ABC of clinical haematology

Platelet disorders

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Platelets are produced predominantly by bone marrow megakaryocytes as a result of budding of the cytoplasmic membrane. Megakaryocytes are derived from the haemopoietic stem cell, which is stimulated to differentiate to mature megakaryocytes under the influence of various cytokines, including thrombopoietin.

Once released from the bone marrow, young platelets are trapped in the spleen for 36 hours before entering the circulation, where they have a primary haemostatic role.

Normal haemostasis

The platelet membrane has integral glycoproteins essential in the initial events of adhesion and aggregation, leading to formation of the platelet plug during haemostasis.

Glycoprotein receptors react with aggregating agents such as collagen on the damaged endothelial surface (for example, blood vessels), fibrinogen, and von Willebrand's factor to facilitate platelet-platelet and platelet-endothelial cell adhesion. Storage organelles within the platelet include the "dense" granules, which contain nucleotides, calcium, and serotonin, and α granules containing fibrinogen, von Willebrand's factor, platelet derived growth factor, and many other clotting factors. After adhesion, platelets are stimulated to release the contents of their granules essential for platelet aggregation. Platelets also provide an extensive phospholipid surface for the interaction and activation of clotting factors in the coagulation cascade.

Congenital abnormalities

Congenital abnormalities can be disorders of platelet production or platelet function. All are very rare.

Fanconi's anaemia is an autosomal recessive preleukaemic condition that often presents as thrombocytopenia with skeletal or genitourinary abnormalities. The cardinal feature is abnormal chromosomal fragility. The condition can be cured only with bone marrow transplantation.

Amegakaryocytic thrombocytopenia presents with severe neonatal thrombocytopenia (platelet count $< 2 \times 10^9/l$), though this often corrects itself after the first year of life. Infants with coexistent absent radii have the thrombocytopenia-absent radii (TAR) syndrome; they may also have the coexistent congenital cardiac defects.

The Wiskott-Aldrich syndrome is an X linked disorder with a triad of thrombocytopenia, eczema, and immunodeficiency. The platelet count is usually $20-100 \times 10^9/l$ and the platelets are functionally abnormal. Like Fanconi's anaemia, this condition can be cured only with bone marrow transplantation.

May-Hegglin anomaly and variants of Alport's syndrome are both characterised by giant platelets. The former is a benign condition, but the latter is associated with progressive hereditary nephritis and deafness.

Glanzmann's thrombasthenia, the Bernard-Soulier syndrome, and platelet-type von Willebrand's disease are characterised by absence or abnormalities of the glycoproteins in the platelet membrane, resulting in defective platelet adhesion and aggregation.

The life span of a platelet is 7-10 days, and the normal count for all ages is $150-450 \times 10^9/l$

Amegakaryocytic thrombocytopenia with absent radii (TAR syndrome).

Giant granular platelets in peripheral blood film as seen in Bernard-Soulier syndrome or May-Hegglin anomaly.

Diseases of the platelet storage pool are deficiencies in either the α or dense granules causing poor secondary platelet aggregation

Acquired abnormalities

Decreased production of platelets due to suppression or failure of the bone marrow is the commonest cause of thrombocytopenia. In aplastic anaemia, leukaemia, and marrow infiltration and after chemotherapy thrombocytopenia is usually associated with a failure of red and white cell production but may be an isolated finding secondary to drug toxicity (penicillamine, co-trimoxazole), alcohol, malaria, or viral infection (HIV, infectious mononucleosis). Viral infection is the most common cause of mild transient thrombocytopenia.

Increased platelet consumption may be due to immune or non-immune mechanisms. Idiopathic thrombocytopenic purpura is a relatively common disorder and the most frequent cause of isolated thrombocytopenia without anaemia or neutropenia. In adults it often presents insidiously, most frequently in women aged 15-50 years, and can be associated with other autoimmune diseases, in particular systemic lupus erythematosus or the primary antiphospholipid (lupus) syndrome. In children the onset is more acute and often follows a viral infection. The autoantibody produced is usually IgG, directed against antigens on the platelet membrane. Antibody-coated platelets are removed by the reticuloendothelial system, reducing the life span of the platelet to a few hours. The platelet count may vary from $< 5 \times 10^9/l$ to near normal. The severity of bleeding is less than that seen with comparable degrees of thrombocytopenia in bone marrow failure due to the predominance of young, functionally superior platelets.

Spontaneous skin purpura in severe immune thrombocytopenia.

Neonatal alloimmune thrombocytopenia is similar to haemolytic disease of newborn infants except that the antigenic stimulus comes from platelet specific antigens rather than red cell antigens. In 80% of cases the antigen is human platelet antigen 1a, and mothers negative for this antigen form antibodies when sensitised by a fetus positive for the antigen. Fetal platelet destruction results from transplacental passage of these antibodies, and severe bleeding including intracranial haemorrhage can occur in utero. Firstborn infants are frequently affected, and successive pregnancies are equally or more affected.

Acquired disorders of reduced platelet production*

- Drug induced
- Leukaemia
- Metastatic tumour
- Aplastic anaemia
- Myelodysplasia
- Cytotoxic drugs
- Radiotherapy
- Associated with infection
- Megaloblastic anaemia

*Due to bone marrow failure or replacement

Disorders with increased platelet consumption

- Disorders with immune mechanism
 - Autoimmune*—idiopathic thrombocytopenic purpura
 - Alloimmune*—post transfusion purpura, neonatal alloimmune thrombocytopenia
 - Infection-associated*—infectious mononucleosis, HIV, malaria
 - Drug-induced*—heparin, penicillin, quinine, sulphonamides, rifampicin
- Thrombotic thrombocytopenic purpura/haemolytic uraemic syndrome
- Hypersplenism and splenomegaly
- Disseminated intravascular coagulation
- Massive transfusion

Bone marrow aspirate showing increased megakaryocytes in immune thrombocytopenia.

Post-transfusion purpura

- This is an acquired abnormality
- It is a rare complication of blood transfusion presenting with severe thrombocytopenia 7-10 days after the transfusion
- Patients are usually multiparous women who are negative for the human platelet antigen 1a
- Antibodies to this antigen develop that are somehow responsible for the immune destruction of the patient's own platelets

Heparin induced thrombocytopenia occurs during heparin treatment in up to 5% of patients. It may become manifest when arterial or venous thrombosis occurs during a fall in the platelet count and is thought to be due to the formation of antibodies to heparin that are bound to platelet factor 4, a platelet granule protein. The immune complexes activate platelets and endothelial cells, resulting in thrombocytopenia and thrombosis coexisting. Heparin induced thrombocytopenia carries an appreciable mortality risk if diagnosis is delayed.

Thrombotic thrombocytopenic purpura and the similar haemolytic uraemic syndrome cause fever, fluctuating neurological signs, renal impairment, and microvascular haemolysis, which results in thrombocytopenia. Red cell fragmentation on the blood film, a reticulocytosis, and the demonstration of an abnormal pattern of von Willebrand's multimers make the diagnosis highly likely.

Disseminated intravascular coagulation usually occurs in critically ill patients as a result of catastrophic activation of the coagulation pathway, often due to sepsis. Widespread platelet aggregation occurs, causing thrombocytopenia.

Massive splenomegaly—The spleen normally pools about a third of the platelet mass, but in massive splenomegaly the proportion can rise to 90%, resulting in apparent thrombocytopenia.

Aspirin and non-steroidal anti-inflammatory agents are the most common cause of acquired platelet dysfunction, and for this reason aspirin is now widely used therapeutically as an antiplatelet drug. It acts by irreversibly inhibiting cyclo-oxygenase activity in the platelet, resulting in impairment of the granule release reaction and defective aggregation. The effects of a single dose of aspirin last for the lifetime of the platelet (7–10 days).

Bleeding in uraemic patients is most commonly from defects in platelet adhesion or aggregation, though thrombocytopenia, severe anaemia with packed cell volume <20%, or coagulation defects can also contribute.

Essential (primary) thrombocytosis and *reactive (secondary) thrombocytosis*—In these conditions the platelet count is raised above the upper limit of normal. A wide range of disorders may cause a raised platelet count ($>1000 \times 10^9/l$), but patients are normally asymptomatic. However, antiplatelet drugs can be useful to prevent thrombosis in high risk patients—for example, postoperatively.

History and examination of patients

Abnormal bleeding associated with thrombocytopenia or abnormal platelet function is characterised by spontaneous skin purpura and ecchymoses, mucous membrane bleeding, and protracted bleeding after trauma. Prolonged nose bleeds can occur, and menorrhagia or postpartum haemorrhage is common in women.

Rarely, subconjunctival, retinal, gastrointestinal, genitourinary, or intracranial bleeds may occur. In thrombocytopenic patients severe spontaneous bleeding is unusual with a platelet count of $\geq 30 \times 10^9/l$.

Investigations

If the bleeding is severe the patient may need urgent hospital referral for prompt evaluation, diagnosis, and treatment, which may entail blood product support. All patients should have a full blood count, blood film, coagulation, and biochemical screen and then further investigations depending on the results of these.

Red cell fragmentation in patient who presented with confusion and lethargy in whom thrombotic thrombocytopenic purpura was diagnosed. She responded well to large volume plasma exchange for one week.

Causes of acquired platelet dysfunction

- Aspirin and non-steroidal anti-inflammatory agents
- Penicillins and cephalosporins
- Uraemia
- Alcohol
- Liver disease
- Myeloproliferative disorders
- Myeloma
- Cardiopulmonary bypass
- Fish oils

Thrombocytosis

- Essential (primary) thrombocytosis
- Reactive (secondary) thrombocytosis
 - Infection
 - Malignant disease
 - Acute and chronic inflammatory diseases
 - Pregnancy
 - After splenectomy
 - Iron deficiency
 - Haemorrhage

Prolonged nose bleeds are more likely in children than in adults

The investigations in a suspected platelet disorder will depend on the presentation and history in each patient

Thrombocytopenia can be artefactual and due to platelet clumping or a blood clot in the sample, which should be excluded in all cases. The bleeding time (including the standard template technique) may or may not be prolonged in congenital or acquired platelet dysfunction, and therefore a normal bleeding time does not exclude these conditions. It is also not a good indicator of bleeding risk perioperatively.

Management

All serious bleeding due to a platelet disorder needs haematological assessment and treatment. Mild or trivial bleeding due to a transient postviral thrombocytopenia or aspirin needs no active treatment and can be managed in the community.

Acquired disorders

In thrombocytopenia due to bone marrow failure or marrow infiltration—for example, leukaemia and cancer—prophylactic platelet transfusions are given to keep the platelet count above $15 \times 10^9/l$, though the threshold is higher in infected or bleeding patients or to cover invasive procedures.

In childhood idiopathic thrombocytopenic purpura spontaneous recovery is common, and treatment is given only in life threatening bleeding. In adults the condition rarely remits without treatment and is more likely to become chronic. Initial treatment is prednisolone 1 mg/kg daily (80% of cases remit) or intravenous immunoglobulin (0.4 g/kg for five days or 1 g/kg for two days), or both. In refractory patients splenectomy has a 60-70% chance of long term remission, and azathioprine, danazol, vinca alkaloids, and high dose dexamethasone have all been tried with variable success.

Post-transfusion purpura may respond to intravenous immunoglobulin (at doses given above), or plasma exchange may be required. Platelet transfusions should be avoided.

Patients in whom heparin induced thrombocytopenia is suspected are often inpatients with ongoing thrombosis who may have complex medical problems. It is essential to withdraw heparin and treat thrombosis with anticoagulants, avoiding all forms of heparin. Warfarin, synthetic heparinoids, or anicrod can be used. Platelet transfusions are contraindicated in heparin induced thrombocytopenia and in thrombotic thrombocytopenic purpura. If the latter is suspected clinically and on the basis of laboratory tests, large volume plasma exchange should be started immediately and continued daily until substantial clinical improvement and all the results of haematological tests have normalised. Aspirin can be started once the platelet count is $> 50 \times 10^9/l$.

With disseminated intravascular coagulation it is essential to treat the underlying cause as well as to support depletion of clotting factors and platelets with blood products.

In pronounced bleeding or risk of bleeding due to the acquired disorders of platelet function platelets usually have to be transfused to provide normally functioning platelets, though desmopressin (DDAVP) and tranexamic acid can also be of value. Usually treatment may only be necessary to cover surgical procedures or major haemorrhage.

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Investigation of suspected platelet disorder.

A neonate or small infant with bleeding must be referred for evaluation as the inherited bleeding disorders (eg haemophilia or von Willebrand's disease) and platelet disorders may present at a very young age

Treatment of platelet disorders

Congenital disorders

- Platelet transfusions (filtered)
- Desmopressin (DDAVP)
- Tranexamic acid

Acquired disorders

- Bone marrow failure—Platelet transfusions if platelet count is $< 15 \times 10^9/l$
- Idiopathic thrombocytopenic purpura (adults)—Prednisolone, intravenous immunoglobulin, splenectomy
- Post-transfusion purpura—Intravenous immunoglobulin, plasma exchange
- Heparin induced thrombocytopenia—Anticoagulation, but without heparin
- Thrombotic thrombocytopenic purpura—Large volume plasma exchange, aspirin when platelets $> 50 \times 10^9/l$
- Disseminated intravascular coagulation—Treatment of underlying cause, fresh frozen plasma, platelet transfusion
- Hypersplenism—Splenectomy if severe
- Platelet function disorders—Platelet transfusion, desmopressin (occasionally useful—for example, in uraemia)

Correction

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A production error and an editorial error occurred in the article on chronic myeloid leukaemia by John Goldman (1 March, pp 657-60). In the box on p 660 the sixth and seventh bullet points should read “ > 10 Blasts...” and “ > 20 Blasts...” respectively. In the line drawing on p 660 the box saying “advanced phase” should read “accelerated phase” (the arrow is correct reading “advanced phase disease”), and the two boxes at the bottom should read “myeloid” and “lymphoid.”