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

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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.

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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