Cutaneous vasculitis occurring in the setting of systemic lupus erythematosus: a multicenter cohort study

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Abbreviations

ACR, American College of Rheumatology

ADICAP, Association pour le Développement de l'Informatique en Cytologie et Anatomo Pathologie

ANCAs, anti-neutrophil cytoplasmic autoantibodies

APS, Antiphospholipid Syndrome

CRP, C-reactive protein

CV, cutaneous vasculitis

ELISA, enzyme-linked immunoassay

EULAR, European League Against Rheumatism classification criteria

IQR, Interquartile range

NRC, National Referral Center

SELENA-SLEDAI, Safety of Estrogens in Lupus Erythematosus National Assessment–Systemic Lupus Erythematosus Disease Activity Index

SLE, systemic lupus erythematosus

SS, Sjögren's syndrome

SSCS, Swiss SLE Cohort Study

SVV, Small vessel vasculitis

UV, Urticarial vasculitis

Abstract

Objectives:

To describe the clinical and pathological features of biopsy-proven cutaneous vasculitis (CV) associated with systemic lupus erythematosus (SLE), focusing on diagnosis classification and impact on overall SLE activity.

Methods:

Retrospective multicentric cohort study including SLE patients with biopsy-proven CV identified by 1) data from pathology departments of three university hospitals and 2) a national call for cases. SLE was defined according to 1997 revised ACR and/or 2019 ACR/EULAR criteria. CV diagnosis was confirmed histologically and classified by using the dermatological addendum of the Chapel Hill classification. SLE activity and flare severity at the time of CV diagnosis were assessed independently of vasculitis items with the SELENA-SLEDAI and SELENA-SLEDAI Flare Index.

Results:

Overall, 39 patients were included; 35 (90%) were female. Cutaneous manifestations included mostly palpable purpura (n=21; 54%) and urticarial lesions (n=18; 46%); lower limbs were the most common location (n=33; 85%). Eleven (28%) patients exhibited extracutaneous vasculitis. A higher prevalence of Sjögren's syndrome (51%) was found compared with SLE patients without CV from the French referral center group (12%, $p<0.0001$) and the Swiss SLE Cohort (11%, $p<0.0001$). CV were mostly classified as urticarial vasculitis (n=14, 36%) and cryoglobulinemia (n=13, 33%). Only 2 (5%) patients had no other cause than SLE to explain the CV. Sixty-one percent of patients had inactive SLE.

Conclusion: SLE-related vasculitis seems very rare and other causes of vasculitis should be ruled out before considering this diagnosis. Moreover, in more than half of patients, CV was not associated with another sign of active SLE.

Keywords: Systemic Lupus Erythematosus, Cutaneous Vasculitis, Lupus Activity, Urticarial Vasculitis, Cryoglobulinemia, Sjögren Syndrome

Key messages

1) Only five percent of patients had no other cause than SLE to explain the CV.

2) During SLE, most of the CV were classified as UV (36%) or cryoglobulinemia-associated CV (33%).

3) During CV occurrence, 61% of patients had inactive SLE and 24% had a severe flare.

Introduction

Vasculitis associated with systemic lupus erythematosus (SLE) is a potentially life-threating condition and considered a sign of activity and severity in most SLE evaluation scales, including the Safety of Estrogens in Lupus Erythematosus National Assessment–Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI) and SELENA-SLEDAI Flare Index (1–3). Few studies have estimated the prevalence of vasculitis during SLE (4–7). In these studies, the prevalence of associated vasculitis ranged from 11% and 36%, and small vessel vasculitis (SVV) of the skin accounted for the most common type observed, 82% to 89% of cases (4,5). This prevalence is probably overestimated because the cutaneous vasculitis (CV) diagnosis was based on clinical descriptions (6,7) or without skin biopsy in about 50% of cases (4,5). Indeed, in the study of Bouaziz *et al.* involving 50 SLE cases with digital involvement, vasculitis was diagnosed clinically in 18 (36%) of cases but was confirmed on skin biopsy in only two (4%) (8). Moreover, other conditions associated with SLE, such as Sjögren's syndrome (SS) and cryoglobulinemia, may also manifest as CV, which leads to difficulties in classifying SLE-associated vasculitis (9,10). In some studies, the presence of CV was reported to be associated with SLE activity (5,11,12). However, these studies did not assess whether SLE was active at the time of CV diagnosis, in particular after excluding the vasculitis item of the SELENA-SLEDAI, which may have affected the results.

Here, we performed a retrospective multicenter study to assess the clinical and immunological features as well as the causes of CV associated with SLE. We also aimed at investigating the SLE activity at CV diagnosis independent of vasculitis-related items.

Patients and methods

Patients, study design and settings

This retrospective multicentric cohort study included SLE patients with histologically proven CV occurring during SLE history. SLE was diagnosed according to the 1997 American College of Rheumatology (ACR) criteria for SLE classification and/or the 2019 ACR/European League Against Rheumatism (EULAR) classification criteria (13,14). Cases were identified by 1) the database of the pathology departments of three university hospitals in Paris (including the French National referral Center for SLE) between 2011 and 2021 using the Association pour le Développement de l'Informatique en Cytologie et Anatomo Pathologie (ADICAP) code 9312 (leukocytoclastic vasculitis) and 4230 (purpura with vasculitis); and 2) a national call for cases from the French Group for the Study of Systemic Diseases in Dermatology (EMSED), a group belonging to the French dermatology society. For the call for cases, an email was sent to all the members of the group in December 2019 with similar inclusion and exclusion criteria than for cases identified in our pathological database. Patients with a CV diagnosis prior to SLE diagnosis were excluded. Associated Sjögren Syndrome was defined according to ACR/EULAR 2016 (15) and Antiphospholipid Syndrome (APS) according to 2006 revised criteria (16).

This study was approved by the ethical committee of Sorbonne Université (CER2021-099), and written informed consent was obtained from all participants according to the Helsinki convention.

Definition and classification of vasculitis

The definite CV diagnosis was based on the presence of perivascular inflammatory infiltrates associated with 1) vessel wall fibrinoid necrosis and/or 2) leukocytoclasia (defined as extensive karyorrhexis of the vascular and perivascular leukocytes) on skin biopsy. Concomitant extra-

cutaneous vasculitis was retained only when confirmed by biopsy and/or arteriography except for mononeuritis multiplex, which was diagnosed by nerve study conduction.

All cases were reviewed by 2 dermatologists, 1 internist and 1 pathologist (PB, MJ, YD and FC). The causes of CV were classified according to the dermatological addendum of the Chapel Hill classification (17). SLE-related CV was diagnosed when no other cause than SLE contributing to CV was identified. Urticarial vasculitis (UV) was defined as CV presenting with lasting (>24 hr) urticarial lesions in the absence of a specific etiology (e.g., drug-induced, infection, sepsis or neoplasm) or serum cryoglobulinemia. Hypocomplementemic UV was distinguished from normocomplementemic UV by the presence of hypocomplementemia (C3 and/or C4) (18). Cryoglobulinemic vasculitis was diagnosed in the presence of CV associated with serum cryoglobulinemia estimated by centrifugation of serum at 4°C after incubation for 7 days. Sjögren Syndrome-related vasculitis was defined as non-cryoglobulinemic, non-urticarial leukocytoclastic vasculitis, as proposed by Ramos-Casals *et al.* (10). An infection-induced vasculitis diagnosis was considered when the onset of CV occurred within 7 days after bacterial or viral infection with sepsis and in the absence of another specific etiology (19). A drug-induced vasculitis diagnosis was retained with temporal association of onset with drug intake and reversibility with discontinuation of the likely etiologic drug. When several causes of CV were identified were available or when there was no consensus in classification, all potential causes were indicated.

Comparison of SLE patients with and without CV

Demographics, SLE historical characteristics and main comorbidities of SLE patients with a diagnosis of CV were compared to 345 consecutive SLE patients from the French national referral center for SLE seen in consultation between December 2018 and 2020 after excluding patients with a definite or suspected CV history. In order to perform a nested case control study with a 4:1 relationship, we randomly selected 156 patients from these 345 controls using JMP

v15 (SAS Institute Inc). Moreover, the characteristics of CV patients were also compared to an external cohort of 133 SLE included in the Swiss SLE Cohort Study (SSCS) (Swiss Ethics review board (PB_2017-01434) seen in consultation between November 2017 and December 2018(20).

SLE activity and flare severity at the time of CV diagnosis and definitions

Demographics, SLE clinical characteristics, the SELENA–SLEDAI (1–3), routine laboratory testing and immunological parameters, including C3, C4, CH50 complement levels; anti-dsDNA autoantibody levels; the presence of cryoglobulinemia; and the received treatments were recorded at the time of the first CV episode. Active SLE was defined with SELENA–SLEDAI $\geq$ 6, and SLE flares were characterized according to the SELENA-SLEDAI Flare Index (2,3). To evaluate SLE activity independent of CV, both the SELENA–SLEDAI and SELENA-SLEDAI Flare Index were calculating without incorporating the vasculitis item. Constitutional signs include fever (defined as a body temperature above 38.5°C in absence of infectious causes), weight loss (defined as a loss of at least 5% of body weight), lymphadenopathy/splenomegaly and anorexia. The class of lupus nephritis was recorded according to the International Society of Nephrology/Renal Pathology Society-2003 (21) and hemophagocytic lymphohistiocytosis was defined according to Henter *et al.* criteria (22).

Treatment for CV and response to therapy

The treatments used for CV were recorded, and response to therapy was assessed for patients with $\geq$ 6 months of follow-up. Cutaneous response was classified as complete remission (complete disappearance of lesions), partial response (improvement compared to baseline based on the physician's opinion) or no response (no improvement or worsening of lesions). Time to treatment failure was measured from the date of treatment initiation to disease relapse requiring a new add-on therapy.

Statistical analysis

Categorical variables are expressed as number (%) and quantitative variables as mean± SD or median (interquartile [IQR]), as appropriate. The Mann–Whitney U-test or Student t-test was used for analysis of continuous data and the Fisher's exact or chi-squared test for categorical data. All tests were two-sided and $p<0.05$ defined significance. Statistical analyses were performed with GraphPad Prism v8.0.1 (GraphPad Software, San Diego, CA, USA),

Results

The search in the database of the pathology departments using the ADICAP codes identified 522 patients with confirmed CV between 2011 and 2021; 25 (5%) had associated SLE **(Flow chart, Supplementary Figure S1**, available at *Rheumatology* online). In addition, 14 patients were included from the national call for cases.

Clinical, biological and histological CV features

Among the 39 patients included in the analysis; 35 (90%) were female and the median age at diagnosis of CV was 43 years (IQR 36-51). Clinical and pathological CV features are in **Table 1**. The main cutaneous findings included palpable purpura in 21 (54%) patients, long-lasting (>24 h) urticarial lesions in 18 (46%), erythematous papules/macules in 12 (31%), ulcerated/necrotic lesions in 8 (21%), livedo reticularis in 5 (13%) and nodular lesions in 1 (2.5%). The most common locations of cutaneous lesions were lower limbs in 33 (85%) patients, followed by trunk and/or abdomen in 13 (33%), arms in 11 (28%) and hands (fingertips and/or palms) in 8 (21%). Extracutaneous vasculitis was reported in 11 (28%) patients, mostly peripheral nerve involvement in 8 (21%) (proven by nerve biopsy, n=1) but also renal (membranoproliferative glomerulonephritis), muscular, and digestive involvement (n=1 each). Other associated manifestations included episcleritis in 3 (8%) patients and angioedema in 3 (8%).

Considering pathological features, all CV cases were classified as SVV. The main histological features included peri-vascular inflammatory cell infiltrates in all 39 patients, with predominant neutrophilic infiltrates in 22 (56%), lymphocytic infiltrates in 15 (38%) and no predominant population in 2 (5%). Overall, 33 (85%) of CV had associated leukocytoclasis, with fibrinous necrosis of the vessel wall in 20 (51%). Direct immunofluorescence assay was performed in 21/39 (54%) patients, and results were positive with perivascular deposits in 15/21 (71%), with

immunoreactivity to C3 in 13/21 (62%), immunoglobulin M or G in 8/21 (38%) and C1q in 5/21 (24%).

SLE characteristics, activity and flare severity at time of CV diagnosis and during follow-up

The main SLE characteristics at the first episode of CV are summarized **in Table 2**. The median age at SLE diagnosis was 31 years (IQR 25-42). SLE was diagnosed before the occurrence of CV in 30 (77%) patients and concomitantly in 9 (23%). The median time between SLE diagnosis and the first CV episode was 6 years (IQR 0-19). After excluding the vasculitis item from the SELENA-SLEDAI, at the first CV episode, SLE was active (SELENA-SLEDAI ≥ 6) in 15/38 (39%) patients. Moreover, according to the SELENA-SLEDAI Flare Index, 15/38 (39%) patients experienced a flare, classified as severe in 9/38 (24%). The most frequent active concomitant SLE features were cutaneous lupus in 17/38 (45%), arthritis in 14/38 (37%) and constitutional signs in 11/38 (29%) patients. Six of 38 (16%) patients had active lupus nephritis, including class I (n=1), class III (n=1), class IV (n=2), class II+V (n=1) and class III + V (n=1) lesions. Two of 38 (5%) patients had hemolytic autoimmune anemia and one (3%) hemophagocytic lymphohistiocytosis.

Immunological findings included decreased complement C3 or C4 levels in 25/33 (76%), increased DNA binding in 20/33 (61%) and positivity for anti-C1q antibodies in 2/9 (22%). Overall, 15/32 (47%) patients had cryoglobulinemia, including type II (n=6), type III (n=5) and untyped (n=4). None of the 33 patients tested were positive for anti-neutrophil cytoplasmic autoantibodies (ANCAs). Biological testing showed frequent lymphopenia (n=28/30; 93%), anemia (n=23/33; 70%), and elevated C-reactive protein (CRP) level (n=20/33; 61%).

Comparison of SLE patients with and without CV

The median follow-up duration of the controls without CV was 13 years (IQR 7-21) for the 156 randomly selected patients from the French NRC and 9.5 (IQR 4-18) for the SSCS compared

with 15 years (9-23.5) for the 39 CV patients (p=0.27 and p= 0.006 respectively). We found significantly higher prevalence of SS (51%) compared with SLE patients without CV from the French NRC (12%, p<0.0001) and the SSCS (11%, p<0.0001). Moreover, patients with CV more frequently had a history of cutaneous lupus (92% vs. 69%; p = 0.0013 (French NRC) and vs. 54%; p<0.0001 (SSCS)) and decreased C3 and C4 levels during follow-up compared to patients from French NRC (80% vs. 48%; p=0.002 and 97% vs. 47%; p<0.0001) (**Table 3**).

Classification of CV

All cases were reviewed by four investigators, and CV was classified by using dermatological addendum of the Chapel Hill classification. In total, 29 (74%) CV cases were classified in one category, mostly UV (n=14, 36%) and cryoglobulinemic vasculitis (n=13, 33%) **(Table 4)**. Of note, among the 13 patients with cryoglobulinemic vasculitis, n=9 (69%) had secondary SS. Only two patients (5%) had no other cause than SLE to explain the CV and therefore cases were classified as SLE-related CV.

For nine (23%) patients, there was no unique diagnosis, and CV was classified as uncertain diagnosis; 5 of these patients had non-cryoglobulinemic, non-urticarial CV with coexisting SS diagnosis and could therefore be classified as SLE or SS-related CV. Moreover, three patients had a concomitant infection: one had pneumonia with sepsis but without bacteriological identification, one had a cytomegalovirus infection and one had *Klebsiella pneumoniae* infection. The latter patient also showed SLE flare concomitant to active neoplasia and type III cryoglobulinemia. Finally, one patient with SLE flare presented non-typable cryoglobulinemia with a very minute cryoglobulin pellet and unusual cryoglobulinemic vasculitis presentation (punctate purpura and livedo reticularis limited to digits and palms) and therefore the case was classified as SLE- or cryoglobulin-related CV.

First-line treatment and CV outcomes

CV treatments and follow-up data were available for 37 patients. First-line treatment consisted of oral corticosteroids for 27 (73%) patients, including 16 who initially received an intravenous infusion **(Table 5)**. Moreover, six patients with a diagnosis of UV received antihistamines therapy, and three (8%) patients received colchicine. Hydroxychloroquine was initiated for 11 (30%) patients, including nine with a concomitant diagnosis of SLE and two had previously diagnosed SLE but undetectable HCQ blood concentration despite a prescription and were therefore considered not receiving HCQ. Twenty (54%) received immunosuppressant agents. When comparing treatments of patients according to SLE activity, patients with active SLE independent of CV more frequently received oral corticosteroids (93% vs. 59%; p=0.0279). After the first-line treatment, cutaneous response was classified as complete for 25 (67%) patients, partial for 10 (27%) and absent for two (5%). After a median follow-up of 75 months (IQR 40.5-106.5), 15 (38%) patients experienced at least one relapse at a median delay of 24 months (IQR 11-48). Relapses concerned patients with cryoglobulinemic vasculitis (n=8; 62%), UV (n=6/13; 46%) and SLE-related vasculitis (n=1; 50%) **(Table 4)**. No patient died from vasculitis complications during the follow-up period.

Discussion

In this study of 39 biopsy-proven cases of CV associated with SLE, we highlighted that SLE itself is rarely the only cause explaining CV. Most of the CV cases occurring in the setting of SLE were classified as UV (36%) or cryoglobulinemia-associated CV (33%).

Although previous studies did not specifically aim to classify CV associated with SLE, Ramos-Casals *et al*. also found a high prevalence of cryoglobulinemic vasculitis (28%) and, less frequently, UV (7%) (5). Furthermore, in our study, SLE patients with CV more frequently had a secondary SS diagnosis as compared with those with SLE without CV, which has also been suggested in other studies (11,23). Moreover, three cases had concomitant viral or bacterial infection, one with simultaneous solid organ malignancy. All these situations have been described as a possible cause of CV (17,24–26).

Regarding the clinical phenotypes of CV, previous studies identified a wide variety of cutaneous lesions, mostly erythematous punctuate lesions, palpable purpura urticarial lesions, necrosis and livedo reticularis (4–7,9,11). Some studies reported erythematous punctuate lesions of the digits as the most frequent lesions (4,5), whereas we more frequently observed palpable purpura of lower limbs, which is the most common skin manifestation of SVV (27,19). This difference could be explained by the fact that the prevalence of CV in digit lesions was overestimated in previous studies without pathological confirmation. Conversely, in our study, a skin biopsy of digital lesion may have been less frequently performed.

Previous works without systematic biopsy identified an association between CV and APS in the setting of SLE (4,5). Such association was not found in the present study and in several others (6,28). Thrombotic lesions of APS and non-vasculitic occlusive vasculopathy may be clinically misdiagnosed as CV (29,30) and thus may have contributed to an overestimation of the prevalence of CV during SLE (8).

As compared with previous studies (5), here we found UV as the most common diagnosis of CV identified (36%). UV is a distinct clinicopathologic entity that could occur in the setting of autoimmune diseases and mostly SLE, up to 54% of published cases (18,31,32). The Jachiet *et al.* study found no significant differences between UV patients with and without SLE, except for more frequent anti-double-stranded DNA antibodies and rheumatoid factor in the SLE group (18). In our study, UV could occur with (38%) and without SLE flare and was often chronic, with a significant risk of relapse (46%).

Of importance, the occurrence of CV is considered a marker of activity in several scores including the SELENA-SLEDAI, the SELENA Flare Index (1–3), the European Consensus Lupus Activity Measurement (ECLAM) (33) and the British Isles Lupus Assessment Group (BILAG) (34). Furthermore, in the SLEDAI, CV is associated with high disease activity because it scores as high as an organic brain syndrome or seizure (3). Regarding the potential association between the occurrence of vasculitis and SLE activity, CV was found to be associated with high disease activity (5,11,12), renal and central nervous system deterioration (12) as well as increased Systemic Lupus International Collaborating Clinics/ACR damage index (6,11,28). However, the association between CV and disease activity was not confirmed in 2 studies of digital vasculitis (7,28), and no major organ involvement was associated with CV in other studies (6,7). The assessment of SLE activity was likely biased by the inclusion of the vasculitis item in the activity scores used in preceding works. In the present study, when assessing SLE activity independent of the vasculitis item of the SELENA-SLEDAI, 61% of SLE patients had inactive disease and patients with CV did not have an increased frequency of severe SLE features included lupus nephritis or neurolupus compared with two control cohorts. In contrast, 24% had a severe flare according to the SELENA-SLEDAI Flare index and six had SLE renal involvement including four proliferative nephritis. SLE activity may differ according to the etiological classification of the CV because 38% of UV cases were associated with active

SLE versus 2/2 (100%) of SLE-related CV but there was not enough patients to perform statistical analyses.

The treatment of CV associated with SLE is not well codified, and only a few studies have focused on CV management during SLE. Ramos-Casals *et al.* reported the use of oral corticosteroids in 87% of vasculitis cases and immunosuppressant agents in 20% (cutaneous and visceral) of cases occurring during SLE (5). In the present study, 73% of patients received corticosteroids, including 43% with intravenous infusion, and 54% had a new immunosuppressant agent use. Surprisingly, we found no significant difference in CV management between patients with active and inactive SLE except for the frequency of corticosteroids use which was higher in the active group. Particularly there was no significant difference in the frequency of prescription of immunosuppressant treatments. We thus hypothesized that some physicians have considered CV as an element of severity by itself even in the absence of extra-cutaneous manifestations of lupus, notably renal or neurological involvement. Therefore, some patients without visceral involvement or SLE flare may have been overtreated considering that compression therapy or hydroxychloroquine or colchicine therapy may be sufficient for UV (18) or skin-limited SVV (19,26).

Limitations of this work include the retrospective design and missing data. This situation resulted in difficulties identifying the cause of CV in some patients. In particular, this study highlights a lack of current classifications to define the origin of vasculitis in SLE associated with SS. However, all cases were reviewed by 4 investigators with the help of the recent dermatological addendum of the Chapel Hill classification (17), and all potential causes of CV were indicated in doubtful cases. Moreover, some patients with definite CV may not have undergone a skin biopsy and therefore our design did not allow for estimating the prevalence of CV among our cohort of SLE. However, we included only biopsy-proven CV cases and estimated the prevalence of SLE at 5% among patients with CV from 3 university hospitals,

which is an important finding of our study. In addition, non-specific signs or symptoms of systemic inflammation, including fever, myalgia and arthralgia, could be associated with SLE or SVV (27), which may have affected our assessment and potentially overestimated SLE activity.

Overall, the occurrence of CV in the setting of SLE is rarely exclusively attributable to SLE. A complete etiological work-up is necessary before concluding that CV is directly related to SLE, excluding in particular SS, UV, cryoglobulinemia, and infectious and drug-induced vasculitis. These results highlight that CV items should be included in activity scores of SLE activity if 1) CV has been confirmed with a skin biopsy and 2) other potential causes of CV have been excluded. This is important for guiding the therapeutic strategy of SLE with associated CV in particular because most SLE cases are inactive after excluding the CV item in activity scores. Further studies are needed to better characterize the spectrum of CV associated with SLE and validate a proper classification and specific guidelines for treatment.

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Conflicts of interest

The authors have declared no conflicts of interest.

Data availability statement

Data are available upon reasonable request by any qualified researchers who engage in rigorous, independent scientific research, and will be provided following review and approval of a research proposal and Statistical Analysis Plan (SAP) and execution of a Data Sharing Agreement (DSA). All data relevant to the study are included in the article.

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Characteristics	
Vasculitis cutaneous features	
Palpable purpura	21 (54)
Urticarial lesions	18 (46)
Erythematous papules/macules	12 (31)
Ulcerated/necrotic lesions	8 (21)
Livedo reticularis	5 (13)
Nodular lesions	1 (2.5)
Association of lesions type	17 (44)
Topography of cutaneous lesions	
Legs/lower limbs	33 (85)
Trunk/abdomen	13 (33)
Arms/upper limbs	11 (28)
Fingertips and/or palms	8 (21)
Face	0 (0)
Association of locations	18 (46)
Associated features	
Angioedema	3 (8)
Episcleritis	3 (8)
Vasculitis visceral involvement	
Mononeuritis multiplex	8 (21)
Membranoproliferative glomerulonephritis	1 (2)
Muscle involvement	1 (2)
Digestive involvement	1 (2)
Biological and immunological features	
Elevated CRP level (>5 mg/L)	20/33 (61) ‡
Cryoglobulinemia $	15/32 (47) ‡
Anti-C1q positive	2/9 (22) ‡
ANCA-positive	0/33 (0) ‡
Histological features	
Inflammatory cell infiltration	39 (100)
predominant neutrophilic infiltrates	22 (56)
predominant lymphocytic infiltrates	15 (38)
predominant eosinophilic infiltrates	0 (0)
no predominant infiltrate	2 (5)
Leucocytoclasia	33 (85)
Vascular fibrinous necrosis	20 (51)
Direct Immunofluorescence features	
Perivascular C3 deposits	13/21 (62) ‡
Perivascular Ig deposits	8/21 (38) ‡
Perivascular C1q deposits	5/21 (24) ‡

Table 1: Clinical and histological characteristics of cutaneous vasculitis in systemic lupus erythematosus (SLE) (n=39)
Data are n (%).
‡ Positive assay/number of patients assessed.
$ n= 6 type II, n= 5 type III, n=4 untyped cryoglobulinemia
ANCA; antineutrophil cytoplasmic antibody, CRP; C-reactive protein, Ig; immunoglobulin

Age at CV diagnosis, years, median (IQR)	43 (36-51)
SLE duration at time of CV diagnosis, years, median (IQR)	6 (0-19)
SLE activity at vasculitis diagnosis	
SELENA-SLEDAI score, median (IQR)	12 (10-17.5)
SELENA-SLEDAI score, median (IQR) after excluding the vasculitis item	4 (2–9.5)
Active SLE (SELENA-SLEDAI score ≥ 6) after excluding the vasculitis item	15/38 (39) ‡
SLE flare excluding the vasculitis item *	15/38 (39) ‡
Mild/moderate flare	6/38 (16) ‡
Severe flare	9/38 (24) ‡
SLE active manifestations at time of CV diagnosis	
Active cutaneous lupus	17/38 (45) ‡
Subacute cutaneous lupus	8/38 (21) ‡
Chronic cutaneous lupus	7/38 (18) ‡
Acute cutaneous lupus	4/38 (11) ‡
Arthritis	14/38 (37) ‡
Constitutional signs	11/38 (29) ‡
Active lupus nephritis§	6/38 (16) ‡
Hemolytic autoimmune anemia	2/38 (5) ‡
Active lupus serositis	1/38 (3) ‡
Hemophagocytic lymphohistiocytosis	1/38 (3) ‡
Active neuropsychiatric lupus	0/38 (0) ‡
Immune thrombocytopenia	0/38 (0) ‡
Biological and immunological features	
Increased DNA binding (above normal range for testing laboratory)	20/33 (61) ‡
Low C3 level	20/35 (57) ‡
Low C4 level	25/33 (76) ‡
Leucopenia (<3 G/L)	6/31 (19) ‡
Lymphopenia (<1.5 G/L)	28/30 (93) ‡
Anemia	23/33 (70) ‡
Thrombocytopenia (<100 G/L)	0/33 (0) ‡
Associated disease	
Concomitant infection #	3 (8)
Active Neoplasia ##	1 (3)

Table 2. Main features of SLE at diagnosis of cutaneous vasculitis (CV) (n=39)
Data are n (%), unless stated otherwise.
‡ Positive assay/number of patients with available data.
* Defined using SELENA-SLEDAI Flare Index
§ including class I (n=1), class III (n=1), class IV (n=2), class II+V (n=1) and class III + V (n=1) lesions according to ISN/RPS-2003.
# 1 *Klebsiella pneumoniae* pneumonia with sepsis, 1 pneumonia with sepsis (no microbiological identification), 1 primo CMV infection.
Adenocarcinoma of the lung; this patient also had bacterial pneumonia and type 3 cryoglobulinemia
DNA, deoxyribonucleic acid; IQR, interquartile range; ISN, International Society of Nephrology; RSP, Renal Pathology Society; SELENA-SLEDAI, Safety of Estrogens in Lupus Erythematosus National Assessment–Systemic Lupus Erythematosus Disease Activity Index; SLE, systemic lupus erythematosus.

	SLE with CV (n = 39) n (%)	Control group (French NRC) (n = 156) n (%)	p value[a]	Control group (SSCS) (n = 133) n (%)	p value[b]
Women	35 (90)	142 (91)	*0.76*	111 (83)	*0,44*
Age at SLE diagnosis, years, median (IQR)	**31 (25-42)**	**25 (18-34)**	***0.001***	32 (23-44)	*0.73*
Follow-up duration, years, median [IQR]	15 (9-23.5)	13 (7-21)	*0.27*	**9.5 (4-18)**	***0.006***
Other autoimmune diseases					
Sjogren's syndrome	**20 (51)**	**19 (12)**	***<0.0001***	**15 (11)**	***<0.0001***
Antiphospholipid syndrome	6 (15)	17 (11)	*0.41*	8 (6)	*0.09*
Historical SLE clinical features					
Lupus arthritis	37 (95)	145 (93)	*1*	**98/132 (74)‡**	***0.004***
Cutaneous lupus (except CV)	**36 (92)**	**107 (69)**	***0.002***	**72 (54)**	***<0.0001***
Lupus nephritis	16 (41)	61 (39)	*0.86*	50/131 (38)‡	*0.85*
Constitutional signs	15 (38)	51 (33)	*0.57*		
Cytopenia (except isolated lymphopenia)	15 (38)	51 (33)	*0.57*	NA	-
Lupus serositis	10 (26)	32 (20)	*0.51*	43 (32)	*0.55*
Neuropsychiatric (except vasculitis-related)	2 (5)	16 (10)	*0.53*	18 (13)	*0.25*
Immunological parameters(ever)					
Increased DNA binding (ELISA)	**34 (87)**	149 (95)	*0.07*	**89/132 (67)‡**	***0.01***
Low C3 level	**31 (80)**	**70/145 (48)‡**	***0.0005***	NA	-
Low C4	**38 (97)**	**80/145 (55)‡**	***<0.0001***	NA	-

Table 3: Main historical features of 39 SLE patients with CV and control groups
Data are n (%), unless stated otherwise.
‡ Positive assay/number of patients assessed.
[a] Estimated by comparing SLE patients with CV to 156 randomly selected SLE controls without CV from the French NCR for Lupus.
[b] Estimated by comparing SLE patients with CV to the 133 SLE included in the Swiss SLE cohort
CV, cutaneous vasculitis; ELISA, enzyme-linked immunoassay; NRC, National Referral Center; IQR, Interquartile range; NA, Non Assessable; SLE, systemic lupus erythematosus; **SSCS,** Swiss SLE Cohort Study
Variables with P<0.05 on univariate analysis are highlighted in bold

	Patients n (%)	Female n (%)	Visceral involvement n (%)	Active SLE n (%)	Predominant cutaneous lesions (%)	Predominant locations (%)	Relapse n (%)	Delay before relapse, median (IQR), months
Retained diagnosis								
Urticarial vasculitis§	14 (36)	14 (100)	1 (7)	5/13 (38)	urticarial lesions (100), palpable purpura (29)	legs (86), trunk/abdomen (71), arms (57), palms/digits (14)	6/13 (46)	36 (16-49)
Cryoglobulinemic vasculitis	13 (33)	12 (92)	7 (54)	3 (23)	palpable purpura (77), ulcero-necrotic (31), urticarial lesions (23)	legs (85), arms (15), palms/digits (15)	8 (62)	24 (10-63)
SLE-related vasculitis	2 (5)	2 (100)	0 (0)	2 (100)	palpable purpura (100)/erythematous macules or papules (50)	legs (100)	1 (50)	11
Drug-induced vasculitis†	1 (3)	1 (100)	0 (0)	0 (0)	urticarial lesions	trunk and abdomen	0 (0)	/
Uncertain diagnosis								
SLE or Sjögren's syndrome-related vasculitis	5 (13)	3 (60)	3 (60)	2 (40)	palpable purpura (80), erythematous macules and papules (20)	legs (100), palms/digits (20)	0 (0)	/
SLE with concomitant infection*	2 (5)	2 (100)	0 (0)	1 (50)	ulcerations (100), necrosis (50), erythematous macules and papules (50)	palms (100), arms (50), legs (50)	0 (0)	/
SLE with concomitant infection, neoplasia and cryoglobulinemia**	1 (3)	0 (0)	0 (0)	1 (100)	erythematous macules and papules with ulcerations	legs	0 (0)	/
SLE or cryoglobulinemic-related vasculitis	1 (3)	1 (100)	0 (0)	1 (100)	palpable purpura and livedo reticularis	palms and digits	0 (0)	/

Table 4. Diagnosis classification of CV in 39 patients with SLE

$ Including n=10 hypocomplementemic urticarial vasculitis, n=1 normocomplementemic urticarial vasculitis and n=3 non-classifiable (insufficient data)

†Related to rituximab injection (serum sickness syndrome)

* One pneumonia with sepsis (no bacterial identification) and one primo-cytomegalovirus infection

** SLE flare with type III cryoglobulinemia associated with *Klebsiella pneumonia* infection revealing lung carcinoma

IQR, interquartile range; SLE, systemic lupus erythematosus

First-line treatment	Total (n=38)	Active SLE (n=15)	Inactive SLE (n=23)	p value[a]
Prednisone introduced or increased	27/37 (73) #	**14 (93)**	13/22 (59) ‡	***0.03***
Prednisone, mg/day, median [IQR]	20 [3.5-60]	50 [10;60]	20 [0;60] ‡	*0.09*
Intravenous methylprednisolone bolus	16/37 (43) ‡	8 (53)	8/22 (36) ‡	*0.33*
Hydroxychloroquine	11/37 (30) ‡†	5 (33)	6/22 (27) ‡	*0.73*
Colchicine	3/37 (8) ‡	1 (7)	2/22 (9) ‡	*1*
Antihistamines	6/37 (16) ‡	1 (7)	5/22 (23) ‡	*0.37*
Immunosuppressive treatment	20/37 (54) ‡	11 (73)	9/22 (41) ‡	*0.09*
Rituximab	6/37 (16) ‡	2 (13)	4/22 (18) ‡	*1*
Mycophenolate mofetil	6/37 (16) ‡*	4 (27)	2/22 (9) ‡	*0.19*
Methotrexate	4/37 (11) ‡	2 (13)	2/22 (9) ‡	*1*
Azathioprine	3/37 (8) ‡	2 (13)	1/22 (4) ‡	*0.55*
Cyclophosphamide	2/37 (5) ‡	1 (7)	1/22 (4) ‡	*1*
Belimumab	1/37 (3) ‡	1 (7)	0/22 (0) ‡	*0.40*
Baricitinib	1/37 (3) ‡	1 (7)	0/22 (0) ‡	*0.40*

Table 5. Therapeutic management of CV in SLE patients

Data are n (%), unless stated otherwise.

‡ Positive /number of patients evaluated

Active SLE was defined according to SELENA-SLEDAI score ≥ 6 after excluding the vasculitis item

Prednisone introduction or increase was associated with immunosuppressant treatment (excluding antimalarials and colchicine) in 17.

† Nine patients had a diagnosis of SLE simultaneously with CV and two had previously diagnosed SLE but undetectable HCQ blood concentration despite a prescription and were therefore considered not receiving HCQ. All but one received another treatment in addition to hydroxychloroquine.

* Two patients received rituximab followed by mycophenolate mofetil. One received cyclophosphamide followed by mycophenolate mofetil.

a: comparing active SLE to inactive SLE patient

IQR, interquartile range; SLE, systemic lupus erythematosus

Variables with P<0.05 on univariate analysis are highlighted in bold