The skin and hypercoagulable states

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Hypercoagulable states (HS) are inherited or acquired conditions that predispose an individual to venous and/or arterial thrombosis. The dermatologist can play a vital role in diagnosing a patient's HS by recognizing the associated cutaneous manifestations, such as purpura, purpura fulminans, livedo reticularis, livedo vasculopathy (atrophie blanche), anetoderma, chronic venous ulcers, and superficial venous thrombosis. The cutaneous manifestations of HS are generally nonspecific, but identification of an abnormal finding can warrant a further workup for an underlying thrombophilic disorder. This review will focus on the basic science of hemostasis, the evaluation of HS, the skin manifestations associated with hypercoagulability, and the use of antiplatelet and anticoagulant therapy in dermatology. (J Am Acad Dermatol 2013;69:450-62.)

Key words: anetoderma; antiphospholipid antibody syndrome; chronic venous ulcer; hemostasis; hypercoagulable states; livedo reticularis; livedo vasculopathy; purpura; superficial venous thrombosis; thrombosis.

HEMOSTASIS

Hemostasis is the physiologic response that minimizes blood loss while maintaining blood flow after an injury to a vessel. Endothelial injury triggers immediate vasoconstriction and exposes tissue factor (TF) and collagen in the subendothelial matrix, providing a surface for platelet adherence and plug formation. Traditionally, coagulation has been described as a cascade of enzyme reactions, consisting of the extrinsic and intrinsic pathways converging on the common pathway to produce an insoluble fibrin clot.[1-3] Although the extrinsic and intrinsic pathways correlate with the laboratory values of prothrombin time and partial thromboplastin time, respectively, this model has shortcomings and fails to describe the importance of cells during the coagulation process.[3] Thus, a "cell-based" model of coagulation has been proposed, which consists of 3 phases: initiation, amplification, and propagation (Fig 1), and results in platelet activation and fibrin clot production.[3] TF, a cell membrane glycoprotein, is responsible for the initiation of coagulation, which occurs on the surface of a TF-bearing cell and results in the production of small amounts of thrombin (activated [a] factor [F] II).[3] During amplification, thrombin generated in the initiation phase activates factors V, VIII, and XI on the negatively charged phospholipid surface of a platelet leading to platelet activation.[3] Finally, in the propagation phase, significant amounts of thrombin are generated on the surface of an activated platelet, resulting in the conversion of fibrinogen into insoluble fibrin.[3-5]

Abbreviations used:

APC:	activated protein C
APLA:	antiphospholipid antibody
APLS:	antiphospholipid antibody syndrome
CVU:	chronic venous ulceration
DIC:	disseminated intravascular coagulation
DVT:	deep venous thrombosis
HIT:	heparin-induced thrombocytopenia
HS:	hypercoagulable states
LMWH:	low-molecular-weight heparin
LR:	livedo reticularis
LV:	livedo vasculopathy
PE:	pulmonary embolism
PF:	purpura fulminans
SVT:	superficial venous thrombosis
TF:	tissue factor
TTP:	thrombotic thrombocytopenic purpura
VTE:	venous thromboembolism

HYPERCOAGULABLE STATES

Venous and arterial thromboses are major causes of morbidity and mortality. Venous thromboembolism (VTE) includes deep venous thrombosis (DVT) and pulmonary embolism (PE). Hypercoagulability, in addition to stasis (slow flow) and endothelial injury,

From the Department of Dermatology, University of Pittsburgh.
Funding sources: None.
Conflicts of interest: None declared.
Accepted for publication January 25, 2013.
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Published online April 11, 2013.
0190-9622/$36.00

http://dx.doi.org/10.1016/j.jaad.2013.01.043

compose the Virchow triad of risk factors for venous thrombosis.[6] Several components can contribute to a thrombophilic state, including genetic and acquired risk factors (Table I), triggering factors, and/or a lack of appropriate pharmacologic or nonpharmacologic prophylaxis. Arterial thrombosis results in an ischemic event, such as acute coronary syndrome, stroke, or limb ischemia. These events are often the consequence of a ruptured atherosclerotic plaque that provides a surface for platelet aggregation that can lead to vessel occlusion.[7] In these high-flow vessels, platelets are the primary mediators of thrombosis.

CAPSULE SUMMARY

- Venous and arterial thrombosis often develop in the setting of a hypercoagulable state and cause significant patient morbidity and mortality.
- Hypercoagulable states can present with a wide variety of cutaneous manifestations.
- Recognizing the cutaneous manifestations of hypercoagulable states can improve patient safety and outcomes.

Hypercoagulable states (HS) can be divided into primary (inherited) or secondary (acquired) conditions (Table I) and are associated with increased risk of venous thrombosis or both venous and arterial thrombosis (Table II). The cutaneous manifestations of HS are generally not specific for a certain condition, but recognition of an abnormal finding can warrant a further workup for an underlying thrombophilic condition or VTE.

The evaluation of HS begins with a thorough history and physical examination. The dermatologist can recognize cutaneous findings that are associated with underlying HS and perform a skin biopsy and laboratory tests to further evaluate. The preliminary laboratory tests used to evaluate for HS are listed in Table III, and include gene mutations, antiphospholipid antibodies (APLAs), and anticoagulant activity levels. In addition to blood work, compression ultrasonography can be used to evaluate the deep venous system if a patient has a suspected DVT or superficial venous thrombosis (SVT). If there are symptoms to suggest PE, imaging studies such as a high-resolution computed tomography scan of the chest with contrast or ventilation perfusion scan may be obtained. For arterial thrombosis, Doppler studies, angiography, or magnetic resonance angiography can be performed. Appropriate referral to specialists should be considered, including the hematologist, internist, or intensivist, depending on the clinical scenario.

Primary HS

Factor V Leiden. Factor V Leiden is the most common primary HS, occurring in 5% to 15% of the population and inherited in an autosomal dominant pattern.[6] Approximately 20% of patients presenting with their initial episode of VTE have a FV Leiden mutation.[8] A point mutation in the FV gene switches guanine (G) to adenine (A) at nucleotide 1691 and codes for glutamine instead of arginine. FV is usually inactivated by activated protein C (APC) by cleavage at 3 sites, however, the FV Leiden mutant is resistant to degradation by APC.[9,10] The FV Leiden mutation accounts for over 90% of APC resistance.[11]

Prothrombin G20210A. Prothrombin G20210A mutation is the second most common primary HS, present in approximately 5% of the population, and also inherited in an autosomal dominant pattern.[11] This mutation is present in approximately 10% of patients presenting with their initial episode of VTE.[8] A mutation at nucleotide 20210 in the 3'-untranslated region of the prothrombin gene causes a guanine (G) to adenine (A) substitution.[12] This mutation is associated with elevated plasma levels of prothrombin and increased thrombin formation.[13]

Methyltetrahydrofolate reductase and hyperhomocysteinemia. Homocysteine is an amino acid, with elevated serum levels leading to increased risk of both venous and arterial thrombosis through an unknown mechanism. Inherited causes are secondary to mutation of the enzyme methyltetrahydrofolate reductase, or less commonly cystathione-β-synthase; the enzyme deficiency in congenital homocystinuria.[11] Patients with a homozygous methyltetrahydrofolate reductase mutation are at increased risk of VTE.[14] Acquired hyperhomocysteinemia can be secondary to renal or thyroid disease, smoking, aging, or a vitamin deficiency (B12, B6, or folate).

Antithrombin III. Antithrombin III deficiency was the first primary thrombophilic state identified, inherited in an autosomal dominant pattern and occurring in less than 0.02% of the population.[11,15] Antithrombin III degrades thrombin (IIa) and multiple other activated coagulation factors (IXa, FXa, XIa, and XIIa), thus a deficiency leads to a thrombophilic state because of increased levels of these activated factors. The heterozygous deficiency can be quantitative (type I) or qualitative (type II). The homozygous condition is usually fatal in the neonatal period. Antithrombin III deficiency, and protein C and S deficiency, can be acquired secondary to consumption (infection, sepsis,