Investigating the patient with thrombocytopenia

Each month we present authoritative advice on the investigation of a common clinical problem, specially written for family doctors by the Board of Continuing Medical Education of the Royal Australasian College of Physicians.

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There are many causes of thrombocytopenia, ranging from an artefact of the collection medium or clot in the sample to rapidly progressive conditions requiring prompt assessment and therapy, such as thrombotic thrombocytopenic purpura (TTP) or acute leukaemia. The presence or absence of symptoms at presentation, together with the platelet count and a review of the peripheral blood film, may indicate the degree of urgency required in investigating the patient.

Thrombocytopenia is defined as a platelet count of less than 150 x 10^9/L, with the normal platelet count range being from 150 to 400 x 10^9/L. Under normal conditions and in the presence of normal platelet function haemostasis does not require a platelet count greater than 30 x 10^9/L, therefore patients may be asymptomatic yet have relatively severe thrombocytopenia.

History and examination

Patients with symptomatic thrombocytopenia present with abnormal bleeding, which most often presents as spontaneous skin purpura and ecchymoses (Figure 1). Bleeding from mucous membranes may also occur, and in the case of nasal mucosa the resulting epistaxis may be severe. In women, menorrhagia can result from thrombocytopenia and, if prolonged, iron deficiency anaemia may ensue.

Although less common than the above symptoms, retinal and subconjunctival haemorrhages may occur in patients with severe thrombocytopenia. Fortunately intracranial haemorrhage is a

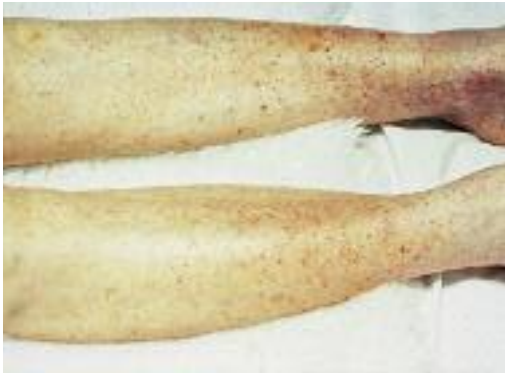

Figure 1. Ecchymoses and purpura in a patient with thrombocytopenia.

IN SUMMARY

- **Thrombocytopenia has many causes ranging from artefacts of the collection process to rapidly progressive and potentially fatal disorders.**
- **A review of the blood film, for diagnostic purposes and to exclude platelet clumping due to a collection artefact, is a necessary initial investigation.**
- **Acquired causes of thrombocytopenia can be classified as due to either decreased platelet production or increased platelet consumption.**
- **Unless the cause of thrombocytopenia is hypersplenism secondary to portal hypertension and liver disease, specialist haematologist referral is usually appropriate.**

rare complication of thrombocytopenia, and is more common in patients who have an associated underlying coagulopathy, for example disseminated intravascular coagulation (DIC).

A thorough patient history may reveal significant contributing factors or causes of thrombocytopenia. The patient's medication history may include medications that can cause thrombocytopenia, such as quinine and heparin (including low molecular weight heparins). Patients should be specifically asked about their intake of tonic water because it contains quinine. Alcohol intake is also important because excess intake may cause thrombocytopenia by several different mechanisms.

Possible exposure to infectious agents should be identified. Hepatitis B and C and HIV infections can result in varying degrees of thrombocytopenia, therefore a history of intravenous drug abuse and sexual contacts may be relevant. Any recent travel to an area where malaria is endemic should be ascertained because the platelet count is often reduced in patients with malaria.

The patient's past history may include a connective tissue disorder such as systemic lupus erythematosus (SLE), which can be associated with thrombocytopenia. However, a finding of thrombocytopenia may precede the diagnosis of a connective tissue disorder or be associated with the presentation of the disease.

Examination should assess the extent of the haemostatic defect and possible aetiological or contributing factors. Acquired disorders that may cause thrombocytopenia (such as splenomegaly, portal hypertension and hepatitis) should be looked for, including examination for stigmata of chronic liver disease. Lymphadenopathy may be related to viral infection or associated with a lymphoproliferative disorder. Evidence of a connective tissue disorder should be sought by assessing the patient for a butterfly rash (associated with SLE), arthritis and vasculitis (including urinalysis).

Although rare, congenital causes of thrombocytopenia may be suspected from clinical assessment. Elfin-like facies suggests Fanconi's anaemia; abnormalities of the radius and thumb are found in thrombocytopenia and absent radii (TAR) syndrome; and eczema occurs in the X-linked Wiskott–Aldrich syndrome.

Table 1. Investigations of thrombocytopenia

Initial tests

- Full blood count
- Review of blood film
- Coagulation studies
- Biochemical profile (including liver function tests and lactate dehydrogenase)

Further tests

- Fibrinogen and d-dimer
- Antinuclear factor
- Lupus inhibitor and anticardiolipin antibodies
- Immunoglobulins and serum electrophoresis and immunoelectrophoresis (EPG and IEPG)
- Vitamin B_{12} and folate assays
- Hepatitis B and C and HIV serology (other serology as clinically indicated)
- Abdominal ultrasound or radionuclide liver/spleen scan
- Bone marrow examination

Initial investigations

The blood film should be reviewed to exclude platelet clumping due to anticoagulant artefact, usually caused by EDTA. If clumping of platelets is found, repeating the platelet count in citrate or oxalate will give a true platelet count. Initial tests should also include coagulation studies and serum biochemistry. Other initial investigations should be directed by causes of thrombocytopenia suggested by the history and examination. The results of these initial tests will determine which further investigations are required (see Table 1).

Further investigations and causes

The causes of thrombocytopenia can be classified into either congenital or acquired. Congenital causes are rare and have been mentioned briefly above. Patients with these conditions need early specialist referral.

Acquired causes of thrombocytopenia can be classified into those due to either decreased platelet production or increased platelet consumption. Clues as to which of these methods is responsible may be apparent in the full blood count and blood film. Isolated thrombocytopenia with no alteration in other indices (that is, normal haemoglobin and white cell counts) may suggest a consumptive thrombocytopenia of immune ongin, whereas accompanying cytopenias may be

Table 2. Causes of reduced platelet production

Ineffective platelet production

- Megaloblastic anaemia (folate or vitamin B_{12} deficiency)
- Myelodysplasia

Reduced platelet precursors

- Leukaemia
- Bone marrow infiltration (e.g. metastatic carcinoma, multiple myeloma)
- Toxins (e.g. radiotherapy, chemotherapy, alcohol)
- Aplastic anaemia

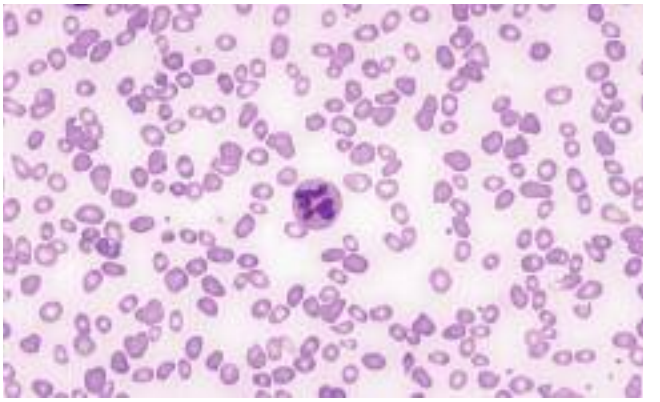

Figure 2. Hypersegmented neutrophil in megaloblastic anaemia.

apparent if there is reduced platelet production by the bone marrow.

Reduced platelet production

Reduced production of platelets may be due to ineffective platelet production or reduced platelet precursors (Table 2).

Table 3. Causes of increased platelet consumption

Immune

Autoimmune

- Idiopathic thrombocytopenic purpura
- Connective tissue disorders (e.g. SLE)
- Lymphoproliferative disorders
- Infections (e.g. HIV, hepatitis C virus, Epstein–Barr virus)

Alloimmune

- Neonatal thrombocytopenia
- Post-transfusion purpura

Drug induced

- Quinine
- Heparin
- Many other drugs (e.g. penicillin, gold salts, rifampicin)

Nonimmune

- Disseminated intravascular coagulation
- Thrombotic thrombocytopenic purpura
- Haemolytic uraemic syndrome
- Hypersplenism
- Massive transfusion

Ineffective platelet production

Ineffective platelet production due to causes such as megaloblastic anaemia or myelodysplasia may be diagnosed or suspected from the initial investigations. Oval macrocytes, hypersegmented neutrophils, anaemia and pancytopenia are features of megaloblastic anaemia (Figure 2). Serum B_{12} and folate levels may clarify the aetiological deficiency, and a bone marrow examination will show diagnostic megaloblastic changes.

In myelodysplasia, other cytopenias (such as anaemia and neutropenia) may also be present. Round macrocytes are characteristic of myelodysplasia, and neutrophils exhibiting a hypogranular cytoplasm may be found. The nucleus of these neutrophils may be bilobed (the pseudo Pelger–Huet anomaly). A bone marrow examination may be diagnostic. In myelodysplasia and megaloblastic anaemia the serum lactate dehydrogenase and bilirubin levels may be elevated.

Reduced platelet precursors

Initial investigations may give a clue to the diagnosis in patients with reduced platelet precursors. A careful assessment of the blood count indices as well as a review of the blood film may be diagnostic, especially in acute leukaemia. However, a bone marrow biopsy is necessary to diagnose other causes, such as marrow infiltration or aplastic anaemia.

Increased platelet consumption

The causes of thrombocytopenia due to increased platelet consumption are either immune or nonimmune (Table 3).

Immune causes

The aetiology of thrombocytopenia due to increased platelet consumption of immune origin may be suggested by the clinical setting and the patient's past medical history, including drug history.

Idiopathic thrombocytopenic purpura (ITP) is a relatively common disorder and is the most frequent cause of isolated thrombocytopenia. It may be associated with a connective tissue disease, especially SLE, and also the antiphospholipid antibody syndrome. In adults, ITP tends to be insidious in onset although it may follow a viral infection, as occurs particularly in children (for example, after Epstein–Barr virus infection). Idiopathic thrombocytopenic purpura is a diagnosis of exclusion. Investigations should include an antinuclear factor, prothrombin time, activated partial thromboplastin time, lupus inhibitor and anticardiolipin antibodies – and also viral serology, because HIV and hepatitis C virus can result in an immune thrombocytopenia. A bone marrow examination may be necessary to exclude other causes of thrombocytopenia before starting treatment.

The alloimmune causes of thrombocytopenia are post-transfusion purpura

and neonatal alloimmune thrombocytopenia. Post-transfusion purpura occurs seven to 10 days after a blood transfusion. The patients are usually negative for human platelet antigen Ia (HPA Ia) and they develop antibodies to this antigen on transfused platelets. Neonatal alloimmune thrombocytopenia occurs in newborn infants most often when the mother is HPA Ia negative and the fetus is HPA Ia positive. Unlike haemolytic disease of the newborn, this disorder can occur with the first pregnancy. The above disorders should be suspected from the clinical setting. Determining the HPA Ia platelet phenotype and testing for anti-HPA Ia antibodies is diagnostic.

Thrombocytopenia can be caused by many drugs and this can be severe, such as thrombocytopenia secondary to quinine use, and heparin induced thrombotic thrombocytopenia syndrome (HITTS). Paradoxically, and of great importance, HITTS is associated with large vessel clotting (especially arterial). Investigations in the setting of exposure to these drugs are aimed at determining if the patient has developed drug-dependent antiplatelet antibodies.

Nonimmune causes

Nonimmune causes of thrombocytopenia may be apparent from initial investigations. Normally, about 30% of platelets are pooled in the spleen. This percentage may rise to more than 90% with massive splenomegaly resulting in thrombocytopenia. History, examination and initial tests may not only elucidate the presence of splenomegaly but also help in identifying the underlying cause. (For example, a history of hepatitis or prolonged excess alcohol intake, or the examination findings of splenomegaly and stigmata of chronic liver disease, may suggest the diagnosis.) Investigations may show round macrocytes and target cells on the blood film, deranged liver function test results and possibly a prolonged prothrombin time.

Thrombotic thrombocytopenic purpura (TTP) and the haemolytic uraemic syndrome (HUS) are disorders characterised by microangiopathic haemolytic anaemia (red cell fragmentation), often severe thrombocytopenia, and clinically by fevers, neurological symptoms and renal function abnormalities. Initial investigations show red blood cell fragments on the blood film and severe thrombocytopenia, although coagulation studies are characteristically normal. Prompt assessment of these disorders by a haematologist is important so that appropriate therapy (for example, plasmapheresis) can be initiated to avoid a fatal outcome or adverse long term sequelae.

DIC is associated with a microangiopathic blood film as well as abnormal coagulation studies, including a prolonged activated partial thromboplastin time and thrombin time, reduced fibrinogen and raised fibrin degradation products. The underlying cause of DIC needs addressing, and could be found among any of a diverse group of causes, such as infections, disseminated malignancies (especially breast and prostate) and some leukaemias.

Conclusion

Thrombocytopenia by its nature may be severe and unpredictable in its clinical course depending on its aetiology. Unless the cause is hypersplenism secondary to portal hypertension and liver disease, specialist referral is appropriate. This is because many causes of thrombocytopenia require bone marrow examination and the initiation of relatively urgent therapy directed at either malignant disorders or life-threatening benign disorders. MT