Clinics in
Dermatology

The rash that becomes purpuric, petechial, hemorrhagic, or ecchymotic

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Abstract Hemorrhagic rashes are observed in a wide variety of conditions, ranging from harmless to life-threatening. This review offers a stepwise approach, which helps limit the possible differential diagnoses based on the clinical manifestations and the clinical picture. The most common and most important conditions, including infectious, coagulation and embolic disorders, vasculitides, and vasculopathies, are briefly reviewed focusing on morphology. Dermatologists often need to distinguish among infectious, reactive, or autoimmune etiologies of the rash and determine if the condition is dangerous or even life-threatening in order to make the right decision. Dermatologic expertise provides vital input in the diagnosis and care of complex interdisciplinary patients, such as those with sepsis, purpura fulminans, and thrombotic thrombocytopenic purpura.
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Introduction

Hemorrhagic rashes include a very wide range of heterogeneous conditions resulting from infectious, reactive, or autoimmune processes. To further complicate the issue, many of the diseases causing such rashes are overlapping, or the interpretation of the morphology of the lesions might be dependent on their evolution; hence, the diagnostic process is not straightforward and could require a large panel of laboratory tests, investigations, and consultations.

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Definitions

A common definition of hemorrhagic efflorescence includes such lesions that cannot be pressed away with a transparent object, for example, a glass slide (nonblanchable). This distinguishes them from simple erythema, which results from widening of the blood vessels; hence, the application of external pressure leads to disappearance of the red color. The hemorrhagic lesions are the result of extravasated erythrocytes, and therefore they do not blanch on pressure.

For example, when analyzing the distribution of the rash, its symmetry provides clues to the diagnosis. A wide variety of conditions may present with a hemorrhagic clinical variant, such as *Herpes zoster* infection or cellulitis, neither of which is

an object of this review. In these two very common conditions, the distribution of the lesions is asymmetric. The hemorrhagic appearance could be a consequence of the toxins produced by the pathogens or just attributable to a concomitant anticoagulant therapy; likewise, a skin necrosis of any etiology might initially become visible as a hemorrhagic area.

A symmetric pattern of secondary hemorrhagic conditions is frequently observed on the legs, especially in elderly patients with varicosities or stasis dermatitis, even without concomitant anticoagulants. Any rash could be secondarily hemorrhagic on the legs in such patients, but the lack of a hemorrhagic component on other body parts helps in recognizing the secondary nature. Similarly, any rash could be secondarily hemorrhagic on the dependent parts (buttocks, back) in bedridden patients, as found in intensive care units or long-term care facilities.

In patients wearing compressive stockings, the areas under the stockings may be spared or less affected by a hemorrhagic rash. Extremities affected by peripheral arterial disease might be less affected, whereas extremities affected by venous stasis could be more involved.

Another important characteristic is the size of the hemorrhagic lesions. The smallest lesions are the petechiae (punctiform hemorrhages with an arbitrary limit of up to 4 mm), followed by purpura (sized up to 1 cm) and ecchymoses, which are larger. The size of the lesions corresponds to the amount of hemorrhage in the tissues. The petechiae stem from the capillaries; the purpuric lesions and the ecchymoses require a larger amount of extravasation of erythrocytes.

When larger vessels are occluded, a netlike appearance or arrangement of purpuric lesions is observed, the so-called retiform purpura. The arrangement of such purpuric lesions resembles the form of livedo reticularis and livedo racemosa. In retiform purpura, the affected vessels are the same size as those producing the livedo pattern.[1] Additionally, retiform purpura forms in the process of confluence in a netlike pattern

of smaller purpuric lesions, such as petechiae and ecchymoses in purpura fulminans and palpable purpura in vasculitis. The retiform purpura may be associated with livedo in conditions such as vasculopathies and vasculitis.[1–3]

Another characteristic of hemorrhagic lesions is their relation to inflammation. In purpura, when there is an inflammatory infiltrate, the lesions are palpable, for example, papules. Palpable purpura is the hallmark of and synonymous with small vessel immune complex vasculitis of the skin (Figures 1-3). In many cases, however, the infiltration might be minimal, and the clinical distinction between plain hemorrhage (petechiae or purpura) and palpable purpura is not always easy. In larger hemorrhagic lesions, such as ecchymoses, the larger amount of blood might make them palpable even without inflammation, or an inflammation may develop later. If necrosis, such as in eschars, develops within the larger hemorrhagic lesions, those become palpable as well.

A distinction is made between inflammatory and noninflammatory retiform purpura. In inflammatory retiform purpura, the early lesions have pronounced erythema due to the inflammation of the blood vessels, for example, in vasculitis (Figure 4). In noninflammatory retiform purpura, for example, that which is anticoagulant induced, there is a plain hemorrhage without inflammation. When the vessel occlusion occurs rapidly, however, even the vasculitis lesions might present with noninflammatory retiform purpura, such as in granulomatosis with polyangiitis (previously Wegener granulomatosis).[3]

Classification and algorithm

Because multiple conditions can have a similar clinical picture, the proposed algorithm in Table 1 might be helpful to limit the number of diagnoses to be considered according to the clinical presentation.

Fig. 1 Palpable purpura in a patient with small-vessel cutaneous vasculitis.

Fig. 2 Palpable purpura developing into larger hemorrhagic areas.

As a first step, it is advisable to exclude secondary hemorrhagic variants of common diseases, such as the cases of hemorrhagic zoster or cellulitis discussed previously. Several other dermatoses might frequently have hemorrhagic clinical variants, such as eczematous eruptions, insect bites, dermatitis herpetiformis, pemphigoid, or cutaneous lymphomas.

Many minor conditions may have hemorrhagic lesions, for which the affected patient may also seek medical attention, for example, senile purpura, where skin atrophy and loss of elasticity of cutaneous vessels due to actinic damage lead to fragility and purpura on chronic sun exposure areas, typically on the back of the hands and forearms. Similar changes may be localized to skin areas treated with topical corticosteroids or generalized in Cushing syndrome. Other benign conditions might include petechial purpura on the eyelids and cheeks due to vomiting or coughing. An acquired blood vessel fragility could be a sign of serious diseases, such as amyloidosis.

Nonfebrile/nontoxic purpuras

Petechial exanthems

An exanthem of tiny nonpalpable and noninflammatory petechiae on the skin and mucosae is typical and a hallmark of the thrombocytopenic purpura, but larger lesions might develop through confluence of the petechiae or after trauma. The afflicted areas are often those with increased static pressure, such as the feet and the legs. The extensor aspects of the extremities and areas under pressure or being rubbed by clothing and shoes are more prone. The mucous membranes can also be involved.

Those patients who develop such exanthems vary from being in good health to those with headache, somnolence, and coma, for example, due to meningeal petechiae, cerebral petechiae, or hemorrhages, respectively. With thrombocytopenia greater than 20,000/μL, there is generally no spontaneous bleeding.[4] With more reduced numbers of platelets, there may be increased bleeding (cutaneous, nasal, gingival, gastrointestinal, metrorrhagia). There are many diseases that cause petechial exanthems, and an overview of those is listed in Table 2. Platelet counts and platelet function tests are necessary to prove the diagnosis, as well as coagulation investigations that include prothrombin time, activated partial thromboplastin time, fibrinogen, and d-dimer to rule out a coagulopathy.

Hemophilic type of noninflammatory hemorrhagic exanthems

In this pattern of hemorrhagic exanthems due to coagulopathies, there are larger ecchymotic lesions.[4] These are usually asymmetrically distributed and sharply demarcated, with mucous membrane involvement, for example, sublingual hematoma in hemophilia, joint and muscle hematomas, and spontaneous bleedings. There are numerous hereditary coagulopathies with genetic deficiencies or functional impairments of almost all coagulation factors. Acquired variants are also known where autoantibodies against coagulation factors may develop in lupus erythematosus, hypothyroidism, bullous pemphigoid,[5] myeloproliferative diseases, and neoplastic diseases.

Mixed type of noninflammatory hemorrhagic exanthems

In this type of noninflammatory hemorrhagic exanthems, both petechial exanthems and extensive hemorrhagic lesions

mixed types of hemorrhagic exanthems, as in disseminated intravascular coagulation (DIC) syndrome and purpura fulminans, which are discussed in the section on febrile toxic hemorrhagic conditions.

Papular hemorrhagic exanthems

Vasculitis diseases with palpable purpura

The morphology of skin lesions in vasculitis corresponds to the size of the involved vessels. Palpable purpura is a typical cutaneous presentation of the small vessel vasculitis.

Palpable purpura lesions usually appear in crops. At the onset, they are flat erythematous macules or small urticarial papules that might resemble maculopapular eruptions. The initial lesions usually range from pinpoint to a few millimeters but might coalesce into large plaques in the course of the eruption. The initial macules and papules rapidly become more infiltrated and develop hemorrhagic dots or get partly or completely hemorrhagic and do not blanch on pressure (examples are shown in Figures 1-3).

Depending on the severity of the condition, necrosis might occur within the hemorrhagic areas; these are usually at first necrotic vesicles or bullae that evolve to shallow ulcerations. The legs are usually affected, as well as dependent areas and areas under pressure. The eruption can spread to the buttocks, arms, or abdomen, but the trunk is seldom affected. The appearance of lesions may be asymptomatic or associated with pruritus and burning.[6,7] The major histologic features are segmental areas of transmural neutrophilic infiltration with karyorrhexis (leukocytoclasis), fibrinoid necrosis, and extravasation of erythrocytes.

Lesions of palpable purpura may develop in various vasculitis conditions, which are briefly reviewed.

Cutaneous small vessel vasculitis

This condition is the most common type of vasculitis of the skin. Lesions of palpable purpura may appear in a single or few crops, and the course of the disease is often self-limiting. The patient's general condition is usually good, but systemic clinical manifestations may include fever, malaise, myalgia, arthralgia, or abdominal pain. The presence of systemic vasculitis, however, precludes the diagnosis of cutaneous small vessel vasculitis, which is, by definition, a single-organ vasculitis limited to the skin.

Systemic involvement should be excluded with history and laboratory tests, such as complement levels to exclude hypocomplementemia and testing for antineutrophil cytoplasmic antibody (ANCA) and rheumatoid factors, which should be negative. Urine tests are especially important because renal involvement may be subtle with no or only light findings. Additionally, a flare of only palpable purpura could be the initial manifestation of a limited form of systemic vasculitis, which

Fig. 3 Palpable purpura - haemorrhagic papules and plaques of different size, detail from the same patient as in Figure 2.

develop on the skin and mucous membranes. These include vessel wall–related hemorrhagic conditions, where mild disease can be petechial only or more prominent disease, including easy bruising and larger hemorrhages after minor and/or unnoticed trauma. These include scurvy, where perifollicular petechiae develop on the legs, along with spontaneous bleeding and easy bruising. Other examples of mixed-type hemorrhagic conditions include such genetic diseases as Ehlers–Danlos syndrome, Marfan syndrome, pseudoxanthoma elasticum, and acquired diseases such as amyloidosis and Cushing disease.

Additionally, significant hemorrhagic disorders, where both coagulation factors and thrombocytopenia occur, lead to

Fig. 4 Palpable purpura and inflammatory retiform purpura in a patient with cryoglobulinemic vasculitis. Necrotic vesicles and bullae have also formed.

may later progress to significant disease, requiring observation for several months subsequently.[8] An algorithm of laboratory tests for the diagnosis of primary cutaneous vasculitis has been proposed.[9]

IgA vasculitis (previously Henoch-Schönlein purpura)

IgA vasculitis is a small vessel immune complex vasculitis where the immune complexes contain IgA. It is the most common vasculitis in childhood, with more than half of all cases occurring before the age of 5 years.[10] Apart from the skin manifestations (palpable purpura), joints, kidneys, and the gastrointestinal tract might be affected as well.[6,8] The skin is always affected, whereas the other target organs are not always involved. The skin lesions in children seldom become necrotic and usually fade within 3 to 10 days.[6,7,10] Renal involvement appears as mild glomerulonephritis, but in 1% to 5% of patients, it might become recurrent and progress to renal insufficiency; this complication is more common in adults.

Table 1 Proposed algorithm based on the general condition and the type of the hemorrhagic exanthem.

1. Exclude:		
Secondary hemorrhagic variants of common diseases (zoster, erysipelas/cellulitis, common dermatoses), hemorrhagic skin necrosis		
Limited or secondary hemorrhagic eruptions (senile purpura - areas with solar damage; topical corticosteroid abuse; petechiae on the eyelids and cheeks due to vomiting)		
2. Define general condition, febrile/toxic?		
3. Define the primary and the predominant morphology		
Morphologic types	Non-febrile/ non-toxic	Febrile/toxic
Petechial	Thrombocytopenic conditions; platelet dysfunction; thrombocythemia; vessel wall conditions	Petechial and "capillary toxic" exanthems- scarlatiniform exanthems; viral hemorrhagic fevers
Hemophilic Type	Genetic and acquired coagulopathies	
Mixed type	Vessel wall related hemorrhagic conditions; scurvy; genetic conditions such as Ehlers Danlos and Marfan Syndromes, etc.	Purpura fulminans
Papular Exanthems	Palpable Purpura – Vasculitis	Systemic vasculitis such as ANCA associated vasculitis; systemic PAN
	Pigmented purpuric dermatoses	Papulonecrotic purpuric exanthems-Osler nodules; ecthyma gangrenosum; disseminated gonococcal infection
Retiform purpura	Embolic conditions; Nicolau syndrome; anticoagulant induced necrosis; calciphylaxis; vasculopathies; anticardiolipin syndrome	Septic vasculitis Purpura fulminans Thrombotic thrombocytopenic purpura; HELLP syndrome

ANCA – antineutrophil cytoplasmatic antibody; HELLP – hemolysis, elevated liver enzymes and low platelet count; PAN – polyarteritis nodosa.

Table 2   Diseases and conditions leading to petechial noninflammatory exanthems

Platelets related	Decreased platelet counts	Idiopathic (immune) thrombocytopenic purpura, autoimmune, (lupus erythematosus), hereditary thrombocytopenic purpura, neoplastic, toxic or drug-induced bone marrow suppression, HIV-associated thrombocytopenia, heparin-induced thrombocytopenia (HIT I and II), increased platelet destruction—secondary splenomegaly, initial stages of consumptive thrombocytopenia (DIC, thrombotic thrombocytopenic purpura, HELLP syndrome), etc.
	Platelet dysfunction	Hereditary, drug-induced, eg, ASA, clopidogrel, metabolic–uremic, alcohol abuse.
	Increased platelet counts	Myeloproliferative conditions with increased platelets accompanied by structural and/or functional abnormalities, ie, essential thrombocythemia, hemorrhagic diathesis, hypercoagulability, thrombophilia. Microvascular occlusion with livedo racemosa, ulcers, acrocyanosis.
Vessel wall related		Petechial or mixed type with more prominent disease, including metabolic conditions, ie, renal insufficiency, scurvy with perifollicular petechiae; Ehlers–Danlos syndrome, pseudoxanthoma elasticum, senile purpura, topical corticosteroid abuse, Cushing disease, amyloidosis.

ASA, acetylsalicylic acid, ; DIC, disseminated intravascular coagulation; HELLP, hemolysis, elevated liver enzymes; HIT, heparin-induced thrombocytopenia.

Vasculitides featuring additional manifestations to palpable purpura

Cryoglobulinemic vasculitis

Cryoglobulinemic vasculitis is a systemic vasculitis where the immune complex deposits contain cryoglobulins and are associated with serum cryoglobulinemia.[11] The cryoglobulins are present in the body as immune complexes, and their deposition in blood vessels triggers complement activation and systemic vasculitis.[6] It usually presents with palpable purpura and hemorrhages, urticarial lesions, arthralgias, and malaise. Acral involvement is more pronounced, up to acral hemorrhagic necroses and gangrene, but the face is usually spared. Apart from palpable purpura described previously, there could be small nodules, retiform purpura (Figure 4), livedo racemosa, and larger skin necroses than usually seen with small vessel cutaneous vasculitis[12] (Figure 2).

On histology from skin biopsy results, there is the additional feature of hyaline plugs in the small arterioles. Apart from skin involvement, peripheral neuropathy and renal involvement, such as nephritic syndrome or membranoproliferative glomerulonephritis, are also common. Diagnostic criteria for cryoglobulinemic vasculitis have been proposed.[13] The major etiologic factor for mixed cryoglobulinemia and cryoglobulinemic vasculitis is the chronic hepatitis C infection, but other viral pathogens, including HIV, connective tissue diseases, lymphoproliferative diseases, and hematologic malignant neoplasms may also cause cryoglobulinemic vasculitis.[14,15]

Urticarial vasculitis

Urticarial vasculitis comprises a spectrum of conditions with the clinical appearance of chronic urticaria and histology of cutaneous small vessel leukocytoclastic vasculitis. It ranges from a mild condition and normal complement levels to hypocomplementemic UV, where some of the patients even fulfil the criteria for systemic lupus erythematosus.[6,7] UV is considered an immune complex–mediated type III hypersensitivity reaction, similar to serum sickness.[6] The current Chapel Hill classification defines only the hypocomplementemic vasculitis and requires the presence of C1q autoantibodies,[11] excluding many of the patients with the more common milder condition (normal complement UV)[16] who nevertheless have a reduced quality of life and search dermatologic treatment.

The skin lesions in UV resemble the typical wheals of chronic urticaria but persist longer than 24 hours and change shape slowly, if at all. Angioedema might accompany the eruptions. Subjectively, there is burning and tenderness rather than itching. The wheals of UV always have a hemorrhagic component, but usually its only expression is the hyperpigmentation left over after the wheals disappear (Figure 5). Less often, the hemorrhagic component of the wheals might be revealed on blanching or even visible as hemorrhagic areas in or on the borders of the wheals. In patients with more pronounced hemorrhagic component, the subsiding of the wheals might undergo the typical color changes due to hemoglobin breakdown with yellowish to greenish hues before the final brownish color is reached. Systemic findings might include arthralgias and joint swelling, fever, abdominal pain, diarrhea, vomiting, and dyspnea, occurring more often with hypocomplementemic UV.[6,17] Whereas normocomplementemic UV is usually confined to the skin, systemic involvement with glomerulonephritis, ocular manifestation (iritis, episcleritis, uveitis), lymphadenopathy, and bronchospasms or obstructive pulmonary disease may be present in patients with hypocomplementemic UV and may be severe enough to cause renal of pulmonary insufficiency.[18]

The diagnosis of UV requires a histologic confirmation of the leukocytoclasis, which might prove difficult because the signs of vascular injury and leukocytoclasis are much milder than in palpable purpura. Alternatively, the detection of C1q antibodies in serum may confirm the diagnosis.

UV might be a skin manifestation of a connective tissue disease such as Sjögren syndrome and systemic lupus erythematosus, or of hematologic malignant neoplasms,

Fig. 5 Urticaria vasculitis - wheals and brownish hyperpigmentation in a patient with hypocomplementemic urticaria vasculitis.

gammopathies, infections (including hepatitis B virus and hepatitis C virus), drug reactions, cold urticaria, etc.[6,7]

Beyond the vasculitis treatments such as corticosteroids, hydroxychloroquine, and immunosuppressants, there is also a place for the modalities for urticaria (including antihistamines and even omalizumab[19]) in the treatment of UV.

ANCA vasculitides

In contrast to the immune complex small vessel vasculitides described previouslyabove, the ANCA associated vasculitides have little or no detectable deposits of immunoglobulins or complement in the vessels on direct immunofluorescence (hence "pauci-immune"[6,11]). The ANCA antibodies are considered "markers" of these diseases and not all of the patients included have detectable ANCAs.[11]

Microscopic polyangiitis

Microscopic polyangiitis is a necrotizing ANCA-associated systemic vasculitis without granulomatous inflammation that may affect the small- and medium-sized arteries in addition to the predominantly affected small vessels.[11]

Skin involvement is found in 30% to 60% of patients with microscopic polyangiitis and is the presenting manifestation in 15% to 30% of patients.[20,21] The cutaneous signs include mostly palpable purpura similar to the small vessel cutaneous vasculitis, but retiform purpura, livedo racemosa, and nodules might be present as well.[21] In contrast to classic polyarteritis nodosa (PAN), in microscopic polyangiitis there are often pulmonary findings and necrotizing glomerulonephritis. Almost 80% of patients are found to have P-ANCA antibodies, which are considered to play a role in the microscopic polyangiitis pathogenesis.[21]

Granulomatous ANCA vasculitides

Granulomatosis with polyangiitis (previously Wegener's granulomatosis) and eosinophilic granulomatosis with polyangiitis (previously Churg–Strauss disease) are included in the group of the ANCA antibody-associated granulomatous vasculitides.

Granulomatosis with polyangiitis (Wegener's granulomatosis)

Granulomatosis with polyangiitis (GPA) is a systemic small to medium vessel necrotizing ANCA vasculitis with granuloma formation and a typical predilection for the upper airways and kidneys.[6,22,23]

In the course of GPA there might be phases of limited disease alternating with severe multiorgan exacerbations.[22,24] Only up to 15% of the patients with limited GPA may show cutaneous involvement, including palpable purpura and ulcerations. Skin lesions are more common in severe multiorgan disease, where up to 50% of the patients develop cutaneous signs. These are variable and range from palpable purpura, subcutaneous nodules, livedo, inflammatory or (seldom) non-inflammatory retiform purpura, ulcers, and digital infarcts. In addition to these unspecific vasculitic lesions, there might be polymorphous necrotic papules and nodules (papulonecrotic lesions) favoring the extensor surfaces of the extremities, for example, mobile nodules in the dermis similar to the rheumatic nodules, which tend to ulcerate and are frequently located over the elbows.[6] Additional signs include mouth ulcers and gingival hyperplasia. An important feature is the pyoderma gangrenosum-like ulcerated nodules, which distinguish the GPA from other vasculitides.[22]

More than 80% of patients with PGA are positive for cANCA, but these are not essential for the diagnosis. The typical histologic features of neutrophilic vasculitis and granulomatous inflammation are characteristic for the different phases and are usually not found simultaneously in the same patient or in the same histologic preparation.[22]

Eosinophilic granulomatosis with polyangiitis (Churg–Strauss disease)

Eosinophilic GPA is a systemic necrotizing ANCA vasculitis of the small to medium vessels with granulomatous inflammation and typically associated with asthma and eosinophilia.[6,22]

Eosinophilic GPA usually has a prolonged course evolving through 3 phases. The first stage represents allergic rhinitis, nasal polyps, asthma, and other atopic conditions and may have prolonged course; however, there are rare nonasthmatic cases or even patients with vasculitis preceding asthma.[22,25] In the second phase, there is tissue eosinophilia affecting one or more organs (for example, eosinophilic pneumonia) and blood, and frequent relapses are typical. In the third phase vasculitis develops involving multiple organs, less frequently the kidneys and more frequently the heart, which is the leading cause of death.[22] Only 30% to 40% of patients have ANCA, but these patients experience more pronounced vasculitis involvement.[25] All the EGPA Patients with necrotizing glomerulonephritis are ANCA-positive.[11] In the vasculitis phase, the skin involvement is often present together with neurologic involvement, usually mononeuritis multiplex.[6,22] The cutaneous manifestations (present in 40% to 70% of patients[26]) include unspecific vasculitis lesions, such as palpable purpura, retiform purpura, livedo, subcutaneous nodules, necrosis, and ulcers. Additionally, there might be urticarial lesions or papulonecrotic lesions, as in GPA, typically on the extensor surfaces of the limbs. A specific cutaneous manifestation in EGPA, absent from other vasculitides, is the development of erythematous and edematous to indurated plaques, reminiscent of Wells syndrome (eosinophilic cellulitis), which may have an active edge and livid center.

Histologically, both granulomatous and vasculitis features might be present simultaneously in contrast to GPA.[6,22] Tissue eosinophilia, granulomatous dermatitis, and eosinophil-rich neutrophilic vasculitis are the cardinal features.

Medium vessel vasculitis

Polyarteritis nodosa

PAN is a rare multisystem necrotizing vasculitis involving mainly the medium-sized vessels. A variety of organs might be affected, but the lungs are spared.[6,11,27] When present, the renal involvement is typically at the level of the preglomerular arteries, causing renal hypertension and/or renal insufficiency without glomerulonephritis, which is the manifestation of the involvement of the smaller vessels.

The cutaneous lesions are typically located on the legs and less frequently on the arms and trunk. Palpable purpura may be present, but the typical findings include livedo racemosa and retiform purpura with starburst pattern of livid to hemorrhagic reticular streaks. Subcutaneous nodules 0.5 to 2 cm in diameter and clusters of nodules forming painful plaques along the involved superficial arteries are also typical and frequently lead to ulceration with "pinched out" ulcers. Digital necrosis and gangrene follow vascular involvement of the middle-sized vessels of the fingers and toes.

In the current classification, PAN is not associated with ANCA, and patients positive for ANCA antibodies should not be classified as having PAN.[11] ANCA, rheumatic factors, and antinuclear antibody are typically negative.

More than 30% of PAN cases are due to hepatitis B virus infection, and these are classified separately because of the importance for the treatment.[11,15] The incidence of PAN is considered to be decreased after the widespread vaccination programs.[15]

Cutaneous PAN

Cutaneous PAN is a rare, benign, single-organ variant of polyarteritis nodosa with a better prognosis and with only skin involvement. Some patients with cutaneous PAN may progress to more limited forms of systemic PAN.

The cutaneous manifestations are the same as in systemic PAN, but the subcutaneous nodules are more common, typically located on the legs, sometimes extending proximally and onto the arms. The nodules are painful, may ulcerate (Figure 6). The prognosis is favorable, but the course may be protracted and relapsing.

Pigment purpura type of hemorrhagic exanthems

Pigmented purpuric dermatoses (PPDs) are a group of rare hyperpigmented dermatoses presented by petechiae and purpura, which usually have a chronic course and a benign prognosis.

The most typical sign of a PPD is discoloration characterized by an orange-brown shade and multiple speckles resembling sprayed cayenne pepper. The standard classification of PPDs includes five clinical entities: Schamberg's purpura (SP), Majocchi's purpura, lichen aureus, Gougerot–Blum purpura, and eczematoid-like purpura of Doucas and Kapetanakis (EPDK).[28] Some other subtypes of purpuric dermatoses are also known, for example, itching purpura of Lowenthal, lichen purpuricus, transitory pigmented purpuric dermatosis, linear pigmented purpuric dermatosis, and a granulomatous variation of PPDs. The places of predilection for PPDs are usually the legs. The only symptom might be pruritus or no sign other than discoloration. It is often hard to differentiate one type of PPD from another due to the subtle markers of distinction, whether

Fig. 6 Livedo racemosa with ulcers in a patient with PAN. PAN - polyarteritis nodosa.

Fig. 7 Pigment purpura on the forearm.

clinical or histopathologic expression. There is also frequent overlapping (Figures 7 and 8).

The etiology and pathogenesis are often in flux.

- SP affects all ages, mostly men, although it is possible for it to appear in preadolescents.[29]
- Purpura annularis telangiectodes of Majocchi (PATM) is mostly limited to girls and young women.
- For the eczematoid-like purpura of EPDK, the data show that the average age of patients is 54.2 years, with a slight prevalence for women. EPDK rarely affects children.[30]
- Gougerot–Blum syndrome (GBS) is typical for men in the age range of 40 to 60 years.
- Lichen aureus commonly occurs in young adults.

Triggers for SP could be medications, medical conditions, such as venous hypertension, gravitational dependency, capillary fragility, and contact allergy to wool, and external factors, such as clothing dyes, trauma, or exercise.[31] The etiology of PATM is unknown, although viral[32] or bacterial[33] infections may increase susceptibility to PATM. As for SP, some drugs (eg, aspirin, carbamazepine, and acetaminophen), gravity, and hypertension may contribute to the condition in an unknown mechanism.[34]

Among the risk factors for EPDK, increased venous pressure, capillary fragility, contact dermatitis to aniline dyes, physical exercise, focal infections, foods with chemical additives, and alcohol intake are all suggested. Medications (eg, infliximab)[35] have also been reported to trigger EPDK (Table 3).

The most important risk factors for GBS are infections, physical exercises, venous hypertension, and capillary fragility.

Clinical presentation

Schamberg's purpura

Synonyms: progressive pigmentary dermatosis of Schamberg, purpura pigmentosa progressiva, Schamberg's disease.

SP is the most widespread of PPDs. The usual localization of SP is the legs, but it can affect the rest of the body as well. Asymmetry is typical for SP; the number of patches differs on both sides. The skin in SP becomes covered with many oval or irregular plaques and patches with orange-brown color. The plaques either become darker or clear by themselves. The color results from the presence of hemosiderin. The pathognomonic "cayenne pepper" macules can be seen inside old lesions and on their borders. The macules are actually petechiae, which may remain after pressure from diascopy.

Fig. 8 Pigment purpura, detail from the same patient as in Figure 7.

The disease takes a chronic course but is usually asymptomatic. There is a subgroup of SP defined as transitory PPD or Schamberg-like dermatitis, which is pruritic and tends to fade within less than a year.[36]

Majocchi's purpura

Synonyms: purpura annularis telangiectodes, Majocchi capillaritis, Majocchi's disease.

Localization of PATM is symmetrical on both legs. In time, the lesions progressively affect the rest of the body. PATM is presented by punctate telangiectatic macules, evolving into annular hyperpigmented patches clarifying in the center. Atrophy could be also noticed but is unusual. The patches have distinctive limits, the diameter is about 1 to 3 cm. Fortunately, neither pain nor itching is experienced.

Eczematoid-like purpura of Doucas and Kapetanakis

Synonyms: eczematoid purpura, eczematoid-like purpura, itchy purpura; disseminated pruriginous angiodermatitis.

In EPDK, the trunk is usually affected along with the extremities. The Doucas and Kapetanakis PPD is known for its widespread, eczematous look and scales on top of the plaques.[37] The pruritus is severe, and lichenification could appear.

Gougerot–Blum syndrome

Synonyms: pigmented purpuric lichenoid dermatitis, pigmented purpuric lichenoid dermatitis of Gougerot and Blum.

Lesions in GBS generally appear on the legs, arms, and trunk. Sometimes, only one leg is affected, whereas in others, the arms and trunk are covered, too. GBS resembles progressive pigmented purpura and differs by having bright undersized, sometimes pruritic lichenoid papules that may progress through pink to orange to brown.

Lichen aureus

Synonyms: lichen purpuricus.

Localization is mainly on the lower legs. Rash is presented by discrete or confluent golden, rust-colored to brownish lichenoid macules and papules. The lesions are often solitary, usually symptomless, and may persist for years.

The granulomatous variation of PPDs is very rare. It has a chronic course and localization to the lower parts of the legs. As opposed to other types, the predilection spot is on the back of the feet, but typical PPD lesions may appear elsewhere.[38] For the granulomatous variation of PPDs, red to brown macules and papules are typical.[39]

Dermatoscopic findings of PPDs showed multiple red to purple globules or dots over a purpuric background, which later become an orange-brown color.[40] The dermatoscopic findings correspond histopathologically to the extravasation of red blood cells and an increased number of blood vessels.

Histopathology: the cause of all types of chronic pigmented purpuric dermatoses is inflammation, involving the upper portion of the dermis. The infiltration consists mainly of lymphocytes and macrophages. Significant variations in the extent, density, and distribution of the inflammatory infiltration are possible. The main population of lymphocytes consists of the CD4+ helper phenotype. The presence of CD1a+ dendritic cells is also notable.[41] Some authors define chronic pigmented purpuric dermatoses as lymphocytic vasculitis, or at least as lymphocytic capillaritis. It should be considered that there are no specific signs of leukocytoclastic vasculitis such as leukocytoclasis and fibrinoid necrosis of the vessel walls. A distinctive mark for early lesions is the extravasation of red blood cells in the papillary dermis. Perls' stain proves the presence of iron (hemosiderin), and Masson–Fontana stain demonstrates the absence of melanin pigment.

In SP, topical and systemic drugs have failed to achieve consistent results until now. Treatment with colchicine proved to suppress relapses. The data from pentoxifylline application seem promising.[42] Narrowband UVB therapy has yet to defend its reputation[43] as an effective method for SP treatment.

As a rule, PATM has a benign prognosis; however, it might be persistent to treat for years. The standard treatment is application of topical corticosteroids. In cases of a large area of affection, systemic steroids may be introduced for a short period of time. Impressive results achieved by narrowband UVB and

Table 3　Pigment purpura type of hemorrhagic exanthems—main features

PPDs	Age and sex	External factors	Drugs	Internal factors	Contact allergy	Usual localization	Clinical characteristics
SP	all ages, mostly men	textile dyes, trauma, exercises	aspirin, carbamazepine, acetaminophen		contact dermatitis to wool	legs, asymmetric distribution	oval or irregular plaques and patches, orange-brown color, cayenne pepper macules
PATM	children and young adults, mostly female	infections: viral or bacterial	aspirin, carbamazepine, acetaminophen	gravity, hypertension	no data	legs, symmetric distribution	Telangiectatic macules, hyperpigmented patches, central clearance
EPDK	average 54 years, female prevalence	physical exercises, focal infections, alcohol intake	infliximab	increased venous pressure, capillary fragility	contact dermatitis to aniline paints	trunk	widespread eczematous-like plaques
GBS	middle-aged men	systemic diseases, infections, foods, physical exercises	no data	venous hypertension, capillary fragility	no data	legs, arms, trunk	minute lichenoid papules
LA	young adults	infections, physical exercises, energy drinks	no data	venous insufficiency, perforator vein incompetence	no data	legs	golden to brownish lichenoid macules and papules

EPDK, eczematoid-like purpura of Doucas and Kapetanakis; GBS, Gougerot–Blum syndrome; LA, Lichen aureus; PPD, pigmented purpuric dermatosis; SP, Schamberg's purpura.

psoralen plus UVA therapy have been acknowledged by some authors.[44]

Multiple therapeutic options have been tested in treating EPDK. There are supporters for narrowband UVB[45] and psoralen plus UVA for topical corticosteroids and tacrolimus. Systemic treatment includes oral intake of cyclosporine, griseofulvin, bioflavonoids, and ascorbic acid.

In GBS, immediate clinical response to steroid cream has been reported multiple times. Psoralen UVA treatment has also achieved contenting results. Another choice is narrowband UVB therapy.[46]

Lichen aureus is usually therapy resistant. Treatment modalities include topical steroids, topical calcineurin inhibitors, and psoralen UVA.

Nonfebrile/nontoxic retiform purpura

Embolic conditions

Embolic conditions of noninfectious etiology, including cholesterol emboli,[47] fat emboli after long bone fracture,[2] or in atrial myxoma, may cause hemorrhagic lesions in an acral distribution and must be distinguished from vasculitis[48] and sepsis.

Drug-induced retiform purpura is a local complication known as Nicolau syndrome, which may be caused by injections with macromolecular substances such as glatiramer acetate.[49] The embolization of vessels is a known complication from injection, usually intramuscular but also intravenous and subcutaneous. Medicaments such as corticosteroids, depot penicillins, vaccinations, interferons, and hyaluronic acid fillers are implicated.[50] Initially, the affected area is pale, accompanied by a strong pain, and with ensuing livedo racemosa, which turns hemorrhagic and into retiform purpura. Necroses develop in the hemorrhagic areas, which might be deep and involve the underlying muscles and leave scars.

Intravenous drug abuse could also cause embolization and Nicolau syndrome, but case series of conditions due to levamisole adulterated cocaine[51] reveal very pronounced retiform purpura on large body areas. Levamisole, used to adulterate the cocaine, is at least partly[52] responsible for some of the cases or for atypical presentations.[53] Cases with drug-induced ANCA vasculitis due to cocaine are also described.[54]

Anticoagulant-induced necrosis

Coumarin-induced necrosis is a rare complication, commonly seen in patients with heterozygous protein C deficiency. Large painful areas of retiform purpura usually develop in areas rich in subcutaneous fat tissue, such as the thighs and abdomen, but the legs could also be affected. A similar condition could be induced by heparin, as in low molecular weight heparins in heparin-induced thrombocytopenia. Type 1 is nonimmunologic and develops within the first days of therapy. Type

II is antibody related, develops after 5 to 14 days of therapy, and might include life-threatening thromboses. The skin could be affected with skin necroses similar to the coumarin necroses. These are usually localized to the injection sites in patients with subcutaneous injections, but distant locations might be observed well after intravenous application.

Calciphylaxis

The vascular occlusion is due to calcium deposits in the blood vessels, which could be seen on histology. The patients are initially diagnosed as having infiltrated subcutaneous plaques, which later become livedo racemosa, evolving into hemorrhagic and retiform purpura. Finally, there may be painful necrosis and ulceration. The predilection sites include areas rich in subcutaneous fat tissue (ie, thighs, abdomen, and the gluteal area). A distal variant[55] of calciphylaxis affects the acral areas and might lead to necroses, gangrene, and loss of digits. This variant might be difficult to differentiate from septic vasculitis or embolic conditions, and capturing the affected vessels with calcium deposits for histology is essential.

Vasculopathies

Vasculopathies include a multitude of conditions due to impaired blood rheology, coagulopathies, and embolization; paraproteinemias; and hypercoagulation states, such as anticardiolipin syndrome, protein C and S deficiencies; and hypergammaglobulinemias. These often induce livedo reticularis or livedo racemosa, in rare cases leading to retiform purpura and skin necroses.

Febrile/toxic hemorrhagic exanthems

Petechial

Scarlatiniform or "capillary toxic" eruptions present with tiny petechial macules on the background of diffuse redness and/or swelling of the skin or blurry red confluent edematous papules; tropical viral hemorrhagic fevers such as Ebola and Marburg hemorrhagic fevers, dengue, yellow fever, Crimean-Congo fevers, and others, which may start as petechial but may progress to ecchymoses or vasculitis-like infections. Sudden onset of fever and myalgias, as well as a history of contact or travel in endemic regions suggest the diagnosis.

Palpable purpura and vasculitis-like infections conditions

Pathogens that cause intracellular infection of the endothelial cells, typically rickettsial diseases, lead to vascular damage either through the pathogenic or the immune response (or both) and a clinical picture very similar to immunocomplex vasculitis. Typically, such rickettsial infections are Rocky Mountain spotted fever and epidemic and endemic typhus are implicated as well as malaria.[15]

Papulonecrotic purpuric exanthems/septic embolic conditions

Septic emboli could arise not only within the acute setting of sepsis but also in patients with subacute endocarditis. Painful hemorrhagic nodules are found on the fingers and toes, usually on the distal phalanges, as a consequence of infected thrombotic embolization, known as Osler nodes. Other acral manifestations are palmar and plantar petechiae, called Janeway macules. Such petechiae are also the reason for splinter hemorrhages. Small petechiae could be seen not only on the acral areas but also on the mucous membranes including the conjunctiva. In bacteremia of any origin there could be septic thrombi on the skin or hematogenic dissemination to the skin, where the lesions appear as hemorrhagic papules and nodules with the tendency to central necrosis and ulceration. These could be similar to palpable purpura or papulonecrotic lesions in GPA, and, as discussed in the paragraph on septic vasculitis, such lesions could show true vasculitis on histology.[17,56] An example could be the disseminated gonococcal infection, where a few disseminated macules with a hemorrhagic component develop to hemorrhagic papules or pustules with central necrosis. Another example is ecthyma gangrenosum, where usually immunosuppressed or neutropenic individuals develop anywhere on the body (perianal areas could be preferred) macules and plaques that progress to hemorrhagic necroses und ulcers.[56,57]

Retiform purpura in febrile or acutely ill patients

Septic vasculitis

Within both the clinical and histopathologic manifestations of sepsis and bacteremia, true immune complex vasculitis may be present [17,58]. Clinically, there may be palpable purpura, retiform purpura, or hemorrhagic nodules that may accompany rapid deterioration of the patient's general condition. Pustules might develop within the hemorrhagic lesions, and the causative microorganisms may sometimes be isolated from the skin lesions. Small- and medium-sized vessels are involved, as well as the superficial and deep vessels of the dermis and subcutis. The hemorrhagic areas might be extensive, and the septic embolization of middle or large vessels may lead to acral infarctions, which present clinically as hemorrhagic necroses. Patients may lose digits or extremities. The condition may quickly progress to purpura fulminans. Blood cultures should be obtained in such patients, and the clinicians should be on alert for signs of sepsis, including fever attacks, blood pressure fall, tachycardia, and somnolence.

Purpura fulminans

Purpura fulminans is a very rare but dramatic and life-threatening syndrome and must be treated as an emergency in internal medicine and dermatology.[59] It is characterized by the sudden development of intravascular thrombosis and hemorrhagic infarction of the skin rapidly leading to DIC with consumption of anticoagulant factors and signs of shock. Purpura fulminans (PF) usually occurs in infants and children, but it has also been reported in adults. It may be classified as (1) neonatal purpura fulminans with heritable protein C and protein S deficiency, (2) purpura fulminans in severe sepsis, or (3) postinfectious purpura fulminans.

Neonatal purpura fulminans with heritable protein C and protein S deficiency

Neonatal PF develops as a complication in approximately 1:500,000 to 1:1,000,000 live births.[60] It is caused by a hereditary deficiency of the natural anticoagulants protein C or protein S. Partial protein C deficiency caused by heterozygous *PROC* mutations has a reported incidence of 1 in 200 to 500 individuals and is a risk factor for adult-onset venous thromboembolic disease.[61] In contrast, PF arises when there is a severe loss of protein C anticoagulant function caused by homozygous or compound heterozygous *PROC* mutations. Severe heritable deficiency of protein S arises from pathologic mutations in the *PROS1* gene and is exceptionally rare.

The onset of neonatal PF is within the first 72 hours after birth, with purpuric lesions over many different skin sites, including the perineal region, the flexor surface of the thighs, and the abdominal skin. PF lesions initially appear as well-demarcated erythematous macules that progress rapidly to develop irregular central areas of blue-black hemorrhagic necrosis typically surrounded by a thin border of erythema. PF lesions become painful, dark, and raised, sometimes with vesicle or bulla formation. Even if early PF lesions may be reversible with adequate therapy, established lesions progress within 24 to 48 hours to full-thickness necrosis of the skin or even deeper soft tissues that may require surgical debridement, fasciotomy, or amputation. Histologically, occlusion of small dermal vessels with microthrombi causing capillary dilation and congestion with red cells is found in early PF. In later stage lesions, there is irreversible endothelial ischemic injury with extravasation of blood cells into the dermis and necrosis.[62]

Thrombocytopenia is often evident. Infants with severe genetic protein deficiency and neonatal purpura fulminans tend to experience recurrent episodes despite therapy with long-term anticoagulation.

Purpura fulminans in severe sepsis

The appearance of PF may be a presenting feature of severe acute sepsis and is a cardinal feature of meningococcal septicemia, which is complicated by PF in 10% to 20% of the cases.[63]

This is the most common form of PF. Less common pathogens are *Streptococcus*, *Haemophilus*, and *Staphylococcus* (including toxic shock syndrome with PF) species, particularly in asplenic patients.[64–66]

The acute inflammatory response in severe sepsis may lead to DIC. Bacteria can be found in damaged vessels, suggesting that vascular wall infection causes endothelial damage and skin lesions in acute sepsis-associated PF.[67] This results in microvascular thrombosis in the dermis causing PF.

PF in severe sepsis may be distinguished from PF of other causes by typically developing in the distal extremities and progressing proximally or appearing as a generalized or diffuse rash affecting the whole-body surface. In the idiopathic purpura fulminans, the thighs, buttocks, and trunk are preferably affected.[68] Initially, PF might show the clinical picture of a palpable purpura, which rapidly progresses to involve large acral areas, and the skin involvement might precede the onset of the septic shock, for example, in approximately 50% of the patients with pneumococcal sepsis.[68,69] The hemorrhagic areas affect the whole fingers or hands, and bluish or black necrosis forms within such areas. Not only the acral areas, but also areas of pressure, lips, cheeks, and broad areas on the trunk might be affected.

PF caused by severe sepsis is also usually accompanied by microvascular thrombosis and hemorrhagic infarction in other tissues, especially the lungs, kidneys, central nervous system, and adrenal glands. The clinical features of sepsis and PF are therefore accompanied by multiorgan failure that is rapidly progressive and associated with high mortality.

Postinfectious purpura fulminans

Most cases of postinfectious PF occur in children, and more than 90% are preceded by a clinically manifested infection, commonly varicella or streptococcal infection. The purpura usually begins suddenly, a few days to weeks after the onset of a febrile infectious disease, with the development of well-demarcated, rapidly enlarging, erythematous, or purplish macules progressing within hours through to hemorrhagic cutaneous necrosis, accompanied by disbalanced coagulation factors. The lesions develop as a rule on the lower body, especially the thighs, legs, and buttocks, as well as on the scrotum and penis. Postinfectious PF typically spares the distal extremities. Systemic microvascular thrombosis and multiorgan failure are uncommon in this form. Affected children typically show a severe acquired deficiency of protein S caused by cross-reacting IgG autoantibodies that increase protein S clearance from the circulation.[70] PF caused by autoantibodies against protein C is rarely reported.[71]

Laboratory tests are the primary diagnostic tools for PF. Typical findings are those of an associated DIC, with prolonged plasma clotting times, thrombocytopenia, reduced plasma fibrinogen concentration, raised plasma fibrin-degradation products, and, occasionally, microangiopathic hemolysis. This pattern of abnormalities is not specific to PF and may occur in DIC of any cause.

Once PF is suspected, workup including blood cultures should begin immediately to identify an underlying infection.

Measurement of protein C and protein S levels are important additional investigations that should be performed at presentation. PF is usually associated with reduced protein C or protein S levels. When PF is suspected in a newborn, urgent measurement of protein C and protein S levels in the parents should be performed. The demonstration of a partial reduction in one of those proteins in both parents is highly suggestive of severe heritable protein C or protein S deficiency in the affected neonate.

In the differential diagnosis of PF, calciphylaxis, coumarin necrosis, necrotizing fasciitis, thrombotic thrombocytopenic purpura (TTP), toxic shock syndrome, vasculitis, and thrombophlebitis have to be considered.

Mortality in PF is high with reports ranging from 60% for distal lesions to as high as 90% for truncal and widespread lesions.[72] Death is usually the result of common and often severe complications, including sepsis, vascular compromise, and limb amputation. Calciphylaxis, if present, is a grave complication that typically results in death. Therapeutic measures such as anticoagulation and clotting protein replacement therapy also have inherent risks, including bleeding and systemic thromboses.

PF of any cause is a hematologic emergency that requires urgent intervention. Most cases of PF in neonates and older children are initially assumed to have a septic cause and are managed with full supportive care involving broad spectrum antibiotics with activity against a variety of pathogens, including *Neisseria meningitidis*, streptococci, and methicillin-resistant *Staphylococcus aureus*, as well as adjunctive therapies. Intravenous immunoglobulin therapy should be considered because these preparations contain significant antibodies against the causative exotoxins.[73] PF with DIC also requires urgent fresh frozen plasma (10-20 mL/kg every 8-12 hours) to replace the procoagulant and anticoagulant plasma proteins that are consumed in the DIC process. Additional transfusion with platelet concentrates or cryoprecipitate may be necessary for significant thrombocytopenia and hypofibrinogenemia, respectively, particularly if there is pathologic bleeding.[74]

Empiric replacement therapy with fresh frozen plasma is also an appropriate initial therapy for postinfectious PF and for neonates presenting with suspected severe heritable protein C or protein S deficiency before definitive diagnosis. Patients with confirmed heritable protein C or protein S deficiency require long-term oral anticoagulation, which, if well tolerated, may be sufficient to permit them to remain free of coagulopathy throughout life.

Similar to burn patients, patients with PF require meticulous fluid management and may quickly develop electrolyte derangements and acid-base disorders. PF lesions that have already progressed to full-thickness skin necrosis require surgical debridement, fasciotomy, amputation, and plastic reconstruction.[64]

Thrombotic thrombocytopenic purpura

Thrombotic thrombocytopenic purpura is a rare life-threatening disease, with an annual incidence in the United States estimated at 4 to 11 cases per million people.[75]

Full-blown thrombotic thrombocytopenic purpura is characterized by microangiopathic hemolytic anemia with fragmented erythrocytes (schistocytes), thrombocytopenia, neurologic and renal abnormalities, and fever. Additionally, there may be bleeding from the nose and gums and nonpalpatory skin purpura.[76]

The disease was first reported in 1924 by Eli Moschcowitz (1879-1964) in a 16-year-old girl, who died 2 weeks after the abrupt onset of petechial bleeding, pallor, fever, paralysis, hematuria, and coma.[77,78] A gene located on the chromosome 9q34 was identified as the metalloproteinase responsible for the cleavage of the von Willebrand factor multimers. When ADAMTS-13 is not present, the resulting abnormally large von Willebrand factor multimers in plasma have a greater ability to react with platelets and cause the disseminated platelet thrombi characteristic of TTP.[79]

Hereditary TTP is caused by homozygous or double heterozygous *ADAMTS-13* mutations. Acquired TTP is often associated with severe, autoantibody-mediated ADAMTS-13 deficiency. The pathogenesis of cases without severe deficiency of the von Willebrand factor–cleaving protease remains unknown, and the affected patients cannot be distinguished clinically from those with severely decreased ADAMTS-13 activity. Acquired TTP has been reported in association with pregnancy, autoimmune disorders such as lupus erythematosus, antiphospholipid antibody syndrome, scleroderma, a drug reaction to quinine, or a cumulative, dose-dependent drug toxicity to mitomycin or gemcitabine.[80] Additionally, an acquired TTP could be associated with allogenic hematopoietic stem cell transplantation or can remain idiopathic.[80]

If untreated, TTP may be associated with high mortality due to multiorgan failure. The mainstay of therapy is immediate daily plasma exchange with fresh frozen plasma, which brings 70% to 90% of patients with idiopathic TTP into remission; however, 20% to 50% of patients will experience a relapse.[81] Patients with TTP experiencing relapse, and patients refractory to therapeutic plasma exchange (10% to 20%) have been treated with corticosteroids, splenectomy, or immunosuppressive agents including rituximab.[82]

Conclusions

Hemorrhagic rashes could indicate life-threatening conditions and require differentiation between infectious and reactive etiology, as well as therapeutic choices before laboratory confirmation. The presence of fever and/or infectious features could suggest a pathogen-related etiology. There is no simple algorithm that can be applied to the broad variety of clinical

pictures with hemorrhagic rashes. Knowledge of the morphology supports the clinical decision making.

Despite the progress in laboratory and instrumental diagnostic methods, good clinical experience and dermatologic expertise keep its principal role in the diagnostic process.

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