Bleeding disorders

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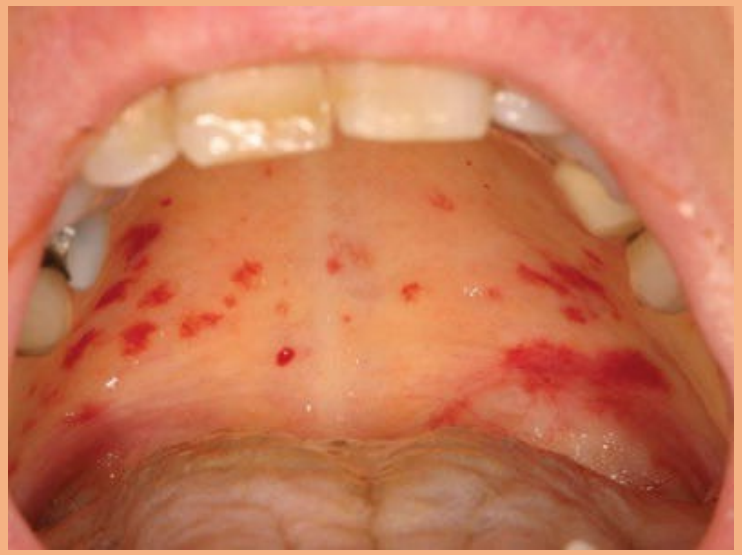
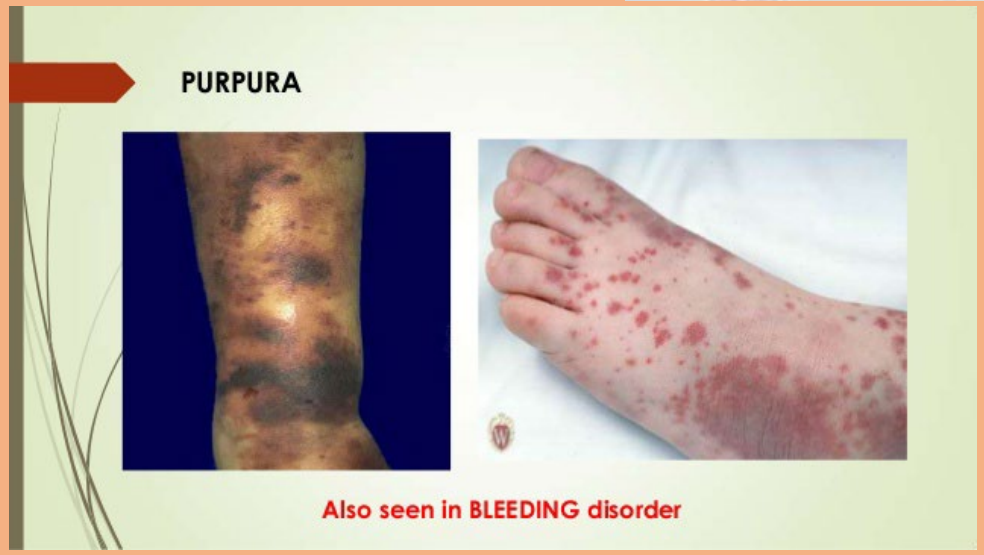
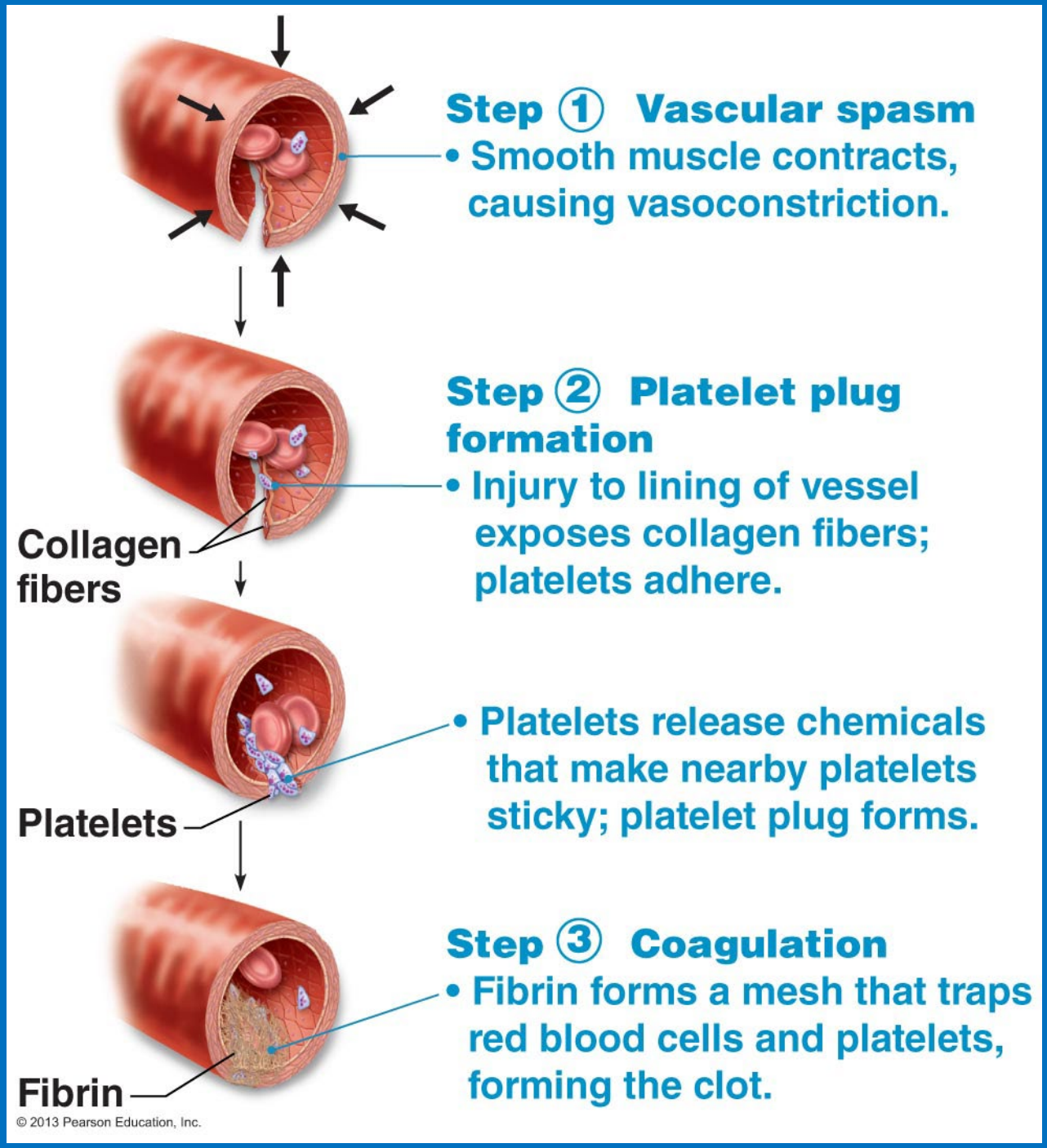




Haemostasis

Blood must be maintained in a fluid state in order to function as a transport system, but must be able to solidify to form a clot following vascular injury in order to prevent excessive bleeding, a process known as haemostasis.

Successful haemostasis is localised to the area of tissue damage and is followed by removal of the clot and tissue repair. This is achieved by complex interactions between the vascular endothelium, platelets, von Willebrand factor, coagulation factors, natural anticoagulants and fibrinolytic enzymes. Dysfunction of any of these components may result in haemorrhage or thrombosis.


Step ① Vascular spasm
• Smooth muscle contracts, causing vasoconstriction.
Step ② Platelet plug formation
• Injury to lining of vessel exposes collagen fibers; platelets adhere.
Collagen fibers
• Platelets release chemicals that make nearby platelets sticky; platelet plug forms.
Platelets
Step ③ Coagulation
• Fibrin forms a mesh that traps red blood cells and platelets, forming the clot.
Fibrin
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Normal hemostasis depends upon

- Vessel Wall Integrity
- Adequate Numbers of Platelets
- Proper Functioning Platelets
- Adequate Levels of Clotting Factors
- Proper Function of Fibrinolytic Pathway

Tests of Hemostasis:

Screening tests:

- Bleeding.T - 2-8min. Platelet count ,function & BV integrity.
- Platelet count (150 000-350 000/ml)
- Prothrombin.T – Extrinsic (10-15 sec)
- aPTT – Intrinsic (25-40 sec)
- Thrombin.T – common path & Fibrinolytic Pathway (9-13 sec) (DIC)

Specific tests:

- Factor assays – hemophilia, fibrinogen
- Tests of thrombosis – FDP, DDA,
- Platelet function studies:PFA -100
- Adhesion, Aggregation, Release tests.
- Bone Marrow study

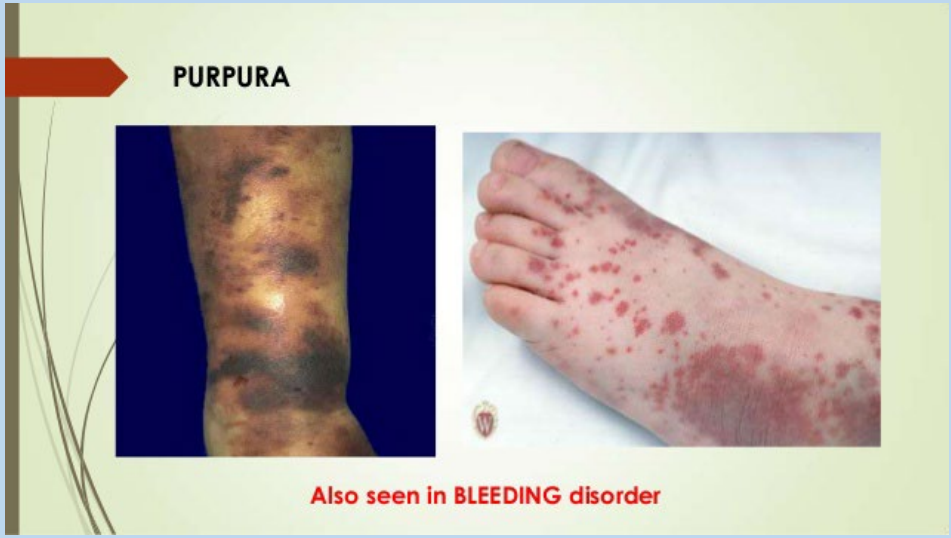
It is important to consider the following points:

Site of bleeding.

1- Bleeding into muscle and joints, along with retroperitoneal and intracranial haemorrhage, indicates a likely defect in coagulation factors.

2-Purpura, prolonged bleeding from superficial cuts, epistaxis, gastrointestinal haemorrhage or menorrhagia is more likely to be due to thrombocytopenia, a platelet function disorder or von Willebrand disease.

3-Recurrent bleeds at a single site suggest a local structural abnormality.



Surgery. Ask about all operations. Dental extractions, tonsillectomy and circumcision are particularly stressful tests of the haemostatic system. Immediate post-surgical bleeding suggests defective platelet plug formation and primary haemostasis, while delayed haemorrhage is more suggestive of a coagulation defect.

However, in post-surgical patients, persistent bleeding from a single site is more likely to indicate surgical bleeding than a bleeding disorder.

Duration of history. **It may be possible to assess whether the disorder is congenital or acquired.**

Precipitating causes. **Bleeding arising spontaneously indicates a more severe defect than bleeding that occurs only after trauma.**

Family history. While a positive family history may be present in patients with inherited disorders, the absence of affected relatives does not exclude a hereditary bleeding diathesis; about one-third of cases of haemophilia arise in individuals without a family history and deficiencies of factor VII, X and XIII are recessively inherited. Recessive disorders are more common in cultures where there is consanguineous marriage.

Drugs. Use of antithrombotic, anticoagulant and fibrinolytic drugs must be elicited. Drug interactions with warfarin and drug-induced thrombocytopenia should be considered. Some 'herbal' remedies may result in a bleeding diathesis.

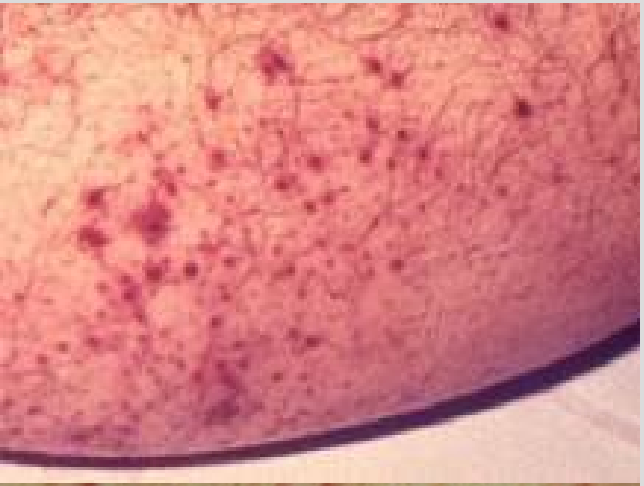
Clinical examination may reveal different patterns of skin bleeding.
-Petechial purpura is minor bleeding into the dermis that is flat and non-blanching .
Petechiae are typically found in patients with thrombocytopenia or platelet dysfunction. –
-Palpable purpura occurs in vasculitis.
-Ecchymosis, or bruising, is more extensive bleeding into deeper layers of the skin. The lesions are initially dark red or purple, but become yellow as haemoglobin is degraded.

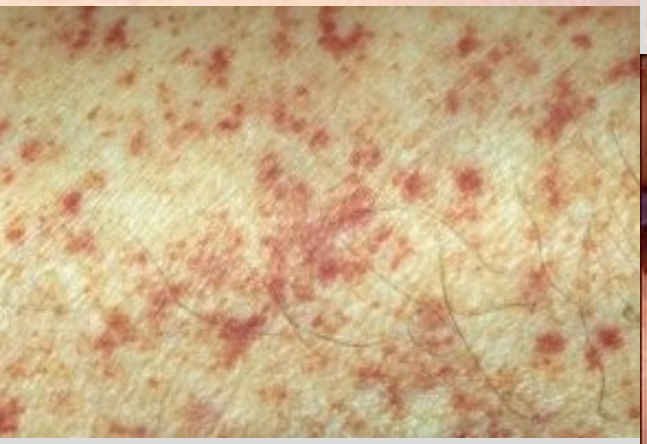
-Retroperitoneal bleeding presents with a flank or peri-umbilical haematoma.
- Telangiectasia of lips and tongue points to hereditary haemorrhagic telangiectasia .
-Joints should be examined for evidence of haemarthroses.
- A full examination is important, as it may give clues to an underlying associated systemic illness such as a haematological or other malignancy, liver disease, renal failure, connective tissue disease and possible causes of splenomegaly

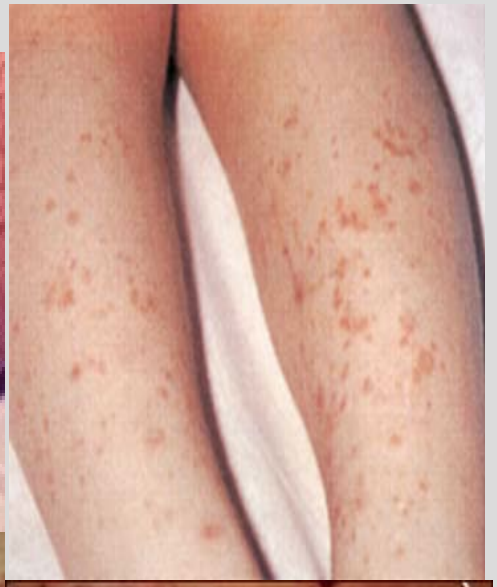
Purpura The spots are caused by bleeding underneath the skin usually secondary to vasculitis or dietary deficiency of vitamin C (scurvy).
They measure 0.3–1 cm (3–10 mm)
Petechiae measure less than 3 mm.
Eccymosis greater than 1 cm.

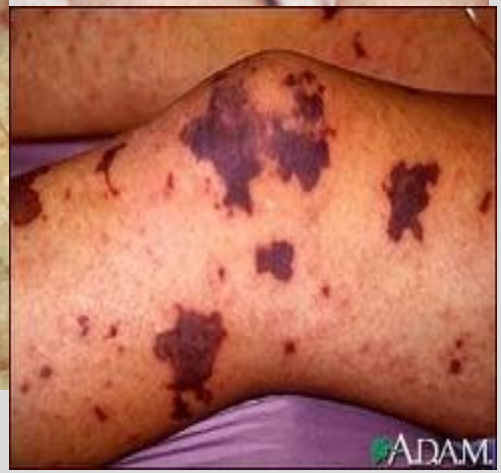
Petechiae

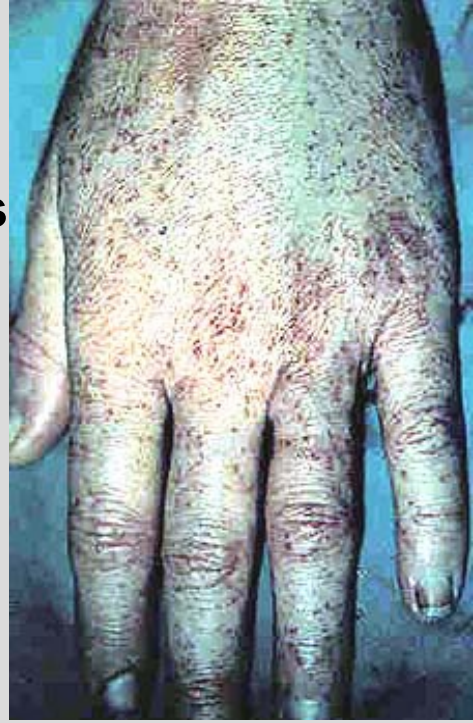
(typical of platelet disorders

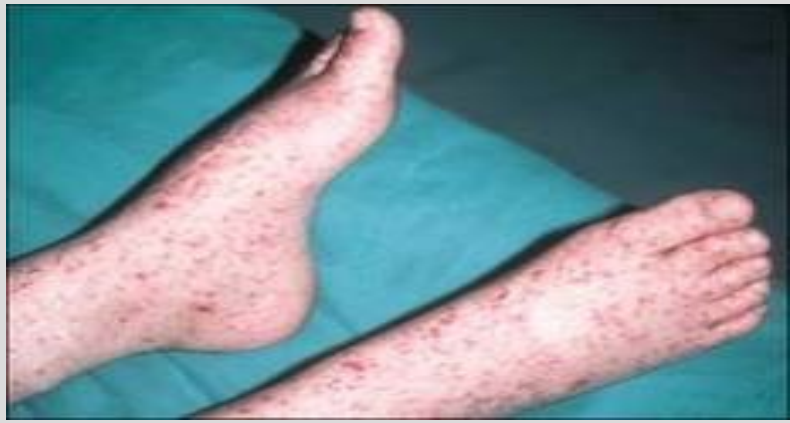






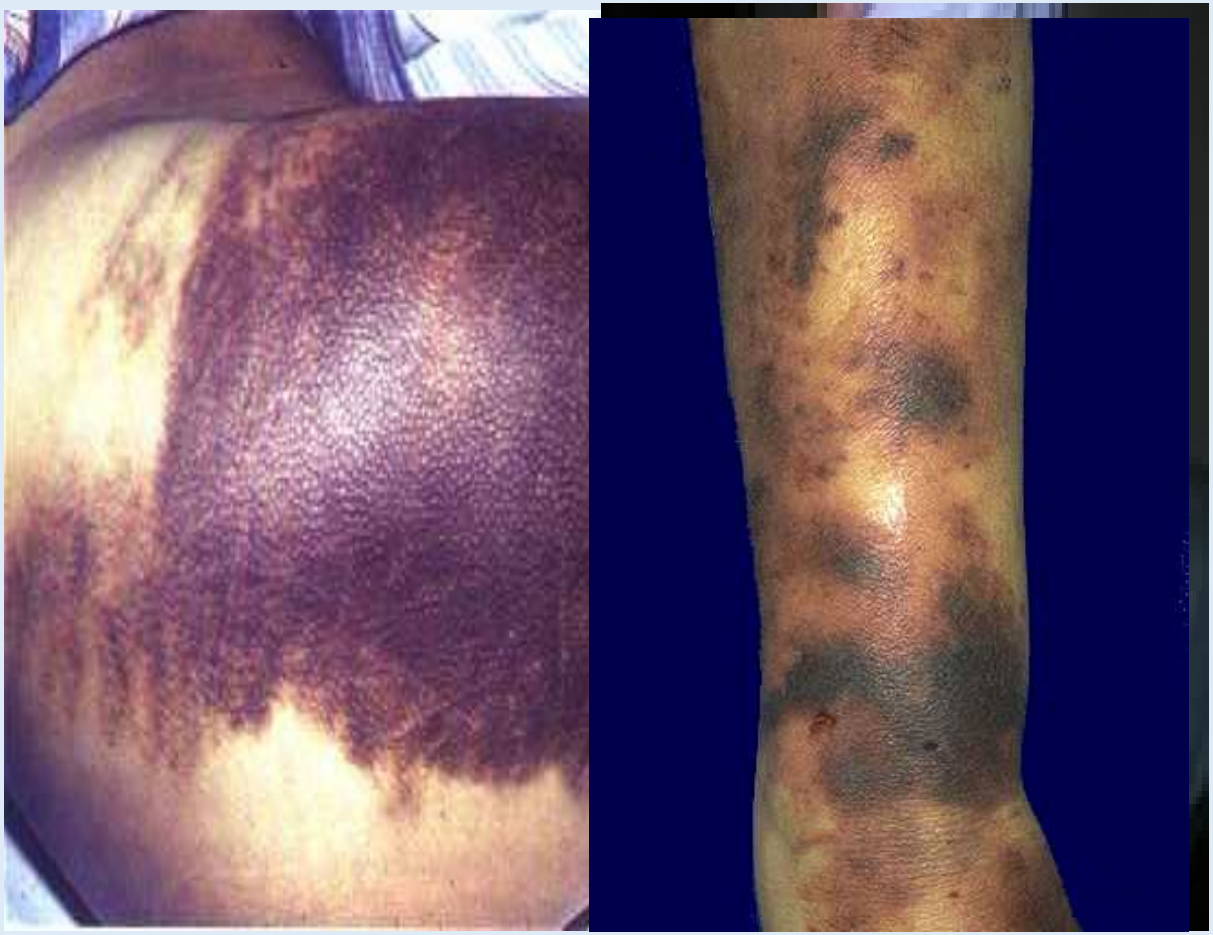




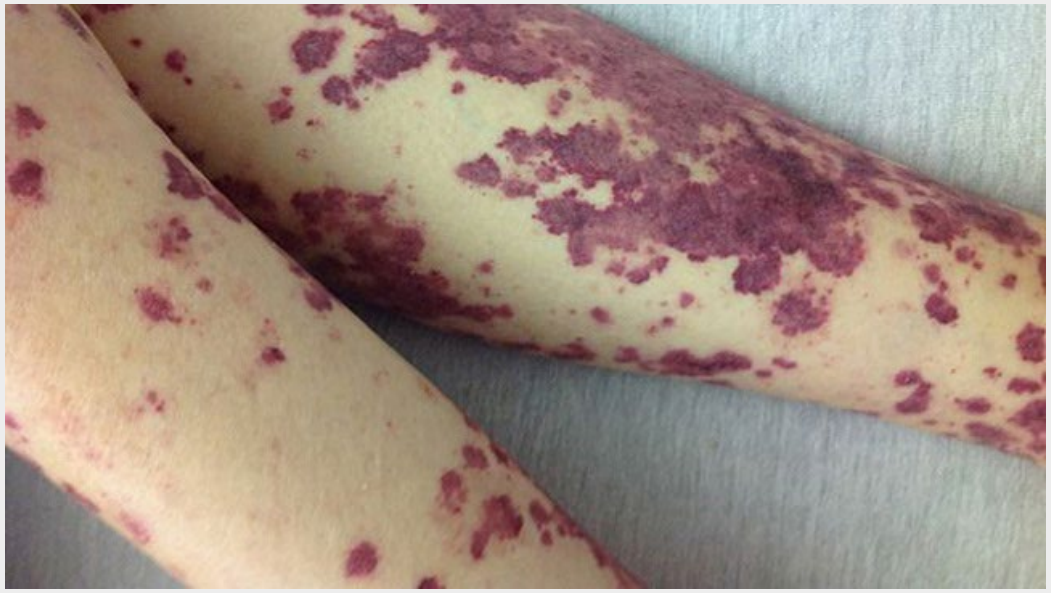


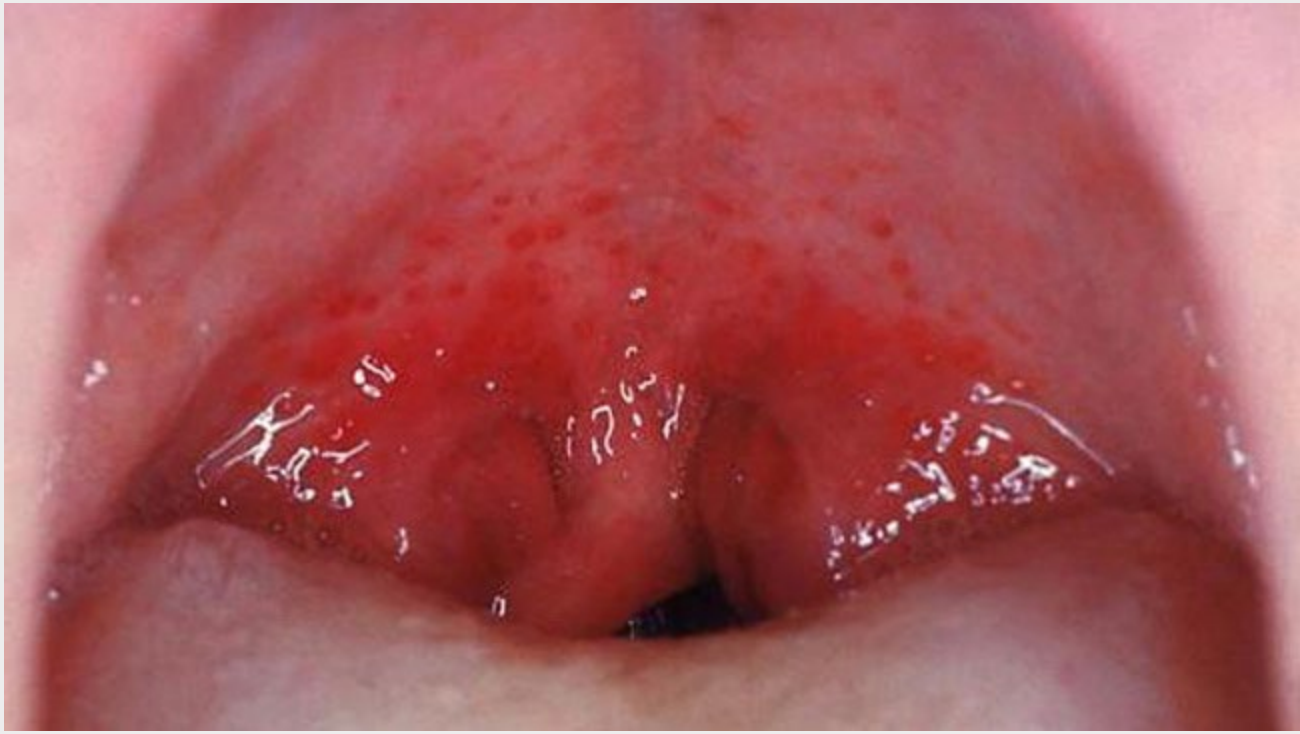
Do not blanch with pressure
(cf. erythema)
Not palpable
(cf. vasculitis)

Ecchymosis



PURPURA





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.

1- Vessel wall abnormalities:

Normal vascular function is necessary for effective haemostasis.

Alteration in the integrity or structure of blood vessel can lead to bleeding diathesis.

Vessel wall abnormalities may be:

- **Congenital, e.g hereditary haemorrhagic telangiectasia**
- **Acquired, as in a vasculitis**

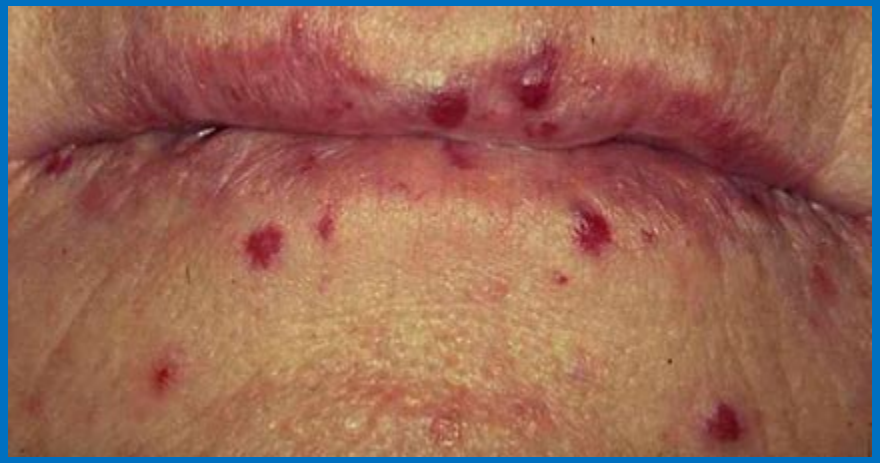
Hereditary haemorrhagic telangiectasia

Hereditary haemorrhagic telangiectasia (HHT) is a dominantly inherited condition caused by mutations in the genes encoding endoglin and activin receptor-like kinase, which are endothelial cell receptors for transforming growth factor-beta (TGF-β), a potent angiogenic cytokine.

Telangiectasia and small aneurysms are found on the fingertips, face and tongue, and in the nasal passages, lung and gastrointestinal tract.

- Significant proportion of these patients develop larger pulmonary arteriovenous Malformations (PAVMs) that cause arterial hypoxemia due to a right-to-left shunt, these predispose to paradoxical embolism, resulting in stroke or cerebral abscess.
- All patients with HHT should be screened for PAVMs; if these are found, ablation by percutaneous embolisation should be considered.
- Patients present either with recurrent bleeds, particularly epistaxis, or with iron deficiency anaemia due to occult bleeding.

- Treatment can be difficult because of the multiple bleeding points but regular iron therapy often allows the marrow to compensate for blood loss.
- Local cautery or laser therapy may prevent single lesions from bleeding.
- A variety of medical therapies have been tried but none has been found to be universally effective.

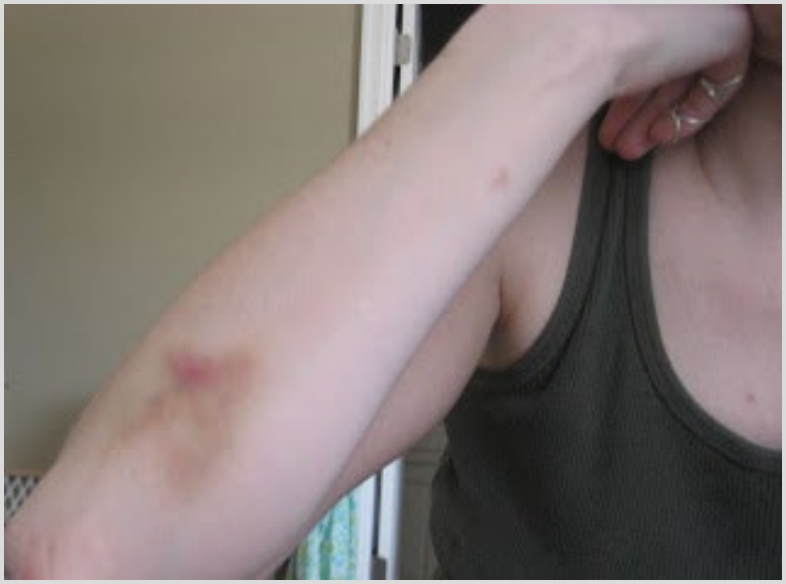


Ehlers-Danlos disease

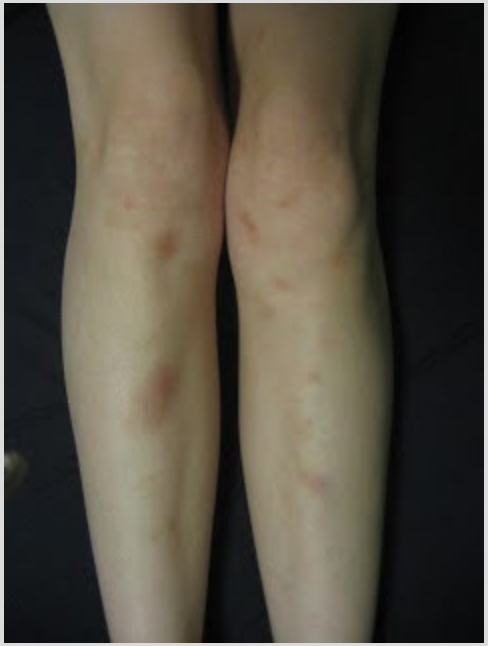
Vascular Ehlers-Danlos syndrome (type 4) a rare autosomal dominant disorder (1 in 100 000) caused by a defect in type 3 collagen which results in fragile blood vessels and organ membranes, leading to bleeding and organ rupture.

Classical joint hypermobility is often limited in this form of the disease but skin changes and facial appearance are typical.

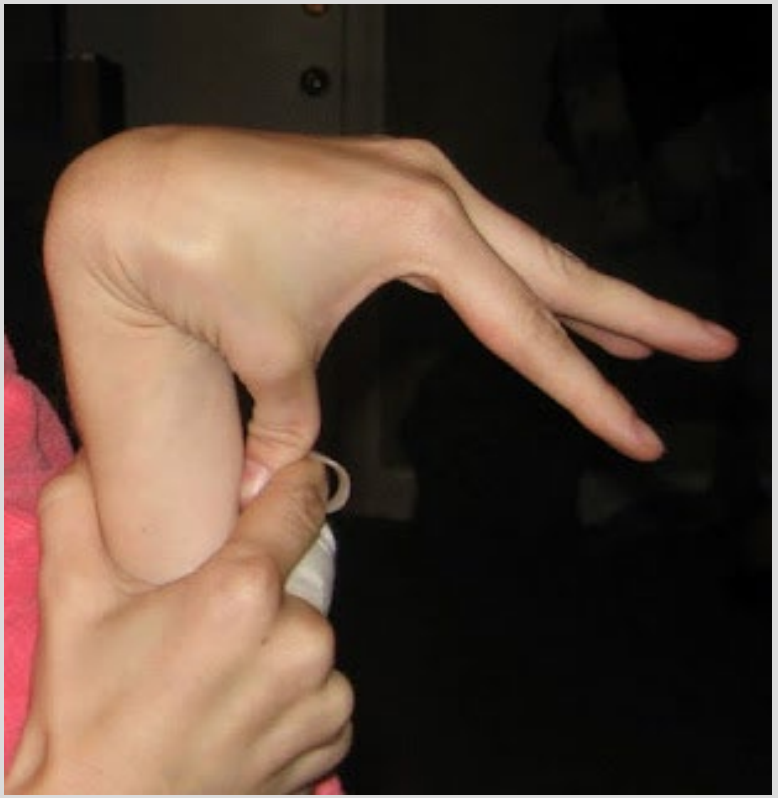
The diagnosis should be considered when there is a history of bleeding but normal laboratory tests.



Easy bruising



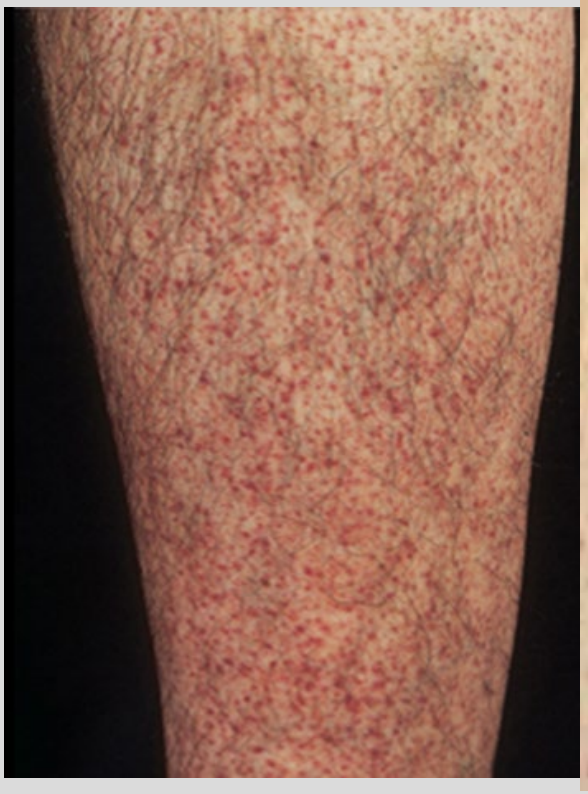
Typical bruising on legs.

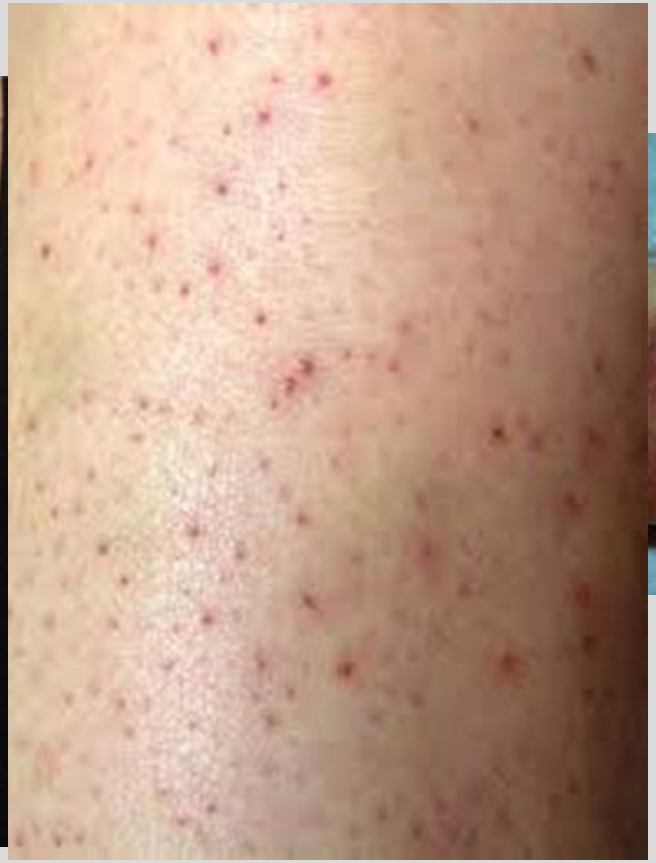


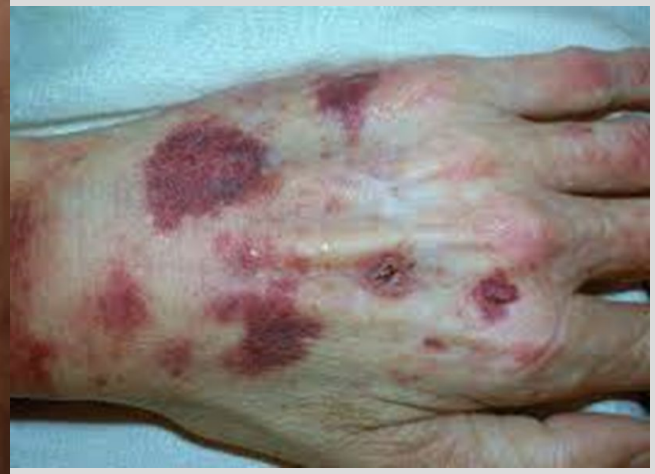
Hypermobile joints.

Scurvy

Vitamin C deficiency affects the normal synthesis of collagen and results in a bleeding disorder characterised by perifollicular and petechial haemorrhage, bruising and subperiosteal bleeding.







Scurvy. Perifollicular hemorrhage on the leg. The follicles are often plugged by keratin (perifollicular hyperkeratosis)

Clinical features

Swollen gums which bleed easily

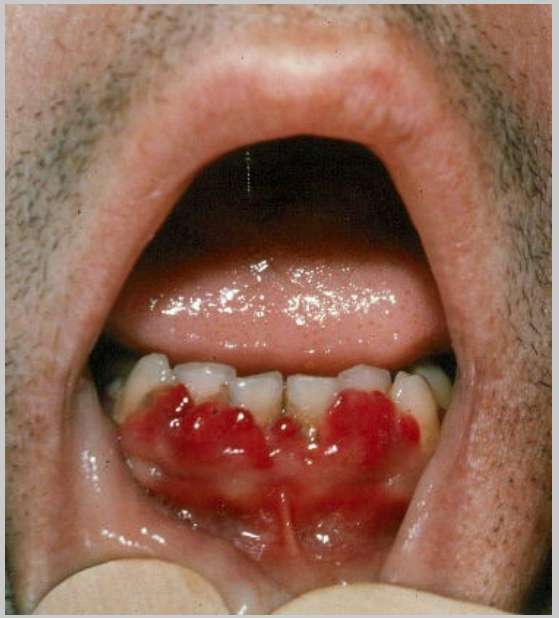
Perifollicular and petechial haemorrhages

Ecchymoses

Gastrointestinal bleeding

Anaemia and Poor wound healing

The key to diagnosis is the dietary history .



Causes of non-thrombocytopenic purpura:

Senile purpura
 Factitious purpura
 Henoch–Schonlein purpura
 Vasculitis
 Paraproteinaemias
 Purpura fulminans, e.g. in disseminated intravascular coagulation secondary to sepsis

Platelet function disorders

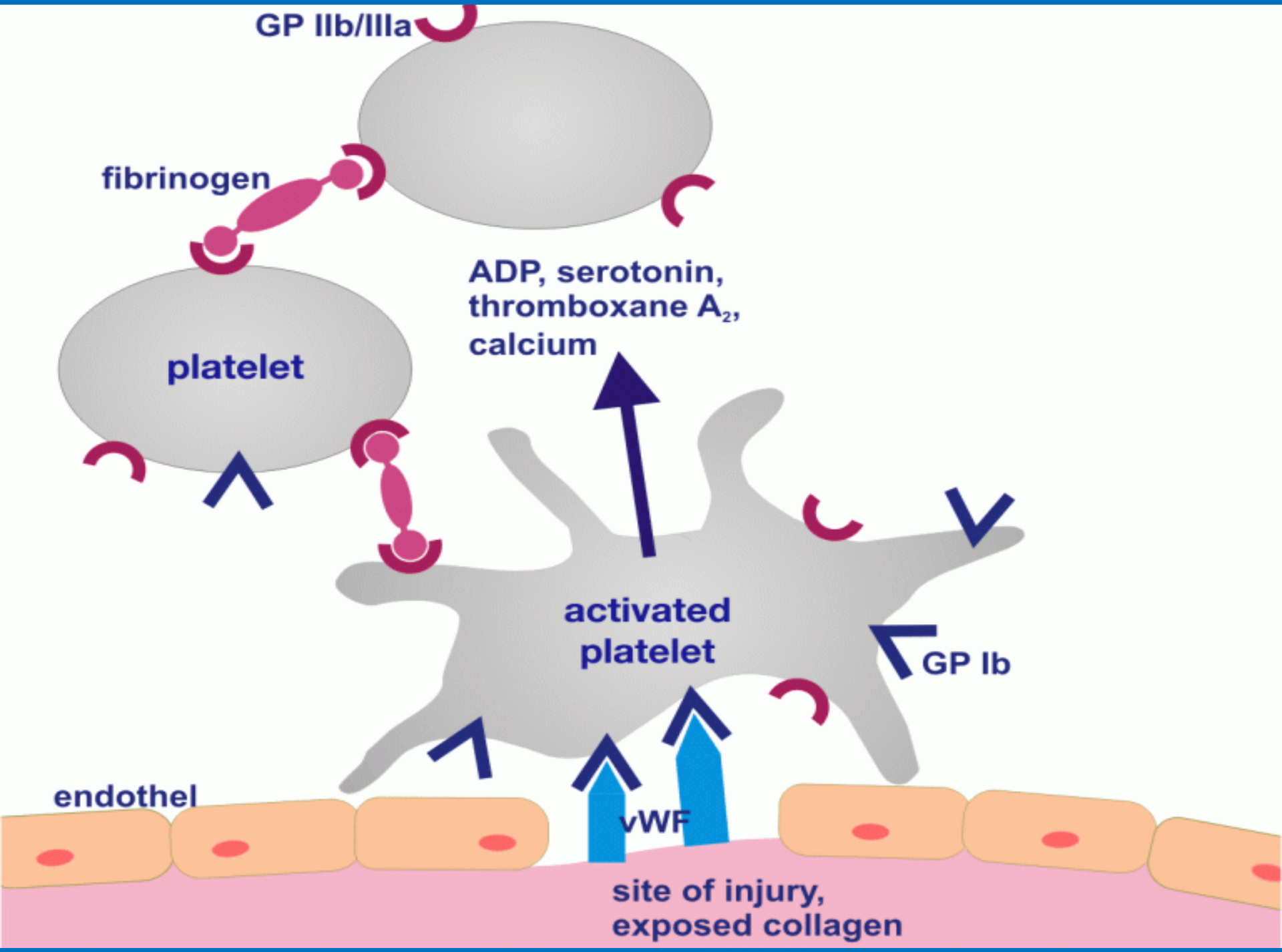
Bleeding may result from thrombocytopenia or from congenital or acquired abnormalities of platelet function.

The most common acquired disorders are iatrogenic, resulting from the use of aspirin,clopidogrel, ticagrelor, dipyridamole and the glycoprotein 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 syndrome (Ib), or due to the presence of defective platelet granules, e.g. a deficiency of dense (delta) granules giving rise to storage pool disorders.

Platelet structure 1

- Membrane glycoproteins
  - IIb-IIIa: integrin, cryptic in resting platelet, after platelet activation binds fibrinogen and other adhesive proteins, necessary for aggregation
  - Ib-IX-V: binds VWF, necessary for platelet adhesion at high shear rates
  - Ia-IIa: integrin, binds collagen, mediates adhesion at low shear rates and platelet spreading (also acts as receptor)


GP IIb/IIIa
fibrinogen
ADP, serotonin,
thromboxane A_2,
calcium
platelet
activated
platelet
GP Ib
endothel
vWF
site of injury,
exposed collagen

Platelet function disorders:

1-Hereditary disorders

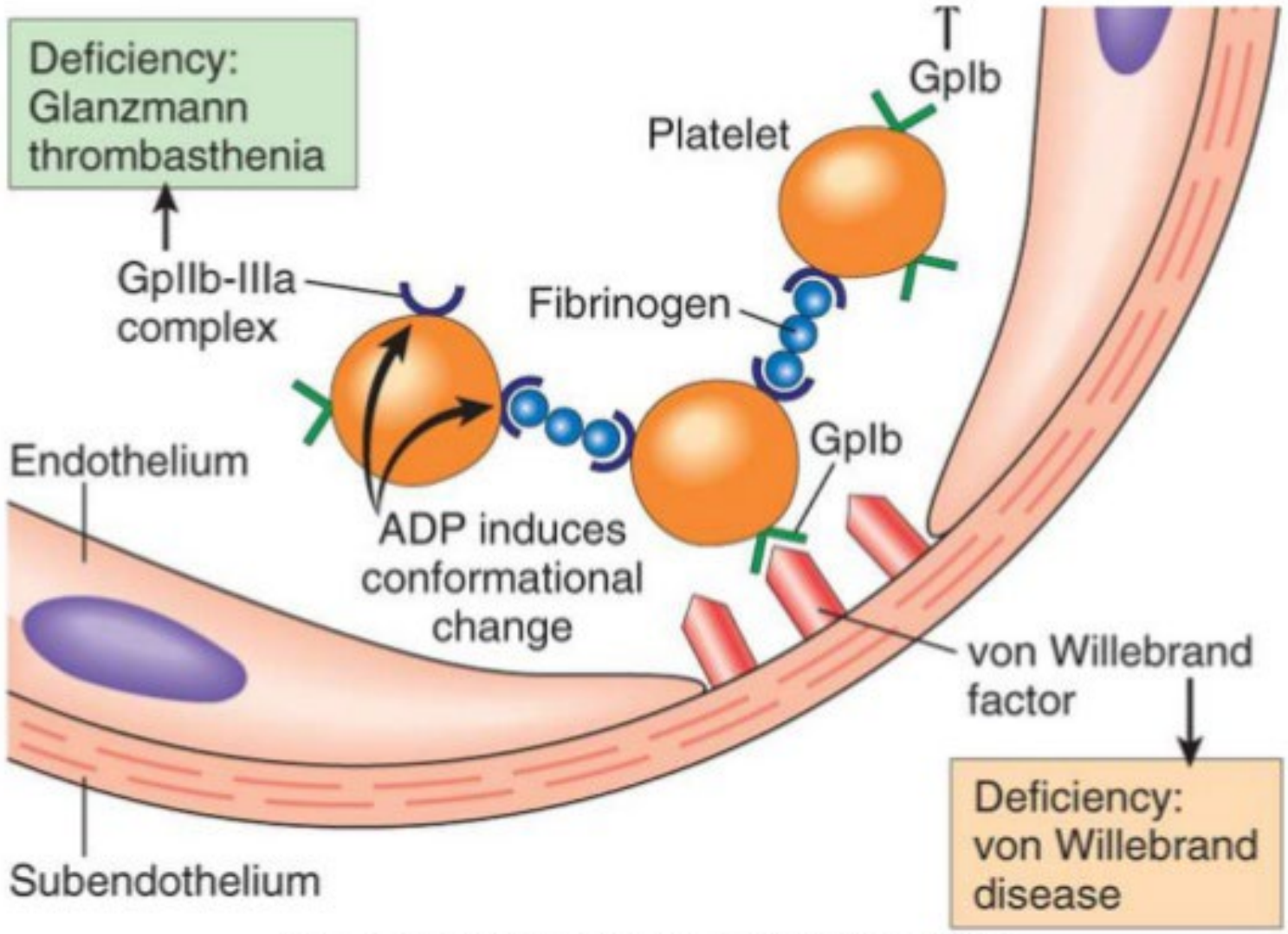
The bleeding history is similar among these Disorders.

Life long history of easy bruising,epistaxis & Prolonged oozing after venipuneture,dental Extraction or other challenges to haemostasis.

Glanzmann's thrombasthenia

is an autosomal recessive condition associated with a variable but often severe bleeding disorder. These conditions are usually managed by local mechanical measures, but antifibrinolytics, such as tranexamic acid, may be useful and, in severe bleeding, platelet transfusion may be required. Recombinant VIIa is licensed for the treatment of resistant bleeding in Glanzmann's thrombasthenia.

Gp IIb-IIIa complex on platelet surface

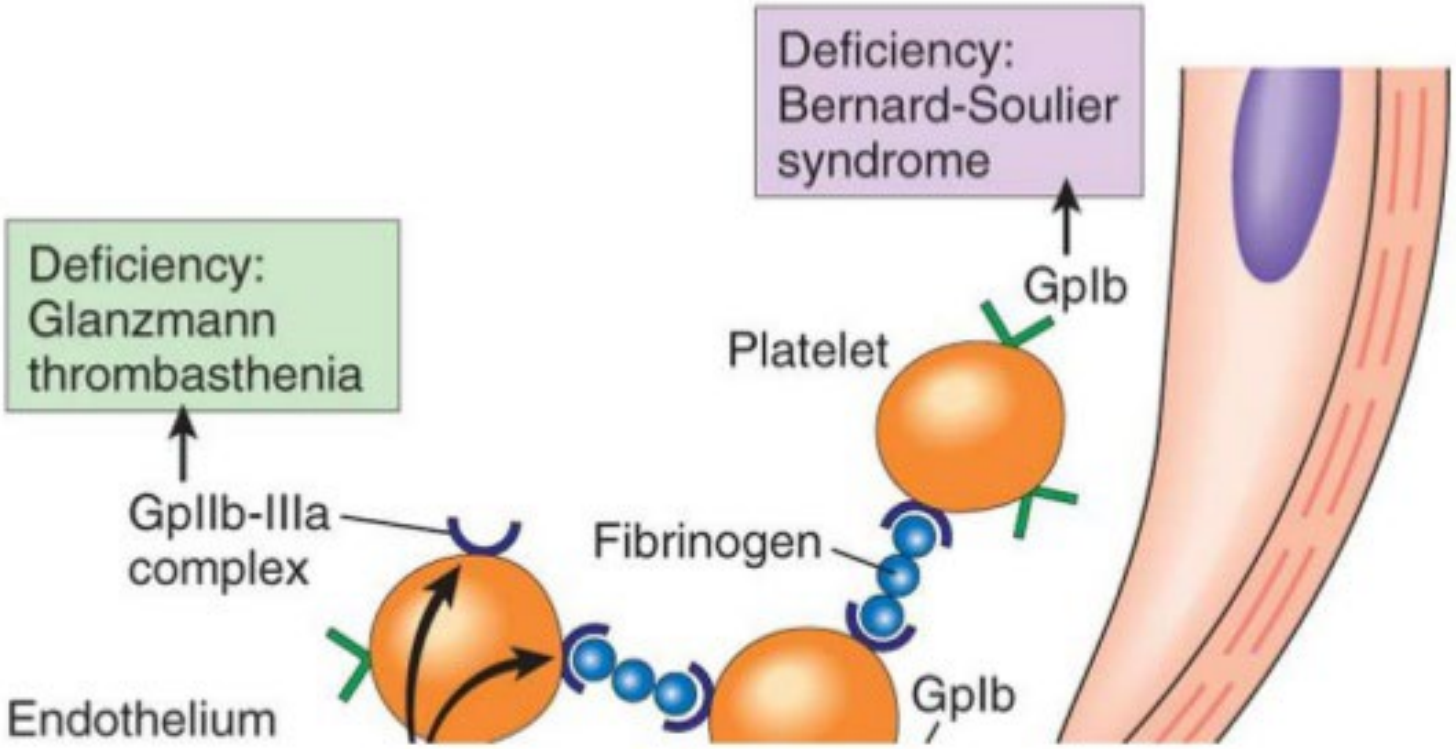


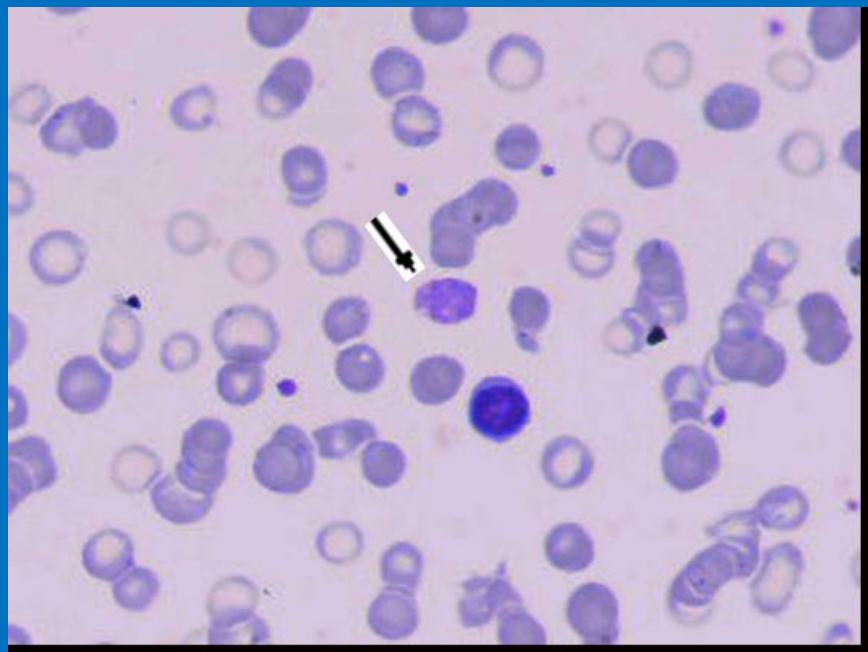
Bernard-Soulier syndrom:

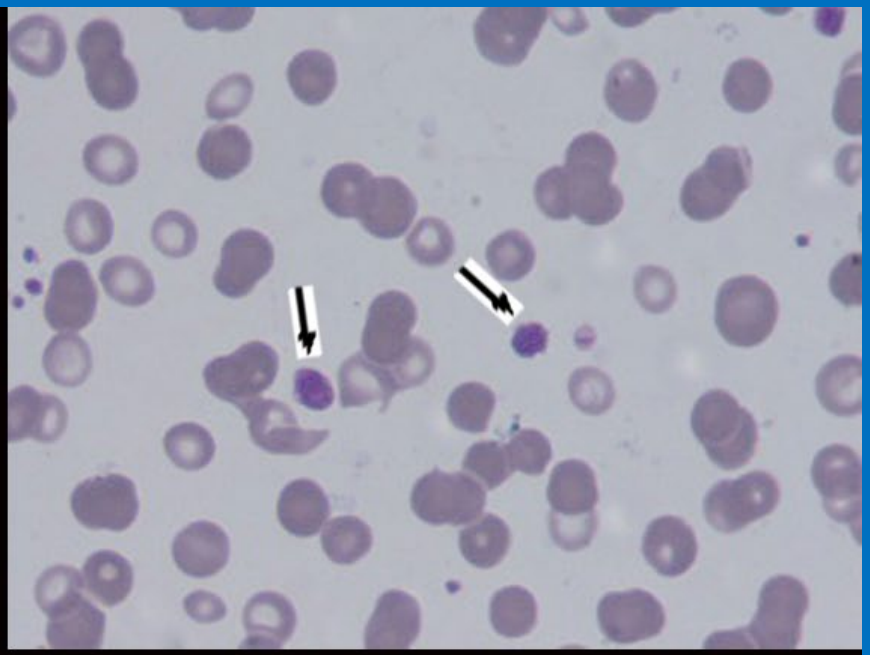
Autosomal recessive

Caused by deficiency of membrane Glycoprotein Complex,GP Ib-Ix,
Platelet count mildly decreased
Platelets aggregate normallyin response to ADP, Collagen ,epinephrine but fail in response to Restocetine.

Gp Ib receptor on platelets

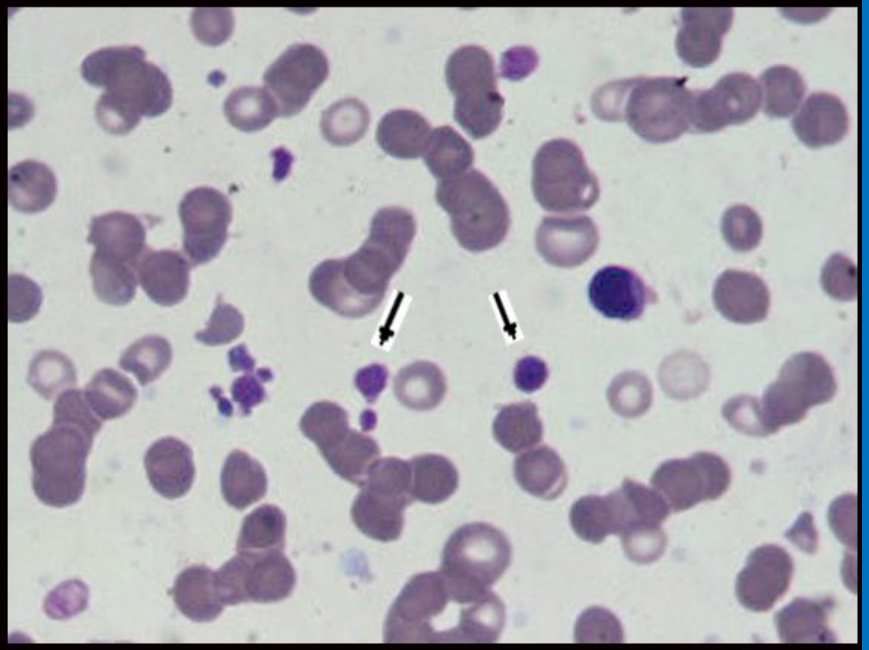






Bernard Soulier Syndrome

(Large-sized Platelets- Arrows)



Storage pool disease:

Autosomal dominant

The presence of defective platelet granules e.g. deficiency of dens(delta) granules.

This gives rise to abnormal platelets aggregation.

Patients present with bleeding of platelet type varies in severity between patients,some presentwith frequent recurrent bleeds whilst otheronly diagnosed because of excessive post-operative haemorrhage.

.

Congenital macrothrombocytopathies that are due to mutations in the myosin heavy chain gene MYH-9 are characterised by large platelets, inclusion bodies in neutrophils (Döhle bodies) and a variety of other features, including sensorineural deafness and renal abnormalities

Acquired disorders of platelets function:

1-drugs inhibited platelet function

-NSAIDs

***Aspirin**

***Indometacin**

***phenylbutazone**

***Sulfinpyrazone**

-Antibiotics

***Penicillins**

***Cephalosporins**

-Dextran

-Heparin

-b-blockers

2-Renal failure

3-Hepatic failure

4-Paraproteinmias

5-Myeloprolifrative disorders

Thrombocytopenia (low platelet count)

Areduced platelet count may arise by one of two mechanisms:

1. Decreased or abnormal production (bone marrow failure and hereditary thrombocytopathies)
2. Increased consumption following release into the circulation (immune-mediated, disseminated intravascular coagulation (DIC) or sequestration

Spontaneous bleeding doesn't usually occur until platelet count falls < 20 × 10^9/L, unless their function is also compromised.

Purpura and spontaneous bruising are characteristic but there may also be oral, nasal, GI or genitourinary bleeding.

Severe thrombocytopenia (< 10 × 10^9/L) may result in retinal haemorrhage and potentially fatal intracranial bleeding, but this is rare.

Causes of thrombocytopenia

I-Decreased production:

1-Marrow hypoplasia

*Childhood bone marrow failure syndromes, e.g. Fanconi's anaemia, dyskeratosis congenita, amegakaryocytic thrombocytopenia

*Idiopathic aplastic anaemia

*Drug-induced: cytotoxics, antimetabolites

*Transfusion-associated graft-versus-host disease

2-Marrow infiltration:

*Leukaemia
*Myeloma
*Carcinoma (rare)
*Myelofibrosis
*Osteopetrosis
*Lysosomal storage disorders, e.g. Gaucher's disease

3-Haematinic deficiency

*Vitamin B_{12} and /or folate deficiency

4-Familial (macro-)thrombocytopathies

*Myosin heavy chain abnormalities, e.g. Alport's syndrome, Fechner's syndrome
*Bernard Soulier disease
*Montreal platelet syndrome
*Wiskott-Aldrich syndrome (small platelets)

II-Increased consumption of platelets Immune Mechanisms

1- immune mechanisms

*Idiopathic thrombocytopenic purpura (ITP)
*Post-transfusion purpura
*Neonatal alloimmune thrombocytopenia
*Drug-associated, especially quinine , vancomycin and heparin.

2-Coagulation activation

Disseminated intravascular coagulation (DIC)

3-Mechanical pooling

Hypersplenism

4-Thrombotic microangiopathies

*Haemolytic uraemic syndrome
*Liver disease
*Thrombotic thrombocytopenic purpura
*Pre-eclampsia / HELLP

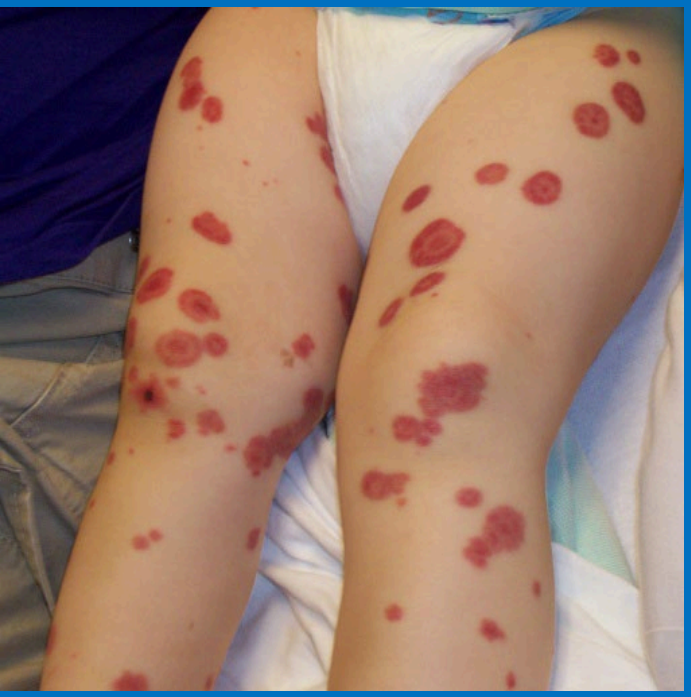
5-Others

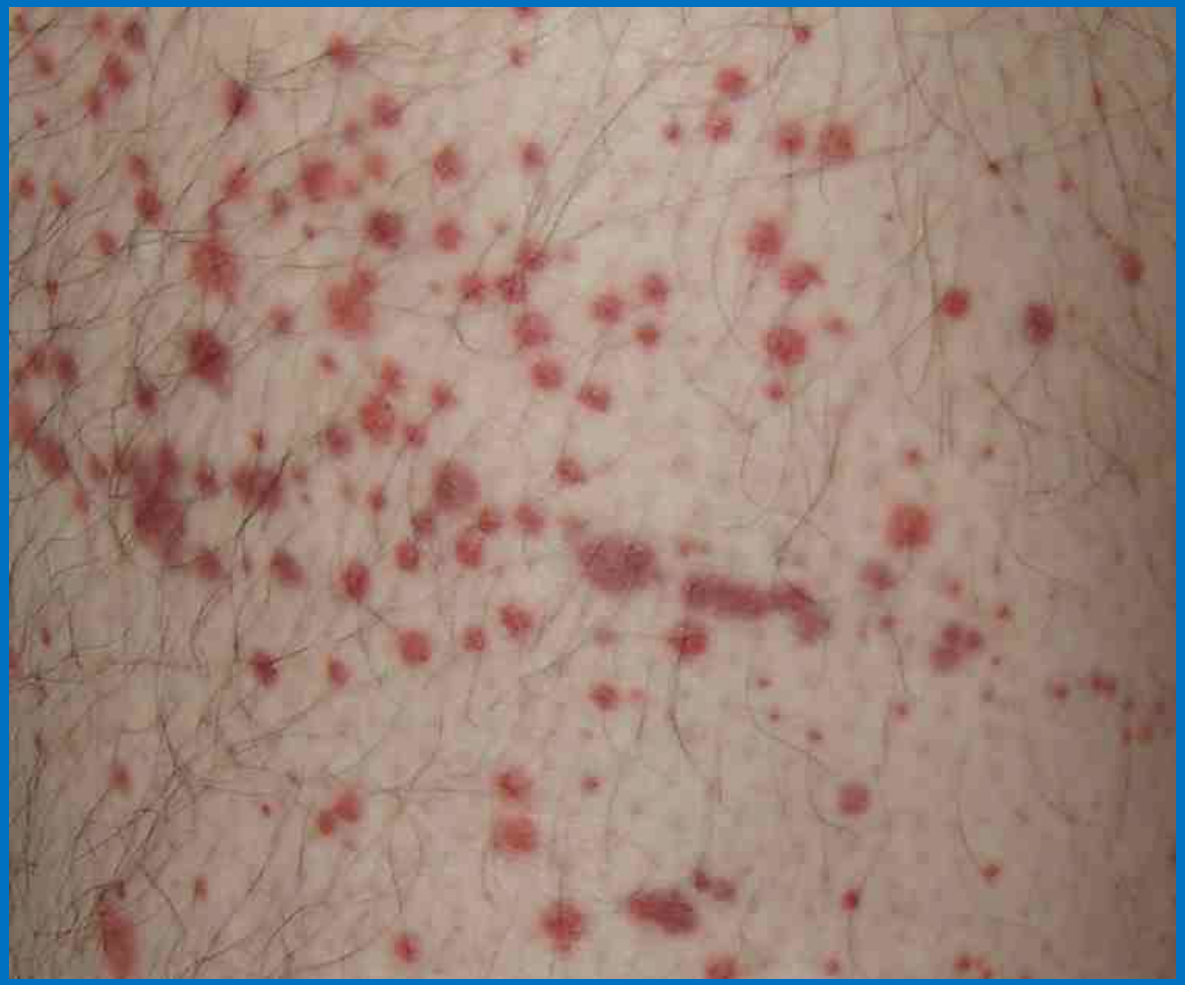
*Gestational thrombocytopenia
*Type 2B von Willebrand disease
*pseudo Von Willibrand disease

Idiopathic thrombocytopenic purpura

ITP is immune-mediated with involvement of autoantibodies, most often directed against the platelet membrane glycoprotein IIb/IIIa, which sensitise the platelet, resulting in premature removal from the circulation by cells of the reticulo-endothelial system.

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 & certain drug therapies.
The clinical presentation & pathogenesis are similar, however, whatever the cause of ITP.





Clinical features & investigations

-Presentation depends on the degree of thrombocytopenia. Spontaneous bleeding typically occurs only when the platelet count is $<20 \times 10^9/L$.

-At higher counts the patient may complain of easy bruising or sometimes epistaxis or menorrhagia.

-Many cases with counts $> 50 \times 10^9/L$ discovered by chance.

-In adults ITP more commonly affects females and has 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.

The development of ITP in the context of COVID-19 infection has been documented

Investigations

1- autoantibody testing performed if a diagnosis of connective tissue diseaseis likely.

2- HIV testing should be considered because a positive result will have major implications for appropriate therapy.

3-The peripheral blood film is normal, apart from a greatly reduced platelet number.

4-bone marrow reveals an obvious increase in megakaryocytes.

Patients aged over 65 years should be considered for a bone marrow examination to look for an accompanying B-cell malignancy

Management

Many patients with stable compensated ITP and a platelet count > 30 × 10^9/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 or Dexamethasone 40 mg daily for 4 days to suppress antibody production and inhibit phagocytosis of platelets by reticuloendothelial cells.

Administration of IV 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 Glucocorticoids alone.

Persistent or potentially life-threatening bleeding should be treated with platelet transfusion in addition to the other therapies.

The condition may become chronic, with remissions and relapses. Relapses should be treated by re-introducing glucocorticoids.

If a patient has two relapses or primary refractory disease, second-line therapies are considered.

The options for second-line therapy include the thrombopoietin receptor agonists (TPO-RA) eltrombopag and romiplostim (which stimulate new platelet formation), the splenic tyrosine kinase inhibitor fostamatinib, splenectomy and immunosuppression.

Splenectomy produces complete remission in about 70% of patients and improvement in a further 20–25% in favourable cases.

The TPO-RAs induce response in around 75% of cases, usually within 10–14 days.

Low-dose glucocorticoid therapy and immunosuppressant such as rituximab, ciclosporin, mycophenolate and tacrolimus may also produce remissions.

Thrombotic thrombocytopenic purpura

Thrombotic thrombocytopenic purpura (TTP) is a disorder in which thrombosis is accompanied by paradoxical thrombocytopenia.

TTP is characterised by a pentad of findings, although few patients have all five components:

-thrombocytopenia
-microangiopathic haemolytic anaemia
-neurological sequelae
-fever
-renal impairment

It is a rare disorder (1 in 750 000 per annum), which may occur alone or in association with drugs (ticlopidine, ciclosporin), HIV, shiga toxins and malignancy.

It should be treated by emergency plasma exchange. Glucocorticoids, aspirin and rituximab also have a role in management.

Caplacizumab, a monoclonal antibody directed against the A domain of vWF, is associated with improved outcomes, less relapse and faster time to recovery in patients with acquired TTP. Untreated mortality rates are 90% in the first 10 days, and even with appropriate therapy, the mortality rate is 20%–30% at 6 months.

THANK YOU