Livedoid Vasculopathy

Further Evidence for Procoagulant Pathogenesis

Bethany R. Hairston, MD; Mark D. P. Davis, MD; Mark R. Pittelkow, MD; Iftikhar Ahmed, MD

Objective: To further characterize the clinical and pathologic features, disease associations, and laboratory abnormalities of livedoid vasculopathy.

Design: Retrospective study of patients identified from our institutional database from January 1, 1990, to December 31, 2000.

Setting: Tertiary care institution.

Patients: Forty-five patients with biopsy-proved livedoid vasculopathy.

Main Outcome Measures: Clinical presentation, histopathologic diagnosis, results of testing for coagulation abnormalities, and assessment of vascular status.

Results: Thirty-two patients (71.1%) were female (mean age, 45 years; age range, 10-85 years). Bilateral lower extremity disease occurred in 36 patients (80.0%), ulceration in 31 (68.9%), and atrophie blanche in 32 (71.1%). In patients tested, transcutaneous oximetry measurements were decreased in 20 (74.1%) of 27, and factor V Leiden mutation (heterozygous) was noted in 2 (22.2%) of 9, decreased activity for protein C or protein S in 2 (13.3%) of 15, prothrombin G20210A gene mutation in 1 (8.3%) of 12, and lupus anticoagulant in 5 (17.9%) of 28. Anticardiolipin antibodies were present in 8 (28.6%) of 28 patients, and elevated homocysteine levels in 3 (14.3%) of 21. Intraluminal thrombosis was observed in 44 (97.8%) of 45 skin biopsy specimens. Direct immunofluorescence disclosed multiple vascular conjugates in 31 (86.1%) of 36 biopsy specimens.

Conclusions: Livedoid vasculopathy was predominantly bilateral, affected the lower extremities, and was associated with ulceration and atrophie blanche. Histologic evidence of intraluminal thrombosis was observed in almost all biopsy specimens reviewed. Laboratory testing revealed numerous heterogeneous coagulation abnormalities, providing further evidence of procoagulant mechanisms.

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LIVEDOID VASCULOPATHY IS A chronic, recurrent, painful cutaneous disease with distinctive clinical features. The initial clinical appearance may include a primary lesion of focal purpura progressing to shallow ulcerations. Atrophic, stellate, ivory to white, scarlike plaques stippled with telangiectasia and surrounded by hyperpigmentation, known as “atrophie blanche,” are commonly identified (Figure 1). Histologic features include hyalinizing vascular changes of the subintimal layer of dermal blood vessels, typically with minimal inflammation (Figure 2).

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Originally described as atrophie blanche en plaque by Milian in 1929, synonyms for this disease have included “livedo reticularis with ulcerations,” “segmental hyalinizing vasculitis,” “livedo vasculitis,” and “livedoid vasculitis.” The pathogenesis is not fully understood. Variable nomenclature and the multifactorial nature of cutaneous ulcerations complicate classification of the disease. It has been described as idiopathic, associated with immune complex–associated diseases, and a result of dermal blood vessel occlusion. Laboratory test result abnormalities have been reported in patients with the disease, including defective release of tissue plasminogen activator, elevated fibrinopeptide A, antithrombin III deficiency, and numerous other thrombophilic abnormalities that are further described in this article. The purpose of our review was to further characterize the clinical features, disease associations, and laboratory test result abnormalities, including coagulation study results, in patients...
with biopsy-proved livedoid vasculopathy whose conditions were evaluated at the Mayo Clinic, Rochester, Minn, from January 1, 1990, to December 31, 2000.

METHODS

INCLUSION AND EXCLUSION CRITERIA

This retrospective review was approved by the Mayo Foundation Institutional Review Board. The medical record database at our institution was searched using the master index diagnoses of “livedo or livedoid plus vasculitis or vasculopathy,” “segmental hyalinizing vasculitis or vasculopathy,” and “atrophie blanche.”

Inclusion criteria were as follows: (1) painful, stellate, shallow ulcerations or crusted erosions on the legs, ankles, or feet; a history of such lesions healing with atrophie blanche; or presence of atrophie blanche; and (2) histologic features of the disease as previously defined,1 including endothelial proliferation and hyalinized degeneration of the subintimal layer of dermal blood vessel walls. Both requirements were fulfilled in 45 patients. Clinical data and biopsy specimens were available for all patients.

Exclusion criteria were as follows: (1) no skin biopsy specimen had been obtained and (2) another cause for the leg ulceration had been elucidated. Examples include primary inflammatory vasculitis (eg, polyarteritis nodosa), pyoderma gangrenosum, sarcoidosis, factitial dermatitis, conditions induced by drugs (eg, hydroxyurea), cryoglobulinemia, and primary antiphospholipid antibody syndrome.

ABSTRACTION OF DATA

Information abstracted from patient medical records included age at onset of disease, sex, clinical manifestations, relevant medical history, histopathologic diagnosis, and results of laboratory and noninvasive vascular testing. Laboratory test result abnormalities were analyzed with emphasis on the presence of an inherited or acquired coagulation abnormality as measured and reported by the coagulation testing laboratory at our institution. This extensive testing for coagulation abnormalities became available during the past decade; therefore, the period from 1990 to 2000 was chosen for this retrospective review.

Vascular status was assessed in the noninvasive vascular laboratory at our institution. Continuous-wave Doppler ultrasonography, a useful method for detection and diagnosis of deep venous insufficiency,10 was used to evaluate 6 vein qualities: patency, spontaneity, phase, augmentation, competency, and pulsatility. The continuous-wave Doppler ultrasonographic data were supplemented with information from exercise strain gauge outflow plethysmography, which adds quantitative information about the severity of venous insufficiency.11 Arterial investigations included transcutaneous oximetry (TcPO2), which measures oxygen tension for determining the degree of ischemia in poorly perfused skin.12 The TcPO2 measurements were graded as normal, mild to moderately reduced, or severely reduced.

Biopsy specimens (stained with hematoxylin-eosin) from all of the patients in this series were reviewed. Direct immunofluorescence testing was performed using conjugate antiserum to IgG, IgM, IgA, complement component 3, and fibrin.

RESULTS

The study group consisted of 32 female and 13 male patients. Their age range was 10 to 85 years (mean age, 45 years).

CLINICAL FEATURES

When patients were first seen, the duration of symptoms ranged from less than 1 year to 45 years (mean, 6.3 years). Atrophie blanche was described in 32 patients (71.1%). Ulcers were noted in 31 patients (68.9%), 25 (55.5%) of whom also had atrophie blanche. Among the 13 patients without classically described atrophie blanche, shallow stellate ulcerations were noted in 6, crusted erosions with history of ulceration in 3, and crusted erosions with purpuric papules or plaques in 4. Edema was present in 8 patients (17.8%), and the disease was bilateral in 36 (80.0%). The lesions involved the lower extremities in all patients, with most having lesions in a combination of the following locations: foot, 28 patients (62.2%); ankle, 30 (66.7%); and leg, 36 (80.0%).
COMORBIDITIES
Of the 45 patients, 23 (51.1%) had no identifiable comorbid diseases. Twenty-one patients (46.7%) reported a smoking history; 6 of these patients had previously smoked and 15 were smokers at the time of diagnosis of livedoid vasculopathy. Clinical histories pertaining to smoking at disease manifestation were unavailable. None of the patients had used or were using nicotine gum or nicotine patches. Medical diseases present in association with livedoid vasculopathy. Clinical histories pertaining to smoking at disease manifestation were unavailable. None of the patients had used or were using nicotine gum or nicotine patches. Medical diseases present in association with livedoid vasculopathy in our study group are listed in Table 1.

HISTOPATHOLOGIC FINDINGS
In all patients, at least 1 cutaneous punch or incisional biopsy specimen was obtained; in 7 patients, a second biopsy specimen was required to make the diagnosis because the initial specimen did not demonstrate the distinctive histopathologic features necessary for the diagnosis. Dermal blood vessel thrombosis was noted in 44 (97.8%) of 45 biopsy specimens.

Direct immunofluorescence testing, performed in 36 of the 45 biopsy-proved livedoid vasculopathy cases, showed multiple vascular conjugates (fibrin > C3 > IgM > other immunoglobulins) in 31 (86.1%) of 36 patients. Most specimens with positive results demonstrated thick, heavy staining of conjugates within the walls of diseased vessels. A detailed review of the histologic and immunopathologic features in our study group has been summarized by 2 of us (B.R.H. and I.A., unpublished data, 2005).

LABORATORY DATA
Overall, 29 patients underwent extensive testing for abnormalities at our coagulation laboratory. Of these, 12 (41.4%) had abnormalities. In 10 patients, the abnormalities were multiple or were noted in conjunction with either anticardiolipin antibody (ACA) or increased concentrations of homocysteine. Specific abnormalities are listed in Table 2.

VASCULAR ASSESSMENT STUDIES
Of the 45 patients, 24 underwent venous studies; 3 of the 24 patients had venous insufficiency. Among the 27 patients evaluated with arterial studies by TcPO2, 8 (29.6%) had a severe to critical reduction in oxygen delivery, 12 (44.4%) had a mild to moderate reduction, and 7 (25.9%) had normal results.

COMMENT
These 45 patients, whose lower extremity ulcerative disease met strict clinical and histologic criteria, had livedoid vasculopathy. The disease was predominantly bilateral, but unilateral disease was also identified. The presence of more severe disease in 1 extremity has been previously reported. Female patients outnumbered male patients by nearly 2:1, a finding similar to that reported in an earlier review. The leg was the most common site of lesions, followed by the ankle. The dorsal surface of the foot was the least common. Most patients had lesions in a combination of these locations.

Atrophie blanche was reported in 32 (71.1%) patients. This clinical pattern has been noted to follow a painful ulcerative stage and has also been described in the absence of previous ulceration. The term atrophie blanche was once synonymous with this disease; however, clinical classification is often difficult because lesions resembling atrophie blanche have been described in diseases other than livedoid vasculopathy. The minority of patients in this series who did not have classic atrophie blanche changes were described as having either multiple stellate shallow ulcers or crusted erosions. Of the 45 patients, 19 had livedoid vasculopathy in association with a comorbid condition, 3 of whom had a combination of associated diseases (Table 1). Previous reviews have described livedoid vasculopathy in association with connective tissue diseases. Among our patients with characteristic clinical and histologic features of livedoid vasculopathy, 6 had associated connective tissue diseases, including scleroderma and rheuma-

Table 1. Associated Medical Diseases in Patients With Livedoid Vasculopathy

<table>
<thead>
<tr>
<th>Disease</th>
<th>No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Venous insufficiency</td>
<td>4</td>
</tr>
<tr>
<td>Deep venous thrombosis</td>
<td>3</td>
</tr>
<tr>
<td>Connective tissue disease</td>
<td>6</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>3</td>
</tr>
<tr>
<td>Scleroderma</td>
<td>1</td>
</tr>
<tr>
<td>Mixed connective tissue disease</td>
<td>1</td>
</tr>
<tr>
<td>Undifferentiated connective tissue disease</td>
<td>1</td>
</tr>
<tr>
<td>Solid organ carcinoma</td>
<td>3</td>
</tr>
<tr>
<td>Colon</td>
<td>1</td>
</tr>
<tr>
<td>Pancreas</td>
<td>1</td>
</tr>
<tr>
<td>Prostate gland</td>
<td>1</td>
</tr>
<tr>
<td>Hematologic malignancy</td>
<td>2</td>
</tr>
<tr>
<td>B-cell lymphoproliferative disease</td>
<td>1</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>1</td>
</tr>
<tr>
<td>Cerebrovascular accident or transient ischemic attack</td>
<td>2</td>
</tr>
<tr>
<td>Mononeuritis multiplex</td>
<td>1</td>
</tr>
<tr>
<td>Peripheral arterial occlusive disease</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 2. Results of Laboratory Testing in Patients With Livedoid Vasculopathy

<table>
<thead>
<tr>
<th>Test</th>
<th>No. of Patients Test</th>
<th>No. of Patients With Abnormal Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor V Leiden gene mutation (heterozygous)</td>
<td>9</td>
<td>2</td>
</tr>
<tr>
<td>Protein C or protein S</td>
<td>15</td>
<td>2</td>
</tr>
<tr>
<td>Prothrombin G20210A gene mutation</td>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td>Homocysteine</td>
<td>21</td>
<td>3</td>
</tr>
<tr>
<td>Anticardiolipin antibody</td>
<td>28</td>
<td>8</td>
</tr>
<tr>
<td>IgG alone</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>IgM alone</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>IgG plus IgM</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Lupus anticoagulant</td>
<td>28</td>
<td>8</td>
</tr>
</tbody>
</table>
It is important to carefully differentiate rheumatoid vasculitis from livedoid vasculopathy because of the potential for widespread damage from systemic vasculitis in severe rheumatoid vasculitis.\textsuperscript{19}

Five patients had associated malignancies (hematopoietic carcinomas in 2 patients and solid organ carcinomas in 3), a finding similar to previously reported associations with solid organ cancers.\textsuperscript{4} Recently, livedoid vasculopathy in association with lymphoproliferative disease was reported in 2 patients (not included in this review) at our institution.\textsuperscript{20}

Four of our patients had venous insufficiency in association with livedoid vasculopathy. Livedoid vasculopathy has clinical and histologic features that enable differentiation from lower extremity disease secondary to venous incompetence\textsuperscript{13}; however, the clinical findings in both conditions may be similar and differentiating them is often difficult. Useful features of distinction may include involvement of bilateral malleoli, the dorsal aspect of the feet, and toes in livedoid vasculopathy, with edema occurring more often with venous insufficiency. Only 8 of our 45 patients with livedoid vasculopathy had lower extremity edema. Noninvasive vascular studies may be used to confirm venous insufficiency. In 3 of our patients, venous insufficiency was confirmed by abnormal results of venous studies at our institution; 1 patient was tested elsewhere. Another feature that is helpful in differentiating these 2 conditions is the presence of segmental hyalinizing vascular change and dermal vessel occlusion in livedoid vasculopathy, as was recognized in our review.

It is important to exclude other causes of lower extremity ulcerative disease, as listed in our exclusion criteria, when diagnosing livedoid vasculopathy. To accurately classify disease in patients who have livedoid vasculopathy and comorbid conditions, it is helpful to use the descriptor “livedoid vasculopathy in association with [the name of the comorbid disease].” Limiting the disease nomenclature to only the idiopathic form has been suggested\textsuperscript{22}; this designation would have excluded several patients in our review who clearly fulfilled clinical and histologic criteria for this disease. Therefore, we included in our diagnosis, albeit carefully and selectively, patients who had comorbid diseases that may independently result in ulcerations of the lower extremity (eg, rheumatoid arthritis and venous insufficiency) if clinical and histologic criteria for livedoid vasculopathy were met.

The factor V Leiden gene mutation, a common cause of activated protein C resistance\textsuperscript{23} and inherited thrombophilia,\textsuperscript{23} was heterozygous in 2 (22.2%) of 9 patients tested. The prevalence of heterozygosity for this mutation is reported to be 3% to 7% in healthy white Americans and persons of northern European ancestry\textsuperscript{23,24} but is less common in individuals of African, Asian, or Native American descent.\textsuperscript{25} Patients with livedoid vasculopathy and the factor V Leiden mutation have also been described.\textsuperscript{26,27} None of our patients, including those with the factor V Leiden gene mutation, had a history of pulmonary embolism.

The prothrombin gene mutation (G20210A), which results in excess procoagulant prothrombin, was detected in 1 (8.3%) of 12 patients tested. Several authors\textsuperscript{23,29,30} have reported that the prevalence of this mutation in patients with deep venous thrombosis is 5% to 18% and that the prevalence in the general population is 1% to 5%. To our knowledge, this mutation has not been reported in patients with livedoid vasculopathy.

Protein C and protein S are vitamin K–dependent plasma proteins that inhibit the coagulation cascade. Deficiency of protein C is present in approximately 0.2% of the general population\textsuperscript{31}; deficiencies of protein C or protein S are reported to occur in approximately 4% to 6% of patients with venous thrombosis.\textsuperscript{32,33} Protein C deficiency has been found in individuals with livedoid vasculopathy.\textsuperscript{34,35} Decreases in the activity of protein C or protein S were detected in 1 patient each in our series.

Hyperhomocysteinemia was present in 3 (14.3%) of our 21 patients. This abnormality has been associated with both venous thrombosis and arterial thrombosis.\textsuperscript{36,37} Investigators\textsuperscript{38} at our institution compared levels of serum homocysteine in male and female patients who had livedoid vasculopathy with levels in healthy male and female subjects. The mean homocysteine level in female patients with livedoid vasculopathy was higher than in control subjects, which raises the possibility that higher levels of serum homocysteine may be associated with an increased risk of cutaneous or other organ small vessel thrombosis.\textsuperscript{39}

Lupus anticoagulant (LA) was noted in 5 (17.9%) of 28 patients tested, and ACAs were present in 8 (28.6%) of 28.5 patients had both ACAs and LA. Individuals with LA are at increased risk of thrombosis\textsuperscript{39}; antiphospholipid antibodies with an inhibitory effect on the activated protein C–protein S complex have been identified.\textsuperscript{40} Cutaneous ulceration and necrosis have been described in association with circulating LA,\textsuperscript{41} and LA and ACAs have been reported in patients with livedoid vasculopathy.\textsuperscript{34,42,43} The prevalence of LA in our study group is higher than that in the healthy population (8%).\textsuperscript{44} Similarly, 28.6% of our patients were found to have ACA, compared with 5% to 12% reported in healthy persons, although 1 study reported a 51.6% prevalence of IgG ACA in healthy elderly subjects.\textsuperscript{44,46}

Patients with congenital thrombophilic conditions may have a higher risk of thrombosis when they are in a hypercoagulable state resulting from medications, disease, or an acquired thrombophilic tendency. Although isolated deficiencies of coagulation factor inhibitors or increased levels or function of coagulation factors detected at screening do not fully explain dermal vessel thrombosis identifiable in livedoid vasculopathy, they may indicate a tendency toward a procoagulant state. The effect of heterogeneous or multiple prothrombotic defects, as we noted in 10 of our patients, may be associated with an increased risk of clinically significant thrombosis.\textsuperscript{25,37} The significance of isolated or heterogeneous coagulation abnormalities noted in patients with livedoid vasculopathy and the details of this etiopathogenetic mechanism are not yet fully understood.

Thrombosis of the dermal blood vessels was almost a uniform histologic feature in the biopsy specimens we reviewed (97.8%). Tissue ischemia from vasculopathic disease is reflected by decreased cutaneous oxygen tension, as evidenced by abnormal TcPO\textsubscript{2} results. Decreased TcPO\textsubscript{2} results were a predominant feature in our patients; 74.1% had abnormalities.
We found direct immunofluorescence examination of skin biopsy specimens to be helpful in the diagnosis of livedoid vasculopathy; 31 of 36 specimens tested had fibrin, complement components, IgM, or other immunoglobulins detected in dermal vessels with conjugate antiserum. Previous studies have described characteristic thick, intense staining of vessel walls corresponding to hyalinized vessels on hematoxylin-eosin–stained sections.46 The deposition of these factors, especially fibrin, may be potentially explained by a prothrombic and fibrinolytic state, as has been supported by the finding of elevated fibrinopeptide levels in patients with livedoid vasculopathy.51 Complement deposition may be a consequence of activation of the coagulation pathway.41 A few reports have also considered complement activation as a mediator of antiphospholipid antibody–induced thrombosis and fetal loss.49,50 Anticardiolipin antibodies were detected in 8 of our patients, with 5 of 7 specimens studied at immunofluorescence testing having complement in vessel walls. Thus, other mechanisms in addition to immune complex formation may yield positive immunofluorescence test results in patients with livedoid vasculopathy. The importance of immunofluorescence testing has been debated because not all biopsy specimens from patients with livedoid vasculopathy have demonstrated positive results.9

An accurate diagnosis of livedoid vasculopathy requires historical, clinical, laboratory, and histopathologic data (Table 3). When preliminary results are suggestive of or consistent with livedoid vasculopathy on the basis of clinical and histopathologic criteria, extensive coagulation screening is recommended to investigate potential acquired and inherited prothrombotic conditions. Because the disease is defined by both clinical and histopathologic criteria, a skin biopsy specimen is of diagnostic importance. However, biopsy specimens of the lower extremity are difficult to obtain and often the area is slow to heal. Care should be taken to avoid obtaining tissue from the base of or too close to an ulceration because granulation tissue or inflammatory cells may obscure the histopathologic features.1 Owing to the focal and segmental nature of the vascular changes, multiple biopsy specimens may ultimately be necessary to identify the distinctive histologic features.

In our series, livedoid vasculopathy was determined to be idiopathic (ie, without known comorbid disease or identifiable procoagulant state identified by abnormal laboratory results) in 19 patients (42.2%); however, we suspect that this is an overestimate of idiopathic cases because extensive coagulation screening was not performed in all patients. Recently, investigators in France determined after a thorough coagulation study that several patients with apparently idiopathic disease had potential thrombogenic mechanisms.31 As technologic advances in the coagulation laboratory continue to evolve, the entity designated idiopathic livedoid vasculopathy may be identified less often. Livedoid vasculopathy should be labeled idiopathic only if potentially comorbid diseases and laboratory abnormalities are absent.

As a retrospective review, our study has several limitations. Clinical features were determined by review of medical histories submitted and described by numerous dermatologists at a tertiary care and referral center. Findings such as atrophie blanche may be underrepresented in our study group if they were not specifically described in the medical record. To our knowledge, our study is the largest clinical and histologic review of patients with livedoid vasculopathy to date; however, not all of the patients underwent extensive thrombotic testing. Larger studies are required to fully determine whether the hereditary deficiencies of coagulation factor inhibitors or abnormal levels or function of the coagulation factors are more prevalent in patients with livedoid vasculopathy than in the general population. With further information, insight into the pathogenic potential for these factors may be clarified.

In summary, livedoid vasculopathy is a chronic, recurrent, painful cutaneous disease. The clinical manifestations of this disorder may represent the end result of multiple processes, including vaso-occlusive, immune complex, or idiopathic mechanisms. Increasing evidence is supportive of thrombophilic abnormalities. Diagnosis relies on both clinical and histologic criteria. A thorough investigation of associated medical diseases and laboratory abnormalities in 45 patients at our institution revealed multiple potential thrombogenic factors, which is further evidence of procoagulant mechanisms in the pathogenesis of livedoid vasculopathy.

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Correspondence: Ifikhar Ahmed, MD, Department of Dermatology, Mayo Clinic, 200 First St SW, Rochester, MN 55905.
REFERENCES


