

Prognostic Factors in Leukocytoclastic Vasculitis

A Clinicopathologic Study of 160 Patients

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Objective: To analyze risk factors for systemic involvement and long-term course in leukocytoclastic vasculitis.

Design: A clinicopathological study of 160 patients with leukocytoclastic vasculitis followed up for at least 3 years. Univariate and multivariate analysis were conducted by logistic regression methods.

Setting: The Bellvitge Hospital, a referral center in Barcelona, Spain.

Patients: One hundred sixty patients with cutaneous leukocytoclastic vasculitis. Patients in the categories cutaneous/systemic vasculitis and acute/chronic cutaneous vasculitis were selected for comparative analysis.

Main Outcome Measures: Clinical, laboratory, and histopathological findings.

Results: Of 89 females and 71 males, aged 14 to 89 years,

systemic involvement was documented in 20% of cases. Perinuclear-staining antineutrophil cytoplasmic autoantibodies were found in 21% of patients and cryoglobulins in 25.4%. Of the patients, 1.9% died of systemic vasculitis. The average duration of cutaneous lesions was 27.9 months. In 67.2%, a cause or associated condition was identified. Of the skin specimens, 59.6% showed vasculitis limited to superficial dermal vessels. Direct immunofluorescence was positive in 84.3% of cases. In the multivariate analysis, paresthesia, fever, and absence of painful lesions were found to be risk factors for systemic involvement. Cryoglobulins, arthralgia, and normal temperature were risk factors for chronic cutaneous disease.

Conclusion: Our results identify prognostic factors in leukocytoclastic vasculitis and may provide some aid in the management of this heterogeneous group of patients.

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LEUKOCYTOCLASTIC vasculitis (LV) is a small-vessel inflammatory disease mediated by deposition of immune complexes. In its pathogenesis, neutrophils expressing appropriate adhesion molecules adhere to activated endothelial cells and infiltrate into vessel walls, with consequent release of lytic enzymes.¹⁻⁶ Lesions are often limited to the skin, but other organs may be involved. The natural course of the cutaneous lesions is unpredictable.⁷⁻¹⁰ The diagnosis of LV includes a heterogeneous group of patients having different vasculitic syndromes, with multiple known causes and associated conditions.^{3,4,10-21} Risk factors to distinguish patients with a poor prognosis from those with a benign course have not been identified, and a rational therapy has not been standardized in this disorder.^{22,23}

We describe the clinical, laboratory, and histopathological features of 160 pa-

tients with LV, 32 of whom had systemic vasculitic involvement. The study was undertaken to determine whether these variables would discriminate (1) patients with

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isolated cutaneous vasculitis from those with systemic involvement and (2) patients with acute cutaneous disease from those with cutaneous vasculitis that persisted for more than 6 months.

RESULTS

CLINICAL FEATURES

Eighty-nine females (55.6%) and 71 males (44.4%), aged 14 to 89 years (average age, 51 years), were included. In 30.5% of the patients, physical activity aggravated the cutaneous disease. The average duration

PATIENTS AND METHODS

PATIENTS

One hundred sixty consecutive patients with histologically proved cutaneous LV were enrolled after they gave informed consent. All patients were seen at Bellvitge Hospital, Barcelona, Spain, a center treating mostly adults, from November 6, 1989, to May 27, 1994. The onset of the disease was determined historically.

CLINICAL STUDY

A complete history and physical examination were performed, according to a standard questionnaire. Laboratory tests and radiological studies at the onset of the study included the following: erythrocyte sedimentation rate; complete blood cell and platelet counts; prothrombin and partial thromboplastin times; serum chemistry profile; serum protein electrophoresis; serum immunoglobulin determination; chest radiography; electrocardiography; urinary sediment; 24-hour urinary protein determination; complement study; determinations of rheumatoid factor (latex), antinuclear antibodies, anti-DNA, anti-Ro, and anti-La antibodies, cryoglobulins, anticardiolipin, and antineutrophil cytoplasmic autoantibodies (ANCA) (indirect immunofluorescence test); and serological determination for human immunodeficiency virus, hepatitis B virus (HBV), and hepatitis C virus (HCV) (enzyme-linked immunosorbent assay and recombinant immunoblot assay).

Renal insufficiency was defined as plasma creatinine level of more than 130 $\mu\text{mol/L}$. Hematuria was defined as 5 or more red blood cells per high-power field in a centrifuged urine sample. Urinary protein excretion greater than 0.3 g/24 hours was considered abnormal. When the results of the physical examination showed a possible mononeuritis, an electromyogram was performed and, if abnormal, a peripheral nerve biopsy was obtained. In patients with severe renal or intestinal disease, a biopsy was performed if extracutaneous involvement had not been histologically documented. Systemic vasculitis was diagnosed when (1) extracutaneous involvement was histologically confirmed, (2) persistent hematuria and abnormal proteinuria were found, with or without increased levels of creatinine and urea, (3) there was electrophysiological evidence of mixed (motor and sensory) neuropathy in a pattern consistent with mononeuritis multiplex, and/or (4) abdominal angiography showed vasculitic changes.

Patients were included in different clinical vasculitis categories according to the criteria for classification of vasculitis.^{3-5,10,12,24}

Patients were followed up for at least 3 years and re-examined periodically.

HISTOLOGICAL STUDY

In each patient, a skin biopsy specimen (4-mm punch) of a cutaneous lesion was obtained for histopathological examination. The diagnosis of LV was confirmed in all patients by presence of an inflammatory infiltrate predominantly constituted by neutrophils, nuclear fragmentation, extravasation of erythrocytes, and necrosis of dermal vessel walls (**Figure 1**).^{3-5,10,25} Histological diagnosis was classified according to the size of the affected vessels as small-vessel LV in superficial dermis or LV involving small and medium vessels in superficial and deep dermis.

Fifty original slides randomly selected were further studied to evaluate semiquantitatively several histological variables. Intensity of the inflammatory infiltrate was evaluated perivascularly and interstitially in the dermis as follows: 1, weak; 2, moderate; and 3, strong. The constitutive cells in the infiltrate were classified according to the predominating cell type as follows: 1, more than 75% neutrophils and less than 25% mononuclear cells; 2, 50% neutrophils and 50% mononuclear cells; 3, less than 25% neutrophils and more than 75% mononuclear cells; and 4, more than 50% eosinophils. Necrosis was graded as follows: 1, mild; 2, moderate; and 3, severe, according to the intensity of necrosis and percentage of necrotic vessels. Intensity of purpura and leukocytoclasia was evaluated, both at the perivascular and interstitial dermis, as 1, mild; 2, moderate; and 3, severe.

In 102 patients, a second lesional biopsy specimen was obtained, snap-frozen in liquid nitrogen, and processed for direct immunofluorescence examination of IgG, IgA, IgM, and C3 deposition in dermal vessel walls. Duration of the lesions examined by biopsy was recorded and varied from less than 24 hours to 4 days.

STATISTICAL ANALYSIS

All clinical, laboratory, and histopathological data were entered into a computer. Each laboratory variable was dichotomized according to a predetermined cutoff value (normal or abnormal value). Patients in the major categories (cutaneous vasculitis/systemic vasculitis; acute/chronic [>6 months] cutaneous vasculitis) were selected for comparative analysis. The χ^2 test was used for comparing qualitative variables initially. To determine whether the significant associated parameters would predict the associated systemic disease or the chronicity of the cutaneous lesions, univariate and multivariate analysis were conducted by logistic regression methods. *P* values less than .05 were considered significant.

of the cutaneous vasculitis when patients were first seen was 17.5 months (median, 1.2 months; range, 1 week to 250 months). Palpable purpura was the most prevalent lesion (89.2%), being confluent in 44.6%. In 30.4%, cutaneous necrosis developed (**Figure 2**). Koebner phenomenon was documented in 22.9% of patients; 20.3% of patients had ulcers; 16.5%, pustules; 10%, nodules; 8.2%, urticaria vasculitis; and 6.3%, livedo reticularis. Dis-

tribution of the lesions was as follows: lower extremities, 62.4%; generalized, 28%; arms, 6.4%; and photoexposed skin, 3.2%. Of the patients, 41.4% complained of pruritus, and, in 30%, lesions were painful. Fever was found in 31.6% of patients and toxic syndrome in 24.7%. Arthralgia occurred in 36.7% of patients, paresthesia in 17%, abdominal pain in 9.5%, dyspnea in 7%, and hypertension in 8.7%.

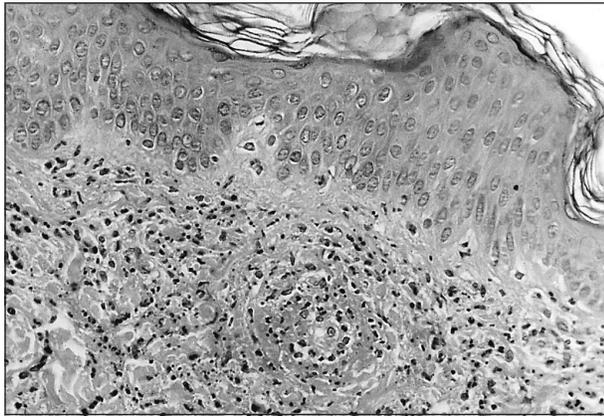


Figure 1. Histological evidence of cutaneous leukocytoclastic vasculitis, with infiltrating neutrophils, nuclear dust, and fibrinoid necrosis of the vessel walls in the superficial dermis (hematoxylin-eosin, original magnification $\times 100$).



Figure 2. Palpable purpura and severe cutaneous necrosis on the legs of a patient with chronic leukocytoclastic vasculitis limited to the skin.

LABORATORY STUDIES

Routine analytical and radiological tests showed an erythrocyte sedimentation rate greater than 20 mm/h in 52.4% of patients; anemia, 37%; leukocytosis, 18%; eosinophilia, 2.5%; thrombocytosis, 10%; urea level greater than 9.7 mmol/L, 16%; creatinine level greater than 130 $\mu\text{mol/L}$, 13%; elevated transaminase levels, 18%; increased levels of α_2 -globulins, 26%; hypergammaglobulinemia (>24 g/L), 20%; monoclonal protein, 2.8%; pathologic urine sediment, 21.7%; 24-hour proteinuria of more than 0.3 g, 19%; and 24-hour proteinuria of more than 3.5 g, 3%. **Table 1** summarizes the immunological features. In 30 patients an electromyogram

Table 1. Immunological Characteristics of 160 Patients With Leukocytoclastic Vasculitis*

Characteristic	% of Patients
ANA	28.5
Anti-DNA antibodies	3.4
Anti-Ro antibodies	8.5
Anti-La antibodies	4.7
Anti-Sm antibodies	1.0
Rheumatoid factor (≥ 40 U/mL)	26.4
Cryoglobulins	25.4
ANCA (n = 145)	
p-ANCA	21.0
c-ANCA	0
Anticardiolipin antibodies (n = 103)	
IgG	15.0
IgM	8.2
IgA	7.0
Increased serum IgA levels	24
Total serum hemolytic complement (decreased)	17
C3 plasma levels (decreased)	6
C4 plasma levels (decreased)	25

*ANA indicates antinuclear antibody; ANCA, antineutrophil cytoplasmic autoantibodies.

was performed, showing mononeuritis multiplex in 17 (56.6%). A biopsy specimen of a peripheral nerve was obtained in 15 patients, showing vasculitis in 9 (60%). A renal biopsy was necessary to confirm systemic involvement in 8 patients and revealed vasculitis in 6 (75%). In 8 patients an intestinal biopsy was obtained, showing vasculitis in 3 (37.5%). Only in 2 patients was an angiographic study undertaken, being positive for vasculitis in 1 patient.

In summary, systemic involvement (other than articular) was documented in 20% of the patients. **Table 2** shows the prevalence of the vasculitic syndromes diagnosed as well as the causes and associated diseases identified.

EVOLUTION OF THE LV

All patients were followed up for at least 3 years (average, 56 months). According to the evolution of the cutaneous vasculitis, the disease was classified as acute (resolved in <6 months) in 46.9% of the patients; chronic (resolved in ≥ 6 months or not resolved at the end of the study) in 43.8%; unavailable for follow-up in 3%; death from systemic vasculitis in 1.9%; and death not related to vasculitis in 4.4%. At the end of the study, 28.8% of patients showed chronic active cutaneous vasculitis. The duration of the cutaneous vasculitis ranged from 1 week to 318 months, with an average (\pm SD) duration of 27.9 ± 49.1 months (median, 3.7 months).

HISTOLOGICAL STUDY

In 59.6% of the specimens, the vasculitis affected dermal vessels of small diameter; in 40.4% of the medium-sized vessels, the deeper dermis were also involved. In most cases, the infiltrate was distributed around the vessels. In 76% of cases, neutrophils accounted for more than

Table 2. Causal Agents, Associated Conditions, and Vasculitis Syndromes Identified

Cause/association	% of Patients
Hepatitis C virus	19.0
Hepatitis B virus	5.0
Other infections	4.0
Drug intake	9.6
Underlying malignant neoplasm	10.0
Connective-tissue diseases	8.4
Behçet disease	2.0
Rheumatological diseases	2.4
Essential mixed cryoglobulinemia	1.3
Inflammatory bowel disease	2.5
Miscellaneous	3.0
Vasculitic syndrome	
Hypersensitivity vasculitis	64.0
Polyarteritis nodosa	6.0
Pustular vasculitis	6.0
Henoch-Schönlein purpura	5.2
Livedo vasculitis	4.5
Urticarial vasculitis	3.2
Rheumatoid vasculitis	3.2
Erythema elevatum diutinum	2.6
Churg-Strauss vasculitis	2.0

75% of the total infiltrating cells. In 2.5% (specimens from vasculitic lesions of more than 48 hours' duration), most infiltrating cells were mononuclear cells. In 3 cases of cutaneous LV in the context of Churg-Strauss vasculitis, the inflammatory infiltrate was mainly constituted by eosinophils. Vascular necrosis was mild in 42% of the patients, moderate in 32%, and marked in 26%. Although leukocytoclasia and extravasation of erythrocytes tended to be more intense around dermal vessels, in almost 50% of patients some diffuse distribution was observed.

Direct immunofluorescence study in 42.2% of the patients showed IgG deposition in the dermal vessels; in 64.7%, IgA; in 49%, IgM; and in 80.4%, C3. In 15.8% of patients, direct immunofluorescence was negative. **Figure 3** shows the inverse relationship between deposition of immunoreactants and duration of the lesion ($P < .01$).

STATISTICAL ANALYSIS

Table 3 shows crude (cRR) and adjusted (aRR) relative risks of long-term evolution of the cutaneous vasculitis for all the factors found to have a significant association in the bivariate analysis, together with the 95% confidence intervals. The following factors were demonstrated to significantly influence the univariate analysis: arthralgia, exacerbation of the disease with physical activity, paresthesia, increased rheumatoid factor, cryoglobulins, and positive serological determinations for HCV. Protective factors found were sex (male), fever, upper respiratory tract infection before developing LV, increased levels of α_2 -globulins, and normal levels of total hemolytic complement and C4.

These factors were controlled for by means of multiple logistic regression analysis, and aRRs were calcu-

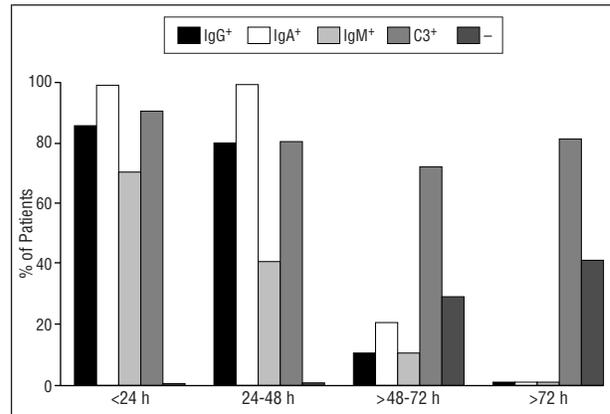


Figure 3. Direct immunofluorescence and duration of the cutaneous vasculitic lesion studied by biopsy. Plus sign indicates positive; minus sign, negative. $P < .001$ for the 4 groups compared.

lated for each factor in a collective model. Cryoglobulins were the most relevant independent risk factor of developing chronic cutaneous LV (aRR, 32.08); detection of HCV and increased levels of rheumatoid factor lost their significance. Arthralgia was the second factor to be considered (aRR, 8.85). Fever continued to be a protective factor by multivariable methods (aRR, 0.03). The aRRs for sex and physical activity did not reach significance.

Table 4 shows the RR and 95% confidence interval of systemic vasculitic involvement for all of the factors with a significant initial association. The univariate evaluation found the following predictors of systemic vasculitic disease: elevated erythrocyte sedimentation rate, leukocytosis, thrombocytosis, increased rheumatoid factor, abdominal pain, paresthesia, positivity of HBV core antibody, fever, and toxic syndrome. Presence of painful skin lesions was a protective factor in this analysis.

When all of these factors were entered in the multivariate analysis, paresthesia was the most relevant independent risk factor for developing systemic vasculitis (aRR, 36.95). Fever also maintained its significance (aRR, 8.88). All of the laboratory variables, presence of abdominal pain, and toxic syndrome lost their influence. Presence of painful cutaneous lesions continued to be a protective factor when tested by multivariate methods (aRR, 0.05).

COMMENT

Our results reflect the diversity of manifestations of LV. Systemic involvement was documented in 20% of patients. A causal agent or an associated condition was identified in 67.2% of the patients. A careful reading of previous reports shows similar percentages.⁷⁻¹⁰ The prevalence of HCV in the Spanish population is 0.8%, and this can explain the high incidence of LV associated with HCV in our series (21.4%). In almost 47% of our patients, cutaneous LV resolved in less than 6 months, and a subgroup of patients (8%) presented with successive crops of cutaneous lesions for more than 10 years. (Exercise aggravated the cutaneous vasculitis in 30.4% of our patients.²⁶) Less than 2% of patients died of systemic vasculitis.

Table 3. Crude and Adjusted Relative Risk of Chronic Evolution of the Cutaneous Vasculitis for All Relevant Factors Examined by Multiple Logistic Regression*

Risk Factor	Crude		Adjusted†	
	RR	95% CI	RR	95% CI
Sex				
Females	1		1	
Males	0.39	0.20-0.75	0.30	0.08-1.12
Upper respiratory tract infection				
Absent	1	0.79-0.10	1	
Present	0.29	0.10-0.79	0.21	0.02-1.66
Physical activity				
Absent	1		1	
Present	3.36	1.60-7.05	3.22	0.73-14.06
Fever				
Absent	1	0.50-0.11	1	0.25-0.01
Present	0.23	0.11-0.50	0.03	0.01-0.25
Arthralgia				
Absent	1		1	
Present	2.50	1.25-4.96	8.85	1.97-39.71
Paresthesia				
Absent	1		1	
Present	3.22	1.26-8.21	2.23	0.46-10.79
α ₂ -Globulins, g/L				
<7	1	0.90-0.19	1	
≥7	0.42	0.19-0.90	0.26	0.05-1.37
Total hemolytic complement, U				
<51	1	0.95-0.11	1	
≥51	0.32	0.11-0.95	1.87	0.21-16.24
C4, g/L				
<0.2	1	0.68-0.11	1	
≥0.2	0.28	0.11-0.68	0.66	0.09-4.77
Rheumatoid factor, U/mL				
<40	1		1	
≥40	5.41	2.03-14.44	3.44	0.54-21.91
Cryoglobulins				
Absent	1		1	
Present	7.76	2.43-24.72	32.08	2.85-360.97
Hepatitis C virus				
Absent	1		1	
Present	2.93	1.09-7.80	1.44	0.17-12.08

*RR indicates relative risk; CI, confidence interval.

†Adjusted risks (95% CI) obtained from a model that contained all other variables included in this table.

As previously stated, the infiltrate was mainly constituted by neutrophils, and the proportion of mononuclear cells significantly correlated with duration of the lesion studied by biopsy ($P < .001$).^{1,2,4,27} Predominance of infiltrating eosinophils was associated with Churg-Strauss disease in our series. We did not find a significant association between the histological variables studied and prognosis.

Direct immunofluorescence test showed vascular deposition of immunoreactants in 84.3% of the vasculitic biopsy specimens studied. Similar positive results were reported previously.^{1,7,28-30} Destruction and removal of immunoglobulins deposited in the affected dermal vessels takes place in less than 48 hours, and direct immunofluorescence studies of vasculitic lesions older than 48 hours are frequently negative.²⁹ The posi-

Table 4. Crude and Adjusted Relative Risk of Systemic Vasculitis Involvement for All Relevant Factors Examined by Multiple Logistic Regression*

Risk Factor	Crude		Adjusted†	
	RR	95% CI	RR	95% CI
ESR, mm/h				
<20	1		1	
≥20	4.15	1.70-10.11	4.21	0.79-22.31
Leukocytes, ×10 ⁹ /L				
<10.5	1		1	
≥10.5	4.33	1.79-10.44	2.70	0.26-27.69
Thrombocytes, ×10 ⁹ /L				
<450	1		1	
≥450	6.9	1.81-26.27	0.93	0.03-23.33
Rheumatoid factor, U/mL				
<40	1		1	
≥40	3.07	1.26-7.49	3.40	0.59-19.33
Abdominal pain				
Absent	1		1	
Present	9.48	2.83-31.77	10.30	0.56-189.38
Paresthesia				
Absent	1		1	
Present	13.27	4.89-36.02	36.95	5.82-234.41
Anti-HBV core antigen				
Absent	1		1	
Present	3.41	1.19-9.74	3.59	0.52-24.40
Painful lesions				
Absent	1	0.68-0.05	1	0.45-0.01
Present	0.19	0.05-0.68	0.05	0.01-0.45
Fever				
Absent	1		1	
Present	3.23	1.41-7.42	8.88	1.46-53.95
Toxic syndrome				
Absent	1		1	
Present	3.07	1.29-7.29	0.75	0.12-4.67

*RR indicates relative risk; CI, confidence interval; ESR, erythrocyte sedimentation rate; and HBV, hepatitis B virus.

†Adjusted risks (95% CI) obtained from a model that contained all other variables included in this table.

tivity of the immunofluorescence test was inversely correlated with the duration of the lesion studied by biopsy ($P < .001$). C3 deposition persisted longer than immunoglobulins did. Unlike previous authors,^{7,10,29} we found that IgA was the immunoglobulin most frequently detected. However, in only 8 patients (2 with Henoch-Schönlein purpura with mesangial IgA deposition, 1 with alcoholic liver disease, 1 with Crohn disease, 1 with sore throat and amoxicillin intake, 1 with Churg-Strauss disease, and 2 with chronic HBV infection), IgA was not associated with IgM or IgG deposition. The finding of IgA deposition in dermal vessels is not restricted to Henoch-Schönlein disease, and its diagnostic value is still a matter of controversy.³¹⁻³⁴ It may also be seen in various vasculitic and nonvasculitic disorders, including chronic glomerular diseases and alcoholic liver disease.³⁵⁻³⁸

Our results suggest that in the context of LV, the finding of IgA fluorescence with additional immunoreactants (IgG, IgM) within the vessel walls has a low specificity for differentiating Henoch-Schönlein disease. However, it can be argued that vascular, isolated IgA (or C3)

staining may be characteristic of Henoch-Schönlein disease.^{1,29,32-34}

As previously reported, we did not find a significant correlation between direct immunofluorescence results and long-term evolution of the cutaneous vasculitis or systemic involvement.^{1,7}

In this study, 21% of patients had positive ANCA. Perinuclear-staining ANCA was the pattern detected in all these cases. Systemic involvement was documented in 40% of the ANCA-positive cases (microscopic polyarteritis, classic polyarteritis nodosa, Churg-Strauss disease, and mixed cryoglobulinemia), but in 60% the disorder remained limited to the skin (idiopathic LV, cryoglobulinemia related to HCV and HBV infection, and paraneoplastic vasculitis). The usefulness of ANCA when diagnosing necrotizing systemic vasculitis is well known.³⁹⁻⁴⁵ However, when considering a patient with cutaneous LV, the presence of perinuclear-staining ANCA does not appear to be a specific enough marker of systemic involvement. None of our patients had cytoplasmic-staining ANCA, a highly specific test for Wegener granulomatosis, but perinuclear-staining ANCA was positive in 15% of patients with LV limited to the skin—in opposition to suggestions made in previous reports⁴⁶⁻⁴⁹—with or without associated connective-tissue disorders, such as systemic lupus erythematosus or scleroderma.^{50,51}

We tested all the variables assessed in this study to identify prognostic factors in LV. The univariate analysis demonstrated a significant association between systemic vasculitic involvement and elevated erythrocyte sedimentation rate (cRR, 4.15), leukocytosis (cRR, 4.33), and thrombocytosis (cRR, 6.9). All these laboratory abnormalities are nonspecific markers of systemic inflammation. When entered in the multiple regression analysis, only erythrocyte sedimentation rate maintained a similar influence in predicting systemic involvement (aRR, 4.21), although the 95% confidence interval was 22.31 to 0.79. Analysis of other laboratory variables showed elevated levels of rheumatoid factor (cRR, 3.07) and positive HBV core antibodies (cRR, 3.41) to have a significant influence in predicting extracutaneous involvement. Both factors lost their mild univariate predictive power when entered in the multivariate model. Concerning the clinical variables, fever (cRR, 3.23), evidence of toxic syndrome (cRR, 3.07), and abdominal pain (cRR, 9.48) were also influential factors when examined individually, but when tested by multivariable techniques only fever reached statistical significance (aRR, 8.88). As expected, paresthesia was the main prognostic factor identified (aRR, 36.95), and in our study 56.3% of patients who complained of paresthesia had positive findings in the electromyogram and/or in the biopsy specimen of a peripheral nerve. The type of cutaneous lesion had no prognostic influence in our series, but patients with pain were more likely to have disease limited to the skin (aRR, 0.05; 95% confidence interval, 0.01-0.45).

It can be argued that pain is related to a more necrotic cutaneous disease, reflecting a greater deposition of circulating immune complexes in the dermis and decreased extracutaneous involvement. Age and sex were not useful predictors of systemic involvement. As

af Ekenstam and Callen⁸ suggested in a clinical observation, duration of cutaneous disease did not significantly increase the risk of systemic involvement. These considerations may provide some help in the management of persistent cutaneous vasculitis.

The results of our study indicate that a subgroup of patients having mixed cryoglobulinemia with arthralgia, increased rheumatoid factor level, and decreased total hemolytic complement and C4 activity has an elevated risk of having cutaneous vasculitis for several months. Most of these patients showed positive serological determinations for HCV in our series. Some authors have proved the association between chronic HCV infection and mixed cryoglobulinemia. It is likely that such persistent infection elicits and maintains the immune-mediated vasculitic disorder.^{15,16} In this sense, detection of cryoglobulins was found to be the most powerful and independent risk factor of chronicity in our statistical analysis. Contrarily, fever may select a subgroup of patients with acute disease. The existence of fever resulting from a curable infection that causes the LV may partially explain this association. Although most autoimmune or immune-mediated diseases show a preponderance of women, the influence of sex in vasculitic syndromes has not been established. Our results allow us to suggest a possible influence of sex in the chronicity of cutaneous vasculitis.

In summary, LV is seen in a heterogeneous group of patients with variable prognosis and a low mortality rate (<2%). The findings on histological examination are time dependent. The multivariate analysis of clinical and histological data found paresthesia and fever to be risk factors for systemic involvement. Painful cutaneous lesions had a protective influence. Interestingly, perinuclear-staining ANCA was not predictive of systemic vasculitis. Cryoglobulins, arthralgia, and normal temperature were the most relevant risk factors for chronic cutaneous disease in this analysis.

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REFERENCES

1. Mackel SE, Jordon RE. Leukocytoclastic vasculitis: a cutaneous expression of immune complex disease. *Arch Dermatol.* 1982;118:296-301.
2. Jennette JC, Charles LA, Falk RJ. The neutrophil and its role in systemic vasculitis. In: Le Roy EC, ed. *Systemic Vasculitis: The Biological Basis.* New York, NY: Marcel Dekker Inc; 1992:65-92.
3. Fauci AS, Haynes BF, Katz P. NIH Conference: the spectrum of vasculitis: clinical, pathologic, immunologic, and therapeutic considerations. *Ann Intern Med.* 1978;89:660-676.
4. Jennette CJ, Milling DM, Falk RJ. Vasculitis affecting the skin: a review. *Arch Dermatol.* 1994;130:899-906.
5. Conn DL. Update on systemic necrotizing vasculitis. *Mayo Clin Proc.* 1989;64:535-543.
6. Sais G, Vidaller A, Jucglà A, Condom E, Peyrí J. Adhesion molecule expression and endothelial cell activation in cutaneous leukocytoclastic vasculitis: an im-

- munohistological and clinical study on 42 cases. *Arch Dermatol.* 1997;133:443-450.
7. Sánchez NP, Van Hale HM, Su D. Clinical and histopathologic spectrum of necrotizing vasculitis: report of findings in 101 cases. *Arch Dermatol.* 1985;121:220-224.
 8. af Ekenstam E, Callen JP. Cutaneous leukocytoclastic vasculitis: clinical and laboratory features of 82 patients seen in private practice. *Arch Dermatol.* 1984;120:484-489.
 9. Cupps TR, Springer RM, Fauci AS. Chronic, recurrent, small-vessel cutaneous vasculitis: clinical experience in 13 patients. *JAMA.* 1982;247:1994-1998.
 10. Gibson LE. Cutaneous vasculitis: approach to diagnosis and systemic associations. *Mayo Clin Proc.* 1990;65:221-229.
 11. Somer T, Finegold S. Vasculitides associated with infections, immunization, and antimicrobial drugs. *Clin Infect Dis.* 1995;20:1010-1036.
 12. Agnello V, Chung RT, Kaplan LM. A role for hepatitis C virus infection in type II cryoglobulinemia. *N Engl J Med.* 1992;327:1490-1495.
 13. Heart-Holmes M, Zahradka SL, Baethge BA, Wolf RE. Leukocytoclastic vasculitis associated with hepatitis C. *Am J Med.* 1991;90:765-766.
 14. Misiani R, Bellavita P, Fenili D, et al. Hepatitis C virus infection in patients with essential mixed cryoglobulinemia. *Ann Intern Med.* 1992;117:573-577.
 15. Popp JW, Harrist TJ, Dienstag JL, et al. Cutaneous vasculitis associated with acute and chronic hepatitis. *Arch Intern Med.* 1981;141:623-629.
 16. Daoud MS, el-Azhary RA, Gibson LE, Lutz ME, Daoud S. Chronic hepatitis C, cryoglobulinemia and cutaneous necrotizing vasculitis. *J Am Acad Dermatol.* 1996;34:219-223.
 17. Karlsberg PL, Lee WM, Casey DL, Cockerell CJ, Cruz PD Jr. Cutaneous vasculitis and rheumatoid factor positivity as presenting signs of hepatitis C virus-induced mixed cryoglobulinemia. *Arch Dermatol.* 1995;131:1119-1123.
 18. Gherardi R, Belec L, Mhiri C, et al. The spectrum of vasculitis in human immunodeficiency virus-infected patients: a clinicopathologic evaluation. *Arthritis Rheum.* 1993;36:1164-1174.
 19. Calabrese LH, Estes M, Yen-Lieberman B, et al. Systemic vasculitis in association with human immunodeficiency virus infection. *Arthritis Rheum.* 1989;32:569-576.
 20. Sanchez Guerrero J, Gutierrez Urena J, Vidaller A, Reyes E, Iglesias A, Alarcon-Segovia D. Vasculitis as a paraneoplastic syndrome: report of 11 cases and review of the literature. *J Rheumatol.* 1990;17:1458-1462.
 21. Greer JM, Longley S, Edwards NL, Elfenbein GJ, Panush RS. Vasculitis associated with malignancy: experience with 13 patients and literature review. *Medicine.* 1988;67:220-230.
 22. Sais G, Vidaller A, Jucglà A, Gallardo F, Peyrí J. Colchicine in the treatment of cutaneous leukocytoclastic vasculitis: results of a prospective, randomized controlled trial. *Arch Dermatol.* 1995;131:1399-1402.
 23. Conn DL. Overview of therapy and management of systemic vasculitis. In: Le Roy EC, ed. *Systemic Vasculitis: The Biological Basis.* New York, NY: Marcel Dekker Inc; 1992:547-574.
 24. Hunder GH, Arend WP, Bloch DA, et al. The American College of Rheumatology 1990 criteria for the classification of vasculitis. *Arthritis Rheum.* 1990;33:1065-1144.
 25. Lie JT, Members and Consultants of the American College of Rheumatology Subcommittee on Classification of Vasculitis. Illustrated histopathologic classification criteria for selected vasculitis syndromes. *Arthritis Rheum.* 1990;33:1074-1087.
 26. Prins M, Veraart JCJM, Vermeulen AHM, Hulsmans FHJ, Neumann HAM. Leukocytoclastic vasculitis induced by prolonged exercise. *Br J Dermatol.* 1996;134:915-918.
 27. Zax RH, Hodge SJ, Callen JP. Cutaneous leukocytoclastic vasculitis: serial histopathologic evaluation demonstrates the dynamic nature of the infiltrate. *Arch Dermatol.* 1990;126:69-72.
 28. Gower RG, Sams WM Jr, Thorne EG. Leukocytoclastic vasculitis: sequential appearance of immunoreactants and cellular changes in serial biopsies. *J Invest Dermatol.* 1977;69:477-484.
 29. Michel BA, Hunder GG, Bloch DA, Calabrese LH. Hypersensitivity vasculitis and Henoch-Schönlein purpura: a comparison between the 2 disorders. *J Rheumatol.* 1992;19:721-728.
 30. Schroeter AL, Copeman PWM, Jordon RE, Sams WM Jr, Winkelman RK. Immunofluorescence of cutaneous vasculitis associated with systemic disease. *Arch Dermatol.* 1971;104:254-259.
 31. Hené RJ, Velthuis P, van de Wiel A, Klepper D, Dorhout Mees EJ, Kater L. The relevance of IgA deposits in vessel walls of clinically normal skin: a prospective study. *Arch Intern Med.* 1986;146:745-749.
 32. Helander SD, De Castro FR, Gibson LE. Henoch-Schönlein purpura: clinicopathologic correlation of cutaneous vascular IgA deposits and the relationship to leukocytoclastic vasculitis. *Acta Derm Venereol.* 1995;75:125-129.
 33. Van Hale HM, Gibson LE, Schroeter AL. Henoch-Schönlein vasculitis: direct immunofluorescence study of uninvolved skin. *J Am Acad Dermatol.* 1986;15:665-670.
 34. Tsai CC, Giangiacomo J, Zuckner J. Dermal IgA deposits in Henoch-Schönlein purpura and Berger's nephritis. *Lancet.* 1975;1:342-343.
 35. Saklayen MG, Schroeter A, Nafs MA, Jalil K. IgA deposition in the skin of patients with alcoholic liver disease. *J Cutan Pathol.* 1996;23:12-18.
 36. Hirbec G, Belghiti D, Wechsler J, Sobel A, Lagrue G. Immunofluorescence study of skin biopsy specimens from patients with chronic renal diseases. *Kidney Int.* 1977;12:374. Abstract.
 37. Swerdlow MA, Chowdhury LN, Mishra V, Kavin H. IgA deposits in skin in alcoholic liver disease. *J Am Acad Dermatol.* 1983;9:232-236.
 38. Thompson AJ, Chan Y-L, Woodroffe AJ. Vascular IgA deposits in clinically normal skin of patients with renal disease. *Pathology.* 1980;12:407-413.
 39. Van der Woude FJ, Lobato S, Permin H, et al. Autoantibodies against neutrophils and monocytes: tool for diagnosis and marker of disease activity in Wegener's granulomatosis. *Lancet.* 1985;1:425-429.
 40. Jennette JC, Falk RJ. Antineutrophil cytoplasmic antibodies and associated diseases: a review. *Am J Kidney Dis.* 1990;15:517-529.
 41. Cohen Tervaert JW, Goldschmeding R, Elema JD, et al. Association of autoantibodies to myeloperoxidase with different forms of vasculitis. *Arthritis Rheum.* 1990;33:1264-1272.
 42. Venning MC, Arfeen S, Bird AG. Antibodies to neutrophil cytoplasmic antigen in systemic vasculitis. *Lancet.* 1987;2:850.
 43. Falk RJ, Jennette JC. Anti-neutrophil cytoplasmic autoantibodies with specificity for myeloperoxidase in patients with systemic vasculitis and idiopathic necrotizing and crescentic glomerulonephritis. *N Engl J Med.* 1988;318:1651-1657.
 44. Savage COS, Winearls CG, Jones S, Marshall PD, Lockwood CM. Prospective study of radioimmunoassay for antibodies against neutrophil cytoplasm in diagnosis of systemic vasculitis. *Lancet.* 1987;1:1389-1393.
 45. Gross WL, Schmitt WH, Csernok E. Antineutrophil cytoplasmic autoantibody-associated diseases: a rheumatologist's perspective. *Am J Kidney Dis.* 1991;18:175-179.
 46. Kemmett D, Harrison DJ, Hunter JAA. Antibodies to neutrophil cytoplasmic antigens: a serologic marker for Sweet's syndrome. *J Am Acad Dermatol.* 1991;24:967-969.
 47. Kemmett D, Hunter JAA. Sweet's syndrome: a clinicopathologic review of twenty-nine cases. *J Am Acad Dermatol.* 1990;23:503-507.
 48. Burrows NP, Lockwood CM. Antineutrophil cytoplasmic antibodies and their relevance to the dermatologist. *Br J Dermatol.* 1995;132:173-181.
 49. Irvine AD, Bruce IN, Walsh M, Burrows D, Handley J. Dermatological presentation of disease associated with antineutrophil cytoplasmic antibodies: a report of two contrasting cases and a review of the literature. *Br J Dermatol.* 1996;134:924-928.
 50. Dolman KM, Gans ROB, Verbaat TJ, et al. Vasculitis and antineutrophil cytoplasmic autoantibodies associated with propylthiouracil therapy. *Lancet.* 1993;342:651-652.
 51. Kawachi Y, Nukaga H, Hoshino M, Iwata M, Otsuka F. ANCA-associated vasculitis and lupus-like syndrome caused by methimazole. *Clin Exp Dermatol.* 1995;20:345-347.