Investigating thrombocytosis

In this series, we present authoritative advice on the investigation of a common clinical problem, specially commissioned for family doctors by the Board of Continuing Medical Education of the Royal Australasian College of Physicians.

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An elevated platelet count is referred to as thrombocytosis. It is often an incidental finding when a full blood count is requested for other reasons. Usually it is reactive, but up to 20% of cases are due to a primary haematological disorder. The cause is often obvious, but diagnosing the underlying problem can be challenging in some cases.

The investigation of patients with thrombocytosis can be carried out by the GP. Referral to a haematologist is recommended for patients in whom the cause remains undiagnosed or a primary haematological disorder is suspected. Other patients may need to be referred to the appropriate specialist for management of the underlying disease causing the thrombocytosis.

The normal platelet count

Platelets are integral to the first phase of clotting. They are produced from the cytoplasm of megakaryocytes in the bone marrow. The normal range for the platelet count is the same in all age groups. The lower limit of normal is 150 x 10^9/L and the upper limit 400 to 450 x 10^9/L. The normal range is defined as the mean plus and minus two standard deviations of the platelet counts of a population of apparently normal, healthy individuals. This calculated normal range includes 95% of the assayed population, but 2.5% of them will have a platelet count above the upper limit of the normal range.

In the absence of pathology, a person tends to have a similar platelet count throughout life. Consequently, some people will always have a platelet count around or just above the upper limit of normal, and this will be normal for them and not indicative of underlying pathology. To exclude such people, most studies of thrombocytosis include only subjects with platelet counts of 500 x 10^9/L or more.

Causes of thrombocytosis

As shown in Table 1, the causes of thrombocytosis are divided into the following:

- physiological
- familial
- autonomous (primary)
- reactive (secondary).

Both autonomous and reactive thrombocytosis are due to increased platelet production.

Most studies of the causes of thrombocytosis have been hospital- rather than community-based, but they have often included both inpatients and

IN SUMMARY

- **Thrombocytosis is more often reactive than due to a primary haematological disorder.**
- **Diagnosing the cause of thrombocytosis is important to enable appropriate management.**
- **The cause of thrombocytosis can often be determined by reviewing previous full blood counts, considering any other abnormalities on the full blood count and taking a detailed history.**
- **There are a small number of patients with thrombocytosis in whom the cause will remain uncertain.**
- **Some laboratory tests may assist in difficult cases; however, there is none that will definitely differentiate reactive from autonomous thrombocytosis.**
- **Patients with a primary haematological disorder and those in whom the diagnosis has not been determined should be referred to a haematologist.**

outpatients. These studies have shown that thrombocytosis is more often reactive than autonomous in both paediatric and adult populations, but the proportion of cases due to primary haematological disorders does increase with age.

Primary haematological disorders are present in only 10 to 20% of people with thrombocytosis. This is true even in studies that have investigated causes in patients with platelet counts of more than 1,000 x 10^9/L. Infection and tissue damage account for most cases of reactive thrombocytosis (between 37 and 56%). Asplenia or hyposplenism account for 10 to 20% of cases, malignancy for 5 to 12%, and blood loss or iron deficiency for 1 to 6%.

Autonomous v. reactive thrombocytosis

The cause of thrombocytosis needs to be diagnosed to allow appropriate management of the patient. Importantly, autonomous thrombocytosis is associated with a risk of bleeding, thrombosis and symptoms because of disturbances in the microcirculation (also known as vasomotor symptoms). The risk of these complications in autonomous thrombocytosis is as high as 30 to 50%.

Conversely, the risk of these complications is very low in patients with reactive thrombocytosis (less than 4%); these complications are usually considered to be due to the underlying disease and independent of the thrombocytosis. Consequently, the management of patients with reactive thrombocytosis does not involve the use of cytoreductive treatment (e.g. chemotherapy) or antiplatelet drugs (e.g. aspirin), whereas these may be appropriate in those with autonomous thrombocytosis.

Causes of autonomous and reactive thrombocytosis are summarised in Tables 2 and 3.

Determining the cause

Review of medical history and full blood counts

The cause of thrombocytosis may be easily determined in many cases by reviewing the medical history. For example, recent surgery or infection may be the cause; the only action required in such cases is to repeat the full blood count in one to two months to ensure the platelet count has returned to normal.

If the cause of the thrombocytosis is not immediately apparent, the results of previous full blood counts should be reviewed to determine whether the thrombocytosis is recent in onset, has been present for a long time or has been increasing over time.

If the thrombocytosis is mild (less than 500 x 10^9/L) and the platelet count has been in the high normal range or mildly elevated over many years, it may be 'normal' for that individual.

Thrombocytosis of recent onset suggests the development of an as yet undiagnosed illness, but the thrombocytosis should be confirmed by a repeat full blood count before further extensive investigation is considered.

A gradually increasing platelet count may indicate a primary haematological disorder.

Clues to the cause of the thrombocytosis may be provided by other abnormalities reported on the full blood count. Microcytosis and/or hypochromia or a fall in the mean cell volume (MCV) and mean corpuscular haemoglobin (MCH) compared with previous results suggests iron deficiency. Spherocytosis suggests the presence of haemolysis.

The abnormalities seen in myeloproliferative disorders are many and varied, including large platelets and megakaryocytic fragments. Further

Table 1. Categories of thrombocytosis

Physiological

Physiological thrombocytosis occurs after vigorous exercise and during childbirth, and is due to mobilisation of platelets from the extravascular pool.

Familial

Familial thrombocytosis is exceedingly rare. In some families it is due to mutations in the gene for thrombopoietin, a cytokine with major effects on megakaryocyte differentiation and maturation.

Autonomous

Autonomous thrombocytosis occurs in primary haematological disorders in which the production of platelets is clonal (neoplastic). These disorders include the myeloproliferative disorders and some forms of myelodysplastic syndrome.

Reactive

Reactive thrombocytosis occurs in the presence of tissue damage, infection, inflammation or asplenia and is due to increased concentrations of haematopoietic growth factors or inflammatory cytokines, particularly interleukin 6. In reactive thrombocytosis the platelet count should return to normal after resolution of the condition, but this may not occur if the underlying illness is chronic or irreversible (e.g. post-splenectomy).

Table 2. Causes of autonomous thrombocytosis

Myeloproliferative disorders
Essential thrombocythemia
Polycythemia rubra vera
Myelofibrosis
Chronic myeloid leukaemia
Myelodysplastic syndromes
Minority of cases only (e.g. 5q-syndrome)

details of these abnormalities are discussed below under 'Primary haematological disorders'. An elevated white cell count may be present in both autonomous and reactive thrombocytosis, but a very high white cell count or marked left shift is more likely in a primary haematological disorder.

Detailed history and examination

If there are no clues to the cause of the thrombocytosis after reviewing the known medical history as well as the previous and current full blood counts, a more detailed medical history and examination will be necessary. Very specific questioning of the patient and the checking of records held by other health facilities (e.g. hospitals) may be useful. For example, a splenectomy may have been performed many years previously and may not have been planned but became necessary during another surgical procedure (e.g. during gastric, pancreatic or left renal surgery).

Recent anorexia, weight loss, night sweats, cough or bone pain may indicate an undiagnosed malignancy. Evidence of blood loss, whether acute, chronic, obvious or occult, should be sought. Thrombosis, particularly if recurrent or involving unusual sites, raises the possibility of a myeloproliferative disorder. Splenomegaly is present in 40% of patients with myeloproliferative disorders, but is much less common in those with secondary thrombocytosis.

There will be some patients for whom the explanation for thrombocytosis remains uncertain even after carrying out all of the above. Unfortunately in these cases there is no laboratory test that can reliably distinguish autonomous from reactive thrombocytosis. The erythrocyte sedimentation rate (ESR) and C reactive protein (CRP) and fibrinogen levels will often be high in reactive thrombocytosis but normal in uncomplicated myeloproliferative disorders (see the flowchart on page 35). However, normal values for these parameters do not exclude a reactive process. An elevated reticulocyte count can be seen in patients with recent blood loss or haemolysis. It is often worth checking the iron studies even if iron deficiency is not considered highly likely based on the full blood count results.

Table 3. Causes of reactive thrombocytosis

Tissue damage
Postoperative
Trauma
Burns
Acute pancreatitis
Inflammation
Rheumatoid arthritis
Vasculitides
Inflammatory bowel disease
Sarcoidosis
Kawasaki disease (in children)
Rapid haematopoietic (blood) regeneration
Acute blood loss
Acute haemolysis
Malignancy
Carcinoma
Lymphoma
Infections
Acute or chronic
Bacterial
– pneumonia
– hepatobiliary
– gastrointestinal
– urinary tract
– soft tissue
– joint or bone
– tuberculosis
Iron deficiency
Rebound from thrombocytopenia
Idiopathic thrombocytopenic purpura
Drug- or ethanol-induced
Following treatment of vitamin B_{12} deficiency
Following chemotherapy
Asplenia or hyposplenism

Asplenia and hyposplenism

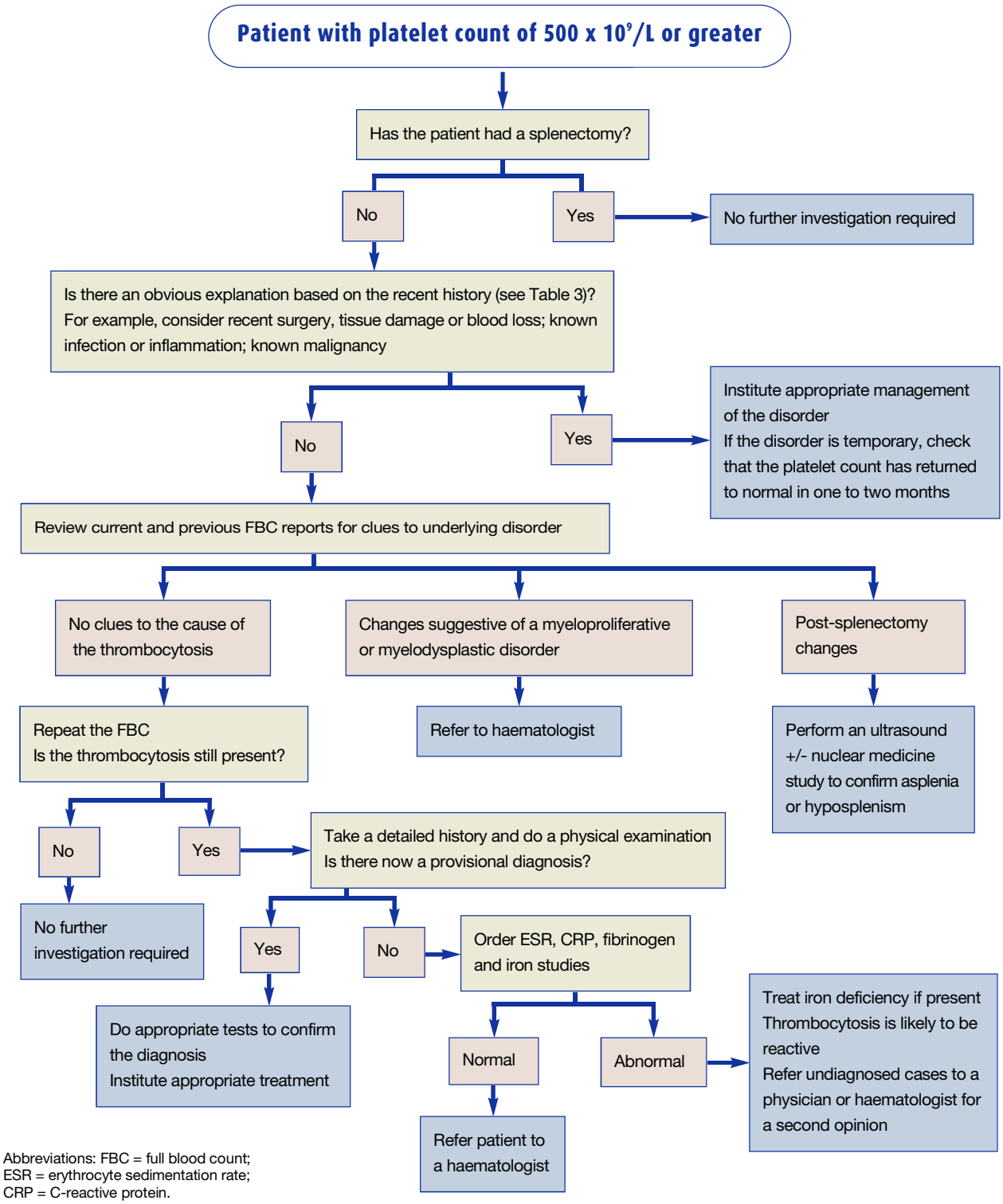
One-third of the total platelet mass of the body is sequestered in the spleen. Consequently, absence or hypofunction of the spleen results in thrombocytosis. Causes of asplenia or hyposplenism are listed in Table 4. The peak platelet count occurs one to three weeks after surgical splenectomy and may be greater than 1,000 x 10^9/L. The platelet count often, but not always, returns to normal, but this may take weeks to years to occur.

The blood film will show target cells, acanthocytes and Howell-Jolly bodies (Figures 1 and 2). There is often also an elevated white cell count. If the blood film is suggestive but there is no history of splenectomy, an upper abdominal ultrasound will confirm the presence or

Table 4. Causes of asplenia and hyposplenism

Absence of spleen
Congenital
Surgical
Hyposplenism
Coeliac disease
Inflammatory bowel disease
Sickle cell disease
Sarcoidosis
Amyloidosis

Investigating thrombocytosis



Abbreviations: FBC = full blood count; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein.

absence of a spleen. However, in hyposplenism the spleen is still present and a nuclear medicine scan (liver spleen scan or red cell scan) may be helpful in demonstrating decreased function.

The dilemma of iron deficiency

Iron deficiency can cause thrombocytosis but, conversely, can also occur in myeloproliferative disorders secondary to bleeding. Patients with thrombocytosis and iron deficiency should be evaluated for the cause and treated with replacement therapy. As well as monitoring for the return of a normal haemoglobin level, red cell indices and iron studies, check that the platelet count normalises. If it does not, the possibility of another process causing reactive thrombocytosis, or iron deficiency complicating a myeloproliferative disorder, must be reconsidered.

Primary haematological disorders

As indicated above, many cases of a primary haematological disorder will be suspected or diagnosed after history, examination and review of the full blood count result. There are specific features to consider when taking a history of bleeding, thrombosis and vasomotor symptoms.

Bleeding

The bleeding most often affects the gastrointestinal tract but may also affect the skin (e.g. when shaving) or other mucosal membranes such as the genitourinary or respiratory tracts (e.g. epistaxis). Counterintuitively, patients most at risk of bleeding are those with platelet counts above 1,500 x 10^9/L.

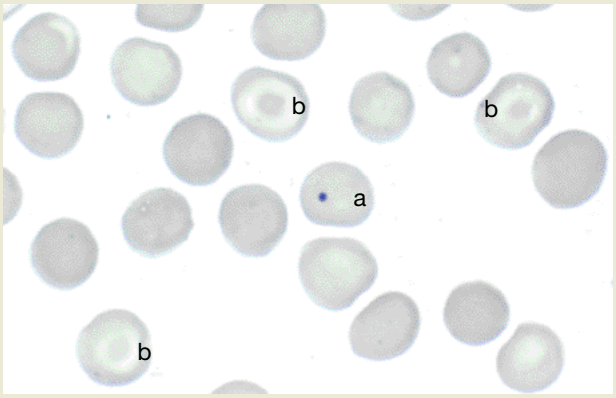
Thrombosis

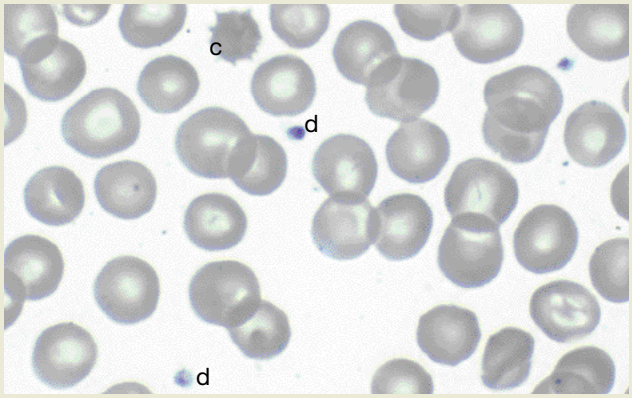
Arterial thrombosis is more common than venous thrombosis. Venous thrombosis is usually deep vein thrombosis and pulmonary embolus, but thrombosis of unusual sites such as the hepatic (Budd-Chiari syndrome), mesenteric or portal veins or cerebral venous sinuses is particularly suggestive of autonomous thrombocytosis. The degree of thrombocytosis does not correlate with the risk of thrombosis; however, treatment to decrease the platelet count does lower the risk.

Vasomotor symptoms

Vasomotor symptoms due to primary haematological disorders include headache, visual symptoms, light-headedness, atypical chest pain and erythromelalgia. Erythromelalgia refers to warm, red,

Investigating thrombocytosis: findings on blood films





Figures 1 (above) and 2 (above right). Blood films showing post-splenectomy changes: Howell-Jolly body (a); target cell (b); acanthocyte (c); normal platelet (d).

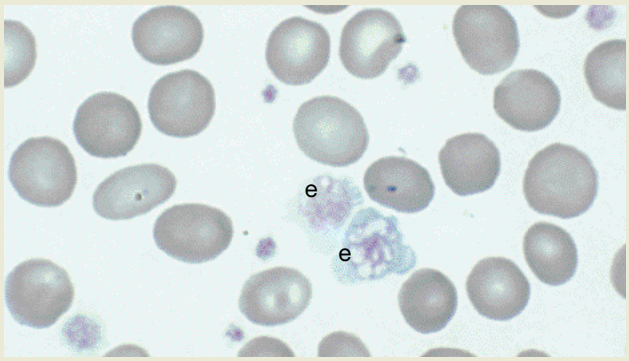


Figure 3 (right). Blood film demonstrating thrombocytosis and large platelets (e) in a patient with a myeloproliferative disorder.

congested extremities often accompanied by throbbing pain or a burning sensation. It may progress to painful acrocyanosis or peripheral gangrene. It affects the lower limbs (predominantly the forefoot sole or toes) more often than the upper limbs. Vasomotor symptoms respond to aspirin treatment.

Haematological testing

In any of the myeloproliferative disorders blood films may show large abnormal platelets (Figure 3) or even megakaryocytic fragments. An elevated haemoglobin level, hematocrit and red cell count indicate polycythemia. A normal haemoglobin level in the presence of microcytosis and hypochromia due to iron deficiency may also occur in polycythemia.

In chronic myeloid leukaemia there will usually be an elevated white cell count with immature white cells – particularly metamyelocytes and myelocytes. An elevated white cell count with a left shift can occur in reactive thrombocytosis but is usually less marked, with the immature forms being predominantly band forms. In myelofibrosis there is often a leukoerythroblastic blood film (immature white cells and nucleated red blood cells) and marked red cell changes including fragments and tear drop poikilocytes. In myelodysplastic syndromes with thrombocytosis there will often also be anaemia with abnormal red cell indices or morphology.

The elusive diagnosis

At the end of the initial assessment process there will be a group of people with persistent thrombocytosis but no provisional diagnosis. This group will include those with:

- reactive thrombocytosis but an as yet undiagnosed underlying illness
- those with a primary haematological disorder with thrombocytosis as the dominant feature.

The patients in the latter group are more likely to have essential thrombocythemia than other primary haematological disorders. These undiagnosed patients need referral for assessment by a haematologist.

There are published criteria for the diagnosis of the myeloproliferative disorders. Applying these criteria requires other tests such as red cell mass, bone marrow aspiration and trephine biopsy with genetic or molecular analysis. However, even at the end of this process there will still be patients in whom a definite diagnosis is not possible. These patients will require monitoring for the development of diagnostic features, sometimes over a period of many years.

Summary

Thrombocytosis is not uncommon and will be encountered numerous times by all medical practitioners. There are many possible causes, but the thrombocytosis is reactive in most patients. Determining the cause allows appropriate management.

In most cases the cause will be obvious and readily determined without the need for extensive investigation. A diagnosis will not be obvious in a small number of patients and it is these people as well as those with primary haematological disorders who need referral to a haematologist for assessment and management. MT

Further reading

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DECLARATION OF INTEREST: None.