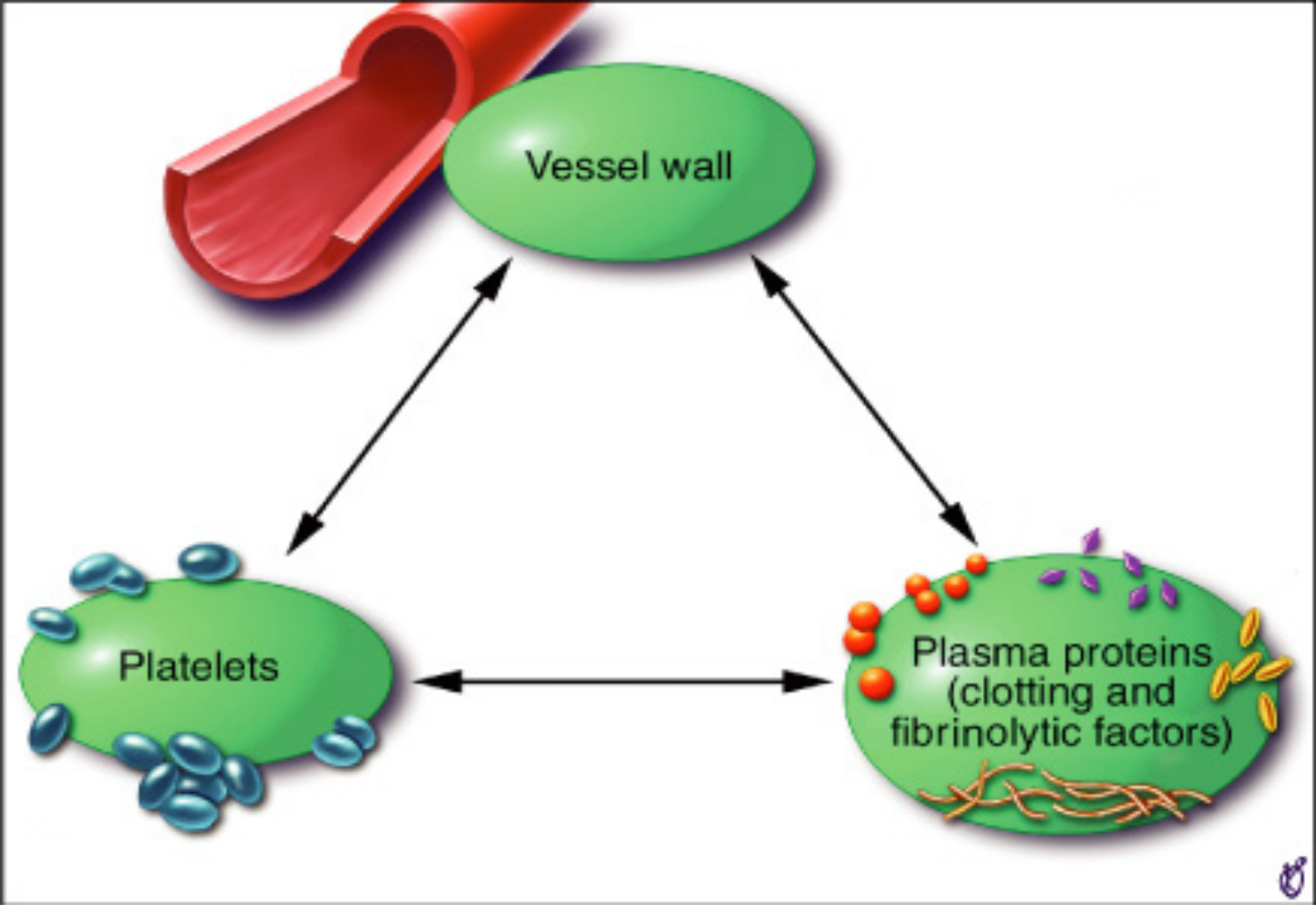
BLEEDING DISORDERS

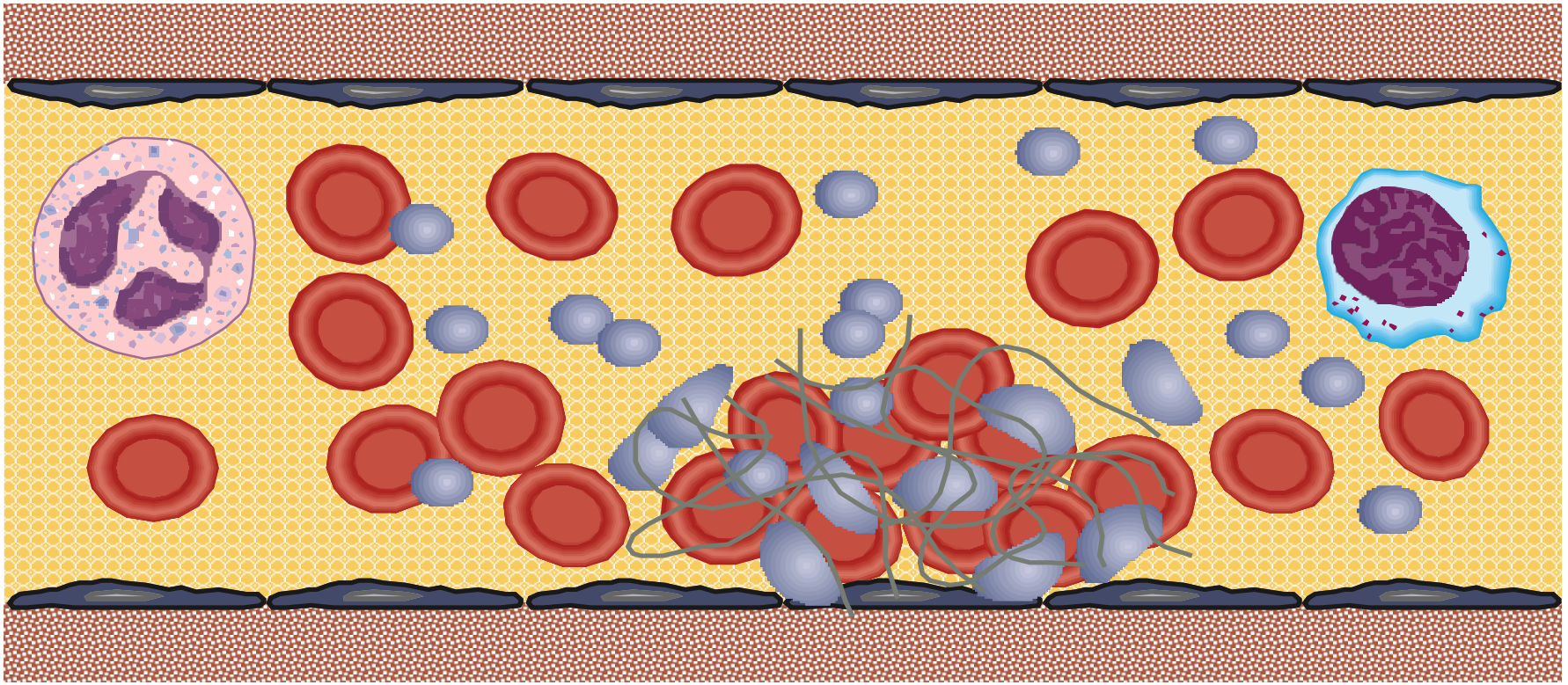
Disorders of primary haemostasis

- **The initial formation of the platelet plug also known as ‘primary haemostasis’) may fail**
- **In thrombocytopenia, von Willebrand disease,**

and also in platelet function disorders and

Diseases affecting the vessel wall.


Vessel wall
Platelets
Plasma proteins
(clotting and
fibrinolytic factors)



Platelet function disorders

- **Bleeding may result from thrombocytopenia. or from congenital or acquired abnormalities of platelet function.**
- **The most common acquired disorders are iatrogenic, resulting from the use of aspirin, clopidogrel, dipyridamole and the IIb/IIIa inhibitors to prevent arterial thrombosis.**

Inherited platelet function abnormalities are relatively rare.

- **Congenital abnormalities may be due to deficiency of the membrane glycoproteins, e.g. Glanzmann's thrombasthenia (IIb/IIIa) or Bernard–Soulier disease (Ib).**

Pathophysiology

- ITP is a disease of increased peripheral platelet destruction, with most patients having autoantibodies against platelet membrane glycoproteins IIb-IIIa and Ib-IX.

- In approximately 60% of cases autoantibodies against platelets can be detected. They are typically of the **IgG** type.

Pathophysiology

- Abnormal T-cell activity is thought to be the stimulus for autoantibody production in ITP.

- Impaired production of the glycoprotein hormone thrombopoietin which is a stimulant for platelet production may be a contributing factor to the reduction in circulating platelets.

In adults, ITP more commonly affects females and may have an insidious onset.
Unlike ITP in children, it is unusual for there to be a history of a preceding viral infection.

Symptoms or signs of a connective tissue disease may be apparent at presentation or emerge several years later.
Patients aged over 65 years should have a bone marrow examination to look for an accompanying B cell malignancy and appropriate autoantibody testing performed if a diagnosis of connective tissue disease is likely.

It is not a single disorder; some cases occur in isolation while others are associated with underlying immune dysregulation.

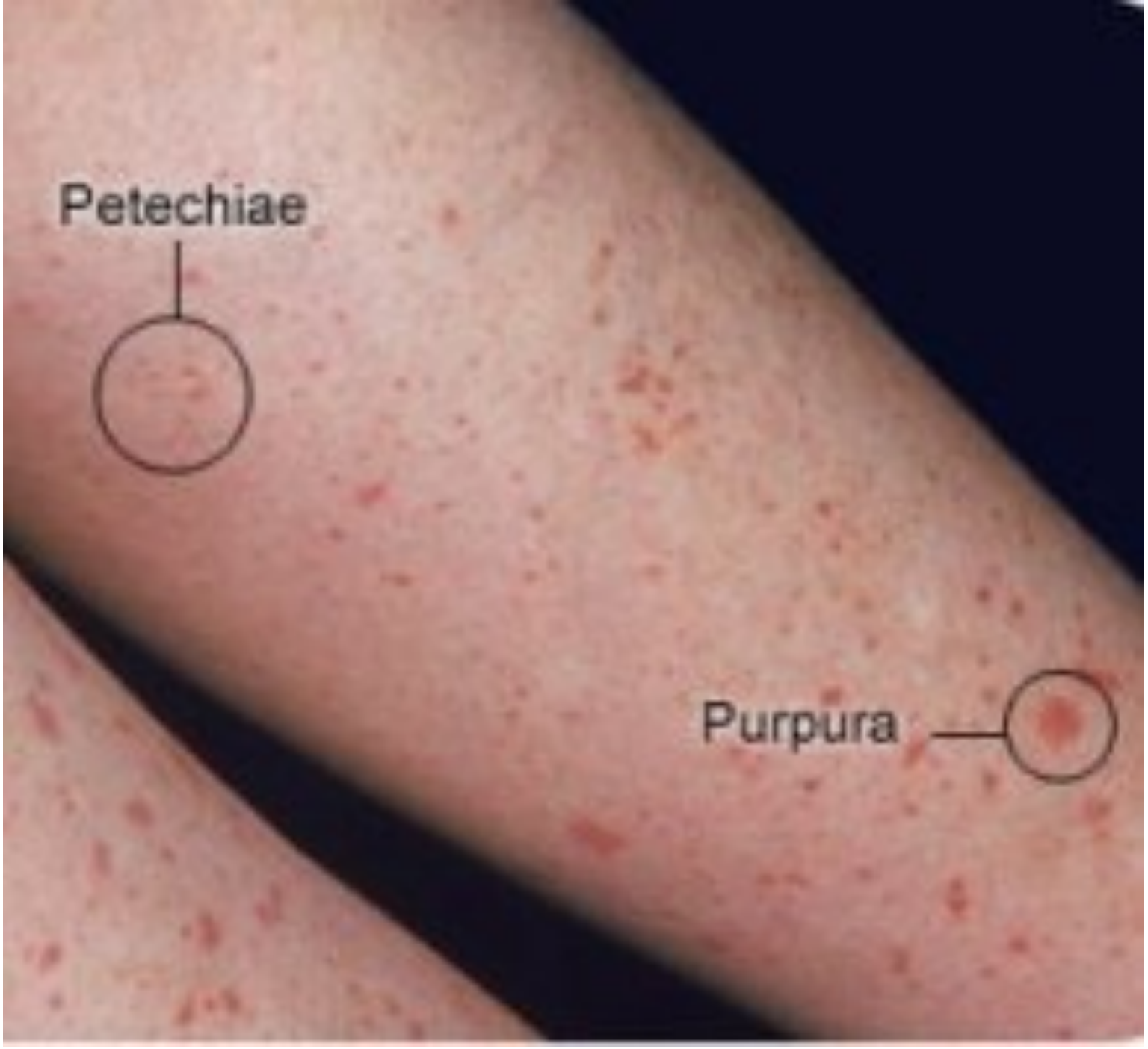
In conditions such as connective tissue diseases, HIV infection, B cell malignancies, pregnancy and certain drug therapies (Heparine).

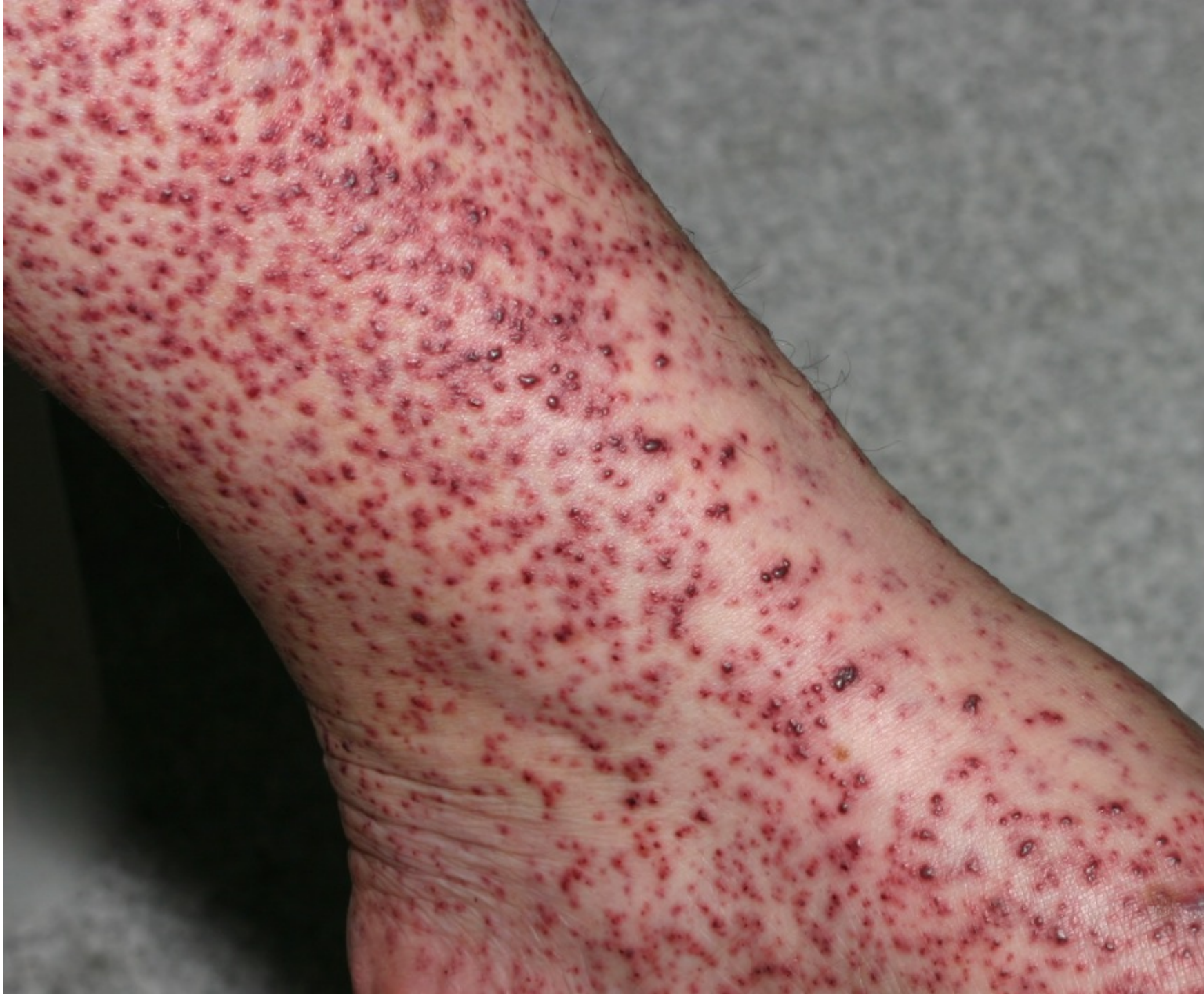
However, the clinical presentation and pathogenesis are similar, whatever the cause of ITP

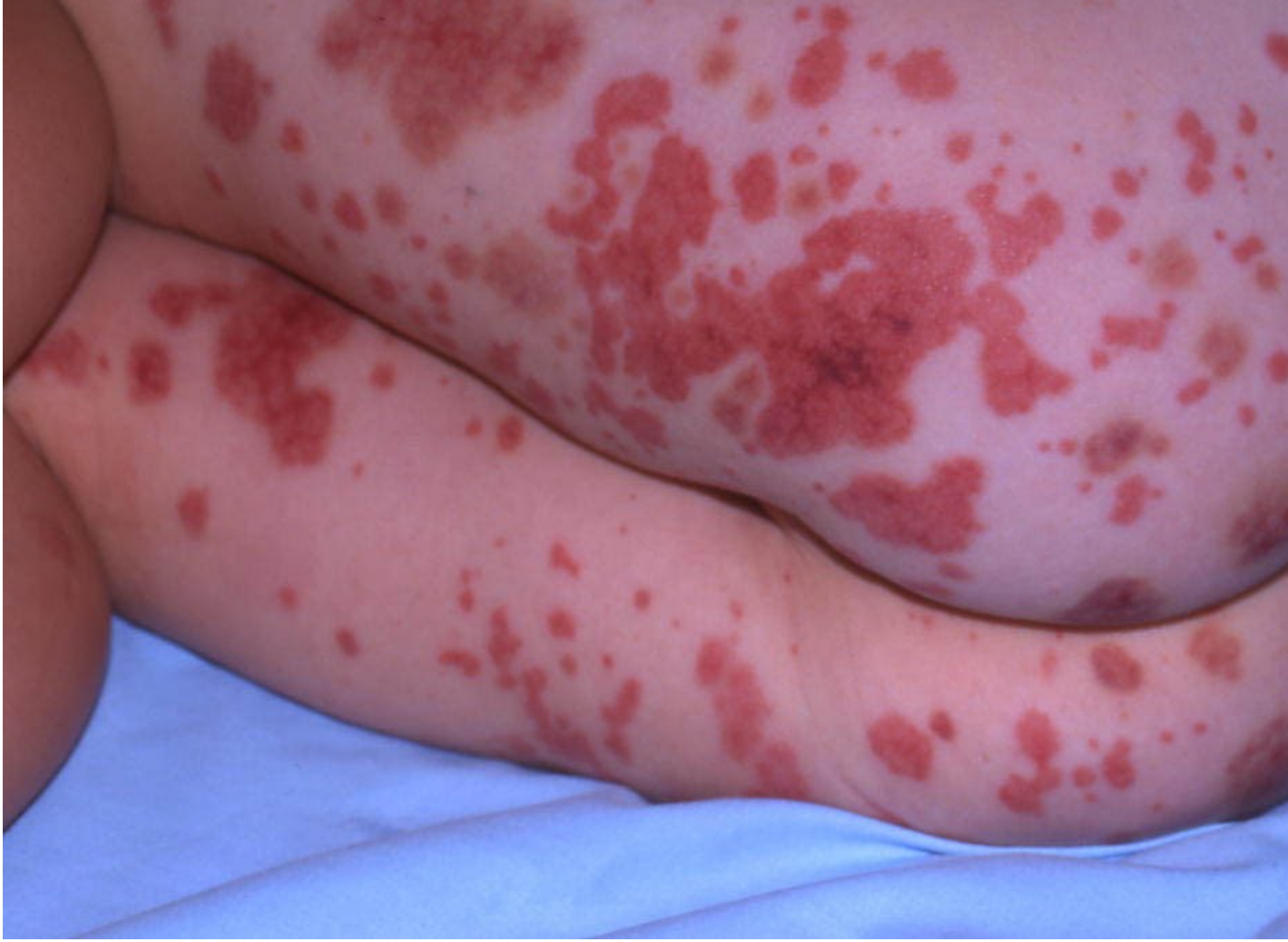
Clinical features and investigations

- **The presentation depends on the degree of thrombocytopenia.**
- **Spontaneous bleeding typically occurs only when the platelet count is below 20 × 109/L.**
- **At higher counts, the patient may complain of easy bruising or sometimes epistaxis or menorrhagia.**
- **Many cases with counts of more than 50 × 10^9/L are discovered by chance.**

occurs if the platelet count is below 20,000 per µl.

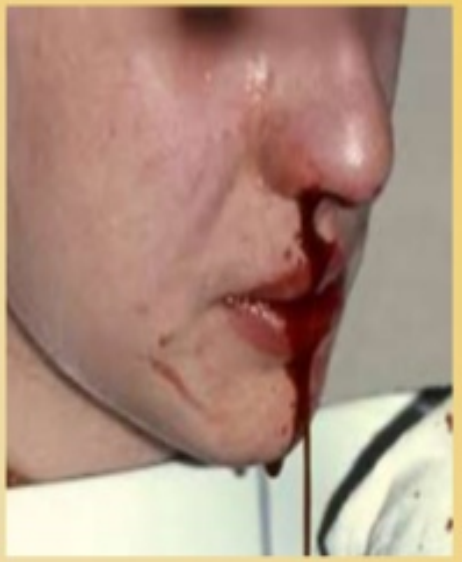

Petechiae
Purpura

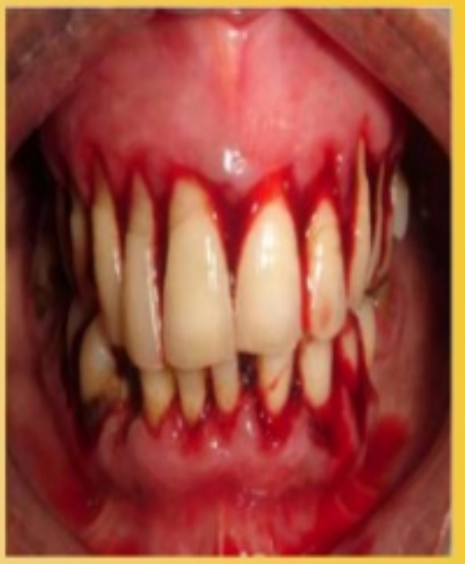


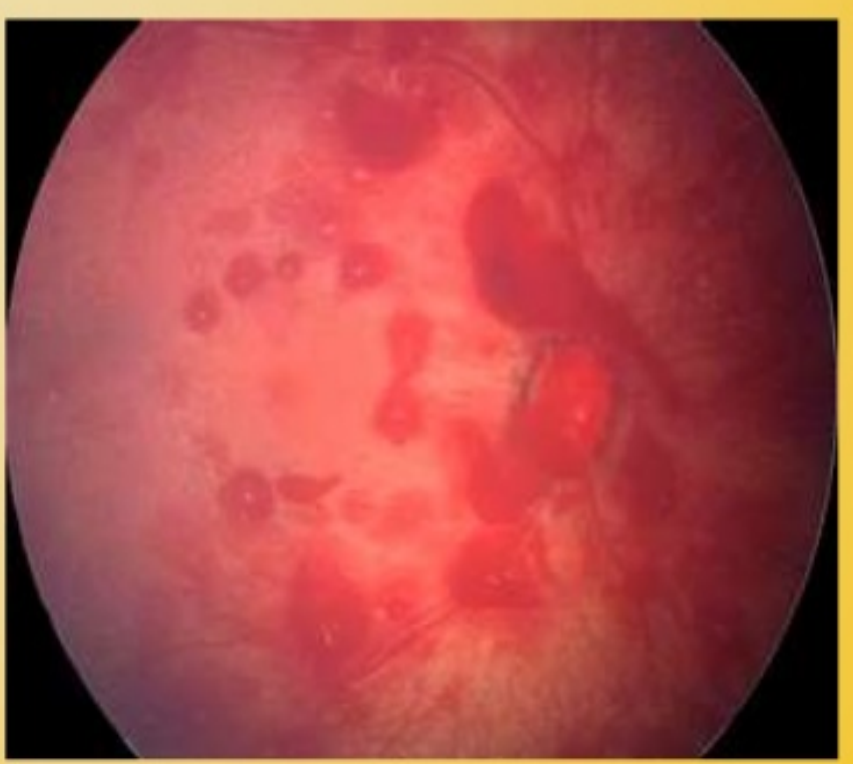


Presentation

- Epistaxis
- Gingival Bleeding
- Signs of GI bleeding
- Retinal Hemorrhage
- Menometrorrhagia/ Menorrhagia
- Spontaneous Bleeding (when platelet count is less than 20,000/mm 3.)

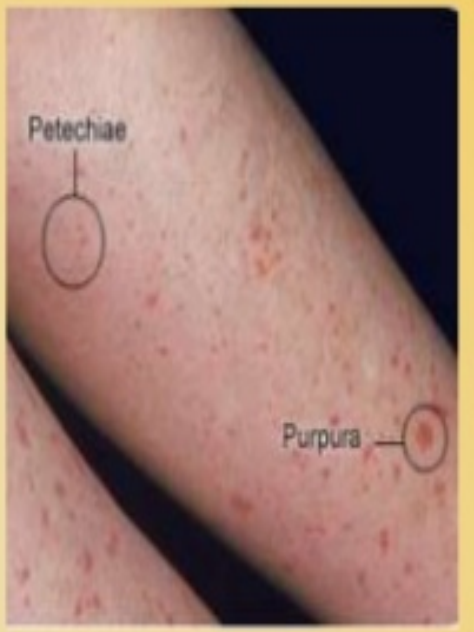


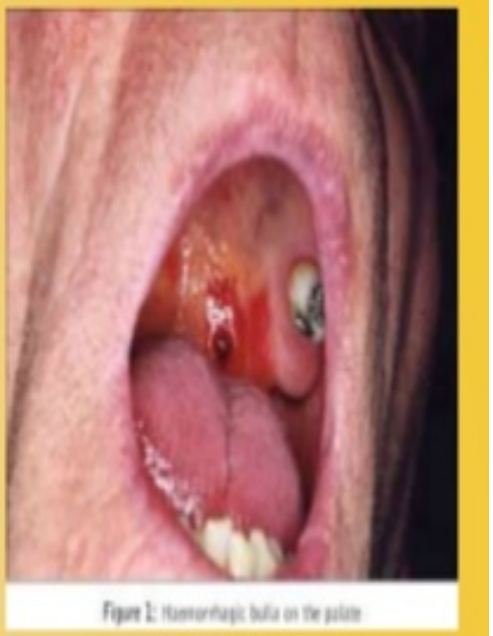


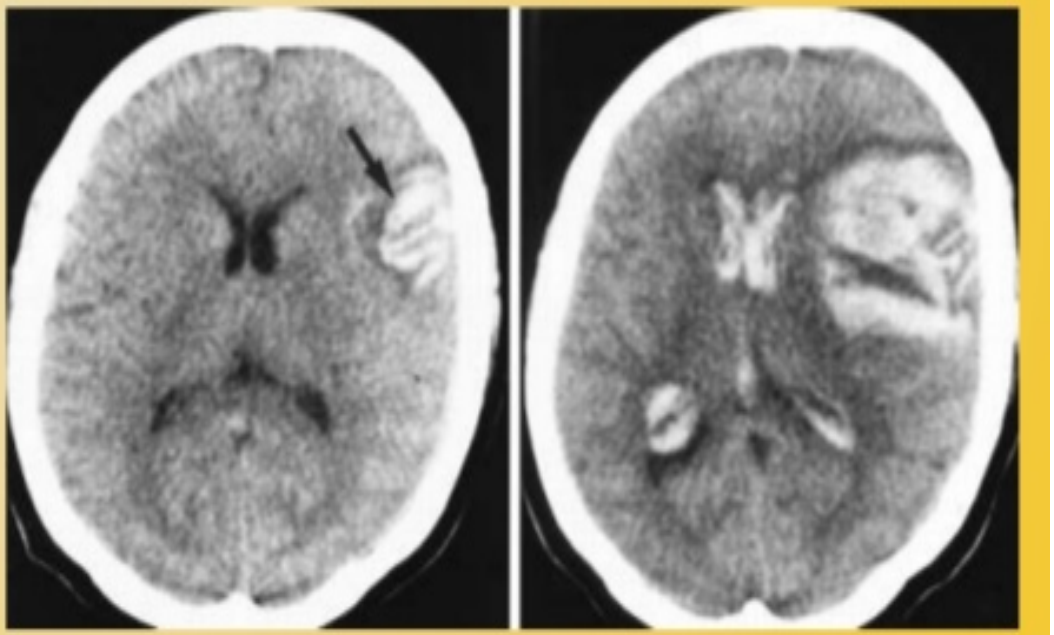


Presentation

- Purpura
- Hemorrhagic Bullae (on mucous membranes)
- **Intracranial Hemorrhage** (with possible neurological symptoms)
- Non-Palpable Petechiae (mostly occur in dependent regions)

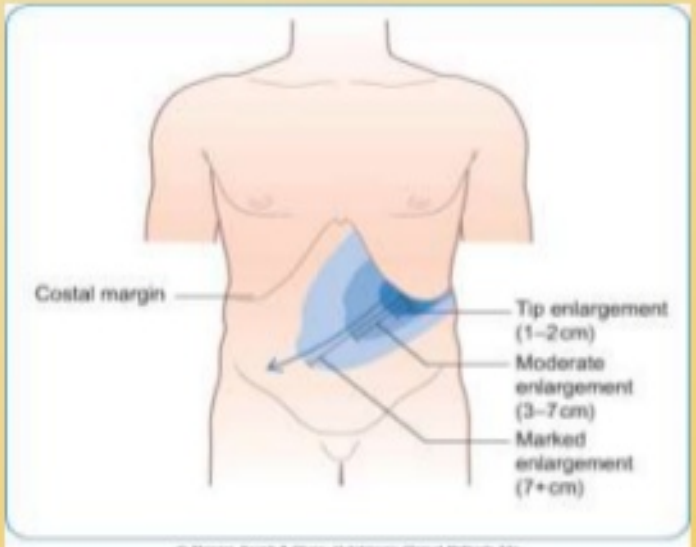






Presentation

- **Non-Palpable Spleen**
  - The prevalence of palpable spleen in patients with ITP is approximately the same as that in the non-ITP population (i.e. 3% in adults, 12% in children.)
  - Despite the destruction of platelets by splenic macrophages, the spleen is normally not enlarged. In fact, an enlarged spleen should lead to a search for other possible causes for the thrombocytopenia.



HIV testing should be considered.

The peripheral blood film is normal, apart from a greatly reduced platelet number, whilst the bone marrow reveals an obvious increase in megakaryocytes

ITP vs. TTP vs. DIC

Parameters	ITP	TTP	DIC
Pathogenesis	Antiplatelet Antibodies	Endothelial Defect	Thrombin Excess
Clinical Condition	Not Sick	Sick	Sick
Red Cells	N	Schistocytes	Schistocytes +/-
PT/INR	N	N/Slightly Increased	Increased
PTT	N	N/Slightly Increased	Increased
Fibrinogen	N	N	Decreased
Fibrin Monomers	N	Slightly Increased	Increased
Fibrin Degradation	N	Slightly Increased	Increased
D-dimer	N	Slightly Increased	Increased

Management

Many patients with stable compensated ITP and a platelet count of more than 30 × 109/L do not require treatment to raise the platelet count, except at times of increased bleeding risk, such as surgery and biopsy.

First-line therapy for patients with spontaneous bleeding is with prednisolone 1 mg/kg daily to suppress antibody production and inhibit phagocytosis of sensitised platelets by reticuloendothelial cells

The condition may become chronic, with remissions and relapses.

Relapses should be treated by reintroducing corticosteroids.

If a patient has two relapses, or primary refractory disease, splenectomy is considered

Splenectomy produces complete remission in about 70%of patients and improvement in a further 20–25%,
Following splenectomy, only 5–10% of patients require further medical therapy.
If severe thrombocytopenia with or without significant bleeding persists despite splenectomy, second-line therapy with the

Thrombopoietin
analogue romiplostim or the thrombopoietin receptor agonist eltrombopag should be considered

Administration of intravenous immunoglobulin (IVIg) can raise the platelet count by blocking antibody receptors on reticuloendothelial cells, and is combined with corticosteroid therapy if there is severe haemostatic failure or a slow response to steroids alone.

Persistent or potentially lifethreatening bleeding should be treated with platelet transfusion in addition to the other therapies

Low-dose corticosteroid therapy, immunosuppressants such as rituximab, ciclosporin and tacrolimus should be considered in cases where the approaches above are ineffective

Management of the splenectomised patient

- **Vaccinate with pneumococcal, *Haemophilus influenzae type* B, meningococcal group C and influenza vaccines at least 2–3 wks before elective splenectomy. Vaccination should be given after emergency surgery but may be less effective**
- **Pneumococcal re-immunisation should be given at least 5-yearly and influenza annually. Vaccination status must be documented**
- **Life-long prophylactic penicillin V 500 mg twice daily is recommended. In penicillin-allergic patients, consider a macrolide**

- **A card or bracelet should be carried to alert health professionals to the risk of overwhelming sepsis**
- **In septicaemia, patients should be resuscitated and given IV antibiotics to cover pneumococcus, *Haemophilus and* meningococcus, according to local resistance patterns**
- **The risk of cerebral malaria is increased in the event of infection**

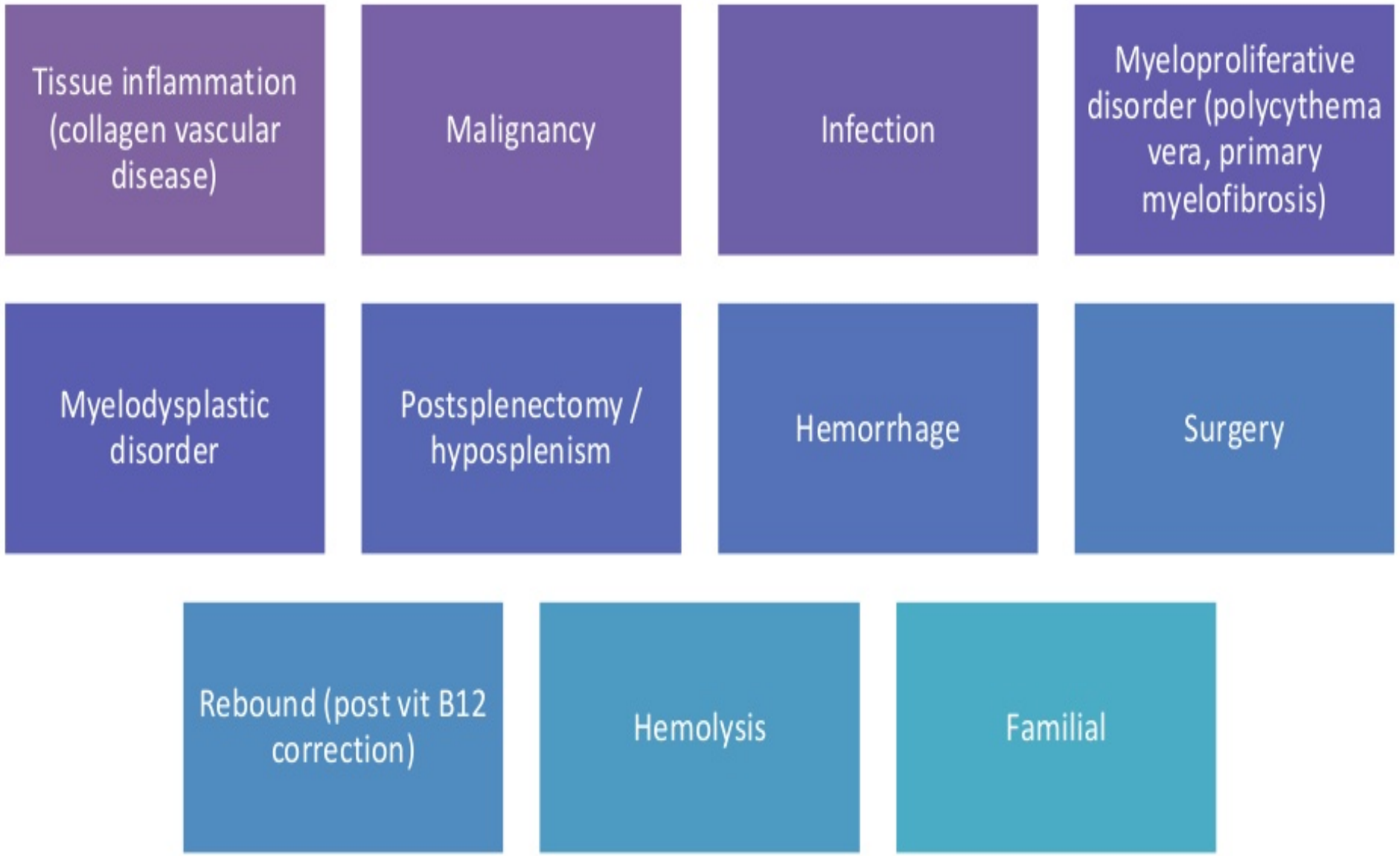
Patients should be educated regarding the risks of infection and methods of prophylaxis

Essential Thrombocytosis

- Non reactive chronic myeloproliferative disorder
- Clonal disorder involving pluripotent hematopoietic progenitor cells
- Manifest clinically by OVERPRODUCTION of platelets
- Isolated thrombocytosis can be the initial clinical manifestation of PV, PMF, or chronic myelogenous leukemia

- First described by Epstein and Goedel in 1934

Causes for Thrombocytosis



EPIDEMIOLOGY

- Incidence: 1-2 / 100 000
- Female predominance (younger patients)

- Median age at diagnosis is 60 years
- Rare in children
- Can occur at any age

mutation

Janus kinase 2 (JAK2) V617F

- 50% in ET patient
- Turn thrombopoietin receptor on permanently, leading to overproduction of megakaryocytes

Calreticulin (CALR)

- 25% of ET patient
- Exclusive of JAK 2 and MPL mutation

Myeloproliferative leukemia virus oncogene (MPL)

- 3-5% of ET patient
- constitutive activation of the thrombopoietin receptor protein

CLINICAL FEATURE

- 25-33% of patients asymptomatic at diagnosis

Hemorrhagic tendency

- Easy bruising
- The gastrointestinal tract is the primary site of bleeding complications
- Other sites of bleeding include the skin, eyes, gums, urinary tract, joints, and brain
- Bleeding is usually not severe and only rarely requires transfusion
- The bleeding is generally associated with a platelet count greater than 1 million/μL

Thrombotic tendency

- Erythromelalgia
- Ocular migraine
- TIA
- Occlusion of the leg, coronary, and renal arteries
- Venous thrombosis of the splenic, hepatic, or leg and pelvic veins may develop
- Pulmonary hypertension may result from pulmonary vasculature occlusion

PHYSICAL EXAMINATION

- Unremarkable

- 40-50% present with splenomegaly
- 20% present with hepatomegaly

INVESTIGATION

Complete blood count

- sustained, unexplained elevation in the platelet count
- Mild neutrophilic leukocytosis

Peripheral smear

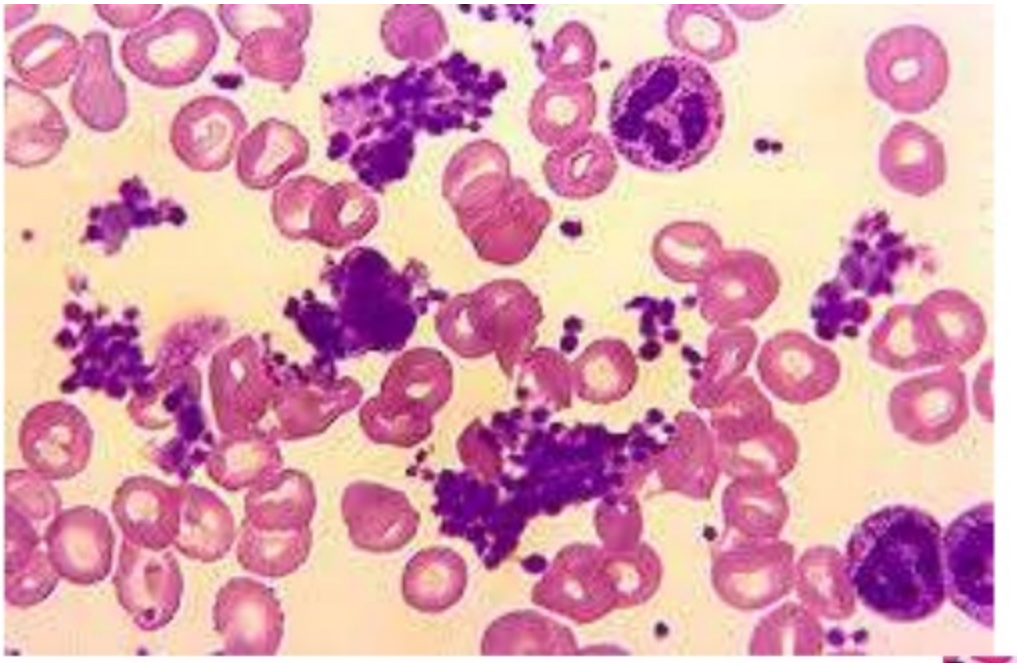
- Increased platelet number
- Large and hypogranular and clumps platelets

Coagulation profile

- PT and aPTT normal

Bleeding time

- Maybe prolonged

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Platelets aggregation studies

- impaired platelet aggregation
- Spontaneous platelets aggregation

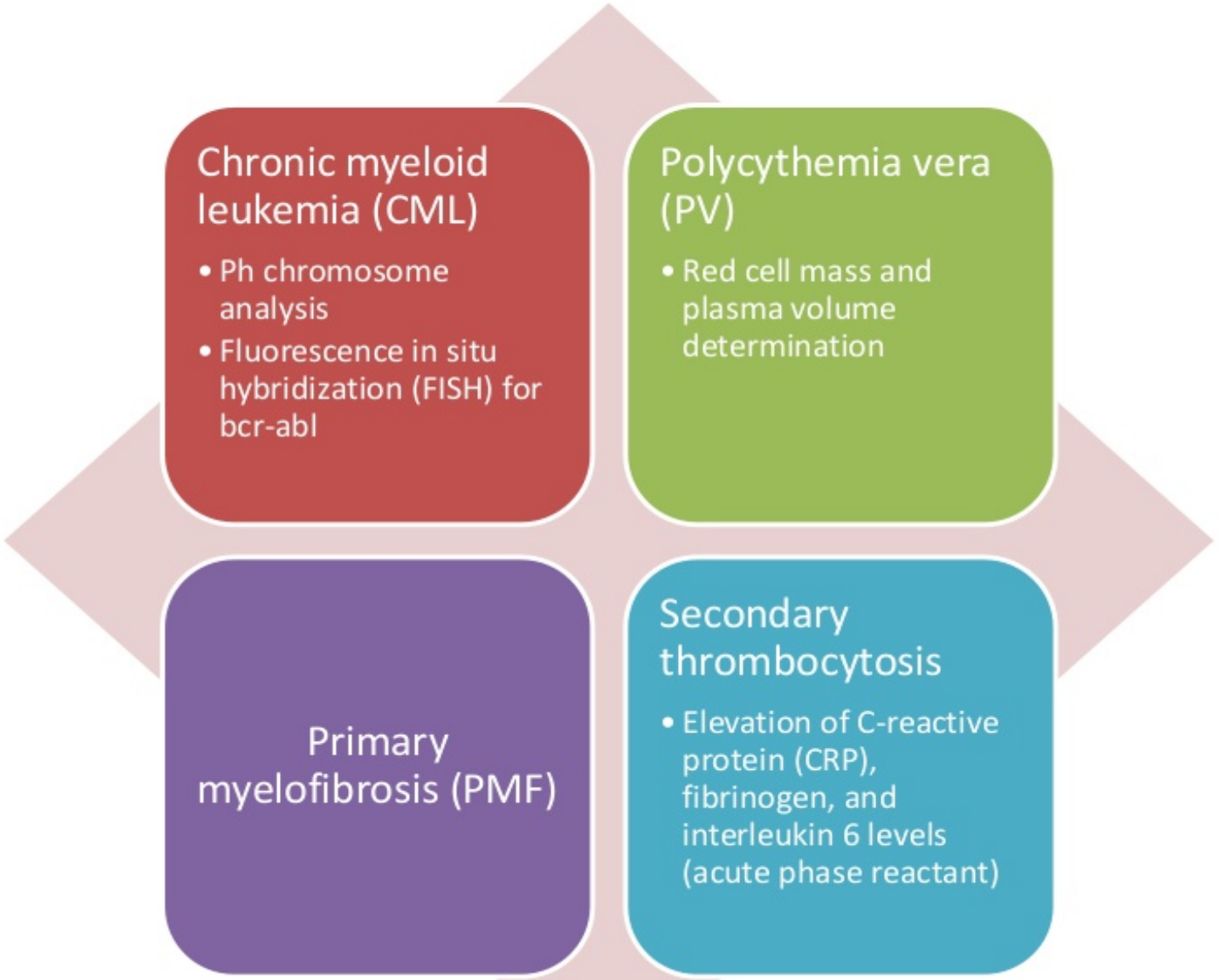
Bone marrow biopsy

- Hypercellular marrow (90%)
- Megakaryocytic hyperplasia
- Giant megakaryocyte with staghorn and hyperlobulated nuclei
- bone marrow iron stain results may be negative even when other studies do not support the presence of iron deficiency (bleeding)

Genetic studies

- JAK2 V617F, CALR, and MPL mutations

DIFFERENTIAL DIAGNOSIS



HIGH RISK FACTOR FOR THROMBOHEMORRHAGIC EVENT

- Age >60 years
- History of thrombosis
- Platelet count >1500 x 10 9/L (1.5 million/µL),
- Obesity
- Cardiovascular RF(smoking, hypertension, and hypercholesterolemia)
- Markers of hypercoagulability (factor V Leiden, antiphospholipid antibodies)
- JAK2 mutation

- Lifestyle modifications should be recommended
- Cytoreductive therapy to decrease the platelet count
  - Hydroxyurea
  - Low dose aspirin
  - Busulfan
  - Anagrelide
  - Interferon alfa
  - Phosphorus-32 (32 P)

LOW RISK PATIENT

- Observation may be appropriate
- Low-dose aspirin may be useful in treating patients with symptoms of microvascular occlusion (erythromelalgia).

PROGNOSIS

- The life expectancy is nearly that of the healthy population.
- A retrospective study revealed:
  - 5-year survival rate of 81%
  - 10-year survival rate of 64%