Acute thrombocytopenia: picking a way through a paucity of platelets

ABSTRACT

Thrombocytopenia is defined as a platelet count under 150x10^9/litre. It may be found as a bystander to other pathology or directly related to an underlying haematological condition. Apart from laboratory artefact, it should be treated seriously as it often reflects serious underlying disease. This review uses short case histories to illustrate how to approach thrombocytopenia during the initial presentation of an adult patient to hospital. This article guides the general hospital physician through the narrow but potentially confusing differential diagnoses related to thrombocytopenia, with particular focus on immune thrombocytopenia, disseminated intravascular coagulation and thrombotic thrombocytopenic purpura. Thrombocytopenia in pregnancy deserves special consideration and will not be discussed in this article.

The principal function of platelets is to form an initial plug at the site of vascular injury – primary haemostasis (Yun et al, 2016). Platelets are derived from the fragmentation of megakaryocytes in the bone marrow under the influence of the hormone thrombopoeitin, which is produced primarily by the liver (Kaushansky, 2005).

The platelet count is determined by the balance of production in the bone marrow, distribution in the body (approximately one third of platelets at any one time are pooled in the spleen) and destruction. In health, normal platelet destruction occurs by apoptosis of senescent platelets, which are subsequently cleared by the liver and spleen. The normal 9–10-day lifespan of platelets may be shortened by pathological processes such as consumption within a thrombus or immune-mediated clearance.

The differential diagnosis of thrombocytopenia is therefore broad, but there are some potentially life-threatening causes which are important for the general physician to recognize. This review provides a structure for approaching the initial clinical assessment and investigation of acute thrombocytopenia using case-based clinical scenarios, and summarizes guidance on platelet transfusions.

Clinical approach to thrombocytopenia

When faced with thrombocytopenia, the first step for a clinician is to exclude an artefactual result by requesting examination of a blood film. Automated platelet counts may produce inaccurate results because of abnormally large or small platelets, or as a result of platelet aggregation or 'clumping'. Platelet clumping is an in-vitro phenomenon also known as EDTA (ethylenediaminetetraacetic acid)-dependent pseudo-thrombocytopenia, with an estimated prevalence of 0.1–2% in hospitalized patients (Fang et al, 2015). Any new finding of thrombocytopenia should have EDTA-dependent pseudo-thrombocytopenia excluded by blood film microscopy. In platelet 'clumpers', the actual platelet count can be quantified by analysis of the full blood count in a citrate sample.

Once a significant artefact has been excluded, the pathophysiology of thrombocytopenia can broadly be categorised into failure of production or shortened survival (*Table 1*), although dilutional thrombocytopenia, e.g. gestational and following massive transfusion, is an alternative but easily recognized explanation for thrombocytopenia.

The presence and pattern of any bleeding should be assessed thoroughly. This should be questioned specifically, including enquiring about symptoms of skin or mucosal bleeding especially from the gastrointestinal or genitourinary tracts. Patients with bleeding secondary to thrombocytopenia typically present with mucocutaneous bleeding (e.g. on brushing teeth) and petechial haemorrhages. This contrasts with haemorrhage into joints or extensive soft tissue bleeding which is more suggestive of a coagulopathy related to impairment of coagulation factors.

There are specific laboratory investigations for patients in acute thrombocytopenia that are essential to inform the diagnosis in addition to routine blood tests. All patients should have a full blood count, blood film microscopy and a full coagulation profile (including fibrinogen). Acutely, the important role of blood film microscopy is to identify life-threatening conditions associated with thrombocytopenia, mainly acute leukaemia (evidenced by circulating blasts) or a thrombotic microangiopathy (e.g. disseminated intravascular coagulation, evidenced by red cell fragments).

Table 2 lists some important distinguishing features in the laboratory assessment of thrombocytopenia to differentiate the three conditions at the centre of this review – immune thrombocytopenia, disseminated intravascular coagulation and thrombotic thrombocytopenic purpura.

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Clinical cases

The following vignettes have been compiled to highlight the key points to appreciate in the presentation of thrombocytopenia to an acute medical take.

Case 1

A 40-year-old woman is referred to ambulatory care by her GP with a 1-week history of bruising, a petechial rash and bleeding gums on brushing her teeth. She has a past medical history of hypothyroidism. She takes only levothyroxine 75 micrograms once daily, with no recent changes to her medications.

On examination she is well, and her clinical observations are normal. Clinical examination reveals bruising as described and, importantly, no palpable lymphadenopathy or organomegaly. Her blood results are shown in *Table 3*.

Table 1. Causes of thrombocytopenia

Failure of production	Marrow failure and suppression	Aplastic anaemia
		Cytotoxic drugs (e.g. co-trimoxazole, ethanol)
		Radiotherapy
		Viral infection, e.g. HIV
	Marrow infiltration	Primary haematological malignancy
		Metastatic carcinoma
	Megaloblastic anaemia – nutritional deficiency	
	Chronic liver disease	
Shortened survival	Increased consumption	Disseminated intravascular coagulation
		Thrombotic microangiopathies, e.g. thrombotic thrombocytopenic purpura, haemolytic uraemic syndrome
		Heparin-induced thrombocytopenia
	Increased destruction	Primary immune thrombocytopenia
		Secondary immune thrombocytopenia, e.g. as a result of autoimmune states (systemic lupus erythematosus, chronic lymphocytic leukaemia, lymphoma), drug-induced (gold, penicillins, digoxin, vancomycin), infection (HIV, hepatitis C, *Helicobacter pylori*, malaria)

Table 2. Comparison of laboratory and clinical features of immune thrombocytopenia, disseminated intravascular coagulation and thrombotic thrombocytopenic purpura

	Immune thrombocytopenia	Disseminated intravascular coagulation	Thrombotic thrombocytopenic purpura
Clinical condition	Stable in absence of bleeding	Unstable	Stable but at risk of sudden deterioration
International normalized ratio	Normal	Increased	Near normal
Activated partial thromboplastin time	Normal	Increased	Near normal
Fibrinogen	Normal	Decreased	Normal
D dimer	Normal	Increased	Slightly increased
Red cell appearances on blood film	Normal	Fragments	Fragments

Diagnosis

Immune thrombocytopenia.

Discussion

Immune thrombocytopenia is an immune-mediated acquired thrombocytopenia (defined by platelets <100x10^9/litre). It can be primary (80% of cases) or secondary (Lambert and Gernsheimer, 2017). Primary immune thrombocytopenia has an incidence of 3.3/100 000 adults per year and results from pathogenic antiplatelet antibodies (Shulman et al, 1965), impaired megakaryocytopoiesis (Khodadi et al, 2016) and T-cell-mediated platelet destruction (Olsson et al, 2003). Secondary immune thrombocytopenia is associated with other autoimmune conditions (e.g. systemic lupus erythematosus and rheumatoid arthritis) and infections, especially HIV, hepatitis C and *Helicobacter pylori*. Clinical features, risk factors and laboratory tests for these are essential in all patients presenting with suspected immune thrombocytopenia (Cines et al, 2009; Lambert and Gernsheimer, 2017).

Drug-induced immune thrombocytopenia is caused by antibody-mediated platelet destruction, which may be a direct drug action or a result of various forms of drug-dependent antibody formation (Aster and Bougie, 2007). It typically occurs within 2–3 days (occasionally within hours) of taking a drug that has been administered previously, or 1–3 weeks after starting a new drug (Stasi, 2012). An

Table 3. Clinical case 1 – admission blood test results

Parameter (units)	Value (normal range)
Haemoglobin (g/litre)	125 (115–165)
White blood cell count (x10^9/litre)	6.3 (4–11)
Platelets (x10^9/litre)	9 (150–450)
Urea and electrolytes	Normal
Liver function tests	Normal
C-reactive protein (mg/litre)	1 (0–5)
Prothrombin time (s)	11.5 (10–13)
Activated partial thromboplastin time (s)	26 (23–30)
Blood film comment	Platelet count confirmed, normal appearances of other cell lines

accurate drug history (including recently discontinued drugs and previous episodes of thrombocytopenia) is therefore essential. In patients who have been previously sensitised, drug-induced immune thrombocytopenia can present with an acute inflammatory reaction and fever. Diagnosis is often clinical and one of exclusion. Treatment involves cessation of the offending drug and supportive measures and thrombocytopenia usually resolves after 4–8 days.

Immune thrombocytopenia in adults is heterogenous and may be diagnosed following an incidental finding of thrombocytopenia on the full blood count, or it may present with bleeding, most commonly mucocutaneous and menorrhagia. Despite low platelet counts, major bleeding is uncommon if the platelet count is above $30x10^9$/litre (Provan and Newland, 2015). Immune thrombocytopenia may be complicated by coincident autoimmune haemolytic anaemia (Evans' syndrome), so a direct antiglobulin test is recommended should anaemia develop.

Management is led by haematologists and first-line acute management usually consists of oral steroids (e.g. prednisolone 1 mg/kg/day), possibly with intravenous immunoglobulin in addition in severe cases with significant bleeding (Cooper, 2017). Platelet transfusions have not been proven to improve mortality rates in immune thrombocytopenia and should be reserved for cases of severe, life-threatening haemorrhage (Goel et al, 2019).

Case 2

An 85-year-old man with a past medical history of chronic obstructive pulmonary disease, hypertension and stage 3 chronic kidney disease presents to the acute medical take with a productive cough, shortness of breath and fever. On admission he is confused, tachycardic and hypotensive. His admission blood tests show raised levels of inflammatory markers, a mild thrombocytosis and normal coagulation profile.

A chest radiograph shows right lower lobe consolidation. He is diagnosed with sepsis secondary to severe community-acquired pneumonia and treated with intravenous fluids and antibiotics. Unfortunately, despite prompt intervention he remains unwell and hypotensive. He is deemed not appropriate for admission to the intensive care unit. Two days after admission the nurses notice that he is bleeding from his two cannulae sites. Repeat blood tests taken are shown in *Table 4*.

He is prescribed low molecular weight heparin as thromboprophylaxis, but no other anticoagulants.

Diagnosis

Disseminated intravascular coagulation in the context of sepsis secondary to pneumonia.

Discussion

Disseminated intravascular coagulation is a syndrome that arises secondary to another physiological insult, e.g. sepsis, trauma or malignancy (Gando et al, 2016). It is characterized by systemic intravascular activation of the coagulation cascade and inhibition of fibrinolysis (by definition not restricted to a specific site of endothelial injury). It is driven by the release of inflammatory cytokines, which in turn leads to microvascular thrombosis and organ dysfunction. This process results in consumption of platelets (producing thrombocytopenia) and coagulation factors, putting patients with disseminated intravascular coagulation at risk of bleeding. Clinical manifestations of disseminated intravascular coagulation are varied and can include haemorrhage (e.g. from wounds and cannula sites), thrombosis and/or organ dysfunction (Wada et al, 2014).

Although the laboratory findings listed in *Table 2* are a useful guide for the general physician, there is no single confirmatory laboratory test for the presence of disseminated intravascular coagulation. Disseminated intravascular coagulation is a dynamic process and laboratory tests, although useful, provide only a snapshot of the clinical picture at one point in time.

The presence of thrombocytopenia is sensitive (but not specific) to disseminated intravascular coagulation and is a feature in up to 98% of cases of disseminated intravascular coagulation (Levi et al, 2009). The prothrombin time or activated partial thromboplastin time is only prolonged in approximately half of cases of disseminated intravascular coagulation at some point during the course of illness (Bick, 1996) and so a normal laboratory coagulation profile does not exclude this diagnosis. Monitoring of fibrinogen levels is often advocated, although as fibrinogen is an acute phase reactant levels can be normal in disseminated intravascular coagulation (Spero et al, 1980). Red blood cell fragments on the blood film are reported in cases of disseminated intravascular coagulation but this feature is also not specific.

Given these complexities, scoring systems (e.g. the International Society on Thrombosis and Haemostasis scoring system for overt disseminated intravascular coagulation, summarized in *Table 5*) have been developed and should be used to aid in the diagnosis, monitoring and assessment of prognosis of patients with disseminated intravascular coagulation (Toh and Hoots, 2007). Perhaps

Table 4. Clinical case 2, bloods on day 3 of admission

Parameter (units)	Value (normal range)
Haemoglobin (g/litre)	110 (130–180)
White blood cell count ($x10^9$/litre)	25 (4–11)
Neutrophils ($x10^9$/litre)	20 (2–7.5)
Platelets ($x10^9$/litre)	35 (150–450)
C-reactive protein (mg/litre)	320 (0–5)
Prothrombin time (s)	18 (10–13)
Activated partial thromboplastin time (s)	55 (23–30)
D dimer (ng/ml)	3000 (<500)
Fibrinogen (g/litre)	0.5 (1.5–4.5)

Table 5. International Society on Thrombosis and Haemostasis scoring system for the diagnosis of overt disseminated intravascular coagulation, applicable when patients have disorders associated with disseminated intravascular coagulation

Parameter		Score
Platelet count (x10^9/litre)	>100	0
	50–100	1
	<50	2
Elevated fibrin-related marker, e.g. D-dimer	No increase	0
	Moderate increase	2
	Strong increase	3
Prothrombin time prolongation (s)	<3	0
Fibrinogen level (g/litre)	>1	0
	≤ 1	1
Score interpretation		
Total score ≥ 5	Compatible with overt disseminated intravascular coagulation, advised to repeat score daily	
Total score < 5	Suggestive (not affirmative) for non-overt disseminated intravascular coagulation, advised to repeat in the next 1–2 days	

From Toh and Hoots (2007)

Table 6. Clinical case 3 – initial laboratory investigations

Parameter (units)	Value (normal range)
Haemoglobin (g/litre)	110 (130–180)
White blood cell count (x10^9/litre)	8 (4–11)
Neutrophils (x10^9/litre)	3.2 (2–7.5)
Platelets (x10^9/litre)	3 (150–450)
Sodium (mmol/litre)	145 (133–146)
Potassium (mmol/litre)	4.5 (3.5–5.3)
Urea (mmol/litre)	20 (2.5–7.8)
Creatinine (µmol/litre)	125 (59–104)
C-reactive protein (mg/litre)	42 (0–5)
Prothrombin time (s)	12 (10–13)
Activated partial thromboplastin time (s)	28 (23–30)
Fibrinogen (g/litre)	2.8 (1.5–4.5)

the most important point is to remember that disseminated intravascular coagulation is a disorder that develops over time and repeated testing of prothrombin time, activated partial thromboplastin time and fibrinogen during a clinical episode is appropriate to monitor the progress of the condition.

The presence of disseminated intravascular coagulation has been shown to be an independent predictor of mortality among critically ill patients (Bakhtiari et al, 2004) and the cornerstone of treatment is management of the underlying predisposing condition.

Case 3

A 62-year-old man presented to hospital with intermittent confusion following an unwitnessed collapse at home overnight in the bathroom, 48 hours before admission. His past medical history was unremarkable apart from gastro-oesophageal reflux disease, for which he took a proton-pump inhibitor. He had never smoked and had not drunk alcohol recently. His family were well and he had not travelled abroad recently. Bedside observations were normal apart from a mild pyrexia of 37.8°C. Physical examination was unremarkable apart from confusion – he was unable to follow three-stage commands and had poor short-term memory. Initial laboratory investigations are shown in *Table 6*.

As the patient had been in such good health before this admission, there were no previous results with which to compare current values. In view of the confusion, a computed tomography head scan was performed, and no intracranial haemorrhage was found. The haematology team was contacted to advise on how to account for the thrombocytopenia.

A blood film prepared urgently revealed fragmented red blood cells which, in combination with altered mental status, deranged renal function and thrombocytopenia, and normal prothrombin time and activated partial thromboplastin time, led to a presumptive diagnosis of thrombotic thrombocytopenic purpura.

Urgent transfer was arranged to a hospital with facilities for plasma exchange (therapeutic apheresis). After arrival at the centre blood tests revealed an absence of ADAMTS13 associated with an inhibitor, allowing the diagnosis to be confirmed.

Diagnosis

Thrombotic thrombocytopenic purpura – immune-mediated

Discussion

Thrombotic thrombocytopenic purpura is a rare condition with an incidence of five cases per million and a 2:1 female:male incidence ratio. The condition may be congenital or acquired, with the latter representing the majority of cases found in adults. Acquired thrombotic thrombocytopenic purpura may be immune-mediated and associated with pregnancy, HIV or other autoimmune disease; or non-immune-mediated and secondary to malignancy or drugs (such as ciclosporin or mitomycin). The key pathological step is inactivation or clearance of the protease ADAMTS13, whose role is to cleave and inactivate circulating von Willebrand factor. This loss of inhibition of von Willebrand factor, especially very large multimers, leads to uncontrolled platelet activation causing

microvascular thrombosis through which circulating red cells are fragmented – microangiopathic haemolysis – a pathological hallmark of the condition.

Diagnosis is confirmed by a low concentration of ADAMTS13. An associated inhibitor confirms an immune aetiology. Key features of the initial blood investigations are a very low platelet count, mild to moderate derangement of renal function and normal routine coagulation indices – a key differentiator from disseminated intravascular coagulation. If the renal function is disproportionately elevated, a diagnosis of haemolytic uraemic syndrome should be considered and discussed with renal physicians.

The rationale of acute management is two-fold. First, to replace the depleted levels of ADAMTS13 via the use of fresh frozen plasma. It is for this reason that baseline blood tests for ADAMTS13 must be drawn and saved before initial therapy. Second, the removal of a pathological autoantibody acutely by plasma exchange in which the plasma of the patient is replaced by pooled donor plasma at least daily until thrombocytopenia resolves. More durable immunosuppression is achieved through the use of very high-dose steroids and rituximab. It is also important to treat the underlying cause (e.g. treatment of HIV infection or discontinuation of a drug).

Thrombotic thrombocytopenic purpura is a medical emergency and must be suspected in the context of thrombocytopenia with associated evidence of intravascular haemolysis. Untreated, mortality approaches 90%, falling to 10% with prompt plasma exchange, so prompt diagnosis is crucial to improve survival, especially as patients often appear clinically stable until a catastrophic thrombotic episode occurs. Case 3 highlights a seemingly innocuous presentation of a patient unless the responsible physician considers and pursues a diagnosis. The diagnosis requires a high clinical index of suspicion and ultimately the involvement of specialized clinicians. For the purposes of initial assessment and work up in the context of general medicine, appropriate first-line investigations should include a full blood count, blood film microscopy (for red cell fragments), coagulation profile (often normal), urea and electrolytes, and routine work up for intravascular haemolysis (reticulocytes, haptoglobin, lactate dehydrogenase, unconjugated hyperbilirubinaemia) (Scully et al, 2012).

Thrombotic microangiopathies are a rare group of conditions which can be associated with thrombocytopenia in the context of acute illness, and include thrombotic thrombocytopenic purpura, haemolytic uraemic syndrome and drug-induced thrombotic microangiopathy. The clinical syndromes are diverse but are characterized by abnormalities in the microvascular blood vessel walls resulting in microvascular thrombosis and producing microangiopathic haemolytic anaemia (with red cell fragments on blood film microscopy), thrombocytopenia (as a result of platelet consumption), and end-organ damage (Kottke-Marchant, 2017). The combination of thrombocytopenia and the presence of red cell fragments (schistocytes) on a blood film examination should prompt consideration of thrombotic thrombocytopenic purpura (i.e. discussion with tertiary centre about ADAMTS13 testing and/or plasma exchange) until excluded. Clinical presentation depends on the underlying thrombotic microangiopathy syndrome. Haemolytic uraemic syndrome is often described following a diarrhoeal illness caused by Shiga toxin-producing strains of *Escherichia coli* and renal impairment is a prominent feature.

When to consider a platelet transfusion

Clinically significant spontaneous bleeding does not usually occur until the platelet count is <20x10^9/litre. Conversely platelet counts >20x10^9/litre are by no means necessarily a guarantee against haemorrhage. Prophylactic platelet transfusions are generally only indicated when the count is <10x10^9/litre.

The first clinical question on encountering a true low platelet count is whether the patient is bleeding. The second question is to consider the aetiology of the thrombocytopenia as consumptive processes, such as found in thrombotic thrombocytopenic purpura or heparin-induced thrombocytopenia, may be worsened by platelet transfusion that fuels the underlying pathology. Third, if a platelet transfusion is considered, whatever else can be done to diminish the risk or consequences of haemorrhage should be considered including discontinuation of drugs that inhibit platelet function, the use of desmopressin or tranexamic acid, or considering less hazardous alternative procedures.

Platelet transfusions are performed infrequently as part of general medical practice and advice should be sought from a haematologist. The thresholds at which platelet transfusion should be considered are clearly described in guidance from the British Society for Haematology - Guidelines for the use of Platelet Transfusions 2016 (Estcourt et al, 2017). This guidance, summarized in *Table 7*, classifies patients based on platelet count, the presence, site and clinical significance

Table 7. British Society for Haematology guidance on platelet transfusion

Offer transfusions in the context of bleeding:	Clinically significant bleeding – platelet count <30 x 10^9/litre
	Patients with severe bleeding - or bleeding in critical sites (such as the CNS) with a platelet count < 100x10^9/litre
Offer prophylactic platelet transfusions (i.e. patient not bleeding):	Patients with a platelet count below 10x10^9/litre who are not bleeding or having invasive procedures or surgery – unless part of a chronic, stable condition
	Patients with a platelet count below 50x10^9/litre who are having invasive procedures or surgery
	Consider a higher threshold (for example 100 x10^9/litre) for patients with a high procedural risk of bleeding – e.g. neurosurgery
	Consider prophylactic platelet transfusions to raise the platelet count above 100x10^9/litre in patients having surgery in critical sites, such as the CNS

From Estcourt et al (2017)

KEY POINTS

- Thrombocytopenia may be the first objective evidence of a medical emergency that requires immediate treatment.
- Essential baseline investigations include a full blood count, blood film and a coagulation profile (including a fibrinogen assay).
- Thrombocytopenia is not necessarily associated with increased bleeding.
- The need for platelet transfusion should be discussed with a haematologist.

of any bleeding (based on the World Health Organization classification system – a five grade scale originally developed to assess bleeding in patients undergoing treatment for cancer (Miller et al, 1981; Fogarty et al, 2012)) and the nature of any procedures planned.

It is recommended to prescribe one dose of platelets at a time unless there is severe thrombocytopenia accompanied by profuse haemorrhage or at a critical site such as intracranially. The platelet count is only one component in the assessment of risk of haemorrhage by a patient. Attention should not be diverted from other contributory factors such as concomitant anticoagulant or antiplatelet agents or the use of ultrasound guidance for invasive procedures, in the narrow pursuit of a platelet threshold.

Conclusions

Thrombocytopenia is common and the causes are varied. Categorising the potential aetiologies in terms of reduced production, abnormal distribution and increased destruction or consumption provides a helpful framework in which to approach thrombocytopenia. The three main considerations upon encountering a patient with thrombocytopenia are checking for artefact, assessment for signs of bleeding, and performing a thorough history and physical examination. Laboratory investigations are important and there are a few specific but readily available laboratory investigations that are essential for informing the differential diagnosis, and for monitoring of these often dynamic disease states. **BJHM**

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