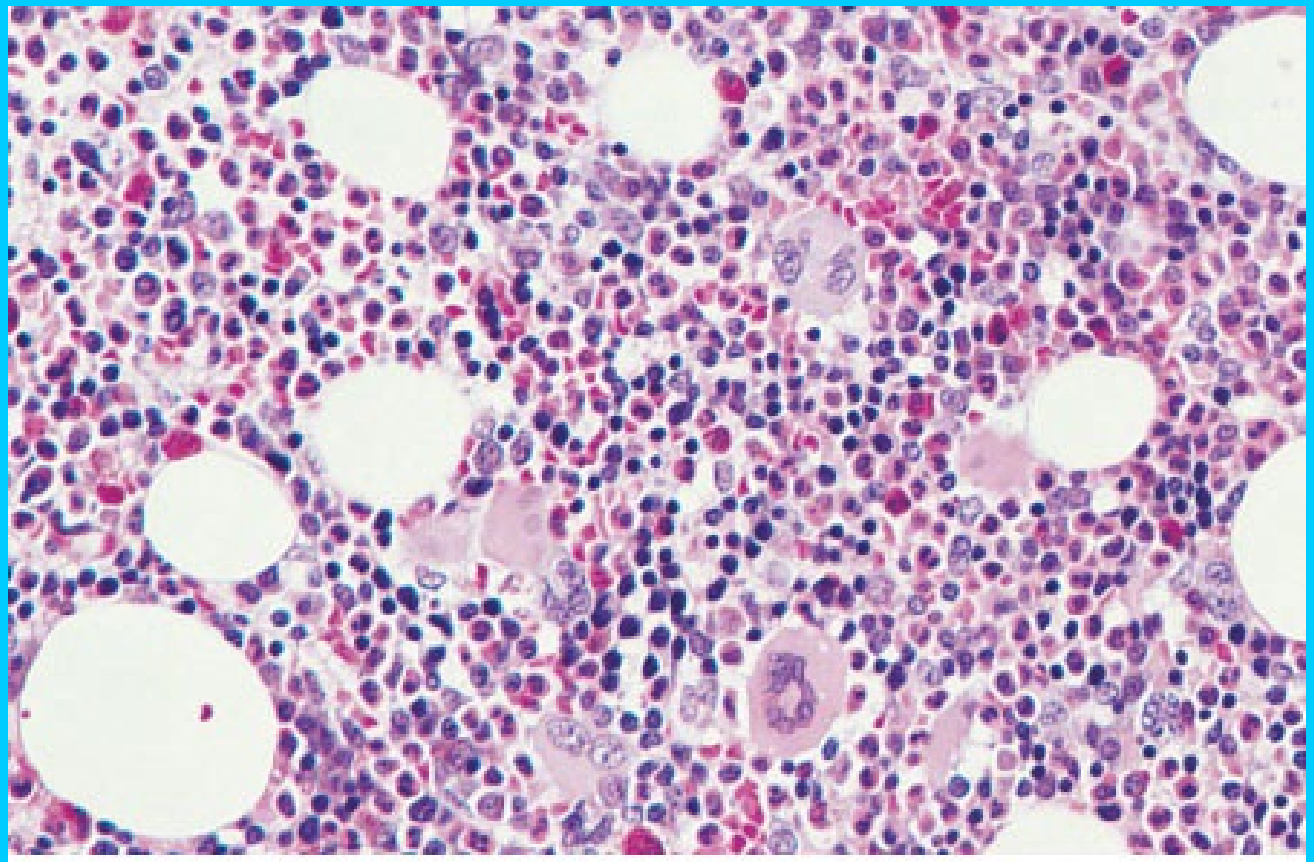
The presence of a pathological JAK-2 mutation supports the diagnosis.


erythroblast
(nucleated rbc or
nrbc)
myelocytes



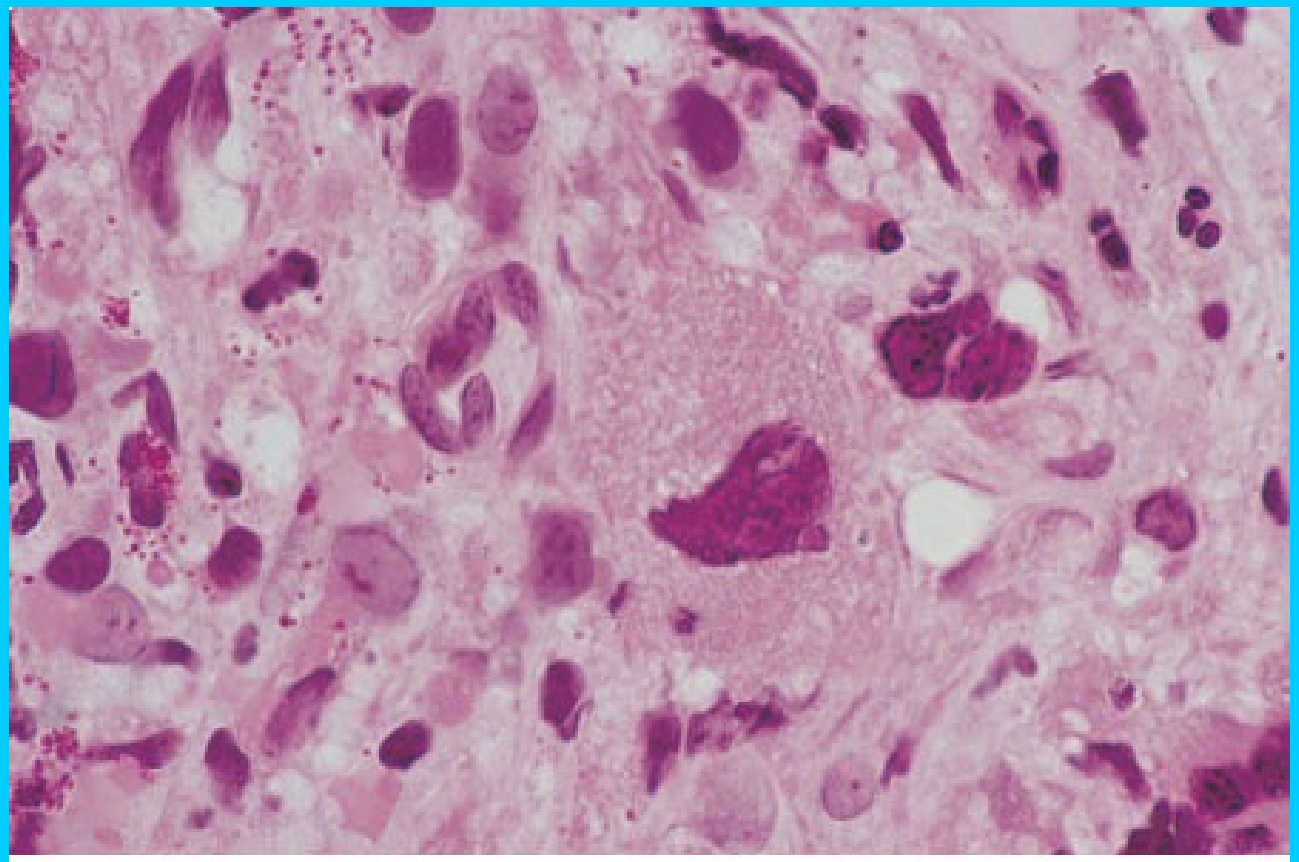






Source: Lichtman MA, Beutler E, Kipps TJ, Seligsohn U, Kaushansky K, Prchal JT: *Williams Hematology*, 7th Edition: http://www.accessmedicine.com

NORMAL BONE MARROW



MYELOFIBROSIS

Treatment : Is directed at control of symptoms.

red cell transfusion for anaemia.
Folic acid to prevent deficiency.
Cytotoxic therapy with Hydroxrycarbamide may help to:
1-control spleen size.
2-WBC count.
3-systemic symptoms.

Splenectomy may be required for grossly enlargedSpleen or symptomatic pan cytopenia secondary to Splenic pooling of cells and hypersplenism.

HSCT transplantation may be considered for Younger patients.

Ruxolitinib, an inhibitor of JAK-2, is effective at reducing systemic symptoms and splenomegaly and may improve life expectancy with longer-term use

PROGNOSIS:

Median survival is 4 years from diagnosis

But range from one year to over 20 years.

Essential Thrombocythemia

Essential thrombocytosis (primary thrombocythemia)

Essential thrombocythaemia:

Uncontrolled proliferation of megakaryocytes
Result in a raised level of circulating platelets
That are often dysfunctional.

Reactive causes of increased platelets should be excluded prior to make the diagnosis.
These are:

Reactive thrombocytosis
Acute and chronic inflammatory disorders
Infection
Malignant disease
Tissue damage
Haemolytic anaemias
Post-splenectomy
Post-haemorrhage

The presence of pathogenic JAK-2 V617F, CALR or, rarely, MPL mutations supports the diagnosis, but is not universal.

Clinical features:

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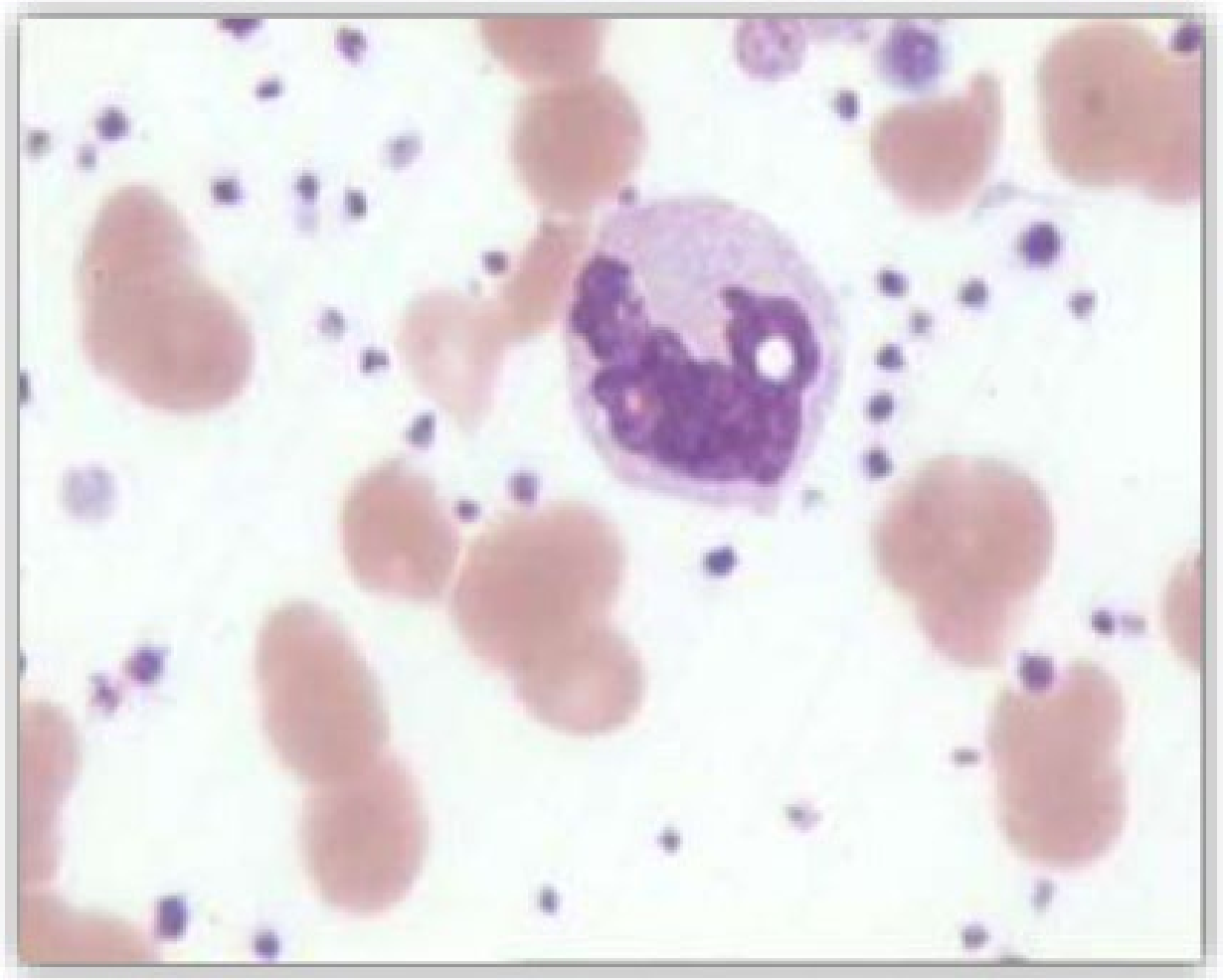
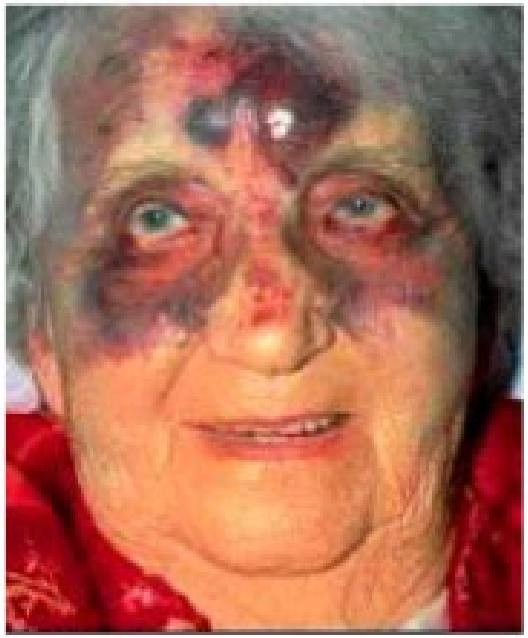
Patients present at a median age of 60 years with vascular occlusion, acrocyanosis (painful discoloured finger tips) or bleeding, or with an asymptomatic isolated raised platelet count.
A small percentage (around 5%) will transform to acute leukaemia and others to myelofibrosis.

Essential thrombocythemia

Plenty of
Platelets in blood →

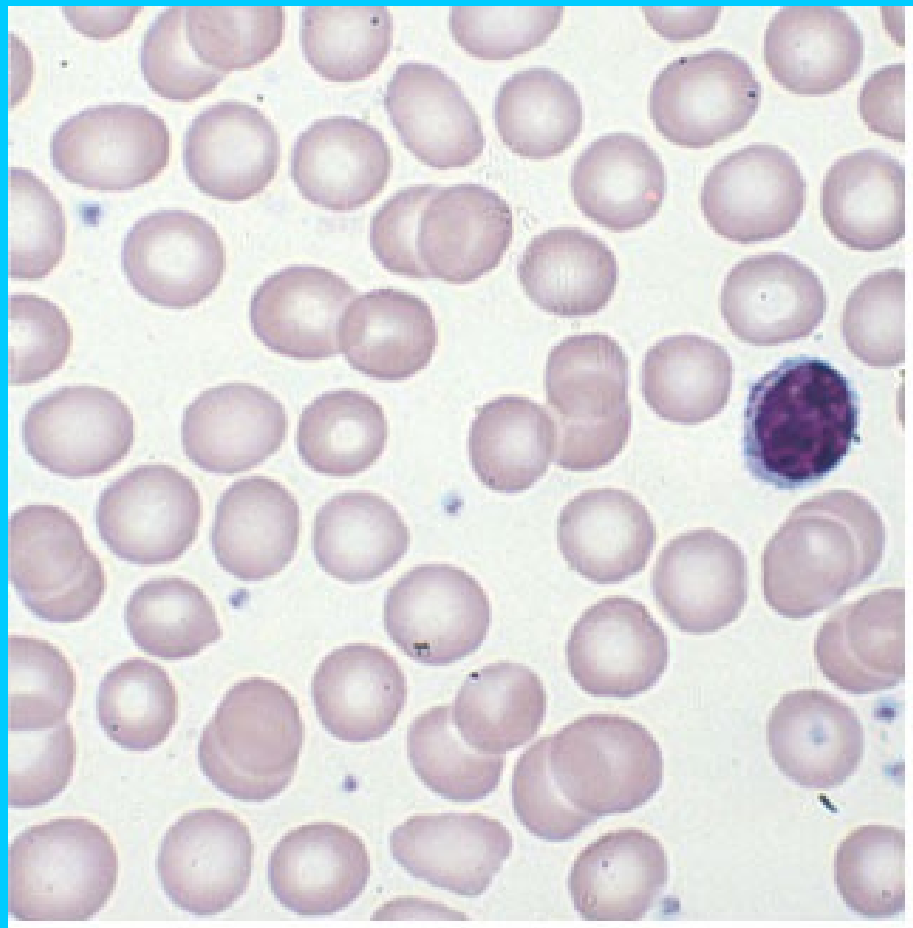




← But clinical bleeding (abnormal platelets)

investigations:

Platelet count usually more than one million per cubic mm.
Haematocrit normal or slightly diminished.
WBC count mildly increased,basophilia and eosinophilia may Occur.
Bone marrow aspirate and biopsy: increased number of large Normally lobulated megakaryocytes.



Source: Lichtman MA, Beutler E, Kipps TJ, Seligsohn U, Kaushansky K, Prchal JT:
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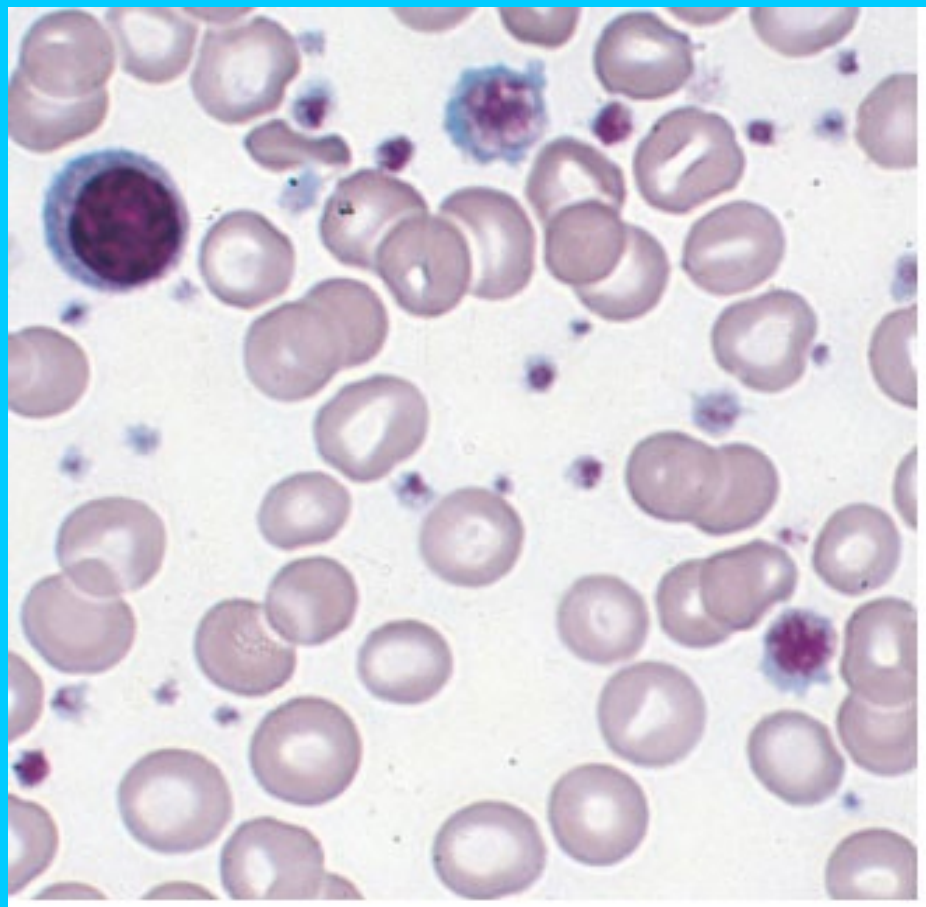
NORMAL PLATELETS



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THROMBOCYTHAEMIA

Treatment :

It is likely that most patients with essential thrombocythaemia benefit from low-dose aspirin to reduce the risk of occlusive vascular events.

Low-risk patients include:

1-age less than40 years.

2- platelet count < 1500 × 10^9/L .

3-no bleeding or thrombosis.

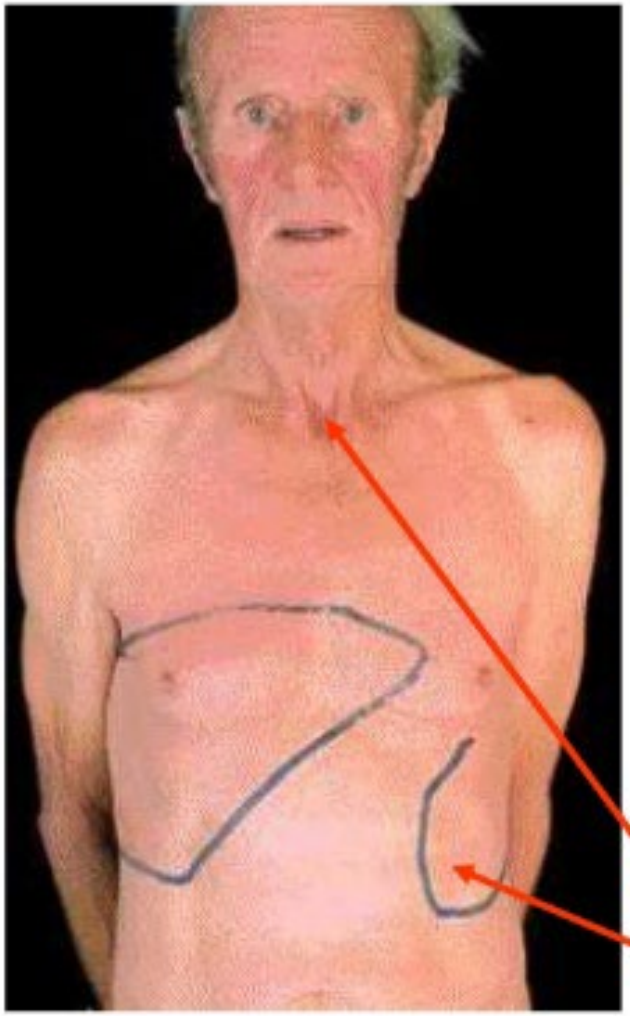
All the above may require no treatment to reduce platelet count.

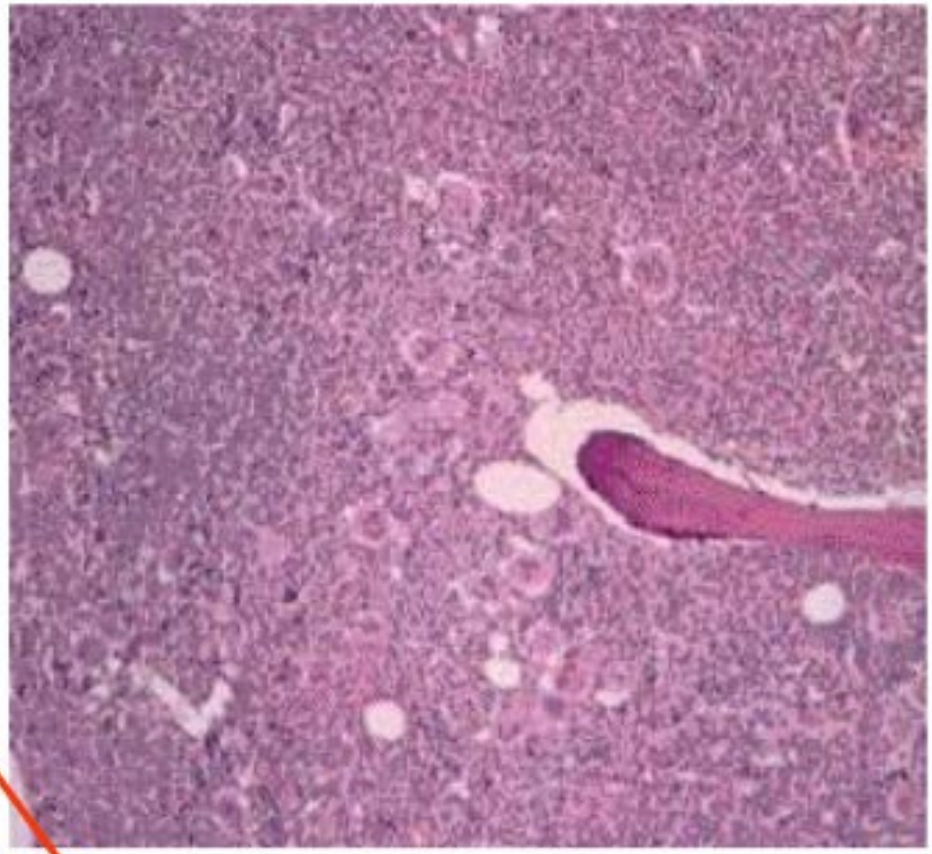
For those with a platelet count > 1500 × 10^9/L, with symptoms, or with other risk factors for thrombosis such as diabetes or hypertension,
treatment to control platelets should be given.
Agents include oral hydroxycarbamide or anagrelide, an inhibitor of megakaryocyte maturation.

Intravenous radioactive phosphorus (32P) may be useful in old age, but is rarely available nowadays, and interferon-alfa has a role in younger patients, including pregnant women and women planning to conceive.

Polycythaemia rubra vera

Polycythemia Rubra Vera (PV)





Hypercellular Marrow,
Red skin & Hepatosplenomegaly

Patients with a persistently raised haematocrit (Hct) (> 0.52 males, > 0.48 females) for more than 2 months should be investigated.

‘True’ polycythaemia (or absolute erythrocytosis) indicates an excess of red cells, while‘relative’ (or ‘low-volume’) polycythaemia is due to a decreased plasma volume.

Causes of polycythaemia are shown next slide.
These involve increased erythropoiesis in the bone marrow, either due to a primary increase in marrow activity, or in response to increased erythropoietin (Epo) levels in chronic hypoxaemia, or due to inappropriate secretion of Epo.
Some athletes improperly use Epo to increase oxygen-carrying capacity and thus enhance their physical performance.
Apparent erythrocytosis with a raised Hct, normal red cell mass (RCM) and reduced plasma volume may be associated with hypertension, smoking, alcohol and diuretic use (Gaisböck syndrome).

Classification and causes of erythrocytosis

	Absolute erythrocytosis	Relative (low-volume) erythrocytosis
Haematocrit	High	High
Red cell mass	High	Normal
Plasma volume	Normal	Low
Causes	*Primary* Myeloproliferative disorder Polycythaemia rubra vera (primary proliferative polycythaemia) *Secondary* High erythropoietin due to tissue hypoxia High altitude Cardiorespiratory disease High-affinity haemoglobins Inappropriately increased erythropoietin Renal disease (hydronephrosis, cysts, carcinoma) Other tumours (hepatoma, bronchogenic carcinoma, uterine fibroids, phaeochromocytoma, cerebellar haemangioblastoma) Exogenous erythropoietin administration Performance-enhancing drug-taking in athletes	Diuretics Smoking Obesity Alcohol excess Gaisbock's syndrome

Clinical assessment and investigations

Males and females with Hct values of over 0.60 and over 0.56, respectively, can be assumed to have an absolute erythrocytosis. A clinical history and examination will identify most patients with polycythaemia secondary to hypoxia.

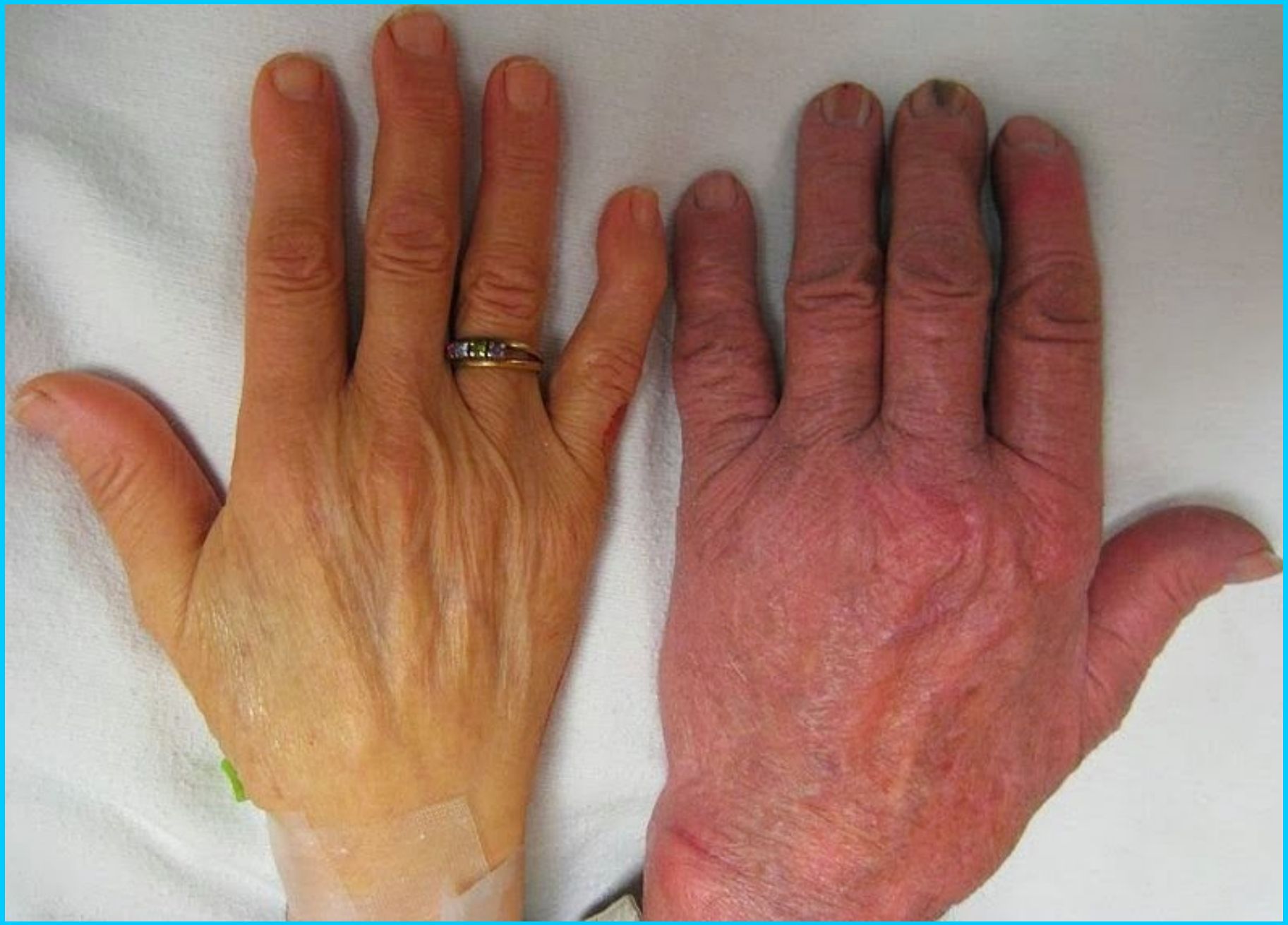
The presence of hypertension, smoking, excess alcohol consumption and/or diuretic use is consistent with low-volume polycythaemia (Gaisbock's syndrome).

Polycythaemia rubra vera

Polycythaemia rubra vera (PRV) occurs mainly in patients over the age of 40 years and presents either as

1-an incidental finding of a high haemoglobin, or

2- symptoms of hyperviscosity, such as lassitude, loss of concentration, headaches, dizziness,blackouts, epistaxis and aquagenic pruritus (worse after a hot bath), hepatosplenomegaly



3-Some patients present with manifestations of peripheral arterial disease or acerebrovascular accident.
4-Venous thromboembolism may also occur.
5- Peptic ulceration is common, sometimes complicated by bleeding.

O/E Patients are often plethoric and many have a palpable spleen at diagnosis.

In polycythaemia rubra vera (PRV), a mutation in a kinase, *JAK-2 V617F, is found in over 95% of cases*

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Investigation

The diagnosis of PRV now rests upon the demonstration of a high haematocrit and the presence of the JAK-2 mutation.

In the occasional JAK 2-negative cases, a raised red cell mass and absence of causes of a secondary erythrocytosis must be established.

If the JAK-2 mutation is absent and there is no obvious secondary cause, a measurement of red cell mass is required to confirm an absolute erythrocytosis, followed by further investigations to exclude hypoxia, and causes of inappropriate erythropoietin secretion. Red cell mass measurement is performed by radiolabelling an aliquot of the patient's red cells, re-injecting them and measuring the dilution of the isotope.

The red blood cell mass is increased if it exceeds 35 mg/kg in males and 31 mg/kg in females. Documentation of an increased red blood cell mass is essential to demonstrate true erythrocytosis.

The spleen may be enlarged and neutrophil and platelet counts are frequently raised, an abnormal karyotype may be found in the marrow and in vitro culture of the marrow can be used to demonstrate autonomous growth in the absence of added growth factors.

Management and prognosis

1-Aspirin reduces the risk of thrombosis.

2-Venesection gives prompt relief of hyperviscosity symptoms. Between 400 and 500 mL of blood (less if the patient is elderly) are removed and the venesection is repeated every 5–7 days until the haematocrit is reduced to below 45%.

Less frequent but regular venesection will maintain this level until the haemoglobin remains reduced because of iron deficiency.

3-Suppression of marrow proliferation with hydroxycarbamide or interferon-alfa may reduce the risk of vascular occlusion, control spleen size
-reduce transformation to myelofibrosis.
4-The JAK-2 inhibitor ruxolitinib is licensed for patients whose disease is not controlled by hydroxycarbamide

Prognosis

Median survival after diagnosis in treated patients exceeds 10 years. Some patients survive more than 20 years; however, cerebrovascular or coronary events occur in up to 60% of patients.

The disease may convert to another myeloproliferative disorder, with about 15%developing acute leukaemia or myelofibrosis.

THANK YOU