Phenylephrine-Induced Microvascular Occlusion Syndrome in a Patient With a Heterozygous Factor V Leiden Mutation

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Background: Cutaneous microvascular occlusion syndromes (MOS) present with noninflammatory retiform purpura with variable outcomes that are dependent on the severity, duration, and specific underlying cause. Transient cases are often associated with few sequelae, while severe forms such as symmetrical peripheral gangrene may be associated with amputation and death.

Observations: A middle-aged man developed MOS after exposure to phenylephrine hydrochloride and experienced complete resolution when treatment with the vasopressor was discontinued. Further evaluation detected a previously subclinical heterozygous factor V Leiden mutation.

Conclusions: We propose that phenylephrine-mediated vasoconstriction superimposed on an underlying thrombotic predisposition precipitated the transient MOS. The role of vasopressors in the development of cutaneous MOS is well documented in the critical care literature; however, it is underrepresented in the dermatologic literature, and, to our knowledge, there are no reports of phenylephrine use inducing MOS. We hope to raise awareness of the potential role of vasopressor medications in causing MOS.

Arch Dermatol. 2007;143(10):1314-1317

Noninflammatory retiform purpura, the clinical manifestation of microvascular occlusion, has a broad differential diagnosis that includes disorders of platelet plugging, cold-related agglutination, vessel-invasive organisms, embolization, local or systemic coagulopathies, and miscellaneous conditions (eg, calciphylaxis, Degos disease, and sickle cell anemia). The cutaneous manifestations and outcomes are various and often depend on the severity and duration of the underlying causative factors.

Report of a Case

A 45-year-old man with diabetes mellitus and hypertension was admitted to the neurosurgical intensive care unit after undergoing a C5-C6 vertebrectomy with postoperative spinal degeneration and infectious complications that required prolonged hospitalization, numerous neurosurgical procedures, and ventilatory and vasopressive support over a 4-month period. His family history included a pulmonary embolism that had occurred in his mother at the age of 35 years. He had previously been treated with norepinephrine bitartrate for vasomotor instability resulting from neurosurgical procedures. However, in the past month, his only vasopressor exposure had consisted of a 2-day course of phenylephrine hydrochloride (at a dosage titrated to maintain target mean arterial pressure), which had been discontinued 1 day before the onset of his rash. It was his first...
and only exposure to phenylephrine. He had been afebrile and hemodynamically stable since the phenylephrine therapy had been discontinued.

His platelet count had decreased from 220 to 105 × 10^3/µL over 2 days, and his D-dimer level was elevated at 1.9 mg/L (normal range, 0-1.5 mg/L). The fibrinogen level, prothrombin time, activated partial thromboplastin time, fibrin split product levels, and results of urinalysis were within normal limits. The leukocyte count was normal, and blood cultures were sterile. A skin biopsy specimen revealed fibrin microthrombi in the superficial and middle dermal vessels, with minimal inflammation and no vasculitis (Figure 2). A diagnosis of microvascular occlusion syndrome (MOS) was made.

Spontaneous improvement began on the second day after the evaluation and was hastened by the addition of lepirudin (a direct thrombin inhibitor used as an alternative to heparin) to the patient’s therapy, resulting in a dramatic resolution of the purpura and superficial sloughing and yielding mildly erythematous erosions. He experienced no further thrombotic complications, and his condition had almost completely resolved 2 weeks later (Figure 3), with no long-term sequelae.

Further evaluation revealed negative results or normal levels for the following laboratory investigations: heparin-induced thrombocytopenia antibodies, protein C, homocysteine, prothrombin 20210a mutation, antithrombin III, cryofibrinogens, cryoglobulins, anticardiolipin antibody, lupus anticoagulant, β2-glycoprotein I antibody, serum protein electrophoresis, antinuclear antibody, rheumatoid factor, hepatitis panel, perinuclear and cytoplasmic antineutrophil cytoplasmic antibodies, parvovirus titers, echocardiography, and lower-extremity Doppler ultrasonography. A heterozygous factor V Leiden (FVL) mutation was found; the erythrocyte sedimentation rate was 33 mm/h (reference range, 0-10 mm/h); the C-reactive protein level was 27 mg/L (reference range, 0-9.0 mg/L); and the functional protein S value (during acute event) was 36% of the normal level. Subsequent functional protein S testing 2 weeks after resolution revealed a normal level.
The FVL mutation is one of the most common causes of inherited thrombophilia, with 4% to 6% of the US population manifesting heterozygous replacement of arginine by glutamine at position 506 of factor V. This mutated gene product, FVL, is resistant to normal physiologic degradation by activated protein C, yielding a hypercoagulable state. The abnormality is transmitted in an autosomal dominant manner, and the risk of thromboembolism is increased 7- and 80-fold, respectively, in individuals who are heterozygous and homozygous for FVL. This baseline-increased susceptibility to thrombotic events is perpetuated by the coexistence of additional genetic or environmental risk factors, including protein C and S deficiencies, antithrombin deficiency, prothrombin gene mutation, elevated levels of factor VIII, hyperhomocystinemia, other coagulation disorders, advanced age, smoking, surgery, immobilization, obesity, pregnancy/postpartum period, or use of oral contraceptives.

Cutaneous MOS presents clinically with noninflammatory retiform purpura, which has a broad differential diagnosis that includes disorders of platelet plugging, cold-related agglutination, vessel-invasive organisms, embolization, local or systemic coagulopathies, or miscellaneous conditions (eg, calciphylaxis, Degos disease, and sickle cell anemia). Factors that affect the disease course include the severity and duration of the specific underlying cause. Transient precipitants can result in reversible MOS, without a significant event; however, considerable morbidity and mortality are associated with symmetrical peripheral gangrene (SPG). In 1891, Hutchinson reported the first case of SPG, which was characterized by acral gangrene occurring in a symmetrical distribution with no evidence of large vessel occlusion or vasculitis. Symmetrical peripheral gangrene, which has been described by some authors as a form of purpura fulminans, is considered a severe form of MOS and is most commonly associated with septic shock and disseminated intravascular coagulation (DIC). Patients with preexisting vascular disorders, such as peripheral vascular disease, diabetes mellitus, Raynaud phenomenon, and prior cold injury, as well as patients who have been exposed to vasoactive medications, are further predisposed to develop SPG. Molos and Hall's review of 71 cases of SPG revealed that 48% of the patients required amputation and 35% cases proved fatal.

Our patient's heterozygous FVL mutation remained subclinical before this event. At the age of 35 years, his mother had experienced a deep venous thrombosis with pulmonary embolism, which was not further investigated. There was no other known family history of thrombotic events. While there was no evidence of sepsis or DIC, his risk factors for MOS included heterozygous FVL, diabetes mellitus, postsurgical status, immobilization, and obesity. An FVL mutation is highly associated with venous thromboses; however, it rarely manifests with MOS. Our patient's underlying neurosurgical issues had required numerous operations and prolonged immobilization over the past 4 months; however, he had only recently developed transient microvascular occlusion. He required intermittent vasopressor support, and treatment with phenylephrine, a pure β-adrenergic agonist that causes intense vasoconstriction and decreased perfusion to the acral vascular beds, had been discontinued just 1 day before the onset of his MOS.

Considering the physiologic effects and temporal relationship of phenylephrine therapy to the onset of our patient's microvascular occlusion, we propose that phenylephrine-mediated vasoconstriction superimposed on his thrombotic predisposition precipitated a transient MOS. Dunser et al reported ischemic skin lesions in only one-third of patients receiving vasopressor medications, suggesting that a combination of predisposing factors must surpass a critical threshold, above which MOS occurs, with the subsequent clinical course depending on the severity and duration of the threshold breach. This model would account for the transient and reversible nature of our patient's MOS: the short-term intense vasoconstriction mediated by phenylephrine therapy resulted in a low-level microvascular occlusion, which spontaneously remitted once the vasoconstriuctive effects of phenylephrine resolved and his cumulative thrombotic tendency returned to below the critical threshold value. It is noteworthy that the patient did not develop MOS from his numerous prior exposures to norepinephrine. Perhaps the β-adrenergic properties of norepinephrine (augmenting cardiac output and thus peripheral perfusion) counteracted the vasoconstriuctive effects, with the cumulative thrombotic tendency remaining below the critical threshold value.

Few cases of cutaneous MOS have been reported in patients who are heterozygous for FVL. Patel et al described an 81-year-old woman with heterozygous FVL who developed extensive acral cutaneous necrosis with no clear precipitant, resulting in septicemia and death. Jackson and Luplow reported 2 cases of heterozygous FVL that were complicated by sepsis and DIC, both of which resulted in digital amputations. To our knowledge, this is the first report of transient MOS precipitated by phenylephrine use in a patient with a heterozygous FVL mutation.

While phenylephrine-induced vasoconstriction is the only identifiable temporally related transient factor associated with our patient's transient MOS, it is possible that additional causative factors were involved. Antiphospholipid antibody syndrome manifests arterial or venous thrombosis of small or large vessels, and while our patient tested negative for anticardiolipin antibodies, lupus anticoagulant, and β2-glycoprotein 1 antibodies, these tests are technically difficult and false-negative results are not rare. Cryoproteins, including cryofibrinogens and cryoglobulins, are other potential contributors in the present case. Again, our patient tested negative for cryofibrinogens and cryoglobulins; however, the sensitivity of these tests is highly dependent on the method of collection. In the presence of protein S, activated protein C inhibits thrombin generation; therefore, a transient deficiency of protein C or S could trigger a thrombotic event. Proteins C and S are acute-phase reactants and are difficult to interpret during acute events; therefore, only an abnormally low level of either protein before the throm-
The role of vasopressors in the development of transient cutaneous MOS is well documented in the critical care literature, however, it is underrepresented in the dermatologic literature. Published reports have associated cutaneous microvascular occlusion with administration of dopamine, epinephrine, norepinephrine, and vasopressin. We have presented a case of transient MOS in a patient with a heterozygous FVL mutation, without active infection, shock, or DIC, and postulate that the transient nature of his MOS was precipitated by phenylephrine-mediated intense vasoconstriction. We hope that this report will raise awareness of the potential role of vasopressor medications in causing MOS. Cutaneous MOS should prompt a search to identify the potentially multiple causative factors, with dermatologists paying special attention to current or prior vasopressor medication use when consulting in the intensive care setting.

Accepted for Publication: May 20, 2007.

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Author Contributions: Drs Kalajian, Turpen, Donovan, Malone, and Callen had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Kalajian, Donovan, and Callen. Acquisition of data: Kalajian, Donovan, and Malone. Analysis and interpretation of data: Kalajian, Turpen, Donovan, Malone, and Callen. Drafting of the manuscript: Kalajian and Turpen.

Critical revision of the manuscript for important intellectual content: Kalajian, Donovan, Malone, and Callen.

Administrative, technical, and material support: Kalajian.

Study supervision: Kalajian, Donovan, Malone, and Callen.

Financial Disclosure: None reported.

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