Coagulation disorders and their cutaneous presentations: Diagnostic work-up and treatment

Ganary Dabiri, MD, PhD,[a] Elizabeth Damstetter, MD,[b] Yunyoung Chang, MD,[b] Emily Baiyee Ebot, MD,[c] Jennifer Gloeckner Powers, MD,[d] and Tania Phillips, MD[b]
Providence, Rhode Island; Boston, Massachusetts; and Nashville, Tennessee

Learning Objectives
After completing this learning activity, participants should be able to identify the indications for diagnostic testing for patients presenting with a cutaneous manifestation of an underlying coagulopathy and describe multidisciplinary treatment strategies for inherited and acquired coagulation disorders.

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Both inherited and acquired hypercoagulable states can present with nonspecific clinical manifestations, such as petechiae, purpura, livedo reticularis, and ulcerations. A good history and physical examination are crucial to diagnoses of these conditions. Inherited conditions tend to present either in neonatal period or later in life, while acquired conditions typically occur later in life. Diagnostic studies are performed to identify the coagulation cascade deficiency or defect. Treatment primarily hinges on anticoagulation and wound care. In this article, we provide an in-depth analysis of the clinical manifestations, diagnostic considerations, and management options of patients in hypercoagulable states. (J Am Acad Dermatol 2016;74:795-804.)

Key words: factor V Leiden mutation; hypercoagulable state; hyperhomocysteinemia; livedoid vasculopathy; protein C deficiency; protein S deficiency; thrombophilia; thrombosis; ulcers; warfarin necrosis.

The incidence of arterial and venous thromboses in patients in hypercoagulable states (HSs) is increased compared to the general population in spite of adequate preventive measures. In addition to macrovascular thromboses, HSs can lead to microvascular thrombi, leading to many nonspecific cutaneous manifestations, most notably ulcerations affecting the lower extremity (LE). However, ulcerations have many other causative etiologies that must be distinguished from a HS. Livedoid vasculopathy (LV) in the LEs is a major distinguishing characteristic of patients with HSs. LV is characterized by recurrent reticulated purpura of the LEs with atrophie blanche (AB).[1] AB can be associated with LV, but also it can occur in the context of chronic venous insufficiency, further complicating the diagnostic picture. Many HSs have been linked to the development of LV (Table I). Here, we review the cutaneous manifestations of HSs and the vasculopathies most often encountered by the dermatologist in both the outpatient and inpatient settings.

From the Department of Dermatology and Skin Surgery,[a] Roger Williams Medical Center/Boston University School of Medicine, Providence; Boston University School of Medicine,[b] Boston; Department of Hematology and Oncology,[c] University Medical Group, Providence; and Vanderbilt University Medical Center,[d] Nashville.
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Reprint requests: Tania Phillips, MD, Department of Dermatology, Boston University School of Medicine, 725 Albany St, Ste 8B, Boston, MA 02118. E-mail: tphill@bu.edu.
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Abbreviations used:

AB:	atrophie blanche
APC:	activated protein C
APS:	antiphospholipid syndrome
AT:	antithrombin
ATIIID:	antithrombin III deficiency
DVT:	deep vein thrombosis
ELISA:	enzyme-linked immunosorbent assay
FVL:	factor V Leiden
FVLM:	factor V Leiden mutation
HIT:	heparin-induced thrombocytopenia
HS:	hypercoagulable state
INR:	international normalized ratio
LE:	lower extremity
LMWH:	low molecular weight heparin
LV:	livedoid vasculopathy
PCR:	polymerase chain reaction
PT:	prothrombin time
PTT:	partial thromboplastin time
SCD:	sickle cell disease
TTP:	thrombotic thrombocytopenia purpura
VTE:	venous thromboembolism

CUTANEOUS MANIFESTATIONS OF HYPERCOAGULABLE STATES

Key points

- **Identifying the different cutaneous presentation of hypercoagulable states**
- **Identifying the histology of livedoid vasculopathy**

Petechiae

Petechiae are pinpoint (≤3 mm), nonblanchable, erythematous macules that manifest as a result of erythrocyte extravasation from small cutaneous vessels. When nontraumatic, petechiae may herald thrombocytopenia, vasculitis, or concomitant anticoagulant therapy. Traumatic petechiae may appear marked relative to the degree of injury if platelets are low or if there is aberrant hemostasis. However, petechiae can appear after trauma or an acute elevation in intravascular pressure with normal platelets and hemostasis.[2] No additional diagnostic tests are usually necessary to identify petechiae. In certain scenarios, obtaining a skin biopsy specimen may help rule out an occult vasculitis. Additional work-up for thrombocytopenia may be warranted.

Purpura

Purpura are nonblanchable, erythematous to violaceous macules or thin papules ranging in size from a few millimeters to several centimeters. Likewise, purpura imply erythrocyte extravasation from dermal or subcutaneous blood vessels.[2] The finding of "palpable purpura" is nondiagnostic, although palpable lesions are often indicative of a vasculitic disorder (Fig 1).[3,4] Both hypo- and hypercoagulable states may present with purpura and can generally be distinguished by the history, physical examination, and basic laboratory tests (eg, partial thromboplastin time/prothrombin time). Hypocoagulable states often manifest as nonpalpable purpura (eg, ecchymoses) occurring at sites of trauma. HS are heralded by the appearance of retiform purpura, or stellate-appearing purpura with an incomplete net-like vascular background.[2] The differential diagnosis for retiform purpura is broad but implies a systemic disease process causing microvascular occlusion, and a thorough work-up must ensue.[5] A biopsy specimen of the skin may reveal features of vasculitis (ie, inflammation of vessel walls, erythrocyte extravasation, fibrinoid necrosis, or leukocytoclasia), vasculopathy (ie, vessel wall abnormalities without inflammation), or occlusion (ie, intraluminal thrombus or atherosclerosis).[6] Purpura fulminans—purpuric lesions that enlarge and become vesiculated—produce hemorrhagic bullae with subsequent necrosis and black eschar formation.

Table I. Hypercoagulable states associated with livedoid vasculopathy*

Factor V Leiden mutation
Prothrombin G20210A mutation
Protein C and protein S deficiency
Antithrombin III deficiency
Hyperhomocysteinemia
Monoclonal cryoglobulinemia
Hepatitis B and C, related to polyclonal cryoglobulins
Cryofibrinogenemia
Antiphospholipid antibodies

*Adapted from Alavi et al.[1]

Livedo reticularis

Livedo reticularis (LR) is an erythematous to violaceous, lacy, net-like, exaggerated venous pattern visible in states of slow venous flow (Fig 2). Classically, it presents on the lower extremities, is exacerbated in cold environments and, in idiopathic cases, reverses with warming the affected area, but once established the discoloration becomes permanent. Although LR may be a physiologic response to cold, in time LR may reflect an upstream occlusive process of arteries or arterioles, such as vasospasm or luminal obstruction (secondary LR). Neurologic disorders affecting vascular tone can also induce LR.[2,6]

Systemic work-up in patients with LR is guided by the history and physical examination.[3,7,8] The term livedo racemosa is used when the vascular patterns are fixed, the lacy pattern includes broken circles, and the patterns do not reverse with warming. This is considered an ominous sign of systemic disease.[2] A skin biopsy specimen obtained from the pale

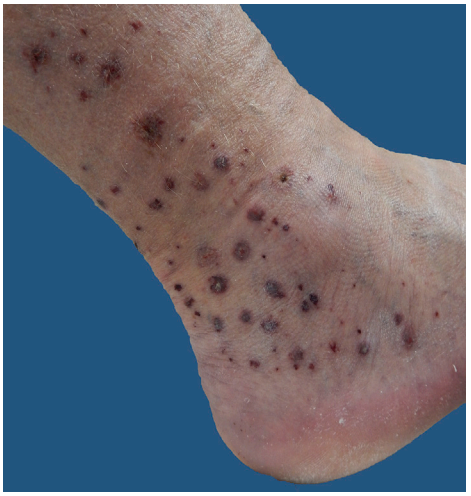

Fig 1. Palpable purpura in a patient with positive lupus anticoagulant showing leukocytoclastic vasculitis on review of the biopsy specimen.

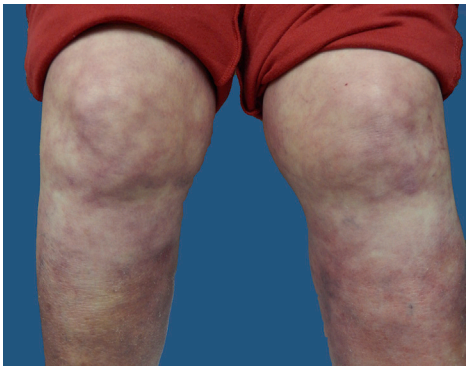

Fig 2. Livedo reticularis in a patient with systemic lupus erythematosus.

perilesional area may reveal changes of vasculopathy or vasculitis, sludging of erythrocytes, intraluminal thrombi, or arterial obliteration and provide insight into the underlying disease process.[9]

Livedoid vasculopathy

LV is a syndrome associated with hypercoagulability comprised of painful, punched out lower leg and foot ulcers on a background of LR or retiform purpura that heal with AB (ie, atrophic, stellate white scars bordered by telangiectasia and hemosiderin deposition; Fig 3).[2,10] A diagnosis of LV compels a broad HS work-up and consideration of underlying connective tissue disease.[1,11] Histologic features of nonulcerated skin classically include intraluminal thrombi and prominent hyalinization of vessel walls with scant perivascular inflammation (Fig 4).[6] Direct immunofluorescence studies are frequently positive for fibrin, complement, and immunoglobulin deposition in dermal vessels.[12]

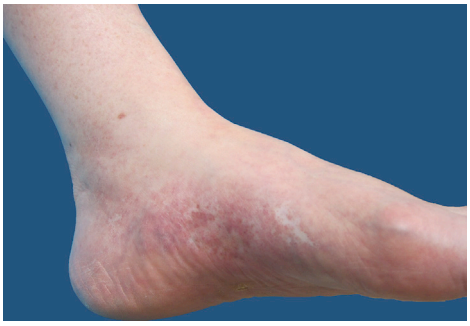

Fig 3. Atrophie blanche. Note the classic stellate white atrophic scars, telangiectasias, and hemosiderin deposition.

Ulcerations

Many primary and secondary HSs can manifest as ulcerations with features of venous or arterial origin. Venous leg ulcers typically appear in the "gaiter area" (ie, medial ankle to mid-calf), are shallow with fibrinous material overlying granulation tissue at the base, and have varying degrees of pain. There is often background pitting edema, venous varicosities, lipodermatosclerosis, and hemosiderin deposition. Chronic venous insufficiency can result from longstanding, recurrent superficial and deep venous thromboses associated with primary or secondary HS, and venous ulcers can be a manifestation of many HSs.[4,11,13-17]

Arterial ulcers classically appear over the lateral malleoli or distal phalanges as painful, punched out ulcers with purpuric borders and prominent eschar.[18] The affected limb may feature pallor and diminished arterial pulses. Upstream arterial occlusion can result from atherosclerosis, vasospasm, an underlying S, or a combination. Histology may implicate an underlying vasculitic or thomboembolic process; intraluminal clefts are seen in cholesterol emboli.[6]

Atypical nonhealing wounds, especially LE ulcers without venous or arterial insufficiency, should prompt work-up for an underlying HS, including cryoglobulinemia, cryofibrinogenemia, and antiphospholipid syndrome (APS).[4,19,20] Calciphylaxis may cause chronic, painful ulcers in patients with an underlying HS, with or without renal failure.[21] Calcification and secondary thrombosis of dermal and subcutaneous small- and medium-sized vessels are seen on wedge biopsy.[22]

INHERITED DISORDERS

Key points

- **Hypercoagulable states can be inherited or acquired**
- **Homozygous mutations can cause purpura fulminans in the neonatal period and can be lethal**

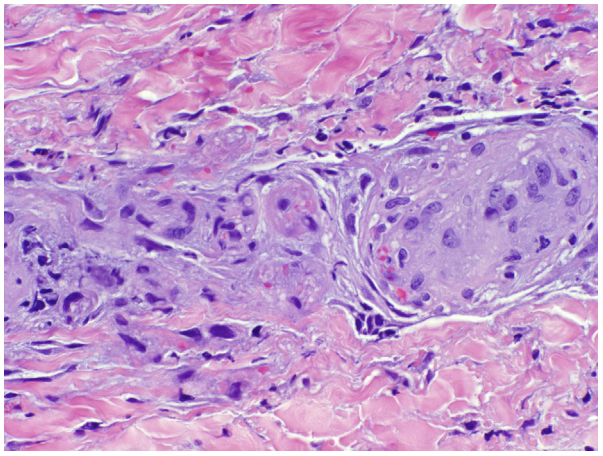

Fig 4. Livedoid vasculopathy revealing hyalinized dermal blood vessel walls with focal perivascular lymphohistiocytic infiltrate and intraluminal thrombus. (Hematoxylin–eosin stain.)

- **Heterozygous mutations result in milder disease presentation**
- **Atrophie blanche is a common presentation of livedoid vasculopathy**

Factor V Leiden mutation

Presentation. FVLM may be associated with any of the nonspecific cutaneous findings listed above, including LV. Cutaneous presentations of FVLM usually occur later in life. If a patient experiences their first thromboembolic event before 50 years of age and has an ulcerative skin lesion, then FVLM should be considered.[23]

Laboratory tests. In a patient presenting with the clinical features described above, in addition to testing for FVLM, a hypercoagulation panel should be performed (Table II). A polymerase chain reaction (PCR)–based assay is used to determine whether FVLM is present. A perilesional skin biopsy can be performed with a narrow and long elliptical excisional biopsy specimen including the reticular dermis and subcutaneous tissue.[24] An ultrasound to rule out a deep vein thrombosis (DVT) is important if a patient presents with asymmetric LE edema.

Treatment. In the absence of a history of thrombosis, long-term anticoagulation is not routinely recommended for patients with an asymptomatic FVLM. In the presence of acute thrombosis, warfarin therapy should be initiated with a goal international normalized ratio (INR) of 2 to 3 for 3 to 6 months, with an initial bridging with heparin.[25] Decisions regarding the duration of anticoagulation are based on an individualized assessment of the risks for venous thromboembolism (VTE) recurrence and anticoagulant-related bleeding.[25] Routine preoperative screening for FVLM or any other thrombophilia is not recommended. However, patients with known thrombophilia should be managed perioperatively with prophylactic anticoagulation.[26] There is no evidence that early diagnosis reduces morbidity or mortality, so decisions regarding testing at-risk family members should be made on an individual basis. Individuals with recurrent thrombosis at an early age with a family history of FVLM should be evaluated because they may need lifelong anticoagulation.[23] When cutaneous ulcerations are present, one should adhere to the basic principles of proper wound care. This includes optimizing granulation tissue formation, decreasing the bacterial burden, decreasing the inflammatory response, and maintaining proper moisture balance.[27]

Prothrombin G202120A mutation

Presentation. Cutaneous presentations of prothrombin gene mutation include tender erythematous and ulcerated papules of the LEs, ankle edema, LV, and AB.[28,29] Cutaneous findings seen with the prothrombin G202120A mutation can mimic chronic LE venous insufficiency, atherosclerotic peripheral arterial disease, inflammatory vasculitides, or pyoderma gangrenosum.[29]

Laboratory tests. A PCR-based assay is used to determine the presence of this specific mutation at nucleotide position 2010 in the prothrombin gene. In addition to testing for this mutation, a hypercoagulation panel should be performed (Table II). An ultrasound to rule out a DVT should also be included in the work-up if warranted.

Treatment. Long-term anticoagulation with warfarin as described above may be indicated in patients who have early or recurrent thrombosis. Skin ulcerations are managed according to the general principles of wound care as described above. A few studies have reported resolution of skin lesions with enoxaparin.[28,30]

Antithrombin III deficiency

Presentation. Cutaneous manifestations are uncommon. Recurrent venous or arterial thromboses at an early age may be signs of antithrombin III deficiency (ATIIID).[31] Neonatal purpura fulminans associated with hereditary ATIIID has been described.[32]

Laboratory tests. An antithrombin (AT) functional assay should be performed if the diagnosis is suspected. An abnormal test result should be repeated at least once, and testing relatives should be considered.[33] Heparin and vitamin K should be discontinued for at least 1 week before repeat testing, because levels will be falsely lower and higher, respectively.[33] All potential causes of

Table II. Hypercoagulation panel

Laboratory evaluation	Key points in interpretation
PT and PTT	Warfarin and other oral vitamin K antagonists and liver disease will significantly prolong the PT. Prolonged PTT could point to antiphospholipid syndrome
Protein C activity	Protein C levels are reduced when patients are taking warfarin
Protein S activity	Acquired causes should be excluded before performing this test. Parents should be screened when questioning a neonate's status. Do not test in acute settings
Homocysteine level	In individuals with an elevated level, it is important to exclude deficiencies in of folate or vitamin B12. An abnormal result should be confirmed on a repeat sample. *MTHFR* mutations can be assayed. Results typically are reported as negative or positive and, if positive, the report will name the mutation(s) present. Often, an interpretation of the results is also provided
Factor V Leiden	There are no reference ranges for a genetic test: the mutation is either present or absent
Antiphospholipid antibody panel (ie, anticardiolipin IgG and IgM, lupus anticoagulant, and β2-glycoprotein-1)	If any of these are positive, the same test should be repeated in 12 weeks (see Table IV)
Cryoglobulin	If results are negative but suspicion is high, make sure the laboratory stored the blood sample at the correct temperature
Cryofibrinogen	If results are negative but suspicion is high, make sure the laboratory stored the blood sample at the correct temperature
Antithrombin III	This is a genetic test; the results are either positive or negative
Prothrombin G202120A	Normal, heterozygous prothrombin [PT] G20210A, homozygous PT G20210A

IgG, Immunoglobulin G; *IgM*, immunoglobulin M; *MTHFR*, methylenetetrahydrofolate reductase; *PT*, prothrombin time; *PTT*, partial thromboplastin time.

acquired ATIIID should be excluded before diagnosing inherited ATIIID.[34]

Treatment. In the absence of a history of thrombosis, long-term anticoagulation is not routinely recommended. Because 42% of episodes of DVT in individuals with ATIIID occur in the setting of transient risk factors, such as surgery, diligent DVT prophylaxis in at-risk patients is important, including longer postoperative DVT prophylaxis in individuals with ATIIID.[35] When prophylaxis cannot be administered before surgery, it is reasonable to administer AT concentrates to a goal activated partial thromboplastin time (aPTT) of 1.5 to 2.[34,36] Long-term anticoagulant therapy with warfarin may be indicated in the setting of recurrent thromboembolic events.[36]

Protein C deficiency

Presentation. Heterozygous protein C deficiency is an autosomal dominant condition that has been shown to be associated with DVT and superficial phlebitis later in life. Homozygous protein C deficiency is a rare but life-threatening bleeding disorder that can present in the immediate neonatal period with purpura fulminans that is usually fatal.[31,37,38] Patients with protein C deficiency may also present clinically with LV.[1,39,40] Acquired protein C deficiency may present as calciphylaxis, with skin findings mimicking warfarin-induced skin necrosis, as discussed below.[3,21]

Laboratory tests. The plasma concentration of protein C in a healthy baby is approximately 40 IU/dL and reaches adult levels after adolescence. A normal plasma concentration of protein C in adults is approximately 65 to 135 IU/dL. Protein C deficiency is considered mild at plasma levels of 20 to 65 IU/dL, moderate to severe deficiency at 1 to 20 IU/dL, and severe deficiency at <1 IU/dL or not detectable.[41] Newborns can have protein C levels <10 IU/dL without manifesting either purpura fulminans or disseminated intravascular necrosis. Protein C levels may be determined quantitatively via enzyme-linked immunosorbent assay (ELISA), which only measures the amount of protein C present and not its functional activity. Functional protein C levels are measured via a clot-based aPTT assay, which measures the time to clot formation after addition of a protein C activator. Functional assays are preferred because they can detect both types of protein C deficiency (type I and II).

Treatment. Management of acute purpura fulminans in the neonatal period involves replacement therapy with fresh frozen plasma or protein C concentrate, intensive wound care, and maintenance anticoagulation therapy that includes low molecular weight heparin (LMWH) and warfarin.[37,38] Adult

patients with purpura fulminans caused by protein C deficiency should be anticoagulated with heparin before the initiation of warfarin.[42] Clinical improvement of ulcerations has been reported with a combination of pentoxifylline, aspirin, and dipyridamole.[40] Oral dapsone reportedly improved skin lesions in 1 case of LV caused by protein C deficiency.[39] Management of calciphylaxis caused by protein C deficiency with LMWH and tissue plasminogen activator showed success in case reports.[3,21] Before elective surgery, patients with protein C deficiency should have adequate anticoagulant prophylaxis to decrease the risk of VTE. When excessive bleeding is anticipated (eg, neurosurgery) and when anticoagulation cannot be safely used, then protein C concentrate can be administered.[43]

Protein S deficiency

Presentation. Like protein C deficiency, homozygous protein S deficiency is associated with purpura fulminans in neonates.[37,44,45] Heterozygous protein S deficiency has been associated with Sneddon syndrome and warfarin-induced skin necrosis.[46-48] Protein S levels can also be low because of chronic kidney and liver disease, vitamin K deficiency, and disseminated intravascular coagulation.[21,49] Postinfectious purpura fulminans with acquired protein S deficiency after varicella has been described.[42,50-53] Patients with protein S deficiency may also present clinically with livedoid vasculopathy.[1]

Laboratory tests. The reference range for protein S in men is >73 U/dL and in women is >63 U/dL. Protein S levels do not reach adult values until approximately 6 months of age. Assays for protein S are functional or immunologic. Functional assays (aPTT-based functional protein S assay) measure only free protein S. Immunologic assays (ELISA) measure both free and bound protein S.[54] Functional assay is again the preferred method of testing.

Treatment. Management of neonatal purpura fulminans involves replacement of protein S with fresh frozen plasma because no protein S concentrate exists.[42] Additional management is as described for protein C deficiency.

Hyperhomocysteinemia

Presentation. Many case reports have documented elevated homocysteine levels in patients presenting with LV in addition to pale or pink skin, a malar rash, and fine hair.[55-57] Hyperhomocysteinemia (HHS) has also been identified as an independent risk factor for psoriasis and mixed cryoglobulinemia.[58,59]

Laboratory tests. Normal homocysteine levels are <11 μmol/L. Intermediate levels are 11 to 14 μmol/L, high levels are 15 to 29 μmol/L, and very high levels are >29 μmol/L.[60] HHS can be diagnosed by high-performance liquid chromatography methods or fluorescence polarization immunoassays.[54,61] In patients with unexpected thrombotic disease, homocysteine levels should be checked as part of the hypercoagulable work-up.[62] If a patient has elevated homocysteine levels, methylenetetrahydrofolate reductase mutation testing may be ordered.

Treatment. B_6, B_{12}, and folate have been shown to effectively decrease homocysteine levels and attenuate thrombin levels.[56,63] When LV is present, clopidogrel in addition to vitamin B supplementation may be indicated to achieve resolution of the skin lesions.[55] Smoking cessation is imperative to normalizing homocysteine levels and resolving skin lesions.

Sickle cell disease

Presentation. Sickle cell disease (SCD) is an autosomal recessive hereditary hemoglobinopathy. Complications of SCD include acute pain episodes, increased rates of vasoocclusive crises, such as stroke, and pregnancy complications. VTE is a common complication of SCD.[64,65] Patients with SCD typically present to the dermatologist with painful leg ulcers with an AB-like appearance with pain out of proportion compared to the clinical presentation.[24] Skin ulcers occur in areas with little subcutaneous fat, thin skin, and decreased blood flow (eg, the anterior aspect of the tibia, dorsal surfaces of the feet, Achilles tendon, or ankles).[64] Patients start presenting with ulcerations around 20 years of age, and men are more likely to develop ulcers than women.[66] The ulcers in SCD resemble venous and arterial ulcers but involves deeper tissue.[24,64]

Laboratory tests. The diagnosis of hemoglobin type is by high-performance liquid chromatography and the sickle test.[67] When a patient with sickle cell anemia presents with ulceration, a complete blood cell count, renal function tests, urinalysis, liver enzymes, D-dimer, folate, iron, vitamin B_{12}, and homocysteine levels (see above) should be evaluated.[64] Biopsy specimens obtained of the ulcer are usually nonspecific; sickled erythrocytes are occasionally present in dermal blood vessels.[64]

Treatment. Therapy for ulcers in patients with SCD should focus on prevention (eg, avoiding trauma, treating venous or arterial disease), wound management, and the treatment of secondary infection. Ulcers in SCD often are resistant to treatment. There is report of a combined split-thickness autologous skin graft with hyperbaric oxygen and blood transfusion as successful in

healing a chronic ulcer on the leg caused by sickle cell anemia.[24] Pentoxifylline has been reported to be helpful in the treatment of sickle cell ulcers.[68] The role of hydroxyurea in the treatment of sickle leg ulcers is unclear; however, the weight of evidence suggests that hydroxyurea does not cause, prevent, or speed healing of these ulcers in patients with SCD.[69] Pain management is also important, and referral to a pain specialist may be necessary.

ACQUIRED HYPERCOAGULABLE STATES

Key points

- **The use of anticoagulants can lead to a hypercoagulable state, resulting in skin necrosis**
- **Retiform purpura is an important physical examination finding in microvascular occlusion syndromes**

Warfarin-induced skin necrosis

Skin necrosis usually occurs 3 to 5 days after initiating warfarin therapy with a large loading dose or without concomitant heparin. Skin necrosis affects areas of the body with high fat content and decreased blood supply, such as the breasts, buttocks, abdomen, thighs, and calves. The first signs are pain and purpura that then progress to full-thickness skin necrosis. Warfarin necrosis can also precipitate calciphylaxis. In order to prevent this from occurring, anticoagulation with heparin should be initiated for 4 to 5 days before starting warfarin.[70] Treatment of warfarin-induced skin necrosis includes discontinuing warfarin, anticoagulation with heparin, and the administration of vitamin K or fresh frozen plasma to reverse the warfarin effect. Local wound care is crucial; depending on the extent of necrosis, surgical debridement and even amputation may be needed.[3]

Heparin-induced thrombocytopenia

Heparin-induced thrombocytopenia (HIT) is an adverse drug reaction characterized by thrombocytopenia and an increased risk of venous or arterial thrombosis. Skin necrosis is the common clinical sign of this entity. There have been reports of skin necrosis caused by HIT without a drop in platelet count. Treatment of HIT involves the cessation of heparin and initiation of another form of anticoagulant, such as lepirudin, agartroban, or rivaroxaban. Good local wound care and other surgical interventions may be necessary depending on the extent of necrosis. A clinical scoring system has been devised to identify patients with HIT (Table III).[71]

Antiphospholipid syndrome

The lupus anticoagulant, anticardiolipin, and anti-β2-glycoprotein-I antibodies have been associated with HSs.[36] Physical examination findings include LV and skin ulcers.[31,72] Patients are often misdiagnosed as having pyoderma gangrenosum and are treated unsuccessfully with antiinflammatory and immunosuppressive agents.[73] The international consensus statement defines clinical and laboratory criteria for antiphospholipid syndrome (Table IV).[74,75] After any single episode of arterial or venous thrombosis, treatment with warfarin is recommended with a goal INR of 2 to 3; treatment duration is controversial.[76]

Thrombotic thrombocytopenia purpura

Thrombotic thrombocytopenia purpura (TTP) can be inherited, acquired, or idiopathic. TTP presents as a pentad of fever, hemolytic anemia, thrombocytopenia, renal failure, and neurologic symptoms. Cutaneous manifestations include petechial and purpuric lesions.[3,77] Cases of suspected TTP can be confirmed by anti-ADAMTS13 antibodies, low platelets, increased bilirubin, increase lactate dehydrogenase, and a negative Coombs test. Successful treatment of TTP includes plasmapheresis and rituximab.[78]

Cryoglobulinemia and cryofibrinogenemia

Clinical signs of cryoglobulinemia and cryofibrinogenemia include cold intolerance, Raynaud phenomenon, purpura, LR, ulcerations, gangrene, and necrosis resulting from thrombosis.20 When testing for cryoglobulins in serum, the blood sample needs to be collected and kept at 37°C before a determination can be made. If the temperature of the serum falls before clot formation, paraproteins will precipitate out, leading to a false-negative test result. In the testing process, the serum is observed at 4°C for formation of cryoprecipitate. Patients that are concomitantly hepatitis C—positive may see improvement in cryoglobulinemia when treated with interferon-alfa and ribavirin.27 However, patients can flare when interferon-alfa therapy is initiated. Testing for cryofibrinogens is as described for cryoglobulins above, except testing is performed on plasma. Treatment options for primary cryofibrinogenemia include stanazolol, prednisone, plasmapheresis, low-dose warfarin, and avoiding cold exposure.[72]

In conclusion, the morbidity and mortality related to HSs is significant. Many forms of HS can be inherited, but acquired forms also exist. Adults in HSs commonly present with LV, which includes LR, ulcer formation, edema, and AB scars. In neonates,

Table III. Four Ts scoring system for heparin-induced thrombocytopenia*

	2 points awarded	1 point awarded	0 points awarded
Thrombocytopenia	Platelet count fall >50% and platelet nadir ≥20	Platelet count 30-50% or platelet nadir 10-19	Platelet count fall <30% or platelet nadir <10
Timing of platelet count fall	Clear onset days 5-10 or platelet fall ≤1 day (previous heparin exposure within 30 days)	Consistent with days 5-10 fall, but not clear (eg, missing platelet counts); onset after day 10; or fall ≤1 day (previous heparin exposure 30-100 days ago)	Platelet count ≤4 days without recent exposure
Thrombosis or other sequelae	New thrombosis (confirmed), skin necrosis, or acute systemic reaction postintravenous unfractionated heparin bolus	Progressive or recurrent thrombosis, nonnecrotizing (erythematous) skin lesions, or suspected thrombosis (not proven)	None
Other causes of thrombocytopenia	None apparent	Possible	Definite

*Adapted from Cuker et al.[71] The 4Ts score is the sum of the values for each of the 4 categories. Pretest probability score: 6-8 indicates high; 4-5, intermediate; and 0-3, low.[71]

Table IV. International consensus statement on preliminary classification criteria for antiphospholipid syndrome[74,75]

Clinical criteria	Laboratory criteria
Vascular thrombosis: • ≥1 clinical episodes of arterial, venous, or small vessel thrombosis, occurring within any tissue or organ • Thrombosis must be confirmed by imaging studies, Doppler ultrasonography, or histopathology, with the exception of superficial venous thrombosis	Anticardiolipin antibodies: • Anticardiolipin IgG or IgM isotype in serum or plasma present in medium or high titer (>40 IgG phospholipid units [GPL]/mL or IgM phospholipid units [MPL]/mL or >99th percentile) β2-glycoprotein I-dependent anticardiolipin antibodies: • Anti-β2-glycoprotein-1 antibody of IgG or IgM isotype in serum or plasma (in titer >99th percentile), present on ≥2 occasions at least 12 weeks apart
Complications of pregnancy: • ≥1 unexplained deaths of morphologically normal fetuses at or after the 10th week of gestation • ≥1 premature births of morphologically normal neonates at or before the 34th week of gestation because of severe preeclampsia or eclampsia, or severe placental insufficiency • ≥3 unexplained consecutive spontaneous abortions before the 10th week of gestation with maternal anatomic or hormonal abnormalities and paternal and maternal chromosomal causes excluded	Lupus anticoagulant antibodies: • Lupus anticoagulant antibodies detected in the plasma on ≥2 occasions at least 12 weeks apart detected in the following steps: ○ Prolonged phospholipid-dependent coagulation shown on a screening test ○ Failure to correct the prolonged coagulation time on the screening test by mixing with normal platelet-poor plasma ○ Shortening or correction of the prolonged coagulation time on the screening test by the addition of excess phospholipid ○ Exclusion of other coagulopathies

Note that antiphospholipid antibody syndrome is considered to be present if ≥1 of the clinical criteria and 1 of the laboratory criteria are met.
IgG, Immunoglobulin G; *IgM*, immunoglobulin M.

purpura fulminans is a major clinical manifestation. Prompt diagnosis is imperative. Treatment is directed based on the inciting factor in addition to anticoagulation. Local wound care is imperative in the management of these patients.

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