Increased incidence of hypercoagulability in patients with leg ulcers caused by leukocytoclastic vasculitis

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Vasculitis is a rare cause of leg ulceration. It is unclear why severe skin infarction develops in some patients with vasculitis, whereas others have only mild symptoms such as purpura, erythema, or urticaria. A coincidence of vasculitis and hypercoagulability may lead to more extensive thrombotic occlusion and hence explain the occurrence of large ulcers in a subset of patients. Our aim was to investigate whether patients with vasculitis ulcers have an increased incidence of hypercoagulability. Thirteen consecutive patients admitted to the hospital with necrotic ulcers caused by histologically confirmed vasculitis were screened for clotting disorders. In 7 of 13 patients (53%), hypercoagulable conditions were found. Five patients had factor V Leiden (38%), and 2 had lupus anticoagulant (15%). The normal frequency of these conditions is 5% to 6% and 3.6%, respectively. These data indicate that there is an increased incidence of hypercoagulable disorders in patients with vasculitis ulcers. We recommend screening these patients routinely for hypercoagulability. (J Am Acad Dermatol 2004;50:104-7.)

Cutaneous vasculitis may present as purpura, erythema, urticaria, noduli, bullae, or skin infarction, leading to ulceration. Fortunately, ulceration is not a common complication in all patients with vasculitis. The extent of tissue damage depends on the amount and size of the vessels involved.[1] Cutaneous ulceration is more common in vasculitis affecting medium-sized arteries (periarteritis nodosa, m. Wegener) than in small-vessel leukocytoclastic vasculitis.[2]

Hypercoagulable disorders may also cause ulceration, either indirectly as a sequel of venous thrombosis (the postthrombotic syndrome), or directly by thrombus formation in small arteries, arterioles, capillaries or venules.[3,4] A growing number of hereditary or acquired conditions predisposing to thrombosis have been identified, such as the antiphospholipid syndrome; deficiency of antithrombin III, protein C, or protein S;[5] or abnormal clotting factors (factor V Leiden, factor II mutant).[4,6-8]

On the basis of some case reports in the literature describing the combined occurrence of vasculitis and clotting disorders,[9-11] we performed routine screening tests for hypercoagulable disorders in all patients admitted to the clinical department of dermatology with skin ulcers caused by vasculitis. The goal of the study was to investigate whether there might be an association between the two entities. From a clinical point of view, such an association would explain why large ulcers develop in some patients, whereas other patients with vasculitis have only purpura, erythema, or wheals.

PATIENTS AND METHODS

Since 1999, all new consecutive patients that were admitted to the hospital (Department of Dermatology, Academic Medical Center, Amsterdam) for skin ulcers caused by vasculitis were included in the study. In all patients, the diagnosis "vasculitis ulcer" was already suspected at the moment of hospital admission because of clinical signs suggestive for vasculitis (usually multiple ulcerations, presence of black necrotic tissue, irregular borders, purple discoloration at the margins (Fig 1), or associated skin signs such as purpura). The diagnosis was confirmed by skin biopsy. All patients were screened for

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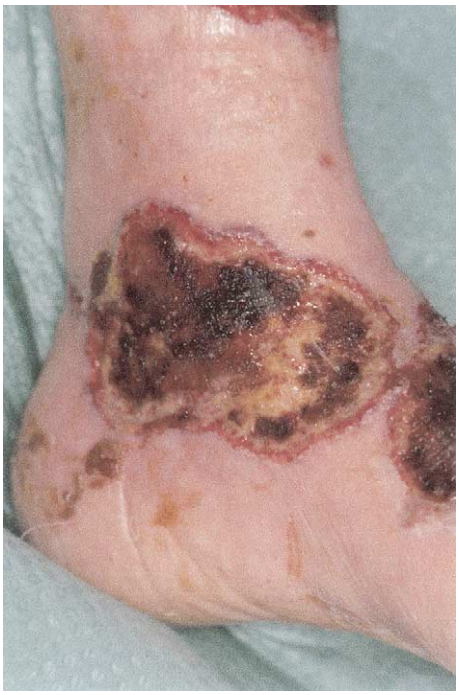

Fig 1. Patient with multiple black necrotic leg ulcers caused by leukocytoclastic vasculitis. At the margins of the ulcers, a purple discoloration can be observed.

the presence of other factors that may cause ulceration, such as venous insufficiency, lower extremity arterial disease, diabetes, hypercholesterolemia, infection, or hypertension. In addition to routine laboratory investigations (hemoglobin, erythrocyte sedimentation rate, leukocyte counts, cholesterol and triglyceride, glucose), patients were screened for underlying disorders associated with vasculitis (urinalysis for proteinuria, hematuria, and cylindruria; routine and immunohistopathologic examination of skin biopsy specimens, kidney, and liver function, antinuclear antibodies [ANA], rheumatoid factor, complement C4, circulating immune complexes, paraproteins, immunoglobulin fractions, antineutrophil cytoplasmic antibodies [ANCA], serologic tests, and cultures for underlying infections)[1,2] and for a selection of disorders associated with hypercoagulability (Table I).

RESULTS

In total, 13 consecutive patients (all white, 5 male, 8 female, mean age 63 years) were included in the study. Most of them (85%) had multiple ulcers (mean: 5.3 ulcers). The average total wound size was 75 cm^2, the average duration of the ulcers at time of admittance was 5.6 months, and the average duration from first onset to total healing was 8.5 months.

Table I. Laboratory screening tests for clotting disorders

Activated partial thromboplastin time (APTT)
Prothrombin time (PTT)
Thrombin time
Factor V (Leiden) mutation ($^{506}R \rightarrow ^{506}Q$)
Factor II (prothrombin) mutation ($^{20210}G \rightarrow ^{20210}A$)
Antithrombin III
Protein C and protein S
Lupus anticoagulant
Anticardiolipin antibody

Common causes of ulceration

Arterial insufficiency, defined as an ankle-brachial index below 0.8, could be ruled out in all patients. Three patients had venous insufficiency, but the clinical aspect of their ulcers was not consistent with venous ulceration (multiple punched-out necrotic ulcers, clinical and histologic signs of vasculitis). Two patients had diabetes, controlled by oral antidiabetic drugs. None of the patients had hypertension. Cholesterol levels were normal.

Underlying disorders associated with vasculitis

In all patients the diagnosis of small-vessel leukocytoclastic vasculitis was made. Underlying disorders explaining the vasculitis were found in 3 patients. Two patients had rheumatoid arthritis, with positive rheumatoid factor, the third patient had ANCA. Two patients had albuminuria; other signs of systemic involvement were absent. Antinuclear antibodies were found in 2 patients, anti-double-stranded DNA was absent in all patients. The other laboratory tests revealed no relevant abnormalities.

Hypercoagulability

In 7 patients (53%), a coagulation disorder was found. In 5 patients an aberrant factor V (factor V Leiden) was detected. Four of them had a history of thromboembolic events (thrombophlebitis, thrombosis, and lung embolism), and 2 of them already used anticoagulant drugs. In 2 patients (the 2 with rheumatoid arthritis) circulating lupus anticoagulant was found. In none of the patients were factor II mutant, antithrombin, protein C or S deficiency, or anticardiolipin antibodies found.

Thrombotic occlusion of small vessels was observed in 4 of the 7 patients with a coagulation disorder and in 1 of the 6 patients without a coagulation disorder.

DISCUSSION

Hypercoagulable disorders were found in 7 of 13 (53%) patients with leg ulcers caused by leukocyto-

clastic vasculitis. Five of them had factor V Leiden (38%). The normal frequency of factor V Leiden in the European population is estimated to be 5% to 6%.[12]

We hypothesize that the following sequence of events is taking place. In vasculitis, the vascular wall is damaged. The vascular damage initiates the coagulation cascade, prothrombin is converted to thrombin, and thrombin activates factor V and VII. Coagulation is normally controlled by circulating antitrombin III and locally by thrombomodulin, which is present on endothelial cells and binds thrombin. The thrombin-thrombomodulin complex activates protein C. Activated protein C (and also protein S) inactivates factor Va en VIIa. But the mutant factor V Leiden ($^{506}R \rightarrow {}^{506}Q$) is resistant to inactivation by protein C. As a consequence, the local protection mechanism against thrombosis is not working adequately.

Lupus anticoagulant was present in 2 patients (16%). The normal frequency in the healthy population is around 3.6%.[13] The presence of lupus anticoagulant is often accompanied by a prolonged prothrombin time and activated partial tromboplastin time, hence the confusing term anticoagulant, but it is associated with an increased risk for thrombosis.[14,15] The lupus anticoagulant has been found in a growing number of diseases, especially autoimmune diseases, including rheumatoid arthritis.[16] The link between lupus anticoagulant and thrombosis has not been conclusively elucidated. It is hypothesized that the lupus anticoagulant binds to negatively charged phospholipids and interferes with the hemostasis system by mechanisms such as binding to thrombin-activated platelets, inhibiting prostaglandin release, or inhibiting protein C activation.[16-18] So both factor V Leiden and the lupus anticoagulant interfere with the local protection mechanisms against thrombosis. This could explain why these patients have severe ulcerations after local damage of the vascular wall by vasculitis.

Even long before clotting disorders such as the lupus anticoagulant or factor V Leiden were known and could be detected routinely, case reports were published suggesting an association between vasculitis ulcers and circulating anticoagulant factors. Johansson et al[19] described in 1977 8 patients with false-positive seroreactions for syphilis and necrotizing purpura with painful superficial star-like ulcers around the ankles. Rocca et al[9] described 4 patients with marked tissue necrosis caused by combination of coagulopathy (antiphospholipids) and vasculitis; 3 of them had systemic lupus erythematosus. Factor V Leiden is a known risk factor for venous thrombosis.[20] As could be expected, the incidence of factor V Leiden in patients with venous leg ulcers, which is considered to be a postthrombotic condition in the majority of cases, is increased (23%-36%).[8,21] Hence, contamination of the study population with a large amount of venous leg ulcers could be confounding the results. This was not the case in our study; 3 patients had postthrombotic syndrome, and in only one of them was factor V Leiden detected.

The majority of patients in this study were treated with immunosuppressants, either prednisone (8 patients) or cyclosporine (4 patients). Four of the 7 patients with coagulopathy already used oral anticoagulant drugs because of thromboembolic events in the past. Although there are no strict guidelines about how to treat patients with coagulopathy and vasculitis, we decided to prescribe oral anticoagulants also to 2 of the remaining 3 patients. In general, the patients had large and deeply necrotic wounds, which required hospitalization and took a long time to heal (8.5 months, on average).

Although it is certainly necessary to expand the number of patients in the future, we concluded that the presence of hypercoagulability in 53% of patients with vasculitis ulcers strongly suggests a pathophysiologic relationship. Therefore we recommend that all patients with severe skin necrosis caused by histologically confirmed vasculitis be screened routinely for hypercoagulable disorders. Because this is a well-defined and rare category of patients, we are not concerned that this recommendation leads to excessive use of diagnostic tests or increased health care costs.

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Tacrolimus effect on rosacea

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Twenty-four patients with erythrotelangiectatic or papulopustular rosacea were treated with 0.1% tacrolimus topical ointment in a 12-week open-label trial. Erythema was significantly improved in both rosacea subtypes ($P < .05$). There was no decrease in the number of papulopustular lesions. Side effects were consistent with those on the tacrolimus topical ointment labeling. (J Am Acad Dermatol 2004;50:107-8.)

The pathophysiology of rosacea is considered to involve the vascular system and immunologic mediation of inflammation.[1] Because of the beneficial effect of tacrolimus treatment in a number of skin inflammatory conditions,[2-4] we investigated its potential effectiveness and acceptability in patients with the two most common presentations of rosacea: erythrotelangiectatic (ET) or papulopustular (PP).[5]

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METHODS

After Institutional Review Board approval of the research plan, we carried out a 12-week open-label clinical trial in which patients with previously diagnosed rosacea were treated with 0.1% tacrolimus topical ointment twice daily. Patients had no confounding topical treatment for rosacea within 30 days or any oral antibiotic within 2 months prior to the study enrollment. All patients agreed not to use any other topical or oral treatment for rosacea while on the study protocol. Dermatologists evaluated erythema on a scale from 0 (none) to 10 (most severe), number of papulopustules and overall severity of rosacea on a scale from 0 (none) to 10 (most severe) at baseline and at the end of the treatment. Analyses of grouped differences for continuous variables were evaluated using an independent sample *t*-test, with paired *t*-test used to evaluate change over time; differences in the number of papulopustules were evaluated using nonparametric tests of significance (signed rank test). A probability less than .05 was considered significant.