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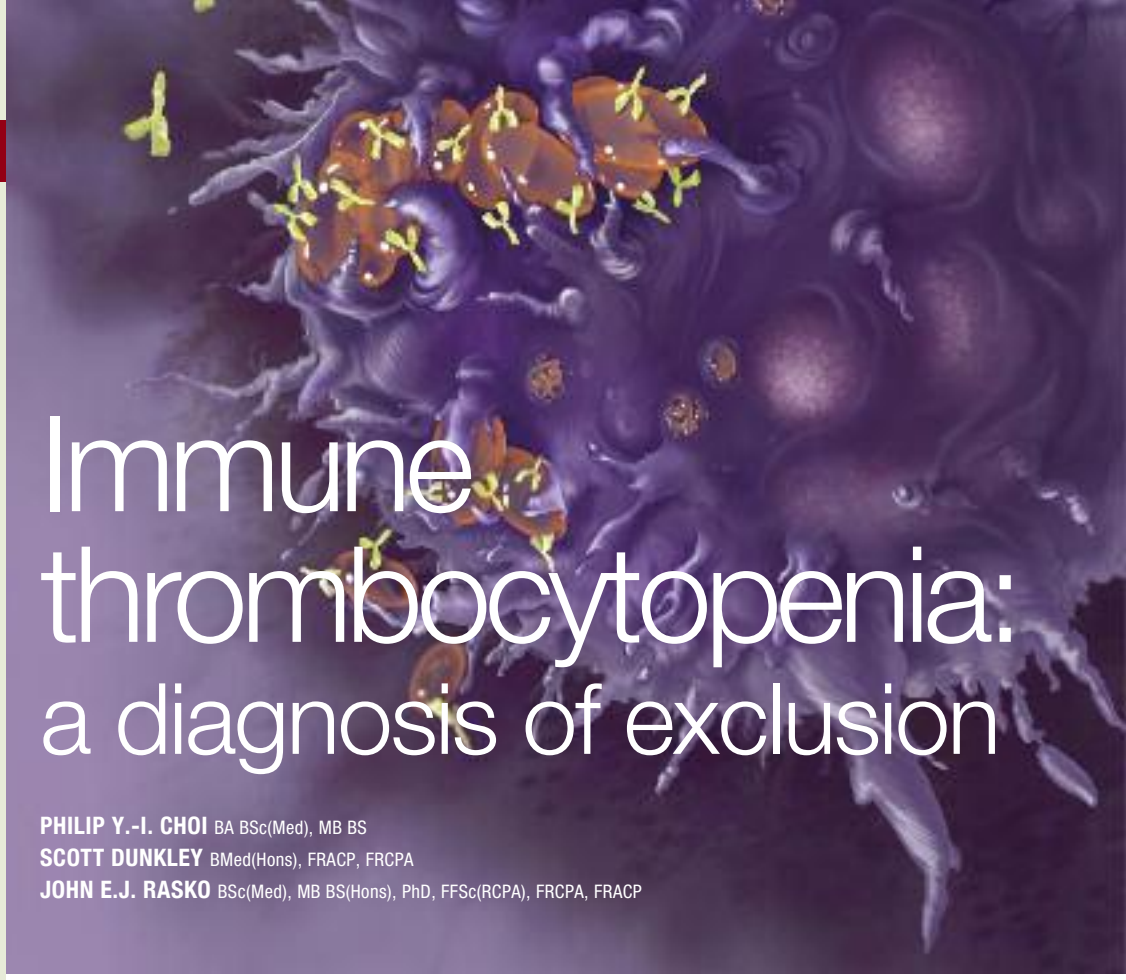

Immune thrombocytopenia: a diagnosis of exclusion

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Key points

- Immune thrombocytopenia (ITP), previously known as idiopathic thrombocytopenic purpura, is not a single disease but instead encompasses a hetero - genous group of disorders with a common manifestation.
- ITP is due to both accelerated platelet destruction and insufficient platelet production.
- The threshold for treatment in ITP is a platelet count of less than 30 x 10^9/L, or any evidence of bleeding with a platelet count of less than 50 x 10^9/L.
- ITP in adults is most frequently chronic.
- Thrombocytopenia in pregnancy has several causes (usually not immune) and careful planning may be required to manage it safely.

The definition of immune thrombocytopenia is changing to reflect our growing understanding of its pathogenesis.

This review provides a brief overview of immune thrombocytopenia (ITP) including current concepts regarding its pathogenesis, future directions in its treatment and the recommended approaches in the management of difficult cases. A review on the other causes of thrombocytopenia was published in the February 2011 issue of *Medicine Today*.

WHAT IS IMMUNE THROMBOCYTOPENIA?

Definition

Since the first description in 1735 by Werlohf of a spontaneous bleeding disorder affecting a young woman, the definition of ITP continues to evolve as more is understood about this disease. ITP is best understood as an immune-mediated disorder of increased platelet destruction and impaired megakaryopoiesis. The International Working Group on ITP has recently recommended a new model for classifying ITP.[1]

Historically, ITP stood for 'idiopathic thrombocytopenic purpura'. However, it is now generally agreed that ITP is an autoimmune condition. The acronym now stands for 'immune thrombocytopenia'. This change removes purpura from the definition because bleeding or bruising does not always accompany the disorder.

Primary ITP is diagnosed in the absence of an identifiable underlying disease. Secondary ITP is further subclassified according to associated findings, such as lymphoproliferative disease (e.g. lymphoma and chronic lymphocytic leukaemia), antiphospholipid syndrome,

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CLASSIFICATION OF IMMUNE THROMBOCYTOPENIA (ITP)[1]

Primary ITP

- Isolated thrombocytopenia (peripheral blood platelet count less than 100 x 10^9/L) in the absence of other causes or disorders that may be associated with thrombocytopenia
- The diagnosis of primary ITP remains one of exclusion
- Bleeding symptoms may not always be present

Secondary ITP

- All forms of immune-mediated thrombocytopenia except primary ITP

DEFINITIONS OF IMMUNE THROMBOCYTOPENIA (ITP)

Newly diagnosed (acute) ITP

- Within three months from diagnosis

Persistent ITP

- Between three and 12 months from diagnosis, without achieving spontaneous remission or maintaining complete response off therapy

Chronic ITP

- ITP lasting more than 12 months

Severe ITP

- Presence of bleeding symptoms at presentation sufficient to mandate treatment, or occurrence of new bleeding symptoms requiring an escalation of therapy

infection or any relationship with drugs (see the box above).[1] The definitions of acute, persistent, chronic and severe ITP are given in the box above right.

Epidemiology

The incidence of ITP in adults is reported at 5.5 per 100,000. The incidence increases with age and ITP is twice as common in those older than 60 years. The female to male ratio is 1.7.

Pathogenesis

In 1951, Harrington and Hollingsworth demonstrated that by injecting the blood of patients with ITP into themselves, they could transiently develop thrombocytopenia.

Primary ITP remains a diagnosis of exclusion. It does not represent a single clinical pathological entity but instead incorporates a heterogeneous cluster of processes that each contributes to the development of thrombocytopenia by the production of platelet autoantibodies. This is due to an error in self-tolerance. Autoreactive lymphocytes develop and these lead to autoantibody production. Platelet reactive T-cell clones have also been demonstrated in this condition but the central role of pathogenic B-cell proliferation is evidenced by the effectiveness of anti-CD20 monoclonal therapy.

Platelet autoantibodies can recognise glycoproteins expressed on the platelet surface such as GPIIb/IIIa and GPIb/IX. In practice, the detection of platelet-bound autoantibodies has poor specificity and is of little clinical utility.

Platelets bound by these antibodies are phagocytosed in the reticuloendothelial system by macrophages via Fc receptors. As such, splenectomy has been shown to provide a sustained response in at least two-thirds of patients.

Secondary forms of ITP are initiated by a diverse range of mechanisms, including immune dysregulation associated with lymphoproliferative disease and molecular mimicry in postinfectious cases. As in primary ITP, these syndromes are ultimately associated with the development of platelet-specific autoantibodies.

Platelet kinetic studies have also demonstrated the spleen to be the major site of platelet clearance, but there is also an inappropriate marrow response to thrombocytopenia. It is postulated that ineffective thrombopoiesis due to antiplatelet antibodies contributes significantly to thrombocytopenia in ITP. New therapies aimed at improving thrombopoiesis have been shown to improve thrombocytopenia and to reduce the reliance on immunosuppressive medications.

Prognosis

Patients with an insidious onset of ITP rarely remit spontaneously, whereas those who present with an acute onset of bleeding generally remit within three months.

An analysis of 152 adult patients with ITP in the Netherlands who were treated according to a well-defined algorithm showed that patients who responded to treatment generally did so within two years of diagnosis.[2] In this study, 85% of patients with primary ITP were able to achieve a platelet count of greater than 30 x 10^9/L despite discontinuation of all therapies. These patients had a long-term mortality risk almost equivalent to that of the general population. However, in the 9% of patients who were refractory to therapy and had a platelet count of less than 30 x 10^9/L, mortality risk was 4.2 times that of the general population.[2] Bleeding and infection were equally important causes for mortality in this group.

DOES MY PATIENT HAVE ITP?

Clinical presentation

Adult patients with ITP typically present insidiously with the development of easy bruising, petechiae, epistaxis, gastrointestinal bleeding or genitourinary bleeding. In contrast, childhood ITP presents acutely with bleeding and generally resolves spontaneously within six months. Mucocutaneous bleeding is common in patients with thrombocytopenia. Life-threatening gastrointestinal and intracranial haemorrhage are feared complications in severe cases.

The latest guidelines from the International Working Group recommend a

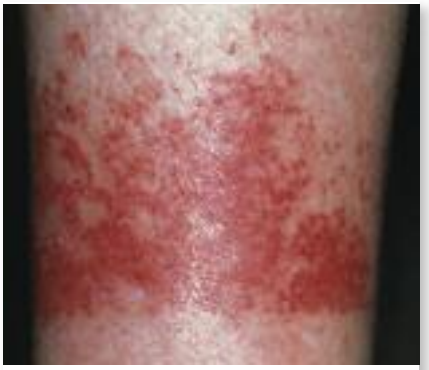

Figure 1. Petechial rash on a woman's leg above the sock line, as can be observed in thrombocytopenia.

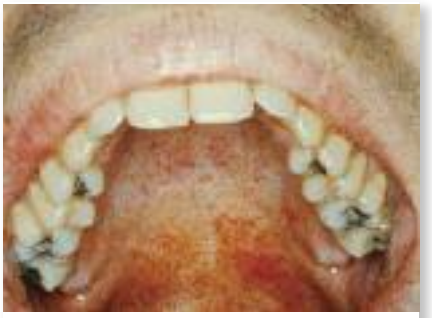

Figure 2. Petechiae on the hard palate. Blood blisters on the lips and tongue can also develop in thrombocytopenia so the mouth should be carefully examined.

threshold thrombocytopenia of 100 x 10^9/L to establish a diagnosis of ITP. Generally, patients with platelet counts close to this level will not experience any increase in bleeding. However, there is great diversity between patients in their propensity to bleed. It is commonly agreed that patients with platelet counts below 30 x 10^9/L require treatment due to an increased risk of bleeding. Some patients will bleed at slightly higher platelet counts and therefore warrant therapy, whereas others avoid bleeding despite platelet counts well below 30 x 10^9/L.

Clinical history and examination

The clinical history should include an enquiry regarding unusual bleeding while brushing teeth, prolonged bleeding from small cuts or abrasions, blood on the pillow on waking, bruising in unusual sites and persistent epistaxis.

It is important to ask about the onset of these symptoms, concurrent medication use (including over-the-counter medications and herbal remedies), dietary and alcohol history, and the presence of any other conditions that are associated with immune-mediated thrombocytopenia. These other conditions include lymphoproliferative disease, common variable immunodeficiency disease, autoimmune diseases including Graves' disease and Hashimoto's thyroiditis and infections such as with *Helicobacter pylori*, HIV and hepatitis C virus, and also recent vaccinations such as for measles, mumps and rubella. A family history of thrombocytopenia or 'a bleeding problem' should prompt family investigations for congenital thrombocytopenia.

Examination of the patient involves looking for evidence of bleeding such as petechiae particularly in dependent areas, purpura and bleeding in the buccal mucosa (Figures 1 and 2). The presence of lymphadenopathy or splenomegaly should prompt a search for a secondary cause for thrombocytopenia. It is estimated that 15 to 20% of ITP is secondary.

Diagnostic tests

ITP is diagnosed in the presence of isolated thrombocytopenia with a platelet count of less than 100 x 10^9/L. It is important to first exclude a false thrombocytopenia called pseudothrombocytopenia by examining the blood film to exclude platelet aggregates. Blasts, fragmented red cells and the presence of giant platelets should alert clinicians to the possibility of alternative diagnoses such as acute leukaemia, intravascular haemolysis or a congenital macrothrombocytopenia. The full blood count should also exclude the presence of other cytopenias.

RECOMMENDED INVESTIGATIONS IN ITP[3]

Basic evaluation

- Patient history
- Family history
- Physical examination
- Complete blood count and reticulocyte count
- Peripheral blood film
- Quantitative immunoglobulin level measurement
- Bone marrow examination in selected patients
- Blood group (Rh)
- Direct antiglobulin test
- *Helicobacter pylori* testing
- HIV and hepatitis C virus serology

Tests of potential use

- Glycoprotein-specific antibodies
- Antiphospholipid antibodies (including anticardiolipin antibodies and lupus anticoagulant)
- Antithyroid antibodies and thyroid function
- Pregnancy test in women of childbearing potential
- Antinuclear antibodies
- Serology or polymerase chain reaction for varicella zoster virus and cytomegalovirus

Tests of unproven or uncertain benefit

- Thrombopoietin levels
- Reticulated platelets
- Platelet associated immunoglobulin G
- Platelet survival study
- Bleeding time
- Serum complement
- Detection of parvovirus B19

Specific confirmatory diagnostic tests are rarely performed in ITP. The box above outlines the current recommendations for investigating ITP from the International Working Group on ITP.[3]

HOW DO WE TREAT ITP?

Initial treatment

The main goal in treating a patient with ITP is to restore haemostasis and prevent symptomatic bleeding. Patients with platelet counts of less than 10 x 10^9/L are usually admitted to hospital at first presentation. Treatment is rarely indicated in patients with a platelet count greater than 50 x 10^9/L. Corticosteroids are the traditional first-line agents used. Up to 90% of patients respond initially but the relapse rate upon withdrawal is approximately two-thirds. These drugs can reduce bleeding independent of their effect on thrombocytopenia by affecting blood vessels directly.

Pooled intravenous immunoglobulin (IVIG) has been demonstrated to provide initial response rates similar to corticosteroids but with a shorter time to response. IVIG is available through the Australia Red Cross Blood Service for use in patients who are corticosteroid refractory or in those with significant bleeding. Corticosteroids administered simultaneously can act synergistically. Intravenous RhD immunoglobulin is a common option worldwide in patients who are RhD positive but is not approved in Australia.

The role of platelet transfusion is limited to the acute control of active bleeding. Due to the rapid destruction of transfused platelets by antibodies, transfusions alone are not effective in maintaining a safe platelet count.

Care should be taken that the patient is not taking other drugs that impair platelet function, such as aspirin, NSAIDs and certain herbal preparations.

If initial treatment fails

Splenectomy has been the gold-standard second-line therapy in ITP; however, this viewpoint is being challenged due to the availability of newer therapies and the fear of infections that may arise from the asplenic state. Initial response rates for splenectomy are 80% and sustained response over five years is achieved in up to 66% of patients, making it still the most efficacious treatment available.[3] Unfortunately, complication rates are significant. Modern laparoscopic methods report a complication rate of 10% and a mortality rate of up to 0.2%.[4] Patients with subsequent thromboembolic risk require postoperative thromboprophylaxis.

The lifelong risk of infection from encapsulated micro-organisms requires preoperative and regular postoperative vaccination. Based on the Australian Immunisation Handbook guidelines[5] and British Committee for Standards in Haematology guidelines,[6] we recommend a standard schedule postoperatively of

pneumococcal and meningococcal vaccinations every five years, annual influenza vaccinations and haemophilus vaccination if previously not performed.

Prompt antibiotic therapy of suspected bacterial infections is strongly recommended. It is our practice to supply patients with an emergency supply of amoxycillin. The role of long-term antibiotic prophylaxis postsplenectomy is controversial. Current Australian guidelines recommend an individualised approach.[7] This is based on risk: patients within two years of splenectomy and those who are immunosuppressed are considered to be at high risk. In contrast, British guidelines are more prescriptive. They recommend that all patients should receive life-long antibiotic prophylaxis, although they concede there is no evidence to support this approach.[8] The use of long-term antibiotics has not been widely adopted by haematologists in Australia.

Future directions in treatment

Future therapies in ITP are aimed at minimising immunosuppression while seeking a durable response.

Rituximab is a monoclonal antibody against the B-cell antigen CD20 that causes immunosuppression. Typically, rituximab has not been associated with increased infection rates but immunoglobulin levels should be measured. Recent concerns regarding the occurrence of progressive multifocal leucoencephalopathy in patients with autoimmune disease highlight our lack of knowledge about the long-term side effects with this therapy. As such, rituximab should not necessarily be considered a benign therapy as compared with splenectomy.[9]

When administered weekly for four intravenous doses, rituximab induces a complete response in over 50% of patients with relapsed or refractory chronic ITP (off-label use).[10] This response was durable for at least five years in one-third of all cases. Furthermore, almost 75% of patients do not require any other therapy for five years.[10]

In contrast, treatment with thrombopoietin-receptor agonists commits patients to an ongoing and indefinite duration of therapy. Thrombopoietin is a megakaryocyte cytokine/growth factor that increases platelet production. Romiplostim (approved for chronic ITP), is a drug that mimics this hormone and has been shown in randomised controlled trials to maintain safe platelet counts in over 80% of cases compared with placebo.[11] Platelet counts are maintained above 50 x 10^9/L for six months continuously in at least 50% of patients taking this drug. Eltrombopag also mimics thrombopoietin but is not yet approved

for use in Australia. Both these drugs are generally well tolerated; however, ongoing surveillance for bone marrow fibrosis, a concern raised in the initial studies, will become more important as younger patients remain on these drugs indefinitely. The use of these drugs is now being studied in other low platelet scenarios such as myelodysplasia and chemotherapy-induced thrombocytopenia.

Other second-line medications that can be used for ITP include azathioprine, mycophenolate mofetil, cyclosporin A, cyclophosphamide, danazol and dapsone (all off-label use for ITP except azathioprine). Each drug exhibits a unique response rate and side effect profile. In general, efficacy of these drugs is inferior to splenectomy.

HOW DO WE MANAGE ITP IN DIFFICULT CASES?

Thrombocytopenia in pregnancy

Gestational thrombocytopenia may affect up to one in 10 of pregnancies, whereas ITP affects one in every 1000 pregnancies. There are many other causes for thrombocytopenia during pregnancy, including pre-eclampsia, haemolysis–elevated liver enzymes–low platelets syndrome (HELLP), thrombotic thrombocytopenic purpura, (TTP), disseminated intravascular coagulation (DIC), drug use, infections and bone marrow infiltration.

Diagnosis and management may require referral of the patient to a specialist haematology/obstetric service. Gestational thrombocytopenia is typically mild and most significant in the third trimester. In general, however, ITP may cause thrombocytopenia in any trimester and will be more severe than gestational thrombocytopenia. The presence of haemolysis, renal impairment, abnormal liver function tests or hypertension should prompt urgent investigation for other causes of thrombocytopenia, such as pre-eclampsia, HELLP, TTP and DIC.

Often the mother will not require therapy during pregnancy but if her platelet count is less than 20 to 30 x 10^9/L, corticosteroid therapy is usually effective and safe (except for an elevated risk of gestational diabetes).

Safe delivery in ITP

Fewer than 5% of babies whose mothers have ITP will have platelet counts less than 20 x 10^9/L at birth and require treatment, despite the fact that platelet autoantibodies can cross the placenta. However, the neonate's platelet count should be determined and monitored.

Maternal ITP is not an indication for caesarean section unless there is a history of the mother having a prior child with severe ITP. It is generally accepted that a platelet count greater than 50 x 10^9/L is safe for normal vaginal delivery, and a platelet count greater than 80 x 10^9/L is safe for caesarean section with epidural anaesthesia. Some mothers whose platelet counts are lower than these safe levels may be successfully treated with corticosteroids and IVIG. Ultimately, some patients will require a planned induction of labour.

ITP and surgery

Although there are no randomised controlled trials to support the practice, it is commonly accepted that a platelet count greater than 50 x 10^9/L is safe for most moderately invasive operations. This practice assumes that the patient has not taken medications that can impair platelet function (such as aspirin, clopidogrel and NSAIDs) and that there is no underlying platelet dysfunction (whether intrinsic by myelodysplasia or extrinsic by renal impairment). It is prudent to perform platelet function testing and coagulation screening if in doubt. Procedures that are likely to be uncomplicated at a platelet count greater than 50 x 10^9/L include laparoscopy, dental extractions, skin biopsies and inguinal hernia repairs.

More invasive surgery such as neurosurgical procedures or thoracotomy will require greater platelet counts. Platelet counts greater than 100 x 10^9/L would be desirable, but objective evidence is lacking. Preoperative therapy with corticosteroids and IVIG could be used to improve the platelet count in preparation for surgery. Platelet transfusions may be necessary to transiently improve the platelet count prior to high-risk procedures.

CONCLUSION

The treatment options in ITP continue to grow. However, most patients currently identified with ITP can be managed with either careful monitoring alone or with traditional first- and second-line therapies with proven efficacy. There remains a significant minority of patients with chronic ITP who are most likely to benefit from recent therapeutic advances in ITP. MT

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A list of references is available on request to the editorial office.

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