Purpura

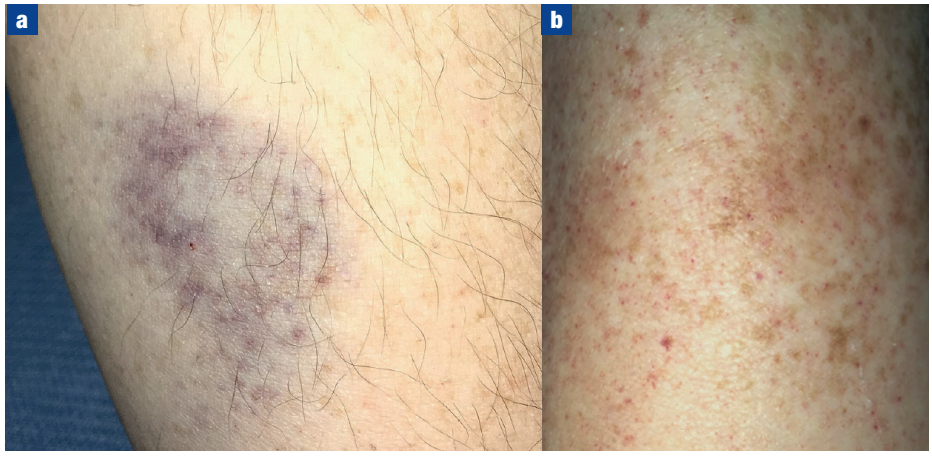

Figure 1. a. Ecchymosis at a venepuncture site in a thrombocytopenic patient. **b.** Petechial rash over the ankle in a thrombocytopenic patient.

Purpura are red-brown lesions caused by localized haemorrhage into the skin. They can be divided by size into petechiae (1–2 mm in diameter) and ecchymoses (>1 cm) (*Figure 1*). There are multiple potential causes, and this article provides a systematic approach to investigating the underlying cause by combining the distribution and features of the rash with additional clinical signs.

Purpura can usually be attributed to a problem with either platelets or blood vessels. Platelet disorders may be quantitative, i.e. thrombocytopenia, or qualitative as the result of an acquired or inherited defect in platelet function. Vascular causes of purpura may be the result of inflammation, vascular fragility, or microvascular occlusion leading to local ischaemia. While disorders of coagulation also cause excessive bleeding and can cause bruising of the skin, the tendency is more towards bleeding into joints and muscles, or excessive bleeding following injury, rather than purpura.

An acute purpuric rash in an unwell patient may indicate a life-threatening diagnosis such as meningococcal septicaemia, clearly necessitating prompt investigation and management, but it may also be an incidental finding in a patient who is not acutely unwell, or the first presentation of a significant multisystem disease. The history may point to an obvious diagnosis, and a careful drug history is particularly important, as many medications can cause purpura through a variety of different mechanisms (*Table 1*).

As well as a general examination, signs associated with the following diagnostic groups should be considered, and their presence commented on in an exam situation:

- Haematological disease (splenomegaly, lymphadenopathy, mouth ulcers (neutropenia), conjunctival pallor)
- Autoimmune rheumatic disease such as rheumatoid arthritis (joint deformities, active arthritis, rheumatoid nodules), systemic lupus erythematosus (malar rash), vasculitis (splinter haemorrhages, ulceration), or Raynaud's syndrome
- Ehlers–Danlos syndrome (hypermobility, skin fragility)
- Liver disease (hepatomegaly, spider naevi, jaundice, ascites)
- End-stage renal failure (fistula, peritoneal dialysis catheter)
- Scurvy (bleeding gums, corkscrew hair).

Dr SC Charrot, Clinical Research Fellow, Centre for Haemato-oncology, Barts Cancer Institute, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, London EC1M 6BQ

Dr RS Sellar, Haematology Specialist Registrar, Department of Haematology, University College Hospital, London

Dr JJ Manson, Consultant Rheumatologist, Department of Rheumatology, University College Hospital, London

Correspondence to: Dr SC Charrot (s.charrot@nhs.net)

Table 1. Drug causes of purpura (not an exhaustive list)

Drug	Mechanism
Allopurinol	Vasculitis (ANCA +)
Aspirin	Disrupts platelet function
Barbiturates	Thrombocytopenia
Clopidogrel	Disrupts platelet function
Gold	Thrombocytopenia, vasculitis
Heparin	Anticoagulant effect, thrombocytopenia
Hydralazine	Vasculitis (ANCA +), drug-induced systemic lupus erythematosus
Non-steroidal anti-inflammatory drugs	Disrupts platelet function, vasculitis
Penicillins	Thrombocytopenia, vasculitis
Phenylbutazone	Vasculitis
Phenytoin	Thrombocytopenia, vasculitis (ANCA +)
Propylthiouracil	Vasculitis (ANCA +)
Quinine	Thrombocytopenia
Steroids	Vascular fragility
Sulphonamides	Thrombocytopenia, vasculitis
Sulphonylureas	Thrombocytopenia
Tetracyclines	Thrombocytopenia, vasculitis
Thiazide diuretics	Thrombocytopenia, vasculitis (ANCA +)
Warfarin	Anticoagulant effect

ANCA = anti-neutrophil cytoplasmic antibody. From Doyle and Cuellar (2003), Colman et al (2006), Valeyrie-Allanore et al (2007), Ramdial and Naidoo (2009)

Table 2. Causes of thrombocytopenia

Increased destruction or consumption	Autoimmune	Immune thrombocytopenic purpura	Presents with purpura, epistaxis, menorrhagia. May be acute (usually in children following an infection), or chronic. Antiplatelet autoantibodies may be present. Bone marrow biopsy (usually unnecessary) may show increased numbers of megakaryocytes. Treatment is with steroids, immunosuppression, intravenous immunoglobulin, and splenectomy in refractory cases. Acute self-limiting cases with mild or moderate thrombocytopenia may not require treatment
		Heparin-induced thrombocytopenia	Presents with venous and arterial thrombosis, and limb ischaemia. Erythematous plaques and skin necrosis more common than purpura, which is not usually present. Usually occurs 5–14 days after starting heparin with mild or moderate thrombocytopenia. Heparin-induced thrombocytopenia antibodies may be detected in serum. Treatment is to stop heparin and start alternative anticoagulation
		Secondary immune thrombocytopenia	Autoimmune-mediated thrombocytopenia can also be seen secondary to a number of other conditions, e.g. systemic lupus erythematosus, chronic lymphocytic leukaemia, APLS, viruses, drugs
	Alloimmune	Neonatal alloimmune thrombocytopenia	Varying degrees of thrombocytopenia, may be mild, or may have haemorrhage at or soon after birth. Maternal antiplatelet antibodies may be present. Resolves after delivery, platelet support if necessary
		Post-transfusion purpura	Purpuric rash and bleeding can occur 2 days to 2 weeks following transfusion, usually in a previously immunized individual. Self-limiting, but can be fatal. Intravenous immunoglobulin or plasmapheresis if necessary. Human platelet antigen-1a negative platelets for future transfusions
	Platelet consumption	Thrombotic thrombocytopenic purpura	Classical pentad is of thrombocytopenia, haemolytic anaemia, fever, neurological disturbance and renal failure, but not all features are necessarily present. Blood film shows red cell fragments. Low ADAMTS13 activity, may have antibodies to ADAMTS13. Treatment in a specialist centre with plasma exchange and steroids
		Disseminated intravascular coagulation	Unwell patient with evidence of bleeding and thrombosis. Deranged clotting, low fibrinogen, raised D-dimer. Thrombocytopenia and haemolytic anaemia. Blood film shows red cell fragments. Treat the underlying condition. Supportive treatment with blood products if bleeding.
		Haemolytic uraemic syndrome	Typical – following a diarrhoeal illness, or atypical – recurrent, may be familial. Thrombocytopenia, haemolytic anaemia, acute renal failure. Blood film shows red cell fragments. Treatment is supportive
Reduced production – marrow failure	Infiltration from solid tumour	May be in a patient with known malignancy or as first presentation. Pancytopenia, bone marrow biopsy shows infiltration. Imaging or histology may indicate the primary tumour. Treatment of underlying malignancy. Supportive treatment with blood products may be required while awaiting marrow recovery	
	Haematological malignancy	Fever, lymphadenopathy, splenomegaly, signs of anaemia, fatigue, weight loss. Full blood count shows pancytopenia, bone marrow biopsy shows infiltration. Treatment of underlying malignancy. Supportive treatment with blood products may be required while awaiting marrow recovery	
	Megaloblastic anaemia	Symptoms of anaemia. May also have neurological symptoms of vitamin B_{12} deficiency. Macrocytic anaemia, thrombocytopenia, hypersegmented neutrophils on blood film. Low serum vitamin B_{12} or folate levels. Treatment is with replacement of the vitamin deficiency	
	Myelodysplasia	Progressive bone marrow failure with deficiencies in myeloid cell lines leading to pancytopenia. Supportive care, chemotherapy and bone marrow transplant are options depending on patient status and percentage of blasts in bone marrow	
	Myelofibrosis	Presents with fever, weight loss, massive splenomegaly and bone marrow failure. May follow other myeloproliferative disorders. Pancytopenia or raised white count, blood film is leukoerythroblastic with tear drop cells, bone marrow trephine shows fibrosis. Treatment is largely supportive with blood products. Bone marrow transplant is an option	
	Aplastic anaemia	Pancytopenia, bone marrow is hypoplastic. Supportive treatment with blood products, immunosuppression and bone marrow transplant	
	Marrow suppression*	Often a predictable side effect in patients undergoing treatment for malignancy. Supportive treatment until the bone marrow has recovered	
Sequestration	Hypersplenism	Caused by splenomegaly of any cause, leading to pancytopenia with haemolysis. Treatment is of the underlying disease	
Dilutional	Massive transfusion	Suspect in a patient who has been transfused a large volume of blood within 24 hours, clotting may be deranged in addition to thrombocytopenia. Treatment is supportive with platelet and fresh frozen plasma transfusions	

*ADAMTS13 = a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; APLS = antiphospholipid syndrome. From Colman et al (2006). * from cytotoxic drugs or radiotherapy.*

Assessing the purpuric rash

Spend some time assessing the rash itself, as the likely aetiology can sometimes be inferred from its distribution and the size, number and morphology of lesions.

Distribution

Most causes of purpura lead to a rash in dependent areas – commonly on the legs, or over the backs of the thighs and buttocks in bed-bound patients (Gonzalez-Gay et al, 2004; Carlson, 2010). This is particularly typical of platelet disorders or immune complex-mediated vasculitis. Non-immune complex-mediated vasculitis typically leads to fewer purpuric lesions in a random distribution. A widespread rash may be drug related or caused by viral infection (Goldsmith et al, 2012).

Petechiae may be seen in areas of high intravascular pressure – for example transient spikes in pressure caused by coughing, vomiting, or the application of tourniquets or blood pressure cuffs (Kaushausky et al, 2010). Ecchymoses are often found in trauma-prone areas such as the shins, lateral thighs and on the extensor surfaces of the arms, and may be further confined to those areas which are also sun-exposed (Goldsmith et al, 2012).

Some features are particularly characteristic, for example peri-orbital purpura in amyloidosis, or peri-follicular haemorrhage in scurvy (Isenberg et al, 2004; Colman et al, 2006). Purpura confined to the peripheries can suggest a cold-occlusion phenomena, but is not specific to this cause (Goldsmith et al, 2012).

Morphology

Lesion size, shape, palpability and the presence of surrounding erythema are important characteristics in assessing the likely aetiology of a purpuric rash. Petechiae often reflect a platelet disorder, while ecchymoses are often trauma related in a pro-coagulant state, or any other underlying predisposition towards purpura. A retiform rash can indicate an occlusive vascular phenomenon, particularly if there is no surrounding erythema (Goldsmith et al, 2012). Palpability is caused by localized oedema, and implies a vascular cause with an inflammatory or ischaemic aetiology – palpable purpura are not usually caused by thrombocytopenia (Kaushausky et al, 2010; Kawakami, 2010; Goldsmith et al, 2012).

Although a purpuric rash is by definition non-blanching (extravasated red blood cells cannot flow and therefore do not disappear on pressure), the lesions may have an element of surrounding erythema which does blanch. This suggests an inflammatory component, but this sign may be present only with early lesions, disappearing as the inflammation subsides (Goldsmith et al, 2012).

Platelet disorders

Purpura as the result of a platelet problem are usually non-palpable petechiae with no element of blanching. The rash is often dependent or distributed in areas of transient high pressure.

Thrombocytopenia

The presence of purpura in thrombocytopenia is largely determined by the platelet count, and it is less common at counts above $10x10^9$/litre (Goldsmith et al, 2012). Causes can be divided into problems with platelet production, excessive consumption or destruction, dilution and sequestration. The cause is also a factor in the severity of any purpuric rash – in conditions with excessive platelet destruction such as immune thrombocytopenic purpura, the circulating platelets are young and healthy, and the platelet count can drop very low before purpura occur, whereas in marrow failure the circulating platelets are older and less effective (Goldsmith et al, 2012).

A full blood count and blood film will identify thrombocytopenia and give further indications towards the cause, and a bone marrow biopsy may be necessary in some cases. Treatment of thrombocytopenia is directed towards the cause, and platelet transfusion is usually only necessary if there is bleeding. Common causes of thrombocytopenia are outlined in *Table 2*.

Inherited or acquired disorders of platelet function

Hereditary platelet function disorders are rare, and clues can be found in the family history, and a history of excessive bleeding from birth. Ecchymoses, mucosal bleeding and excessive bleeding following injury are characteristic (Colman et al, 2006). The platelet count is usually normal or raised. Platelet morphology can be assessed on a blood film, but often more specialist tests are necessary.

Acquired defects of platelet function are relatively common by comparison, and can be caused by common drugs, either with therapeutic intent, such as aspirin, or as a side effect, such as non-steroidal anti-inflammatory drugs. A list of platelet dysfunction disorders can be found in *Table 3*.

Vascular disorders

Vascular defects can be caused by inflammation (i.e. vasculitis), occlusion or a deficiency in vascular support.

Vasculitis

Vasculitis can have a number of cutaneous manifestations, including nodules, livedo

Table 3. Disorders of platelet dysfunction

Inherited disorders	Glanzmann's thrombasthenia – defective platelet aggregation caused by deficient glycoprotein IIb/IIIa (fibrinogen receptor)
	Bernard–Soulier syndrome – defective platelet adhesion caused by deficient glycoprotein 1b (von Willebrand factor receptor). Giant platelets visible on blood film
	von Willebrand disease – deficient or abnormal von Willebrand factor leading to defective platelet adhesion and rapid destruction of factor VIII:C
	Platelet storage pool diseases – e.g. gray platelet syndrome, Chédiak–Higashi syndrome, Hermansky–Pudlak syndrome
Acquired causes	Drug induced
	Liver failure – also causes thrombocytopenia and deranged coagulation
	Uraemia
	Myeloproliferative disorders – essential thrombocythaemia, polycythemia vera, chronic myelogenous leukaemia
	Acute leukaemias and myelodysplastic syndromes – although bleeding is more commonly caused by thrombocytopenia
	Paraproteinaemia

From Colman et al (2006)

reticularis, ulceration, vesicobullous lesions, splinter haemorrhages and purpura (Gonzalez-Gay et al, 2004; Carlson et al, 2006; Kawakami, 2010). Purpura are most commonly associated with small vessel disease affecting the superficial vessels of the dermis (Kawakami, 2010). Lesions are often palpable and may have prominent surrounding blanching erythema or preceding urticarial rash (Isenberg et al, 2004).

If vasculitis is suspected, assess carefully for associated signs and symptoms, such as fever, arthralgia, arthritis, Raynaud's disease, abnormal neurology, abdominal pain or gastrointestinal bleeding, pulmonary involvement with pulmonary haemorrhage, ear nose and throat disease, and signs of renal replacement therapy. Vasculitis can be primary, or secondary to an autoimmune rheumatic disease, so signs suggestive of rheumatoid arthritis or systemic lupus erythematosus should also be sought and commented upon. Types of vasculitis likely to cause purpura are outlined in *Table 4*, with more detail available online (https://doi.org/10.12968/hmed.2017.78.10.C147). Vasculitis is also the pathological finding in many infective causes of purpura, although purpura fulminans, the classical pattern associated with meningococcal septicaemia, is characterized by disseminated intravascular coagulation, vascular thrombosis and haemorrhagic necrosis (Colman et al, 2006; Carlson, 2010).

Skin biopsy, with samples sent for histology and immunofluorescence, is an essential test in the diagnosis of cutaneous vasculitis. It is important to biopsy an active lesion of recent onset, as the diagnostic yield is highest and most specific within the first 24–48 hours (Carlson, 2010). Histologically, vasculitis can be divided according to the size of vessel affected and the type of inflammatory cell infiltrate, and immunofluorescence will give further information on the presence and nature of immune complexes. Leukocytoclastic vasculitis is the usual histological finding in cases of small vessel vasculitis with a variety of causes, and the disease is only classified as cutaneous leukocytoclastic angiitis if no systemic involvement is found (Gonzalez-Gay et al, 2004; Carlson et al, 2006). Other important investigations to differentiate between the different types of small vessel vasculitis are the serum anti-nuclear antibody, anti-neutrophil cytoplasmic antibody and cryoglobulins.

Table 4. Types of cutaneous vasculitis commonly associated with purpura

Vasculitis	Typical presentation of the rash
Cutaneous leukocytoclastic angiitis	Palpable purpura. Skin involvement only
Hypersensitivity vasculitis*	Develops around 7–10 days following trigger with a widespread purpuric rash
IgA vasculitis (Henoch–Schönlein purpura)	Usually in childhood with palpable purpura symmetrically over the legs and buttocks. Skin involvement in almost all cases
Urticarial vasculitis	Urticarial rash initially which may leave residual purpuric lesions after 24–72 hours
Paraneoplastic vasculitis	Recurrent episodes of palpable purpura, may pre-date the diagnosis of malignancy
Granulomatosis with polyangiitis (previously Wegener's granulomatosis)	Palpable purpuric rash in a generalized distribution including the upper limbs. Also necrotic papules, subcutaneous nodules and ulcers. Skin involvement in 50%
Microscopic polyangiitis	Palpable purpuric rash in a generalized distribution including the upper limbs. Also splinter haemorrhages, palmar erythema
Eosinophilic granulomatosis with polyangiitis (previously Churg–Strauss syndrome)	Palpable purpuric rash in a generalized distribution including the upper limbs. Subcutaneous nodules
Cryoglobulinaemic vasculitis	Recurrent palpable purpura, Raynaud's syndrome
Vasculitis secondary to autoimmune rheumatic disease	Variable depending on the underlying disease. Palpable purpura on the lower limbs is typical
Septic vasculitis	Purpuric rash may be widespread
Polyarteritis nodosa	Tender nodules, livedo and ulceration. Purpura is relatively uncommon

**Some classification systems do not consider hypersensitivity vasculitis to be a separate entity to cutaneous leukocytoclastic angiitis. From Gonzalez-Gay et al (2004), Isenberg et al (2004), Carlson et al (2006), Valeyrie-Allanore et al (2007), Ramdial and Naidoo (2009), Carlson (2010), Kawakami (2010)*

Microvascular occlusion

Purpura caused by cutaneous microvascular occlusion are often palpable without blanching, and may be retiform with necrosis (Goldsmith et al, 2012). Vessels can be blocked by platelet plugs, septic, fat or cholesterol emboli, or cold agglutinins. Several causes of thrombocytopenia also cause microvascular occlusion as a result of the same process of microthrombi formation that leads to platelet consumption. These include disseminated intravascular coagulation, thrombotic thrombocytopenic purpura and heparin-induced thrombocytopenia. Antiphospholipid syndrome may cause thrombocytopenia, but rarely severe enough to cause purpura alone; however, necrotizing purpura can be seen in this condition as a result of cutaneous microthrombi (Colman et al, 2006).

Vascular fragility

This is often caused by loss of vascular supporting tissue as a result of age, sun damage or drugs. It typically causes non-palpable, non-blanching ecchymoses, often in the context of minor trauma (Goldsmith et al, 2012). Examples include scurvy, senile purpura, solar purpura, which is limited to sun-exposed areas, steroid-induced purpura, amyloidosis and Ehlers–Danlos syndrome (De Paepe and Malfait, 2004; Isenberg et al, 2004; Carlson, 2010).

Investigation

As there is an extensive differential for a purpuric rash, initial investigations are wide ranging, and include full blood count and blood film, coagulation profile, inflammatory markers, renal and liver profiles. Anti-nuclear antibody, anti-neutrophil cytoplasmic antibody, cryoglobulins, serum protein electrophoresis, D-dimer and fibrinogen may

also be necessary, and the need for further investigations such as skin biopsy or bone marrow biopsy will be guided by the results.

A flow diagram for the assessment and investigation of purpura is shown in *Figure 2*.

Conclusions

Purpura are a non-specific clinical sign with many potential causes. Clues to the aetiology can be gathered from the morphology and distribution of the rash, and associated clinical signs. **BJHM**

Conflict of interest: none.

KEY POINTS

- Purpura usually indicate a platelet or vascular disorder.
- Signs of systemic disease should be actively sought.
- Palpable purpura suggest a likely vascular cause, and partial blanching suggests inflammation.
- A thorough drug history is essential.
- Purpura in an unwell patient may be a sign of life-threatening disease.

Carlson JA (2010) The histological assessment of cutaneous vasculitis. *Histopathology* **56**(1): 3–23. https://doi.org/10.1111/j.1365-2559.2009.03443.x

Carlson JA, Cavaliere LF, Grant-Kels JM (2006) Cutaneous vasculitis: diagnosis and management. *Clin Dermatol* **24**: 414–429. https://doi.org/10.1016/j.clindermatol.2006.07.007

Colman RW, Morder VJ, Cloves AW, George JN, Goldhaber SZ, eds (2006) *Haemostasis and Thrombosis. Basic Principles and Clinical Practice.* 5th edn. Lippincott Williams and Wilkins, Philadelphia

De Paepe A, Malfait F (2004) Bleeding and bruising in patients with Ehlers–Danlos syndrome and other collagen vascular disorders *Br J Haematol* **127**(5): 491–500.

Doyle MK, Cuellar ML (2003) Drug-induced vasculitis. *Expert Opin Drug Saf* **2**(4): 401–409

Goldsmith LA, Katz SI, Gickrest BA, Paller A, Leffell DJ, Wolff K, eds (2012) *Fitzpatrick's Dermatology in General Medicine.* 8th edn. Vol 2. McGraw-Hill, New York

Gonzalez-Gay MA, Garcia-Porrua C, Pujol RM (2004) Clinical approach to cutaneous vasculitis. *Curr Opin Rheumatol* **17**: 56–61

Isenberg DA, Maddison PJ, Woo P, Klars D, Breedveld FC, eds (2004) *Oxford Textbook of Rheumatology.* 3rd edn. Oxford University Press, Oxford

Kaushausky K, Lichtman MA, Beutler E, Kipps TJ, Seligsohn U, Prchal J, eds (2010) *Williams Haematology.* 8th edn. McGraw-Hill Companies, New York

Kawakami T (2010) New Algorithm (KAWAKAMI algorithm) to diagnose primary cutaneous vasculitis. *J Dermatol* **37**: 113–124. https://doi.org/10.1111/j.1346-8138.2009.00761.x

Ramdial PK, Naidoo DK (2009) Drug-induced cutaneous pathology. *J Clin Pathol* **62**: 493–504. https://doi.org/10.1136/jcp.2008.058289

Valeyrie-Allanore L, Sassolas B, Roujeau J-C (2007) Drug-induced skin, nail and hair disorders. *Drug Saf* **30**(11): 1011–1030.

Figure 2. Flow diagram for assessing the aetiology of a non-traumatic purpuric rash. DAT = direct antiglobulin test; MAHA = microangiopathic haemolytic anaemia.

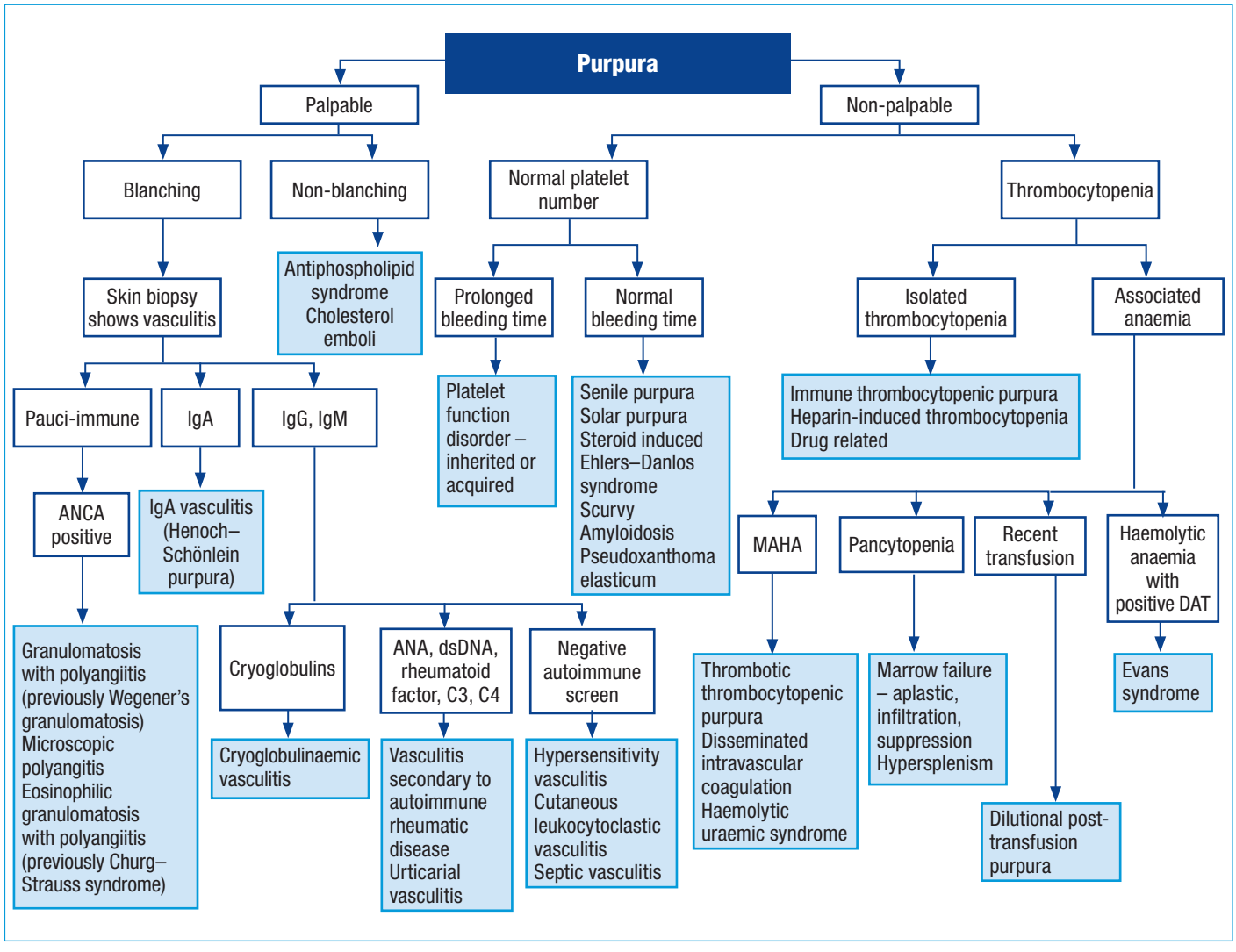

Table 4. Types of cutaneous vasculitis commonly associated with purpura (extended online version)

Vasculitis	Typical presentation of the rash	Size of vessel involved	Inflammatory cell infiltrate	Immune complexes	Blood tests	Systemic involvement	Aetiology or associations
Cutaneous leukocytoclastic angiitis	Palpable purpura. Skin involvement only	Small	Neutrophilic	IgM, IgG, C3		None	Idiopathic
Hypersensitivity vasculitis*	Develops around 7–10 days following trigger with a widespread purpuric rash	Small	Neutrophilic or lymphocytic Tissue eosinophilia	IgM, IgG, C3		Usually none, may have arthralgia	Reaction to a drug or infectious trigger
IgA vasculitis (Henoch–Schönlein purpura)	Usually in childhood with palpable purpura symmetrically over the legs and buttocks. Skin involvement in almost all cases	Small	Neutrophilic	IgA		Gut, renal, joints	Often a preceding viral or bacterial infection
Urticarial vasculitis	Urticarial rash initially which may leave residual purpuric lesions after 24–72 hours	Small	Neutrophilic	IgM, IgG	Low C3, C4	Pulmonary, joint, renal, ocular, angio-oedema	SLE, Sjögren's syndrome, complement deficiencies, viral infections, drug reaction, malignancy (particularly haematological)
Paraneoplastic vasculitis	Recurrent episodes of palpable purpura, may pre-date the diagnosis of malignancy	Small	Neutrophilic	Pauci-immune		Variable dependent on neoplasm	Malignancy
Granulomatosis with polyangiitis (previously Wegener's granulomatosis)	Palpable purpuric rash in a generalized distribution including the upper limbs. Also necrotic papules, subcutaneous nodules and ulcers. Skin involvement in 50%	Small and medium	Neutrophilic	Pauci-immune	cANCA, PR3	Pulmonary, renal, neurological, upper respiratory tract, ocular	Unknown aetiology
Microscopic polyangiitis	Palpable purpuric rash in a generalized distribution including the upper limbs. Also splinter haemorrhages, palmar erythema	Small and medium	Neutrophilic	Pauci-immune	pANCA, MPO	Pulmonary, renal, ocular, gut, neurological	Unknown aetiology
Eosinophilic granulomatosis with polyangiitis (previously Churg–Strauss syndrome)	Palpable purpuric rash in a generalized distribution including the upper limbs. Subcutaneous nodules	Small and medium	Neutrophilic or eosinophilic	Pauci-immune	ANCA, eosinophilia	Pulmonary, renal, neurological, cardiac, upper respiratory tract	Asthma
Cryoglobulinaemic vasculitis	Recurrent palpable purpura, Raynaud's	Small and medium	Neutrophilic	IgM, C3	Cryoglobulins, low C4, rheumatoid factor	Renal, joint, neurological, gut, cardiac	Hepatitis C infection, autoimmune rheumatic disease, lymphoproliferative or myeloproliferative disorders
Vasculitis secondary to autoimmune rheumatic disease	Variable depending on the underlying disease. Palpable purpura on the lower limbs is typical	Small and medium	Neutrophilic	IgM, IgG, C3	ANA, anti dsDNA, rheumatoid factor, C3, C4	Variable dependent on underlying disease	SLE, rheumatoid arthritis, Sjögren's syndrome (common), dermatomyositis, scleroderma (less common)
Septic vasculitis	Purpuric rash may be widespread	Small and medium	Neutrophilic	IgG, IgM, IgA		Variable dependent on infection	Infective endocarditis, septicaemia
Polyarteritis nodosa	Tender nodules, livedo and ulceration. Purpura is relatively uncommon	Medium	Neutrophilic	C3		Neurological, joint, renal arteries, gut	Hepatitis B

*ANA = anti-nuclear antibody; ANCA = anti-neutrophil cytoplasmic antibody; SLE = systemic lupus erythematosus. *Some classification systems do not consider hypersensitivity vasculitis to be a separate entity to cutaneous leukocytoclastic angiitis. From Gonzalez-Gay et al (2004), Isenberg et al (2004), Carlson et al (2006), Valeyrie-Allanore et al (2007), Ramdial and Naidoo (2009), Carlson (2010), Kawakami (2010)*