Purpura: Mechanisms and Differential Diagnosis

22

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INTRODUCTION

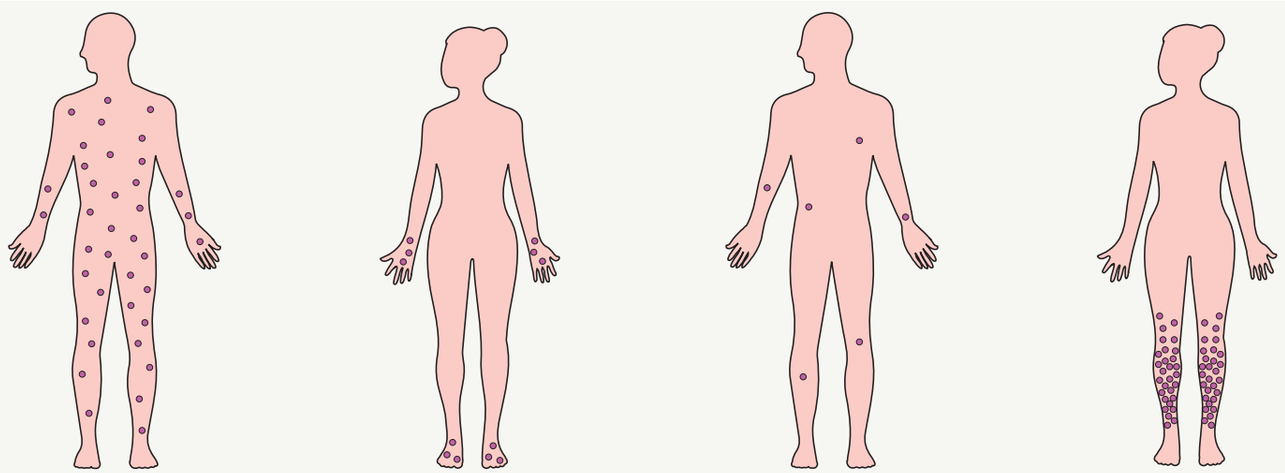
This chapter addresses the evaluation and classification of patients presenting with purpura, defined as visible hemorrhage within the skin or mucous membranes. The differential diagnosis presented in this chapter is directed toward syndromes of primary purpura, where the hemorrhage is an integral part of lesion formation, rather than hemorrhage secondary to causes such as trauma and scratching or hemorrhage into established lesions due to dependency (e.g. stasis dermatitis, eczema craquelé).

This chapter outlines a diagnostic approach based upon lesion number and distribution pattern, with a further focus on the morphology of the purpuric lesions. The initial goal is to identify the most plausible of three broad categories: simple hemorrhage (vascular breach), inflammatory hemorrhage (vessel-directed inflammation), or microvascular occlusion/ischemia. Assigning the patient to one of these three major categories facilitates a more directed, efficient, and accurate evaluation to prove or disprove the suspected pathomechanism and it serves to narrow the list of possible diagnoses.

Figure 22.1 illustrates this diagnostic approach based upon lesion number and distribution pattern. Interpretation of these clinical findings is then modified by lesional morphology, extracutaneous findings, and clinical context. For example, petechiae appearing in a generalized pattern requires exclusion of severe thrombocytopenia or perhaps thrombotic thrombocytopenic purpura, but they are most often due to a viral or drug eruption.

When *widespread*, purpuric lesions in a severely ill patient raise concern for serious drug eruptions (e.g. Stevens–Johnson syndrome) or some vasculitides whereas generalized retiform purpura in the setting of multi-organ disease suggests fulminant microvascular disease (e.g. catastrophic antiphospholipid syndrome) or sepsis-associated disseminated intravascular coagulation (DIC) with purpura fulminans. *Predominantly acral* lesions are divided into two subsets: (1) involvement of the ears and nose as well as the hands and feet, typically triggered by cold exposure; and (2) a more widespread distribution pattern with prominent involvement of the hands and feet, typically in the absence of cold exposure. A *pauci-random* distribution pattern is typical

APPROACH TO THE PATIENT WITH PURPURIC LESIONS BASED UPON NUMBER OF LESIONS AND DISTRIBUTION PATTERN



Multiple and generalized/widespread	Predominantly acral	Pauci-random	Multi-dependent
• Viral exanthem • Drug eruption • If only petechiae, severe thrombocytopenia • If retiform purpura & systemically ill patient, - Purpura fulminans - Sepsis/DIC - Catastrophic APLS - Fulminant ANCA-associated vasculitides	A) Multiple acral sites; typically cold-induced & retiform purpura due to vascular occlusion • Cryoglobulinemia, primarily type I • Rarely due to cryofibrinogens or cold agglutins B) Predominantly hands & feet • Viral exanthem, e.g. parvovirus • Erythema multiforme, including RIME/MIRM variant • Sepsis/DIC with hypotension; thromboses localized to vasoconstricted sites	• Usually <25 lesions • ANCA-associated vasculitides • Lymphomatoid papulosis • Occasionally, cutaneous PAN (more commonly pauci-dependent) • If favors areas with increased adipose tissue, - Warfarin-induced skin necrosis - Calciphylaxis	• 25–100 lesions • If macular & non-blanching, - Thrombocytopenia - Hypergammaglobulinemic purpura of Waldenström - Pigmented purpura - Occasionally, immune complex vasculitis* • If palpable & partially blanchable, - Immune complex vasculitis* - Occasionally, pigmented

*Presents similarly whether skin-limited or systemic, so clinical and laboratory evaluation of extracutaneous signs and symptoms required (see Ch. 24).

Fig. 22.1 Approach to the patient with purpuric lesions based upon number of lesions and distribution pattern. APLS, antiphospholipid antibody syndrome; DIC, disseminated intravascular coagulation; MIRM, *Mycoplasma*-induced rash and mucositis; RIME, reactive infectious mucocutaneous eruption; PAN, polyarteritis nodosa.

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Fig. 22.2 Clinical examples of petechiae and purpura. A Round to oval petechiae, <3 mm in diameter. **B** Solar (actinic) purpura in sites of actinic damage plus trauma. **C** Palpable purpura due to cutaneous small vessel vasculitis (inflammation plus hemorrhage). **D** Non-inflammatory (bland) retiform purpura as well as hemorrhagic bullae in a patient with disseminated intravascular coagulation (DIC). *B, Courtesy Kalman Watsky, MD; D, Courtesy Judit Stenn, MD.*

of ANCA-associated vasculitides, various microvascular occlusive diseases, or lymphomatoid papulosis, and occasionally cutaneous polyarteritis nodosa (PAN). *Multi-dependent* patterns can result from severe thrombocytopenia but in the practice of dermatology is most commonly due to cutaneous small vessel vasculitis (see Ch. 24).

In 1989, the term *retiform purpura* was coined to describe a sign of certain vasculitic subsets, but nowadays it is generally used to denote a frequent marker of thrombotic or occlusive microvascular disease[1–3]. The morphologies of purpuric lesions are divided into two major subsets: (1) exclusively macular, whose shapes can be round, oval, irregular, or geometric; and (2) palpable and/or retiform. The macular group consists of petechiae (Fig. 22.2A, Table 22.1)[2], macular purpura (Table 22.2), and macular ecchymoses (Fig. 22.2B, Table 22.3). The palpable and/or retiform group consists of palpable purpura (Fig. 22.2C, Table 22.4), non-inflammatory retiform purpura (Fig. 22.2D; Table 22.5), and inflammatory retiform purpura (Table 22.6). In this chapter, lesions in the macular group are categorized on the basis of size and are defined as non-blanching and non-palpable; those in the palpable and/or retiform group can range in size from a few millimeters to several centimeters in diameter, may be palpable, and may partially blanch with pressure. The relevance of these morphologic subsets when sorting through the differential diagnosis is depicted in Figure 22.3.

Two major causes of purpura – microvascular occlusion syndromes and vasculitis – are discussed in Chapters 23 and 24[4]. Occlusion is important to recognize because it may mimic vasculitis but requires a very different approach to determine its etiology and appropriate therapy. The most typical presentation of microvascular occlusion syndromes is retiform purpura (see Table 22.5).

Livedo reticularis is a reflection of the physiologic anatomy of slow flow states. The three-dimensional structure and flow regulation of the dermal and subcutaneous vasculature give rise to the net-like pattern of livedo reticularis (see Fig. 106.1). The diameter of the almost-circular to polygonal individual units within the net-like grid varies from 2 cm or larger on the back to 5 mm or less on the palms or soles.

Retiform purpura morphology results from involvement of the same vessels that produce the livedo reticularis pattern. While the former was traditionally considered a component of livedo reticularis, the two should be distinguished based upon the presence or absence of purpura, hence the term "retiform purpura"[1,2]. Given the size of dermal vessels, the clot within the vessel is too small to be seen grossly. What is actually observed is hemorrhage around the dermal vessels, presumably due to ischemia with hemorrhage prior to complete occlusion of the vessel. A complete reticulate pattern is seen infrequently. Instead, the morphology of retiform purpura is composed of "puzzle pieces" of the livedo reticularis pattern. While some lesions have a branching appearance, very few, if any, are truly stellate, i.e. a central area of necrosis or hemorrhage with a radiating star-like pattern composed of straight lines.

Retiform lesions can be inflammatory or non-inflammatory, but the age of the lesion may blur this morphologic distinction, so in practice both groups of diagnoses need to be considered (see Tables 22.5 & 22.6). Inflammatory retiform purpura is accompanied by peripheral erythema, but the wound healing response can eventually lead to erythema and leukocytoclasis in lesions initiated by non-inflammatory occlusion (Fig. 22.4). As a corollary, vasculitis sometimes produces lesions that have minimal early erythema and lesions lose erythema during resolution.

Lastly, the retiform lesions of immune complex vasculitis are invariably sparse in number and are accompanied by many round purpuric lesions. In addition, these retiform lesions are typically more finely branched than either occlusive or ANCA-associated retiform purpura. However, when within confluent areas of purpura, they may have more intense branching hemorrhage or necrosis. Of note, vasculitic retiform lesions do not simply represent the crowding or collision of more classic round purpuric lesions, and they may occur with or without cutaneous arteritis.

The presence of a multi-dependent round and retiform pattern (many round/few retiform lesions) is seen most commonly with three types of immune complex vasculitis: (1) IgA-predominant; (2) autoimmune connective tissue disease-associated; and (3) mixed cryoglobulinemia. This pattern of round and retiform purpuric lesions may occasionally

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DIFFERENTIAL DIAGNOSIS OF MACULAR PETECHIAE (≤4 MM IN DIAMETER)
Hemostatically relevant thrombocytopenia (<10 000–20 000/mm³)*
Major etiologies†

• Idiopathic thrombocytopenic purpura
• Thrombotic thrombocytopenic purpura
• Other acquired thrombocytopenias, including drug-related
  • Peripheral destruction (e.g. quinine, quinidine)
  • Drug-induced decreased production, idiosyncratic or dose-related (e.g. chemotherapy)
  • Bone marrow infiltration, fibrosis, or failure
• Disseminated intravascular coagulation (early sign)

Abnormal platelet function
Major etiologies†

• Congenital or hereditary platelet function defects
• Acquired platelet function defects
  • Aspirin, NSAIDs
  • Renal insufficiency
  • Monoclonal gammopathy (uncommon)
• Thrombocytosis secondary to myeloproliferative disorders (often >1 000 000/mm³)

Non-platelet etiologies
Major etiologies†

• Spiking elevations of intravascular venous pressure (Valsalva maneuver-like, e.g. repetitive vomiting, childbirth, paroxysmal coughing, seizure)
• Fixed increased pressure (e.g. stasis, ligatures) or intermittent pressure (e.g. blood pressure cuff – Rumpel–Leede sign)
• Trauma (often linear)
• Fat embolism syndrome
• Perifollicular (vitamin C deficiency)
• Mildly inflammatory conditions
  • Pigmented purpuric eruptions
  • Hypergammaglobulinemic purpura of Waldenström

*Platelets provide factors necessary for hemostasis of endothelial cell junctions. When counts fall below 10 000–20 000/mm³, inadequate platelet support leads to degradation of junction function, increased permeability, and hemorrhage³. †Partial list.

Table 22.1 Differential diagnosis of macular petechiae (≤4 mm in diameter). NSAIDs, nonsteroidal anti-inflammatory drugs.

DIFFERENTIAL DIAGNOSIS OF INTERMEDIATE MACULAR PURPURA (5–9 MM)
Major etiologies*
• Hypergammaglobulinemic purpura of Waldenström • Infection/inflammation in patients with thrombocytopenia • Rarely, minimally inflamed cutaneous small vessel vasculitis (usually dependent distribution)
*Partial list.

Table 22.2 Differential diagnosis of intermediate macular purpura (5–9 mm).

be seen in microscopic polyangiitis or granulomatous polyangiitis, but the lesions are fewer in number and more randomly distributed. The combination of many round/few retiform lesions is not seen with simple hemorrhage or microvascular occlusive disease.

THE TIME COURSE OF PURPURA

The three subsets of macular (non-palpable) purpura (see Tables 22.1–22.3) typically develop via simple hemorrhage, with extravasated red blood cells and minimal inflammation observed in biopsy specimens. These lesions simply evolve from initial hemorrhage to steady clearing of red blood cells and hemoglobin. Clinically this correlates with fading of lesions and, in larger lesions, transition of color from red–blue or purple to green, yellow, or brown before complete fading.

In syndromes of inflammatory hemorrhage, such as cutaneous small vessel vasculitis, as well as in microvascular occlusion, the evolution and

DIFFERENTIAL DIAGNOSIS OF MACULAR ECCHYMOSES (≥1 CM)
Procoagulant defect plus minor trauma
Major etiologies*
• Anticoagulant use • Hepatic insufficiency with poor procoagulant synthesis • Vitamin K deficiency • Disseminated intravascular coagulation (some)
Poor dermal support of vessels plus minor trauma
Major etiologies*
• Solar (actinic, senile) purpura • Corticosteroid therapy, topical or systemic • Vitamin C deficiency (scurvy) • Systemic amyloidosis (light chain-related, transthyretin-related; see Tables 47.1 & 47.2) • Ehlers–Danlos syndrome
Platelet disorders plus minor trauma
Major etiologies*
• Platelet function defects, including von Willebrand disease and those induced by medications and metabolic diseases • Acquired or congenital thrombocytopenia
Miscellaneous
• Papular purpuric gloves and socks syndrome
*Partial list.

Table 22.3 Differential diagnosis of macular ecchymoses (≥1 cm).

PALPABLE PURPURA: INFLAMMATORY PURPURA WITH PROMINENT EARLY ERYTHEMA
Leukocytoclastic vasculitis due to immune complex disease (see Fig. 24.1)
Small vessels only
• Idiopathic, infection- or drug-associated IgG or IgM complexes • Idiopathic IgA complexes (HSP), or IgA complexes associated with drugs or infection • Hypergammaglobulinemic purpura of Waldenström • Urticarial vasculitis: often minimally purpuric • Pustular vasculitis (e.g. bowel bypass syndrome)
Small- and medium-sized (macroscopic) vessels may be involved
• Mixed cryoglobulinemia • Rheumatic vasculitides (LE, RA, Sjögren syndrome)
Pauci-immune leukocytoclastic vasculitis (see Fig. 24.1)
ANCA-associated
• Granulomatosis with polyangiitis • Microscopic polyangiitis • Eosinophilic granulomatosis with polyangiitis (Churg–Strauss syndrome)
Other
• Erythema elevatum diutinum • Sweet syndrome (vasculitis unusual)
***Not* leukocytoclastic vasculitis**
Small vessels only
• Erythema multiforme • Pityriasis lichenoides et varioliformis acuta (PLEVA) • Pigmented purpuric eruptions • Hypergammaglobulinemic purpura of Waldenström (although some lesions have histologic evidence of leukocytoclastic vasculitis)
Classic target lesion – usually erythema multiforme, but can be small vessel vasculitis, especially IgA-associated

Table 22.4 Palpable purpura: inflammatory purpura with prominent early erythema. HSP, Henoch–Schönlein purpura; LE, lupus erythematosus; RA, rheumatoid arthritis.

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DIFFERENTIAL DIAGNOSIS OF NON-INFLAMMATORY RETIFORM PURPURA
Occlusion primarily due to platelet-related thrombopathy
Major etiologies*
• Heparin-induced thrombocytopenia syndrome (HITS) • Thrombocytosis secondary to myeloproliferative disorders • Paroxysmal nocturnal hemoglobinuria • Thrombotic thrombocytopenic purpura (though platelet plugs form primarily in visceral vessels, and skin hemorrhage is due more often to thrombocytopenia)
Cold-related precipitation or agglutination
Major etiologies*
• Cryoglobulinemia, usually monoclonal (early lesions of mixed cryoglobulinemia are more often inflammatory and leukocytoclastic due to immune complex deposition) • Cryofibrinogenemia (though most cryofibrinogens are incidental findings in hospitalized patients) • Cold agglutinins (rarely cause occlusion; usually cause hemolysis or are asymptomatic)
Occlusion due to organisms growing in vessels
Major etiologies*
• Vessel-invasive fungi (e.g. *Mucor* spp., *Aspergillus* spp.; usually in immunocompromised patients) • Ecthyma gangrenosum (often *Pseudomonas* spp. or other Gram-negative bacilli proliferating in adventitia of subcutaneous arterioles) • Disseminated strongyloidiasis • Lucio phenomenon of Hansen disease • Rocky Mountain spotted fever, other rickettsial spotted fevers
Systemic alteration in control of coagulation
Major etiologies*

• Disseminated intravascular coagulation, often in the setting of sepsis
• Protein C- and S-related
  • Homozygous protein C or protein S deficiency (neonatal purpura fulminans)
  • Acquired protein C deficiency (some patients with sepsis-associated DIC)
  • Warfarin necrosis† (protein C dysfunction)
  • Postinfectious purpura fulminans (protein S dysfunction)
• Antiphospholipid antibody, lupus anticoagulant
• Levamisole-adulterated cocaine‡

Vascular coagulopathy
• Livedoid vasculopathy/atrophie blanche (may also have a systemic prothrombotic component) • Malignant atrophic papulosis/Degos disease (antiphospholipid antibody syndrome can mimic this disease) • Sneddon syndrome (can be related to antiphospholipid antibody syndrome) • Deficiency of adenosine deaminase 2 (ADA2)
Embolization or crystal deposition
Major etiologies*
• Cholesterol emboli • Oxalate crystal deposition (rare) • Marantic endocarditis, atrial myxoma, crystal globulins, hypereosinophilic syndrome (all rare)
Reticulocyte, red blood cell occlusion
• Sickle cell disease • Severe malaria (usually *Plasmodium falciparum*)
Miscellaneous
• Cutaneous calciphylaxis • Brown recluse (*Loxosceles*) spider bite reaction • Intravascular B cell lymphoma • Hydroxyurea (rare)
*Partial list. †Also referred to as Coumadin® necrosis. ‡Early lesions primarily thrombotic, but vasculitis can also occur; retiform purpura can be inflammatory.

Table 22.5 Differential diagnosis of non-inflammatory retiform purpura. DIC, disseminated intravascular coagulation; RBC, red blood cell; vWF, von Willebrand factor.

clearing of lesions is more complicated. This is outlined in Figure 22.4. Because of the different evolution of these two processes, it is possible for a biopsy specimen of a late lesion of vasculitis to resemble an early lesion of occlusion histologically. Conversely, a late lesion of occlusion with some resulting dermal necrosis may on histologic examination show features characteristic of leukocytoclastic vasculitis (LCV). This means that *both* the clinical morphology and the histopathology of a purpuric lesion must be interpreted within the context of the lesion's age and clinical setting.

HEMOSTASIS/COAGULATION

Primary hemostasis consists of adhesion, activation, and aggregation of platelets at the site of vascular injury. This leads to the formation of a platelet plug sufficient for routine minor injuries to the microvascular system. Platelets are also essential for maintaining the integrity of small blood vessels. There is molecular signaling crosstalk between megakaryocytes and endothelial cells, with platelets delivering megakaryocytic factors that are important for endothelial health.

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Petechial hemorrhage due to severe thrombocytopenia (typically platelets <20 000/mcl) results from reduced delivery of these megakaryocyte/platelet factors to the endothelium, thereby impairing endothelial cell function and widening of the gaps between endothelial cells[5]. This probably also explains why platelet dysfunction does not typically result in petechial hemorrhage, since platelet number and factor delivery remain normal, but rather ecchymoses develop because platelet plugs fail to form at sites of injury.

When a platelet plug is inadequate due to the size of the vessel or the size of the injury, **secondary** hemostasis with clot formation is needed. Secondary hemostasis classically includes the intrinsic and extrinsic coagulation pathways that then converge into a common pathway, driving the formation of fibrin from fibrinogen via stepwise amplifications (Fig. 22.5)[6,7]. The *intrinsic* (contact activation) pathway is the longer of the two; it begins with factor XII activation, typically due to injury-related exposure of endothelial collagen. This pathway is assessed by the activated partial thromboplastin time (aPTT). The *extrinsic* pathway is triggered by tissue factor released from endothelial and other cells, which converts factor VII to factor VIIa, and then as the extrinsic pathway converges with the intrinsic pathway to form the common pathway, factor X is converted to factor Xa. The extrinsic pathway is monitored by the prothrombin time (PT).

Whereas insufficient clotting can lead to death via hemorrhage, inappropriate clotting produces thrombosis, embolus, and/or necrosis. Uncontrolled clotting with fibrinolysis can produce both thrombosis and hemorrhage, as in DIC. Ideally, a thrombus should form rapidly at sites of injury, but should not extend beyond where it is needed. Clotting factors that escape the local injury site must be prevented from triggering clotting at distant sites. As might be expected for a system that requires exquisite regulation to perform properly, the control of coagulation is multifaceted. Basal coagulation encompasses the constant low-level activation of some components of the procoagulant, natural anticoagulant, and fibrinolytic pathways, so that these systems are primed for a rapid response when needed. While Figure 22.5 appears complicated enough for a dermatologist, there are additional modifiers of coagulation including prekallikrein, C1 esterase inhibitor (see Fig. 18.6), factor XIII, and protein Z/protein Z-dependent protease inhibitor[6].

The initiation phase of clotting is down-regulated by *tissue factor pathway inhibitor* (TFPI) and *antithrombin III* (ATIII). TFPI and ATIII are bound to heparan sulfate molecules on the surface of endothelial cells (see Fig. 22.5). Their presence in close proximity to sites of desired clot formation allows them to capture activated clotting factors and prevent them from leaving the area. ATIII can neutralize thrombin as well as factors IXa, Xa, and XIIa; this process is greatly enhanced by heparan sulfate or heparin binding to ATIII.

The *thrombomodulin/protein C/protein S* system is the other major natural anticoagulant pathway. While both ATIII and protein C pathways

DIFFERENTIAL DIAGNOSIS OF INFLAMMATORY RETIFORM PURPURA
Vasculitis
Primarily dermal vessels
• IgA vasculitis
Dermal and subcutaneous vessels usually involved
• Mixed cryoglobulinemia • Rheumatic vasculitides (LE, RA) • Polyarteritis nodosa • Microscopic polyangiitis • Granulomatosis with polyangiitis • Eosinophilic granulomatosis with polyangiitis (Churg–Strauss syndrome)
Dermal vessel inflammation/occlusion/constriction
• Livedoid vasculopathy • Septic vasculitis • Chilblains (pernio) • Pyoderma gangrenosum

Table 22.6 Differential diagnosis of inflammatory retiform purpura. LE, lupus erythematosus; RA, rheumatoid arthritis.

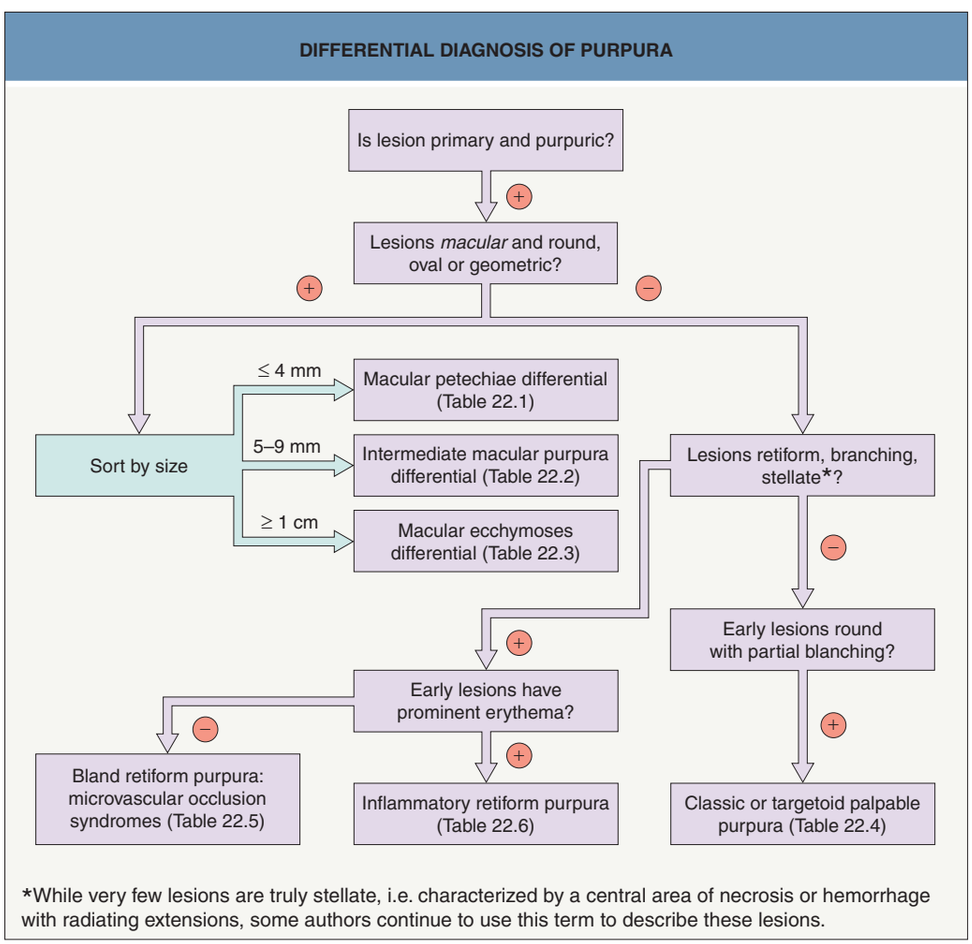


Fig. 22.3 Differential diagnosis of purpura. Morphology can be used as a primary sorting method, but combining morphology with an initial pattern approach as depicted in Figure 22.1 can improve accuracy. When discrepancies between the two arise, additional investigation is warranted.

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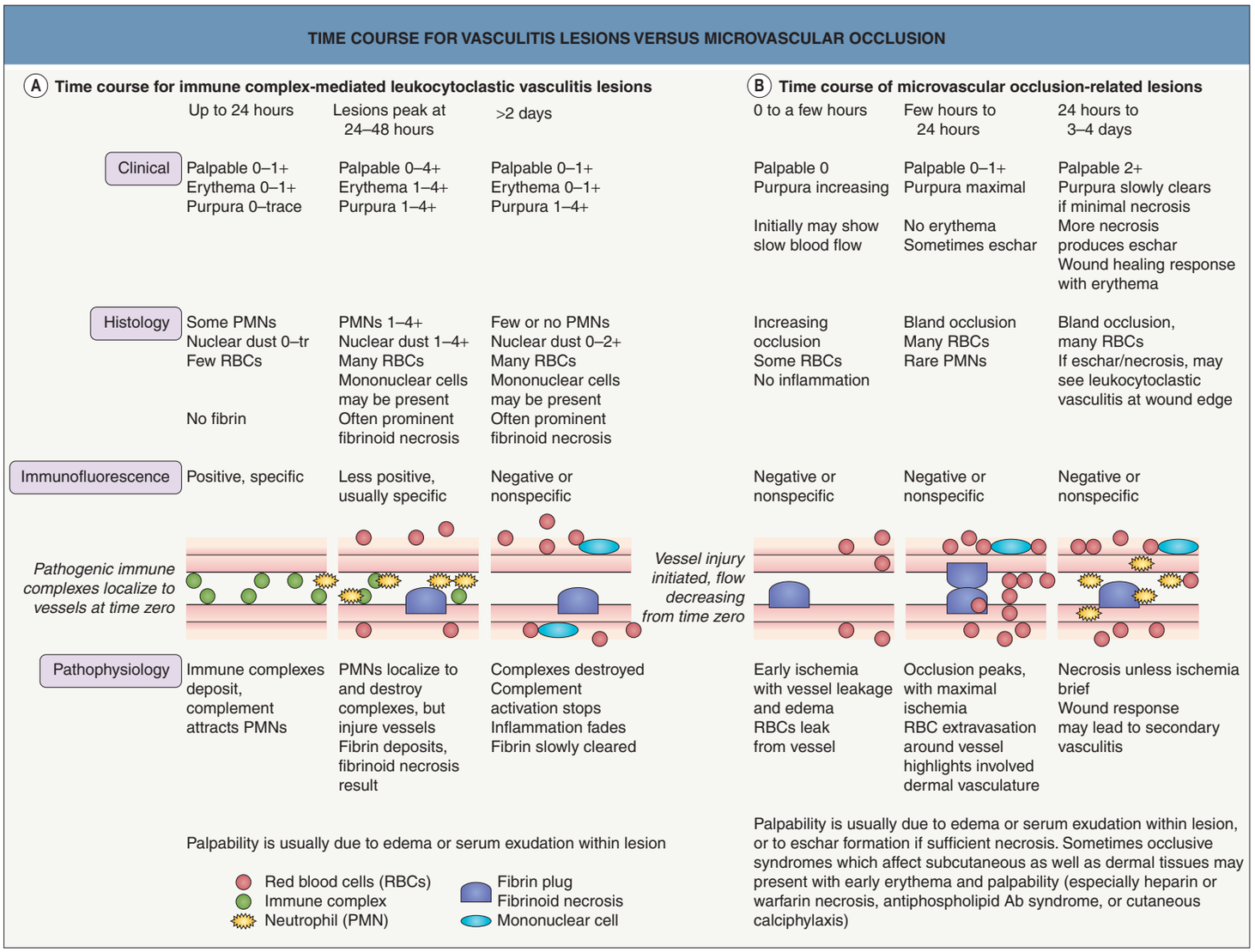


Fig. 22.4 Time course for skin lesions due to vasculitis versus microvascular occlusion. A Time course for lesions due to immune complex-mediated leukocytoclastic vasculitis. **B** Time course for lesions due to microvascular occlusion. Ab, antibody; tr, trace.

are important in large vessels, the protein C system seems to be critical for normal function of the microvasculature. Thrombin that escapes the clot site can bind to thrombomodulin on the endothelial cell surface. Once bound to thrombomodulin, thrombin no longer activates procoagulant factors, but instead avidly binds and activates protein C, a vitamin K-dependent anticoagulant protein (see Fig. 22.5). The anticoagulant function of activated protein C is enhanced by binding to a phospholipid surface, a high-density lipoprotein (HDL), and protein S (another vitamin K-dependent anticoagulant). This complex then inactivates factors Va and VIIIa. The factor V Leiden mutation is a single amino acid change at the site of cleavage by activated protein C, and this change renders it much more resistant to inactivation, thus explaining the associated prothrombotic state. In other patients, a polymorphism in the prothrombin gene, specifically 20210A within an untranslated region, increases the level of prothrombin and can lead to a prothrombotic state.

OVERLAP OF COAGULATION AND INFLAMMATORY VESSEL DISEASE

Hemostasis is one aspect of the host response to injury. It is clear that inflammatory injury can lead to fibrin deposition in vessels, as exemplified by fibrinoid necrosis in vasculitis (see Fig. 22.4). Both platelets and coagulation factors play an important role in vascular integrity, innate immunity, inflammatory responses, and wound healing[8,9]. For example, thrombin is a procoagulant factor, but it also acts to promote monocyte, fibroblast, and endothelial cell migration into an area of recent injury to begin removal of damaged tissue and initiate wound repair. Thrombin bound to thrombomodulin activates protein C, which in addition to its potent anticoagulant action also has important anti-inflammatory properties. In addition, a powerful angiogenesis inhibitor, angiostatin, is a cleavage product of plasminogen. Thromboinflammation is an expanding concept that recognizes the complex and vital integration of coagulation, inflammation, and wound healing pathways[8,9].

TESTS FOR COAGULATION

A thorough history (including family history) and physical examination are important in the proper selection and interpretation of tests measuring coagulation and anticoagulation parameters. A basic laboratory assessment of clotting includes a platelet count, PT, and aPTT (Table 22.7). Platelet function tests (e.g. bleeding time, ristocetin-induced platelet aggregation studies) are performed in settings suggesting platelet function defects unexplained by medications (e.g. aspirin, nonsteroidal anti-inflammatory drugs [NSAIDs]) or metabolic disorders such as renal failure. Another example would be the platelet dysfunction observed in Hermansky–Pudlak syndrome. Laboratory tests that are employed in the evaluation of thrombophilia/hypercoagulability are outlined in Table 105.9.

ANTIPLATELET AND ANTICOAGULANT AGENTS

Antiplatelet agents are used in specific clinical settings to reduce the risk of thrombosis. Medications that dermatologists are most likely

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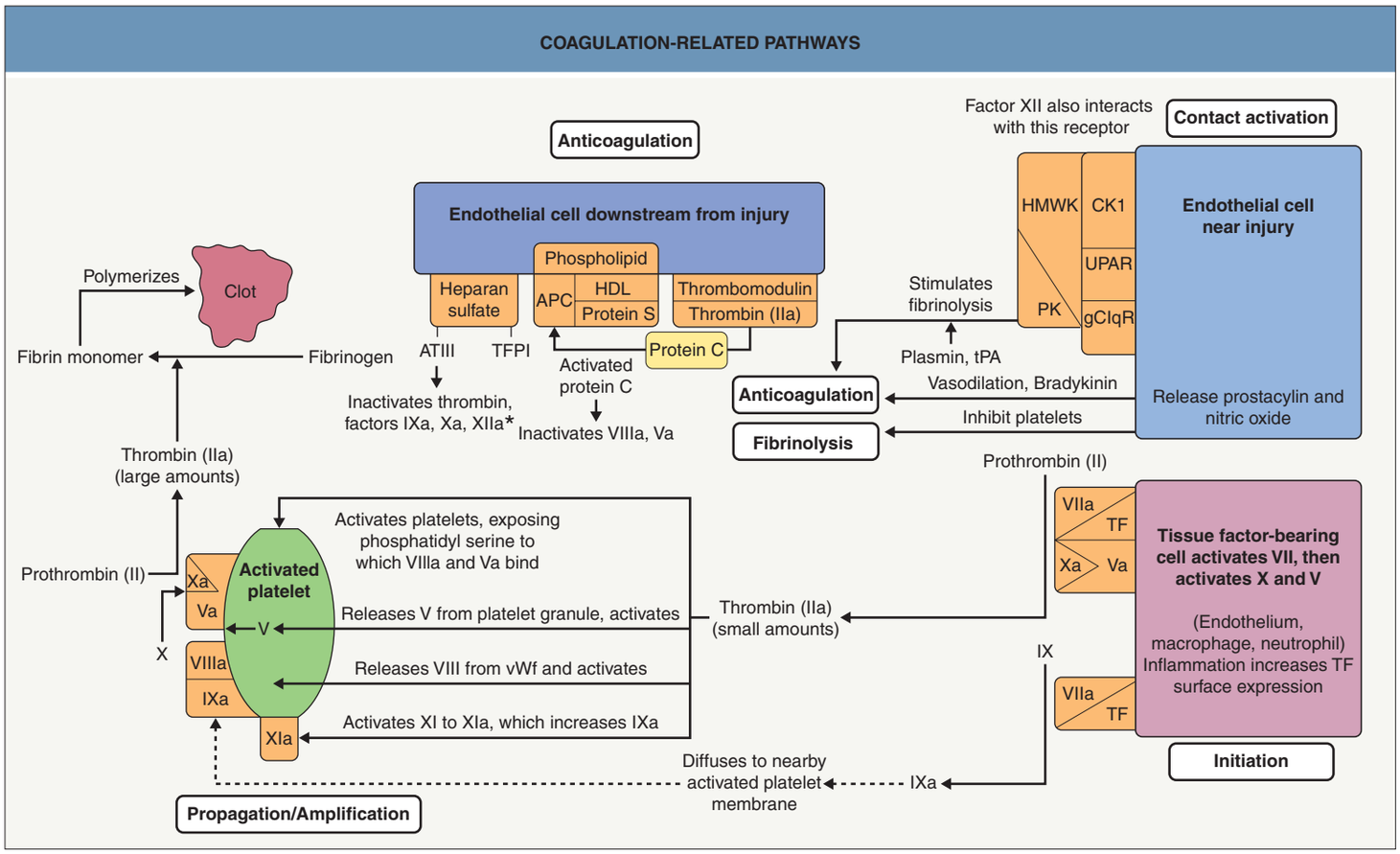


Fig. 22.5 Coagulation-related pathways. TFPI can inactivate factor Xa, and the TFPI–factor Xa complex can inhibit VIIa. *Enhanced by binding of heparin to ATIII. APC, activated protein C; ATIII, antithrombin III; CK1, cytokeratin 1; gC1qR, globular head of the C1q receptor; HDL, high-density lipoprotein; HMWK, high-molecular-weight kininogen; PK, prekallikrein; TF, tissue factor; TFPI, tissue factor pathway inhibitor; tPA, tissue plasminogen activator; UPAR, urokinase plasminogen activator receptor; vWF, von Willebrand factor.

INTERPRETATION OF PROTHROMBIN TIME (PT) AND ACTIVATED PARTIAL THROMBOPLASTIN TIME (APTT)	
Coagulation test results	**Most likely etiologies**
Normal PT, prolonged aPTT	Heparin administration Lupus anticoagulant* Acquired factor VIII inhibitor von Willebrand disease (defective platelet adhesion and functional deficiency of factor VIII) Significant deficiency of one of following: • Factor VIII, IX, XI, or XII • High-molecular-weight kininogen (HMWK) • Prekallikrein
Prolonged PT, normal aPTT	Factor VII deficiency Low-dose oral anticoagulant
Prolonged PT and prolonged aPTT	Deficiency or inhibitor of: • Fibrinogen • Prothrombin • Factor V or X Combined deficiency of multiple procoagulant factors: • Severe vitamin K deficiency • High-dose oral anticoagulant
*Other tests, such as the dilute Russell viper venom time, may help confirm the presence of lupus anticoagulant activity.	

Table 22.7 Interpretation of prothrombin time (PT) and activated partial thromboplastin time (aPTT). Repeating the test using a 1:1 mixture of the patient's plasma and normal plasma will usually normalize the time if there is a factor deficiency, but the time will remain prolonged if an inhibitor is present.

to use to treat microvascular involvement in livedoid vasculopathy or antiphospholipid antibody syndrome include acetosalicylic acid (ASA, aspirin; inhibits cyclooxygenase), dipyridamole or pentoxifylline (both increase cAMP), and clopidogrel (blocks ADP). *Anticoagulant* medications are listed by their mechanisms of action in Table 22.8[10–12], and their sites of interaction are illustrated in Figure 22.6. Unlike warfarin, dabigatran and direct oral anticoagulants (DOACs) that inhibit thrombin or factor Xa, respectively, do not require monitoring of the international normalized ratio (INR), i.e. prothrombin ratio[10]. Given their popularity, specific reversal agents became a priority and are now commercially available while others are in development (see Table 22.8)[11–14]. In addition to LWMH, DOACs are now being used more frequently for select syndromes with prominent microvascular cutaneous involvement such as livedoid vasculopathy.

SELECTED PURPURA SYNDROMES

Some syndromes that are not traditionally discussed in chapters on microvascular occlusion (Ch. 23) or vasculitis (Ch. 24) will be addressed here.

Pigmented Purpuric Dermatoses

Synonyms: ■ Pigmented purpuric eruptions ■ Capillaritis ■ Purpura pigmentosa chronica ■ Purpura simplex ■ Majocchi–Schamberg disease

Variants:
- Schamberg disease: Schamberg purpura, progressive pigmentary dermatosis of Schamberg, purpura pigmentosa progressiva
- Purpura annularis telangiectodes of Majocchi: Majocchi's disease
- Pigmented purpuric lichenoid dermatitis of Gougerot and Blum
- Eczematid-like purpura of Doucas and Kapetanakis: eczematoid purpura, itching purpura
- Lichen aureus: lichen purpuricus

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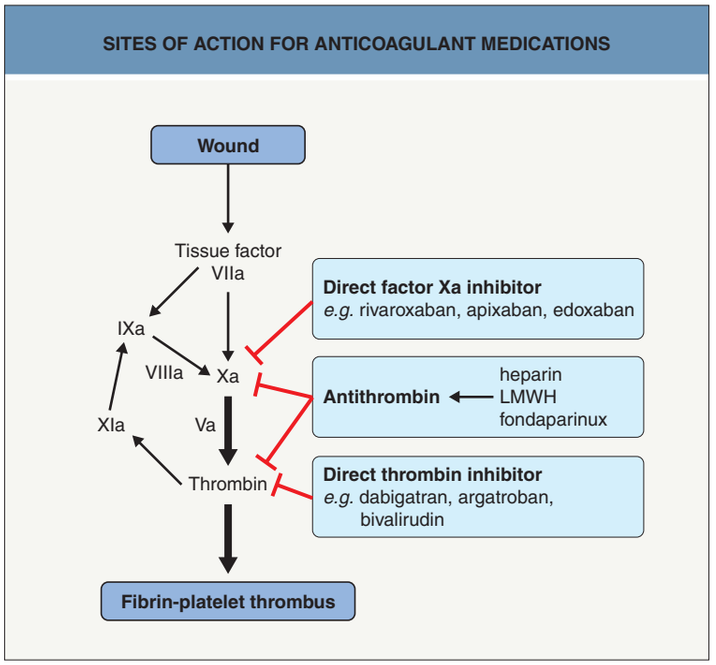


Fig. 22.6 Sites of action for anticoagulant medications. LMWH, low-molecular-weight heparin.

ANTICOAGULANTS		
Agent	**Route of administration**	**Reversal agent**
Interact with antithrombin to primarily inhibit factor IIa (thrombin) and/or factor Xa		
Unfractionated heparin	IV	Protamine sulfate
Enoxaparin (LMWH)	SC	Protamine sulfate (partial)
Dalteparin (LMWH)	SC	Protamine sulfate (partial)
Tinzaparin (LMWH)	SC or IV	Protamine sulfate (partial)
Fondaparinux (synthetic pentasaccharide)	SC	
Inhibit gamma carboxylation of vitamin K dependent factors: II, VII, IX, X, protein C, & protein S		
Warfarin	Oral	Vitamin K Urgent reversal: PCC, FPP, or recombinant factor VIIa
Direct thrombin inhibitor		
Dabigatran (NOAC*)	Oral	Idarucizumab
Argatroban	IV	Can be hemodialyzed
Bivalirudin (synthetic hirudin analogue)	IV	Can be hemodialyzed
Direct factor Xa inhibitor (DOAC)		
Rivaroxaban	Oral	Specific: Andexanet† Nonspecific: PCC
Apixaban	Oral	Specific: Andexanet† Nonspecific: PCC
Edoxaban	Oral	Nonspecific: PCC
Betrixaban	Oral	Nonspecific: PCC
Binds factor XI and XIa		
Abelacimab**	SC or IV	

*NOACs include DOACs plus dabigatran.
**Currently under investigation.
†Under evaluation for broader use.

Table 22.8 Anticoagulants. Ciraparantag is being evaluated as a possible reversal agent for heparin, LMWH, fondaparinux, and DOACs. DOAC, direct oral anticoagulant; FPP, fresh frozen plasma; IV, intravenous; LMWH, low-molecular-weight heparin; NOAC, novel oral anticoagulant or non-vitamin K oral anticoagulant; PCC, prothrombin complex concentrate; SC, subcutaneous.

Key features

- Clustered petechial hemorrhage
- Often a background of yellow–brown discoloration due to hemosiderin deposition
- The location and pattern depends on the particular variant

Introduction

Pigmented purpuric eruptions represent a group of diseases characterized by petechial hemorrhage thought to be secondary to capillaritis[15–18]. These diseases have no systemic findings, but they occasionally lead to a patient evaluation to exclude thrombocytopenia or vasculitis because of the purpuric (usually petechial) nature of the lesions and clinical misdiagnosis, especially of the rarer forms.

Pathogenesis

These diseases all result from minimal inflammation and hemorrhage of superficial papillary dermal vessels, usually capillaries. The reason for the inflammation is unknown.

Clinical features

The characteristics of the various forms of pigmented purpuric eruptions are outlined in Table 22.9 and illustrated in Figures 22.7 and 22.8. This disorder occurs in both children and adults[18].

Pathology

Histopathologic features include red cell extravasation, endothelial cell swelling, a perivascular lymphocytic infiltrate, and hemosiderin-containing macrophages (Fig. 22.9). The lichen aureus and Gougerot–Blum variants are characterized by a lichenoid infiltrate, and epidermal spongiosis with patchy parakeratosis is often observed in the latter as well as in eczematid-like purpura of Doucas and Kapetanakis. A rare granulomatous variant has also been described[17].

Differential diagnosis

The clinical picture is often sufficient for diagnosis, but a biopsy specimen may be required to distinguish the lichenoid variant from cutaneous small vessel vasculitis. Although usually on one extremity, angioma serpiginosum may occasionally be misdiagnosed as pigmented purpura. Lesions resembling capillaritis have been reported in patients with mycosis fungoides; allergic contact dermatitis (e.g. due to rubber or azo dyes); non-allergic reactions to topical medications (e.g. fluorouracil or eutectic mixture of local anesthetics [EMLA]); drug eruptions (e.g. carbromal, meprobamate, acetaminophen, infliximab, bezafibrate, glipizide, pseudoephedrine, NSAIDs, diuretics, creatine supplementation, medroxyprogesterone injections) based primarily on case reports; suction-induced purpura (e.g. cupping); rheumatoid arthritis; lupus erythematosus; hypergammaglobulinemic purpura of Waldenström; and perhaps due to diet (e.g. apple–cherry fruit spritzer)[16].

Pigmented purpuric eruptions on the legs must be differentiated from dermal hemorrhage secondary to venous hypertension, which presents with petechiae superimposed on diffuse hemosiderosis (Fig. 22.7B) rather than the discrete yellow–brown patches that characterize Schamberg disease. It also needs to be distinguished from exercise-induced vasculitis, also known as golfer's vasculitis, hiker's rash or ankle heat rash, which occurs with prolonged exercise in hot weather[19]. Histologically, findings in exercise-induced vasculitis range from urticarial vasculitis to frank LCV. Since exercise or prolonged standing may also induce recurrent macular vasculitis (see below), it is possible that there is some overlap between these two disorders.

Treatment

Topical corticosteroid therapy is occasionally helpful, especially in patients who report pruritus or have more evident erythema. Effective treatment of more extensive pigmented purpuric eruptions with narrowband UVB and PUVA has been described. Successful therapy with ascorbic acid (500 mg twice daily) plus rutoside (50 mg twice daily) has also been reported. While multiple treatments have been recommended, to date none have proven to be reproducibly effective.

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TYPES OF PIGMENTED PURPURIC DERMATOSES			
Type	**Age/Sex**	**Morphology**	**Location**
Schamberg disease	• Most common form • Can occur in children • Peak frequency in middle-aged to older men	• Yellow–brown patches with an oval to irregular outline (Fig. 22.7A) • Pinpoint petechiae within patches – likened to "cayenne pepper" • Successive crops	• Favors lower legs • Can also involve thighs, buttocks, trunk, and arms
Purpura annularis telangiectodes of Majocchi	• Uncommon • Adolescents and young adults, especially women	• 1–3 cm annular plaques that may slowly expand • Punctate telangiectasias and petechiae within the border (Fig. 22.8A)	Trunk, proximal lower extremities

Pigmented purpuric lichenoid dermatitis of Gougerot and Blum	• Rare
	• Middle-aged to older men
		• Admixture of two types of lesions:
		  • Schamberg-like
		  • Purpuric red–brown lichenoid papules
		• Chronic
		• Occasionally pruritic
			On lower extremity, may be confused with cutaneous small vessel vasculitis

Eczematid-like purpura of Doucas and Kapetanakis	• Rare • Middle-aged to older men	• Scaly petechial or purpuric macules, papules, and patches (Fig. 22.8B) • Pruritic	Primarily lower extremities
Lichen aureus	• Rare	• Solitary patch • Color varies from golden to rust to purple–brown	Usually lower extremity, often over a perforator vein
Linear pigmented purpura	• Rare • Can occur in children and adolescents	• Linear array, usually unilateral (Fig. 22.8C) • Individual lesions similar in appearance to lichen aureus or Schamberg disease	Often a single extremity
Granulomatous pigmented purpura	• Very rare	• Brown patches with superimposed hemorrhagic papules*	Lower legs

*Histologically, hemorrhagic granulomatous inflammation in upper dermis.

Table 22.9 Types of pigmented purpuric dermatoses. Rarely, the first two types are familial.

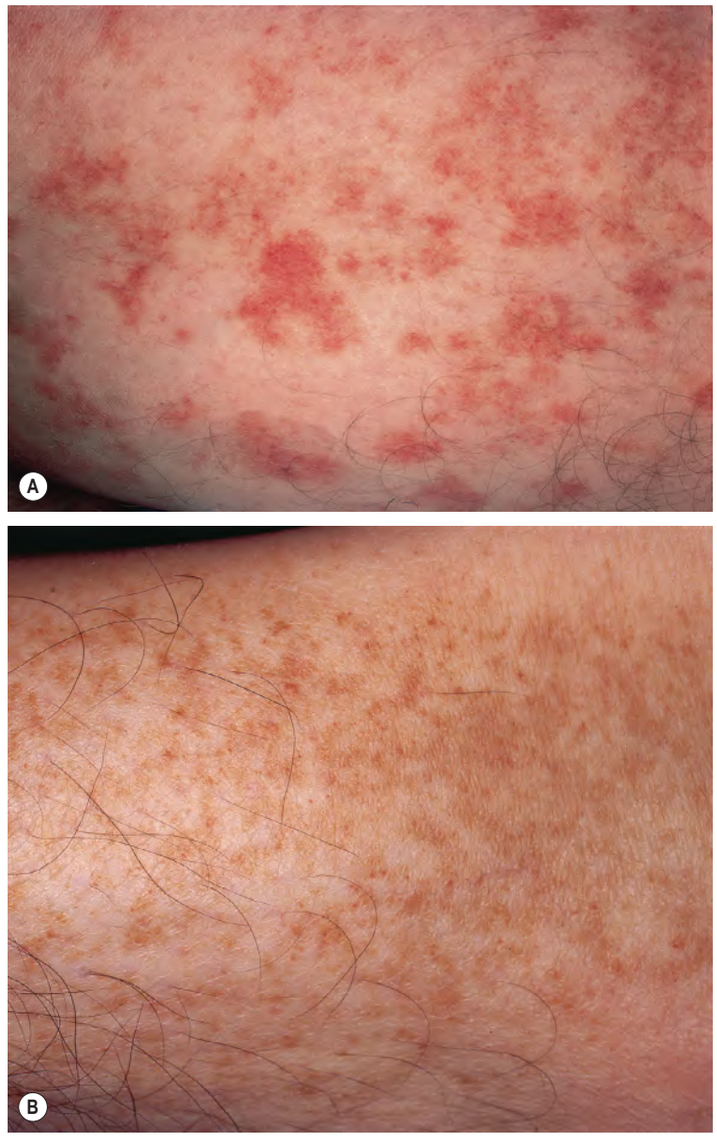


Fig. 22.7 Schamberg disease versus petechiae and hemosiderin secondary to venous hypertension. A Discrete yellow–brown and yellow–pink patches with superimposed petechiae in Schamberg disease. **B** Petechiae superimposed on more diffuse hemosiderin deposits in venous hypertension, referred to as "stasis purpura". *B, Courtesy Jean L. Bolognia, MD.*

Benign Hypergammaglobulinemic Purpura of Waldenström

Synonym: ▪ Recurrent macular vasculitis in hypergammaglobulinemia

Key features

- Usually affects women
- Recurrent crops of petechiae and larger purpuric macules on the lower extremities, which often burn or sting
- Patients typically have polyclonal hypergammaglobulinemia and may have elevated IgG or IgA rheumatoid factor (RF), but not necessarily IgM RF (the standard RF test)
- An autoimmune connective tissue disease develops in a subset of patients

Introduction

This syndrome was first described in 1943 by Waldenström, who reported three women with chronic relapsing purpura, hypergammaglobulinemia, an elevated ESR, and mild anemia. Hypergammaglobulinemic purpura of Waldenström is often associated with an autoimmune connective tissue disease (AI-CTD), especially Sjögren syndrome. In the most recent cutaneous vasculitis classification, this disorder has been renamed *recurrent macular vasculitis in hypergammaglobulinemia*[4].

Pathogenesis

Although associated with hypergammaglobulinemia, a strong argument can be made that a more specific feature of this condition is the presence of small circulating immune complexes, which often contain IgG or IgA rheumatoid factor (RF). Complexes of this size have also been identified in individuals with a clinical presentation that fits this syndrome but who lacked polyclonal hypergammaglobulinemia[20,21]. IgG and IgA RFs are highly soluble, which might explain the rapidity with which lesions appear and then resolve. The presence of monoclonal RF early on in the disease in some patients as well as the tendency of affected individuals to develop autoimmune and (less often) lymphoproliferative disorders supports the presence of a mild immune dysregulation syndrome.

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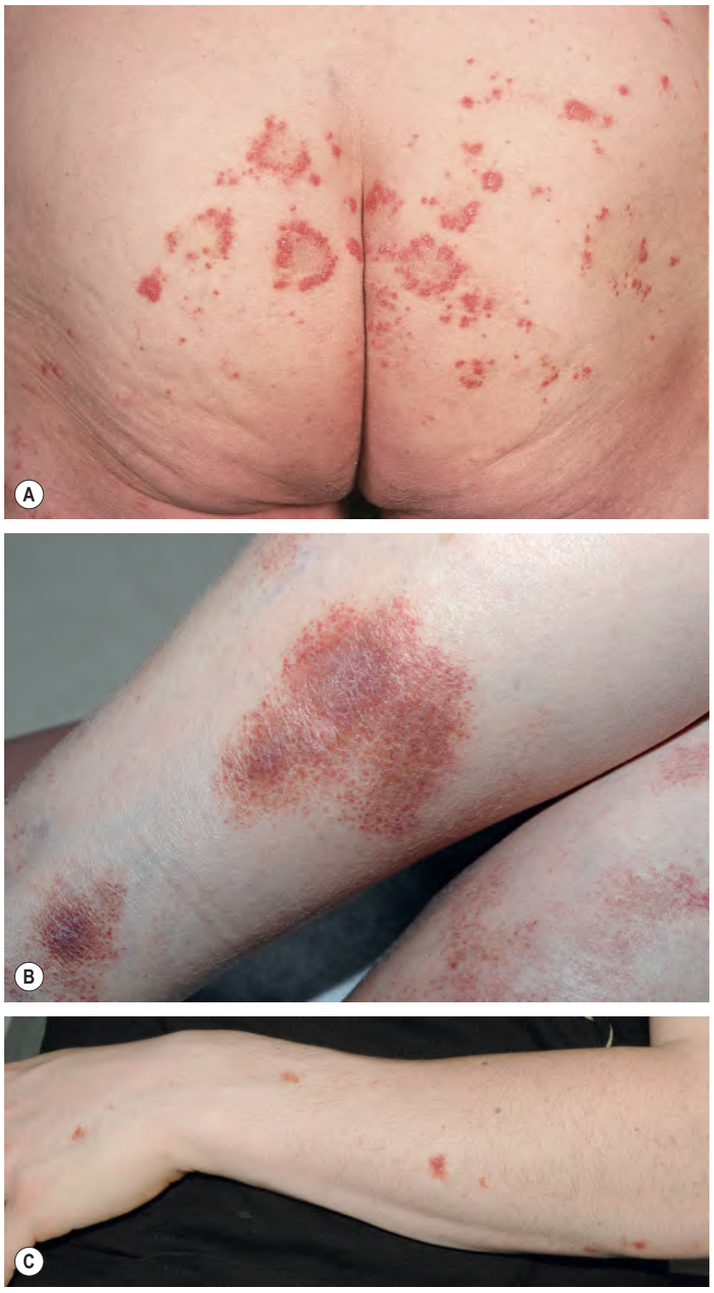


Fig. 22.8 Less common forms of pigmented purpuric eruptions (capillaritis). **A** Purpura annularis telangiectodes of Majocchi characterized by annular plaques with cayenne pepper petechiae in the border. **B** Eczematid-like purpura that often presents with pruritus. **C** Linear pigmented purpuric dermatosis in which there is a linear array of yellow–brown macules and patches with superimposed petechiae and small, red–brown purpuric papules on the arm of a child. The eruption had been present for several months and was limited to this segment of skin. *B, Courtesy Kalman Watsky, MD; C, Courtesy Julie V. Schaffer, MD.*

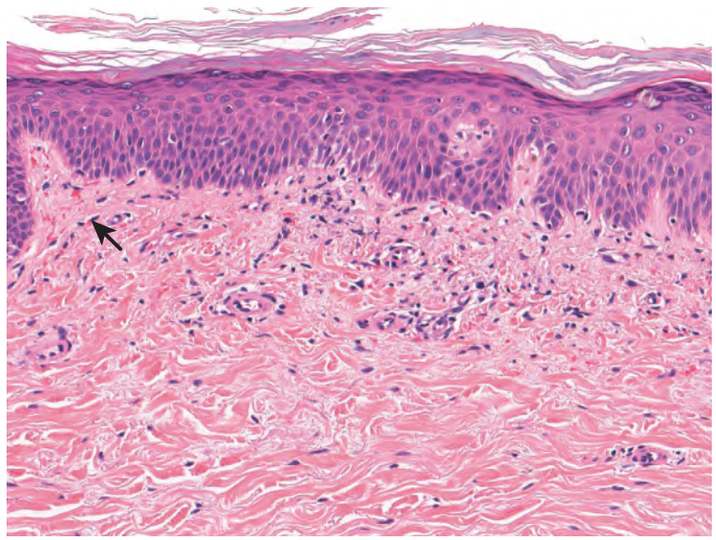


Fig. 22.9 Pigmented purpuric eruption – histopathologic features. Minimal perivascular lymphocytic infiltrate with extravasation of red blood cells (arrow) and hemosiderin deposits. *Courtesy Lorenzo Cerroni, MD.*



Fig. 22.10 Hypergammaglobulinemic purpura of Waldenström. This young woman with Sjögren syndrome had recurrent crops of petechiae on her lower legs. Note the hemosiderin deposition at sites of older lesions. *Courtesy Julie V. Schaffer, MD.*

Clinical features

The purpura is often preceded by a slight itch, mild tingling or burning, and it may be aggravated by tight-fitting garments, prolonged standing, and heat. Macular hemorrhage (e.g. petechiae or larger purpuric macules) on the lower extremities represents the most common presentation, but the lesions may be fleeting (Fig. 22.10). Some patients have palpable purpura with histologic evidence of vasculitis (see below), which has led many authors to classify this entity as a subset of cutaneous small vessel vasculitis[22].

Recurrent macular vasculitis can be primary or secondary[22]. In younger patients it is usually primary, but over time some patients develop evidence of an AI-CTD, most frequently Sjögren syndrome and occasionally rheumatoid arthritis or lupus erythematosus. Much less often, a monoclonal gammopathy or very rarely, a lymphoma or multiple myeloma develops. Children with recurrent macular vasculitis frequently have an associated AI-CTD and it may also develop in patients with cystic fibrosis[23].

Laboratory evaluation typically reveals polyclonal hypergammaglobulinemia and an elevated ESR. Standard RF assays identify only IgM RF, so they will not detect the IgG and IgA RFs that are frequently found in this syndrome (although specific tests for IgG and IgA RF can be performed). Anti-SSA/Ro and -SSB/La antibodies are commonly present and may predict a higher likelihood of developing an associated AI-CTD.

Pathology

Simple hemorrhage is most frequently seen. Occasionally a mild perivascular lymphocytic infiltrate or rarely LCV may be present.

Differential diagnosis

The clinical picture is often characteristic. Some patients develop palpable purpura mimicking classic cutaneous small vessel vasculitis syndromes, but most patients present with recurring crops of burning or stinging macular hemorrhage. Exercise-induced vasculitis is also in the differential diagnosis[19].

Treatment

Some agents used to treat this syndrome, such as aspirin or support stockings, have also been reported to exacerbate the condition. Avoidance of precipitating factors such as alcohol and prolonged

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standing may be helpful. In secondary cases, treatment is aimed at the underlying disease. When there is evidence of LCV histologically, treatment with colchicine or dapsone can be considered.

Gardner–Diamond Syndrome

Synonyms: ■ Psychogenic purpura ■ Autoerythrocyte sensitization

Key features

- Typically affects girls and young women with an underlying psychiatric illness and triggering stressors
- Painful, swollen ecchymoses occur spontaneously or at trauma sites

Introduction

In 1955, Gardner and Diamond described four women with an abnormal response to bruising characterized by the development of painful ecchymoses at sites of trauma followed by progressive erythema and edema.

Clinical features

This condition is seen almost exclusively in girls and young women, and in the majority of patients, it has been associated with psychiatric illnesses, especially depression[24,25]. Individuals report a sudden onset of painful, swollen bruises of variable size in any area of the body. Sometimes there are also prodromal symptoms. The lesions most commonly involve the extremities (lower > upper), usually resolve within a 2-week period, and typically recur. Original reports described appearance of these atypical purpuric lesions at sites of injection of a patient's own blood or other agents, hence the term autoerythrocyte sensitization. However, more recent reports have challenged the reproducibility of this finding.

Pathology

The histologic features of early lesions consist of edema, a minimal perivascular mononuclear infiltrate, and extravasated red blood cells in the upper dermis.

Differential diagnosis and treatment

Gardner–Diamond syndrome is a diagnosis of exclusion. Both child abuse and domestic abuse need to be considered[25]. Some clinicians view this disorder as a factitial disease, but proving a factitial origin is generally difficult. Gentle probing for an underlying, and potentially treatable, psychiatric condition may prove more productive than confronting the patient. Laboratory evaluation is generally unremarkable and histologic findings non-diagnostic. Patients may develop a lesion at the site of an intradermal injection of autologous washed erythrocytes. Some series report a high degree of success with psychological therapy, coupled with medications, most commonly selective serotonin reuptake inhibitors (SSRIs).

Paroxysmal Finger Hematoma

Synonyms: ■ Acute blue finger ■ Achenbach syndrome

Key features

- Recurrent acute episodes of painful ecchymoses on the palmar surface of one or more fingers

Clinical features

This idiopathic syndrome shares some similarities with Gardner–Diamond syndrome as it occurs primarily in females and may be preceded by prodromal symptoms such as pain, tingling, or itching. However, it has an older mean age of onset (48 years).

Recurrent painful ecchymoses develop on the palmar surface of the hand, primarily the fingers[26–28]. The right index finger is the most common site of involvement, and swelling may precede or accompany the ecchymoses. Evaluation is routinely negative, including Doppler ultrasonography, and is usually not indicated.

Differential diagnosis

Trauma, pernio, acrocyanosis, Raynaud phenomenon, and vascular insufficiency are often suspected, but the history, localization to the palmar surface, and time course aid in excluding these entities.

Treatment

While a variety of therapies have been tried, there is no specific successful treatment. The bleeding generally stops spontaneously, but pressure may be helpful. Typically, there is resolution within two weeks.

Onyalai

Onyalai is a Bantu name for a disease that often presents with hemorrhagic blisters in the mouth. It results from the consumption of sorghum grains contaminated with the fungus *Epicoccum sorghinum*. This fungus produces compounds which inhibit platelet aggregation and angiogenesis[29]. Onyalai may run a course indistinguishable from acute immune thrombocytopenic purpura (ITP). Literature regarding Onyalai is limited, treatment is unclear, and it appears to be less responsive to corticosteroids than is ITP.

Mondor Disease

Synonym: ■ Mondor syndrome of superficial thrombophlebitis

Key features

- Superficial thrombophlebitis affecting the anterolateral thoracoabdominal wall
- Pathogenic factors include trauma, surgical procedures, infections, and breast carcinoma
- Presents with the sudden onset of chest pain and subsequent appearance of a cord-like thrombosed vein

Introduction

Mondor disease is characterized by superficial thrombophlebitis of subcutaneous veins within the anterolateral thoracoabdominal wall, i.e. lateral thoracic, thoracoepigastric, and superior epigastric veins. Though previously reported by others, Henry Mondor provided a very detailed description of this condition in 1939[30]. A similar cord-like superficial thrombophlebitis can occur in other sites (e.g. the upper and lower extremities, abdomen, groin, penis).

Pathogenesis

Common pathogenic factors in chest wall thrombophlebitis include trauma, excessive physical activity, a surgical procedure on the breast, mastitis, a breast abscess, and pendulous breasts[30]. Up to 10% of patients with Mondor syndrome have an underlying breast carcinoma. Occasionally, the condition is associated with rheumatoid arthritis, filariasis, pregnancy, oral contraceptive use, intravenous drug use, intravenous catheters, a non-breast malignancy, or a hypercoagulable state (e.g. hereditary protein C deficiency, anti-cardiolipin antibodies).

Clinical features

A sudden onset of chest pain followed by the appearance of one or more visible or palpable cords (representing thrombophlebitic veins) typify this syndrome. Associated findings include tenderness, a sensation of tension, erythema, ecchymosis, pruritus, arthralgia, and rarely fever. Symptoms worsen on pulling the skin or elevating the breast and the ipsilateral upper extremity. The condition is usually unilateral and is three times more common in women than in men.

Pathology

A biopsy is rarely required. The process may involve arteries and lymphatic vessels as well as veins. Sclerosing endophlebitis with complete

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or partial obliteration of the lumen by thrombus and inflammatory cells is typical. The time period between the onset of the condition and ultimate recanalization of the affected vessels varies from 2 weeks to more than 6 months.

Differential diagnosis

The clinical presentation is unique, and etiologic factors should be identified. Recurrent superficial thrombophlebitis (migratory thrombophlebitis) is frequently associated with an underlying malignancy (Trousseau syndrome; most often pancreatic or lung carcinoma), a hypercoagulable state (inherited or acquired), or an inflammatory condition (e.g. Behçet disease).

Treatment

The disease is usually benign and self-limited, except when associated with breast cancer. Aching pain typically ends within 10 days, but the cord often persists for weeks to months and may be tender. Local heat, rest of the arm, and breast support can improve symptoms. The rate of recurrence is ~5%.

Additional figures available in our eBook (see inside front cover for access code).

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eFig. 22.1 Pigmented purpuric dermatosis (capillaritis). Schamberg disease with pinpoint petechiae within lesions. *Courtesy Kalman Watsky, MD.*



eFig. 22.2 Linear pigmented purpura. Linear array of yellow–brown macules. Clinically, the pinpoint hemorrhages were subtle but easily seen by dermoscopy. *Courtesy Jean L. Bolognia, MD.*



eFig. 22.3 Purpura annularis telangiectodes of Majocchi. Annular plaques with pinpoint petechiae within the border. *Courtesy Frank Samarin, MD.*



eFig. 22.4 Purpura annularis telangiectodes of Majocchi. Annular plaques with petechiae within the border. *Courtesy Julie V. Schaffer, MD.*

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eFig. 22.5 Capillaritis. Because the lesions were plaques and the patient was elderly, the possibility of a capillaritis-like presentation of mycosis fungoides was excluded. *Courtesy Kalman Watsky, MD*.



eFig. 22.6 Retiform purpura with bullae formation due to disseminated intravascular coagulation in association with *Klebsiella* pneumonia (A, B).

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