Histopathologic differences between cutaneous vasculitis associated with severe bacterial infection and cutaneous vasculitis secondary to other causes: a study of 52 patients

J. Loricera[1], C. González-Vela[2], R. Blanco[1], J.L. Hernández[3], S. Armesto[4], M.A. González-López[4], V. Calvo-Río[1], F. Ortiz-Sanjuán[1], J.F. Val-Bernal[2], S. Hermana[2], A. Onaindia-Pérez[2], M.A. González-Gay[1]

Departments of Rheumatology[1], Pathology[2], Internal Medicine[3] and Dermatology[4], Hospital Universitario Marqués de Valdecilla, IDIVAL, University of Cantabria, Santander, Spain.

Javier Loricera, MD, PhD*
Carmen González-Vela, MD, PhD*
Ricardo Blanco, MD, PhD
José L. Hernández, MD, PhD
Susana Armesto, MD, PhD
Marcos A. González-López, MD, PhD
Vanesa Calvo-Río, MD, PhD
Francisco Ortiz-Sanjuán, MD
J. Fernando Val-Bernal, MD, PhD
Sandra Hermana, MD
Arantza Onaindia-Pérez, MD
Miguel A. González-Gay, MD, PhD

*J. Loricera and C. González-Vela shared first authorship.

Please address correspondence to:
Dr Miguel A. González-Gay,
Rheumatology Division,
Hospital Universitario Marqués
de Valdecilla, IDIVAL,
Avenida de Valdecilla s/n,
39008 Santander, Spain.
E-mail: miguelaggay@hotmail.com

ABSTRACT

Objective. To determine if cutaneous vasculitis (CV) associated with severe infection has some histopathologic findings that may help us to differentiate patients with this condition from other patients with CV.

Methods. We reviewed the skin biopsy specimens of patients with leukocytoclastic CV associated with a severe bacterial infection. Histopathologic findings of these patients were compared with those observed in leukocytoclastic CV secondary to other causes. Biopsy-proven leukocytoclastic CV were stratified as follows: group a): CV associated with severe underlying bacterial infection; group b): CV without severe bacterial infection but with systemic involvement; group c): CV without systemic involvement. Slides were reviewed by expert pathologists that were blind to the clinical information. The severity of vascular lesions was measured according to a semiquantitative scale (Hodge index). A comparative study between group a) and the other groups was conducted.

Results. group a) included 12 patients (2 women/10 men), mean age± SD 56±15 years; group b) 21 patients (10 women/11 men), 52±18 years; and group c) 19 patients (12 women/7 men), 59±24 years. Presence of neutrophilia was significantly increased in biopsies from group a) when compared with the other two groups. Also, a trend to higher frequency of pustular dermatosis was found in patients from group a). Hodge index, degree of inflammatory infiltrate and deep arterioles involvement were similar in all groups.

Conclusion. Neutrophilia is common in skin biopsies of patients with CV associated with severe bacterial infection. No other histopathological findings help us to establish the presence of a severe underlying infection.

Introduction

Cutaneous vasculitis (CV) comprises a wide and heterogeneous group of conditions characterised by predominant involvement of the skin with histopathologic findings that have in common vascular inflammation and blood vessel damage (1-9). There is a wide spectrum of entities that may be associated with CV such as drug reactions, infections, connective tissue diseases, autoimmune disorders and malignancies (1-11).

Skin biopsy is the gold standard for the diagnosis of CV. However, the presence of a leukocytoclastic vasculitis .in the skin biopsy is not sufficient to establish the specific underlying aetiology (12). An isolated CV is usually a benign process. However, in some cases CV may be associated with systemic disorders and severe underlying infections (4, 6, 9, 10). In this regard, whereas treatment with high doses of corticosteroids, with or without cytotoxic agents, may be effective in patients with CV associated with severe systemic manifestations, these medications can cause deleterious effects in patients in whom CV is a manifestation of a severe underlying bacterial infection.

To determine if CV associated with severe infection has some histopathologic findings that may help us to differentiate patients with this condition from other patients with CV, in the present study we reviewed the skin biopsy specimens of patients with leukocytoclastic CV associated with a severe bacterial infection. Histopathological findings of these patients were com-

pared with those observed in leukocytoclastic CV secondary to other causes.

Patients and methods

We reviewed the clinical records of all the patients diagnosed with CV at a tertiary-care teaching hospital from Northern Spain, between January 1990 and December 2014. Methods were similar to those previously reported (1, 4-7, 13). We assessed 3 different groups of patients that had been included in a large series of patients with CV: *group a)* CV associated with severe underlying bacterial infection; *group b)* CV without severe bacterial infection but with systemic involvement; and *group c)* CV without systemic involvement (hypersensitivity vasculitis).

CV was considered associated with severe bacterial infection when it occurred in the setting of a severe underlying infection and antibiotic therapy led to resolution of the infection and the vasculitic syndrome. Severe bacterial infection was considered to be present when the patient required hospitalisation and received oral or intravenous antibiotics. In the present study, we only included patients with available histopathology slides. Biopsy specimens were reviewed by two dermatopathologists (CGV & SH) who were blind to the clinical information. Histological sections were stained with haematoxilin-eosin (H&E) and periodic acid Schiff (PAS). According to Hodge *et al.* (14), we recorded the following histopathological findings: *a)* inflammation on the vessel wall, *b)* erythrocyte exocytosis, *c)* depth of the inflammatory infiltrate, *d)* amount of leukocytoclasis, *e)* amount of fibrinoid necrosis, *f)* epidermal necrosis, and *g)* fibrin thrombi. The set of all these elements is known as Hodge index. Each feature was judged on a scale of 0 to 3+, and the Hodge index was obtained by adding the score of each feature, thus the Hodge index could vary from 0 to 21. Besides Hodge index, we also recorded the presence or absence of the following histopathological findings: tissue eosinophilia; tissue neutrophilia; tissue lymphocytosis; intensity of inflammatory infiltrate; pustular dermatosis; and involvement of deep arterioles. A grad-

ing (severity) semiquantitative scale (range 0 to 3+) was used for each histopathologic finding. Histopathological features of patients included in *group a)* (leukocytoclastic CV vasculitis in the setting of severe bacterial infection) were compared with those of the other two groups of leukocytoclastic CV (*group b)* and group c)).

Clinical and laboratory definitions
a) Fever was defined as an axillary temperature > 37.7ºC. *b)* Constitutional syndrome: asthenia, and/or anorexia, and weight loss of at least 4 kg. *c)* Joint manifestations included arthralgia and/or joint effusion. *d)* Gastrointestinal manifestations: bowel angina (diffuse abdominal pain worsening after meals), gastrointestinal bleeding (melena, haematochezia, or positive stool Guaic test), nausea and/or vomiting. *e)* Nephropathy if patients had haematuria (≥5 red cell/high power field) and/or proteinuria. *f)* Anaemia was defined as a haemoglobin level ≤11 g/dL. *g)* Leukocytosis if a white cell count was ≥11,000/mm^3. *h)* Westergren Eryth-

rocyte Sedimentation Rate (ESR) in mm/1st hour was considered elevated when it was higher than 15 or 20 mm/1st hour for men or women, respectively.

Data collection
Data on clinical, laboratory and histopathological features, aetiology, treatment and outcome were retrieved from the clinical charts and stored in a computerised database. To minimise entry error all data were double checked and reviewed for diagnosis confirmation. When available, data on the immunological profile, which included rheumatoid factor (RF); antinuclear antibodies (ANA); serum complement C3 and C4, antineutrophil cytoplasmic antibodies (ANCAs) and cryoglobulins, were assessed.

Statistical analysis
Continuous variables were expressed as mean ± standard deviation (SD) or median [interquartile range (IQR)] as appropriate, and analysed by Kruskal-Wallis test. Categorical variables were expressed as percentages and com-

Table I. Comparative study of the main demographic, clinical and laboratory features between the three groups.

Main features	CV associated with severe infection *Group a)* (n=12)	CV with systemic involvement *Group b)* (n=21)	CV without systemic involvement *Group c)* (n=19)
Demographic data			
Age, mean±SD (years)	56 ± 15	52 ± 18	59 ± 24
Sex, Women/Men; n (%)	2 (16.7)/10(83.3)	10 (47.6)/11 (52.4)	12 (63.2)/7 (36.8)*
Clinical features ; n (%)			
Skin lesions	12 (100)	21 (100)	19 (100)
Palpable purpura	12 (100)	20 (95.2)	14 (73.7)
Others	0 (0)	6 (28.6)	10 (52.6)*
Constitutional syndrome	2 (16.7)	3 (14.3)	1 (5.3)
Fever	12 (100)	4 (19)*	3 (15.8)*
Joint manifestations	8 (66.7)	7 (33.3)	5 (26.3)
GI Involvement	5 (41.7)	6 (28.6)	0 (0)*
Nephropathy	7 (58.3)	9 (42.9)	6 (31.6)
Laboratory parameters; n (%)			
Raised ESR	12 (100)	11 (52.4)*	6 (31.6)*
Anaemia	6 (50)	4 (19)	5 (26.3)
Leukocytosis	12 (100)	4 (19)*	6 (31.6)*
Immunologic tests, number cases/number tested (%)			
Positive ANA	3/9 (33.3)	5/17 (29.4)	5/12 (41.7)
Positive RF	2/7 (28.6)	6/15 (40)	2/13 (15.4)
Low C3 and/or C4	1/8 (12.5)	2/13 (15.4)	0/11 (0)
Cryoglobulins	2/5 (40)	3/17 (17.6)	0/8 (0)
Positive ANCAs	0/6 (0)	0/13 (0)	1/9 (11.1)

ANA: antinuclear antibodies; ANCAs: anti-neutrophil cytoplasmic antibody; ESR: erythrocyte sedimentation rate; GI: gastrointestinal; RF: rheumatoid factor, *$p<0.05$ *vs*. group a.

Table II. Main histological findings of the three groups of leukocytoclastic CV.

	CV associated with severe infection Group a) (n=12)	CV with systemic involvement Group b) (n=21)	CV without systemic involvement Group c) (n=19)
Hodge index, median [IQR]	6 [5-8.5]	6.5 [5-9.5]	6 [5-8]
Tissue eosinophilia	0 (0%)	3 (14.3%)	5 (26.3%)
Tissue neutrophilia	12 (100%)	14 (66.7%)*	10 (52.6%)*
Tissue lymphocytosis	0 (0%)	2 (9.5%)	4 (21.1%)
Intensity of inflammatory infiltrate, median [IQR]	1 [1-2]	1 [1-2]	1 [1-1]
Pustular dermatosis	5 (41.7%)	4 (19.1%)	3 (15.8%)
Deep involvement of arterioles	2 (16.7%)	2 (9.5%)	1 (5.3%)

*$p<0.05$ *vs. group a)* *vs. group* b) and *group c)*.

pared between groups by using Fisher's exact test. STATA 12/SE software (StataCorp, College Station, TX) was used in all the calculations. Differences were considered statistically significant at $p<0.05$.

Results

Demographics
We studied 12 patients (2 women/10 men) with severe bacterial infection (*group a)*. The mean age ± SD was 56±15 years (range: 31-78 years). The severe underlying bacterial infections were: pneumonia (n=5), meningitis (n=3), urinary tract infection (n=1), infectious arthritis of the knee (n=1), abdominal sepsis (n=1) and mediastinitis (n=1). *Group b)* included 21 patients (10 women and 11 men) with systemic involvement unrelated to severe bacterial infection. The mean age was 52±18 years (range: 20-83 years). The underlying conditions in this group were: Henoch-Schönlein purpura (n=9), polyarteritis nodosa (n=4), microscopic polyangiitis (n=2), cryoglobulinaemic vasculitis (n=2), malignancy (n=2), systemic lupus erythematosus (n=1) and Sjögren's syndrome (n= 1). *Group c)* comprised 19 patients (12 women and 7 men) patients with hypersensitivity vasculitis; mean age of 59±24 years (range: 5-86 years).

Clinical and laboratory findings
Clinical and laboratory differences between patients with leukocytoclastic CV associated with severe bacterial infection and those from the other two groups are shown in Table I. Palpable purpura was the only cutaneous lesion observed in patients from *group a)*. In the other two groups, in particular in those from *group c)*, other cutaneous lesions such as blisters, erythema, urticaria and ulcers were observed. Fever was present in all patients with severe bacterial infection. Constitutional syndrome, joint manifestations, gastrointestinal involvement and nephropathy were also more frequent in the group of patients with severe bacterial infection (*group a)*, although differences did not reach statistical significance.

Anaemia, leukocytosis and raised ESR were also more commonly found in patients from *group a)*, as well as the presence of serum cryoglobulins. The frequency of positive ANA was similar in the three groups of patients. Positive RF and a low C3 and/or C4 values were more frequent in patients with systemic involvement without severe bacterial infection (*group b)*. Positive ANCAs (anti-MPO, at low titer) was only observed in 1 patient from *group c)* without systemic involvement.

Histopathologic findings
All patients had histopathological features in the skin consistent with small-vessel leukocytoclastic vasculitis. The main histological findings of the three groups of patients are described in Table II. Samples from patients with CV associated with severe bacterial infection (*group a)* showed tissue neutrophilia more commonly than the other two groups (*p<0.05*). Furthermore, skin biopsy specimens from patients with severe bacterial infection had more frequently pustular dermatosis than those from the other two groups, although the difference did not reach statistical significance. Unlike skin biopsies from patients included in *group b)* and *group c)*, none of the patients with CV associated with severe bacterial infection showed tissue eosinophilia or tissue lymphocytosis. However, the differences were not statistically significant. Moreover, the intensity of

Table III. Histological findings of patients with leukocytoclastic CV. Hodge index (13).

Histopathologic characteristics	CV associated with severe bacterial infection Group a) (n=12)				CV without infection but with systemic involvement Group b) (n=21)				CV without systemic involvement Group c) (n= 19)			
	0 (Absent)	+ (Mild)	++ (Moderate)	+++ (Severe)	0 (Absent)	+ (Mild)	++ (Moderate)	+++ (Severe)	0 (Absent)	+ (Mild)	++ (Moderate)	+++ (Severe)
Inflammation of the vessel wall	0 (0%)	8 (67%)	4 (33%)	0 (0%)	0 (0%)	16 (76%)	3 (14%)	2 (9%)	0 (0%)	13 (68%)	6 (32%)	0 (0%)
Exocytosis of erythrocytes	0 (0%)	8 (67%)	4 (33%)	0 (0%)	0 (0%)	15 (71%)	5 (24%)	1 (5%)	0 (0%)	15 (79%)	4 (21%)	0 (0%)
Depth of infiltrate	0 (0%)	6 (50%)	6 (50%)	0 (0%)	0 (0%)	8 (38%)	12 (57%)	1 (5%)	0 (0%)	11 (58%)	7 (37%)	1 (5%)
Leukocytoclasis	0 (0%)	7 (58%)	4 (33%)	1 (8%)	0 (0%)	15 (71%)	5 (24%)	1 (5%)	1 (5%)	10 (53%)	6 (32%)	2 (10%)
Fibrinoid necrosis	3 (25%)	6 (50%)	3 (25%)	0 (0%)	1 (5%)	14 (67%)	3 (14%)	3 (14%)	4 (21%)	9 (47%)	6 (32%)	0 (0%)
Epidermal necrosis	10 (83%)	2 (17%)	0 (0%)	0 (0%)	17 (81%)	4 (19%)	0 (0%)	0 (0%)	18 (95%)	1 (5%)	0 (0%)	0 (0%)
Fibrin thrombi	11 (92%)	1 (8%)	0 (0%)	0 (0%)	20 (95%)	1 (5%)	0 (0%)	0 (0%)	17 (89%)	2 (10%)	0 (0%)	0 (0%)

inflammatory infiltrate and the involvement of deep arterioles involvement were similar in the three groups.

No significant differences in the Hodge index among the different groups were seen.

Table III shows the histological findings of patients with leukocytoclastic CV included in the Hodge index.

Figure 1 illustrates the typical histopathological features of leukocytoclastic vasculitis observed in skin biopsies of patients with CV associated with severe bacterial infection.

Discussion

The skin is the most common target organ for vasculitis (15-18). However, different types of injury can cause identical responses in the vessel. The different cutaneous manifestations (palpable purpura, urticarial papules and plaques, nodules, ulcers, livedo reticularis) that can be observed depend on the size of the involved vessels and the extension of the vascular bed that is affected.

A basic principle for the histopathologic diagnosis of CV is the morphological evidence of both angiocentric infiltration of inflammatory cells and damage of the vessel wall (15-16). In this regard, the inflammation of small vessels is characterised by endothelial oedema, intra and perivascular inflammatory infiltrate, vascular wall necrosis, fibrin deposition and sometimes the extravasation of red blood cells.

Several studies have attempted to correlate the histopathologic findings found in the skin biopsy specimens of patients with cutaneous small-vessel vasculitis with the clinical course of the disease (14, 19-27). With respect to this, Hodge *et al*. (14) observed that patients with urticarial skin lesions tended to have milder histopathologic findings. They also disclosed that patients with deep infiltrates had more commonly cutaneous ulceration and pulmonary involvement than those patients with CV who had superficial inflammatory infiltrates. In their series of 54 patients with cutaneous leukocytoclastic vasculitis, the clinical severity was predicted by the degree of vessel wall changes, amount of exocytosis, depth of the inflammation, amount of leukocytoclasis, sever-
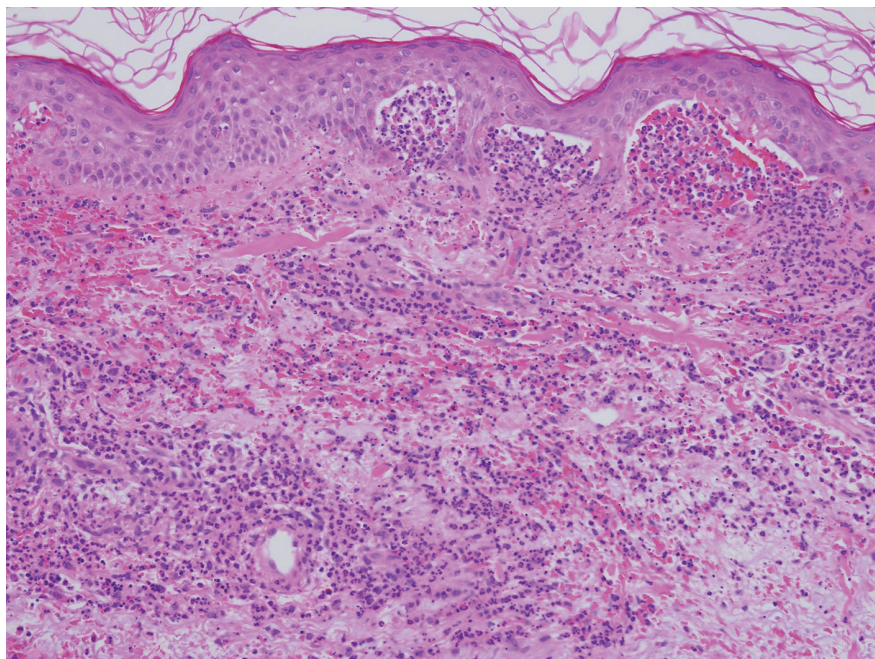

Fig. 1. We observed an intense inflammatory neutrophil infiltrate associated with leukocytoclastis and intraepidermal pustule. There is red cell extravasation and the blood vessels show fibrinoid necrosis.

ity of fibrinoid necrosis and the overall histopathologic score (14). However, Cribier *et al*. (23) could not find any significant link between the severity of the histopathological changes and the systemic involvement in a series of 184 patients with biopsy-proved cutaneous leukocytoclastic vasculitis. In contrast, Ratnam *et al*. (24) described a correlation between the severity of the vascular changes and the clinical lesions, although none of their 61 patients had visceral involvement. Based on the findings observed in a series of 29 patients with Henoch-Schönlein purpura (HSP), Byun *et al*. (21) suggested that the severity of leukocytoclasia may correlate with the risk of relapse of cutaneous small-vessel vasculitis. However, these authors did not analyse the potential correlation of histological findings observed in the skin biopsy with the severity of systemic involvement in their patients. On the other hand, another group suggested that histopathological features on skin biopsies could predict internal vasculitic involvement (25). They observed that patients older than 40 years with HSP without eosinophils on the skin biopsy samples had a nearly 3-times increased risk of renal involvement compared to patients who did not have these characteristics (25).

Sánchez *et al*. (22) reported that the presence of histopathologic findings of vasculitis extending deep into the reticular dermis or the subcutaneous tissue may be associated with systemic disease and that the inflammatory infiltrate in skin biopsies of patients with CV and hypocomplementemia was constituted almost exclusively by neutrophils. In our series, we also observed that patients with systemic involvement (with or without severe bacterial infection) had a moderate depth of infiltrate more frequently than patients with hypersensitivity vasculitis (Table III). Recently, Podjasek *et al*. (26) published that cutaneous small-vessel vasculitis associated with solid-organ malignancies tend to have deeper dermal involvement compared to cases not associated with solid-organ malignancy. In addition, these biopsies were less likely to demonstrate papillary dermal inflammation and papillary dermal oedema in comparison with biopsies of patients with cutaneous small-vessel vasculitis without solid-organ malignancy.

Any infectious agent, including viruses, bacteria and parasites, may potentially cause or trigger a vasculitic syndrome (4, 9, 10, 28).

In the present work, we reviewed the histopathological findings of 12 pa-

tients with CV associated with severe bacterial infection. According to our findings, CV associated with severe underlying bacterial infection has more tissue neutrophilia than CV unrelated to severe infection.

Magro and Crowson (27) reported 19 patients with leukocytoclastic vasculitis and history of infection from a series of patients with IgA-associated vasculitis, suggesting that infection-triggered leukocytoclastic vasculitis shows more commonly subcorneal, intraepidermal and subepidermal neutrophilic pustules, tissue neutrophilia and less eosinophils and lymphocytes than cutaneous leukocytoclastic angiitis. These findings are consistent with our results. However, unlike our series, all cases of CV reported by Magro *et al*. were associated with mild infection.

The most important results obtained in our study consisted of differences in laboratory data, such as elevated ESR and leukocytosis, and the presence of fever, which were observed in all patients with CV associated with severe infection. In addition, the histopathologic findings observed in our study suggest that patients with CV associated with severe bacterial infection have more tissue neutrophilia, which can be explained considering that neutrophils form the first line of host defense against pathogens and they are rapidly mobilised to sites of infection where they help marshal host defenses and remove bacteria by phagocytosis. In addition, the samples of biopsies from patients with infection of our series tended to develop more pustular dermatosis compared with those without a severe bacterial infection. The lack of statistical significance of this result may be related to the small patient cohort and, due to this, it is possible that a larger patient group could have allowed us to reach more solid conclusions.

Our study has potential limitations derived from its retrospective nature and the small sample size. Nevertheless, to the best of our knowledge, histopathological findings specifically focused on a series of patients with CV associated

with severe bacterial infection have not previously been reported. In an attempt to better establish clues that help us to identify CV associated with severe bacterial infection, prospective studies encompassing larger series of patients are needed to confirm the clinical relevance of our results.

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