Cutaneous vasculitis associated with severe bacterial infections. A study of 27 patients from a series of 766 cutaneous vasculitis

J. Loricera[1], R. Blanco[1], J.L. Hernández[2], V. Calvo-Río[1], F. Ortiz-Sanjuán[1], C. Mata[1], J. Rueda-Gotor[1], L. Alvarez[3], M.C. González-Vela[4], M.A. González-López[5], S. Armesto[5], T. Pina[1], M.A. González-Gay[1]

Departments of [1]Rheumatology, [2]Internal Medicine, [3]Paediatrics, [4]Pathology and [5]Dermatology, Hospital Universitario Marqués de Valdecilla, IDIVAL, Santander, Spain.

*Javier Loricera, MD**
*Ricardo Blanco, MD, PhD**
José L. Hernández, MD, PhD
Vanesa Calvo-Río, MD
Francisco Ortiz-Sanjuán, MD
Cristina Mata, MD
Javier Rueda-Gotor, MD
Lino Alvarez, MD
M. Carmen González-Vela, MD, PhD
Marcos A. González-López, MD, PhD
Susana Armesto, MD, PhD
Trinitario Pina, MD
Miguel A. González-Gay, MD, PhD

**These authors made an equal contribution to this study.*

***R. Blanco and M.A. González-Gay shared senior authorship.*

Please address correspondence to:
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

Received on August 1, 2014; accepted in revised form on December 1, 2014.

Clin Exp Rheumatol 2015; 33 (Suppl. 89): S36-S43.

Key words: cutaneous vasculitis, infection, leukocytoclastic vasculitis

Funding: this study was supported by a grant from the "Fondo de Investigaciones Sanitarias" PI12/00193, Spain.
Itwork was also partially supported by RETICS Programs, RD08/0075 (RIER) and RD12/0009/0013 from the "Instituto de Salud Carlos III" (ISCIII), Spain.

Competing interests: none declared.

ABSTRACT

Objective. *To assess the clinical spectrum of severe bacterial infections presenting as cutaneous vasculitis (CV) in a defined population.*

Methods. *Unselected series of 766 patients with CV diagnosed at a single university referral center.*

Results. *An underlying severe bacterial infection was diagnosed in 27 (22 men/5 women; mean age± standard deviation [SD]: 53±18 years) of 766 cases presenting with CV (3.5%). These infections were: pneumonia (n=8), endocarditis (n=6), meningitis (n=4), intra-abdominal infections (n=3), septic arthritis (n=2), septicaemia (n=2), septic bursitis (n=1), and urinary tract infection (n=1). All the patients were admitted for suspected CV. The median delay from admission to the diagnosis of infection was 4 days. A typical palpable purpura without relevant visceral vasculitic involvement was the main clinical manifestation. Patients with severe bacterial infections were older, with male predominance, had more frequently fever, constitutional symptoms, focal infectious features, and leukocytosis with left shift and anaemia than the remaining patients with CV. Although antibiotics were prescribed in all the patients, seven also required the use of low-dose corticosteroids to achieve complete resolution of the cutaneous lesions. Most patients experienced full recovery but two of them underwent prosthetic cardiac valve replacement, and another two died due to infection-related complications.*

Conclusion. *CV may be the presenting manifestation of a severe underlying bacterial infection. Physicians should keep in mind this fact to make an early diagnosis of infection and, consequently, prevent life-threatening complications.*

Introduction

Cutaneous vasculitis (CV) is mainly characterised by palpable purpura, usually involving the lower extremities (1-3). It may occur as a primary process or be secondary to a wide and heterogeneous group of disorders. Thus, CV can be a clinical manifestation of a severe underlying infection. Any infectious agent including viruses, bacteria and parasites, may potentially cause or trigger a vasculitic syndrome (4).

Current pharmacological treatment of primary CV is mainly based on corticosteroids, although, in the most severe cases, immunosuppressive agents can be added. However, when the vasculitis is the result of an underlying bacterial infection this classic therapeutic approach may lead to deleterious consequences for the patient.

Most studies encompassing CV associated with severe underlying bacterial infection include case reports, or small case series (5-18). In the present study we assessed the frequency and clinical characteristics of severe bacterial infections associated with CV from a large unselected series of 766 patients diagnosed with CV at a single university referral hospital. An analysis of the potential differences between patients with CV associated with severe bacterial infections and the remaining individuals with CV was also performed. We propose a work-up including some "red flags" that could help the clinicians to suspect the presence of an underlying infection in patients with CV.

Patients and methods

Patients and study protocol

We analysed the clinical records of all the patients diagnosed with CV at a tertiary-care teaching hospital from Northern Spain, between January 1976 and December 2011. The study was ap-

proved by the Ethics Committee (Cantabria, Spain), and informed written consent was obtained in all the cases. All adult patients were hospitalised and those under 20 years old were admitted to hospital or remained at least 24 hours under observation at the Department of Paediatrics. In our hospital, all adults in whom a CV is suspected, including those presenting with typical palpable purpura, are admitted to hospital to have performed the appropriate complementary testing without delay and to reduce the potential risk of complications due to the systemic involvement in the setting of a CV.

Methods were similar to those previously reported (1, 19-22). Briefly, the diagnosis of CV was based on either *a)* a skin biopsy showing characteristic histological findings of vasculitis (neutrophilic infiltration, leukocytoclasia, fibrinoid necrosis or erythrocyte extravasation into the vessel wall) or

b) the presence of typical non-thrombocytopenic palpable purpura.

Most patients with suspected CV were sent to the hospital by general practitioners or self-referred to the Emergency Department. Dermatology consultation was requested in most cases. Patients with CV were asked for the use of drugs before and during the onset of the vasculitis, as well as about other symptoms or signs that might suggest the presence of a systemic vasculitis or a connective tissue disease.

CV was considered associated with severe bacterial infection when it occurred in the setting of a severe infection and antibiotic therapy led to resolution of both 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. *Systemic inflammatory response syndrome* (SIRS) was defined when 2 or more of the following variables were present:

a) temperature ≥38°C or <36°C;

b) heart rate >90 beats per minute;

c) respiratory rate >20 breaths per minute or $PaCO_2$ <32 mm Hg or

d) white blood cell count >12000/mm^3 or <4000/mm^3 or >10% immature forms. *Sepsis* was defined as SIRS with evidence or suspicion of a microbial origin. *Severe sepsis* was established when it was associated with evidence of hypoperfusion or dysfunction of at least one organ system (23).

Clinical and laboratory definitions

a) Patients >20 years were considered *adults*. This cut-off age was chosen because it was proposed as a criterion by the American College of Rheumatology (ACR) (24, 25).

b) Fever: axillary temperature >37.7ºC.

c) Constitutional symptoms: asthenia and/or anorexia, and weight loss of at least 4 kg.

d) Joint symptoms: arthralgia and/or joint effusion.

e) Gastrointestinal manifestations: bowel angina (diffuse abdominal pain worsening after meals), gastrointestinal bleeding (melena, haematochezia, or positive stool Guaiac test), nausea and/or vomiting.

f) Nephropathy was categorised as mild or severe. Mild nephropathy was defined by the presence of microhaematuria (≥5 red cell/hpf) without fulfilling the criteria for nephritic syndrome (see below), and/or non-nephrotic proteinuria. Severe nephropathy was defined by the presence of nephrotic syndrome (plasma albumin levels ≤25 g/litre and either, 1 g of proteinuria/day/m^2 of body surface area in children, or >3.5 g/day in adults), or nephritic syndrome (haematuria with at least two of the following: hypertension, increased plasma urea or creatinine levels, and oliguria). Renal insufficiency was defined as a serum creatinine level above 125% of the upper limit of normal.

g) Anaemia: haemoglobin level ≤11.0 g/dL.

h) Leukocytosis: blood cell count was ≥11000/mm^3.

i) Elevated erythrocyte sedimentation rate (ESR) if it was higher than 15 or 20 mm/1st hour for men or women, respectively.

j) Increased IgA levels were defined as a total serum IgA level >400 mg/dL.

k) Relapse: a new flare of cutaneous lesions in a patient asymptomatic for at least one month.

Data collection

Data on clinical, laboratory and histopathological features, etiology, treatment and outcome were obtained from the medical records according to a prespecified protocol, and then stored in a computerised database. To minimise entry error, all data were double checked and reviewed for diagnosis confirmation. Regarding laboratory studies, complete blood cell count, coagulation tests, liver and renal function tests, ESR and urinalysis, were performed at the time of diagnosis in almost all the patients.

An immunological profile was carried out in most adults (but only in a minority of children). It included rheumatoid factor (RF), performed until the late eighties by quantitative latex agglutination test, and later by nephelometry; antinuclear antibodies (ANA), by indirect immunofluorescence using rodent tissues as substrate until the late eighties and since then by Hep-2 cells; serum levels of C3 and C4 (initially by radial immunodiffusion and more recently by nephelometry); and cryoglobulins. The composition of the cryoprecipitate was determined by double immunodiffusion with specific antibodies. Antineutrophil cytoplasmic antibodies (ANCAs) were assessed initially by indirect immunofluorescence on alcohol-fixed neutrophils and, later, by ELISA with purified proteinase-3 and myeloperoxidase. ANCAs were only assessed since 1990. Other tests, such as anti-nDNA antibodies (by immunofluorescence with Crithidia luciliae as substrate), blood cultures, stool guaiac test, hepatitis B, C, or human immunodeficiency virus infection serology, bone marrow biopsy, and chest radiographs were performed based on the judgment of the attending physician.

Statistical analysis

Normal distributed variables were expressed as mean±standard deviation (SD), and those not normally distributed as median and interquartile range (IQR). Continuous variables were compared with the two-tailed Student's *t*-test or Mann-Whitney U-test, as appropriate. Dichotomus variables were analysed by means of chi-square test or Fisher exact test. A p-value <0.05 was considered statistically significant.

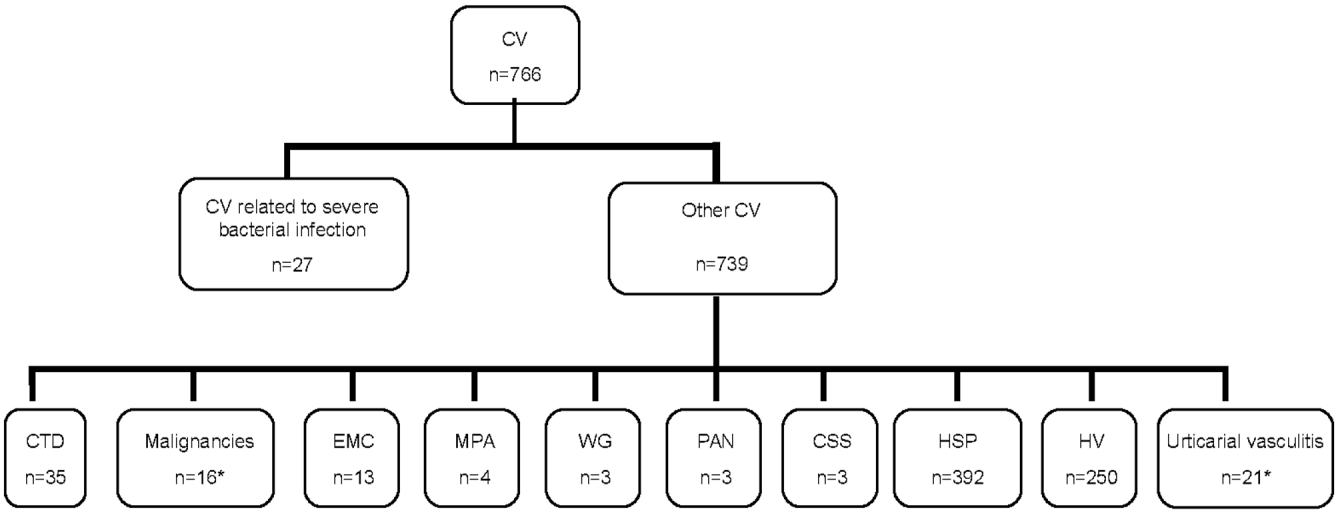

Fig. 1. Flow chart of 766 patients with cutaneous vasculitis.

Analysis was performed with the STATISTICA software package (Statsoft Inc. Tulsa, OK, USA). A comparative study between infection-related CV and the remaining patients with CV was also performed. Finally, a PubMed database search (National Library of Medicine, Bethesda, MD) was conducted to review the studies on CV associated with severe infection published in English between 1988 and 2012.

Results

Seven hundred and sixty-six unselected patients (346 women and 420 men) diagnosed with CV during the study period were included. Figure 1 shows the clinical distribution of these patients. The mean-age of the overall series was 34±28 years (range 1-95 years). Four-hundred and twenty-one patients (178 women and 243 men) were older than 20 years, with a mean age of 56±18 years (range 24–95 years). Twenty-seven cases (22 men and 5 women; mean age at diagnosis 53±18 years [range 9–81]) of the 766 patients (3.5%) had an associated severe bacterial infection. Twenty-five of them were older than 20 years (20 men and 5 women; mean age 56±13 years [range 31–81 years]). They constituted 5.9% of all our adult population with CV. The corresponding rate in those aged 20 or under was 0.6% (2 out of 345).

All the 27 patients were admitted to hospital because of suspected CV. The median (IQR) delay from admission to the diagnosis of the underlying severe bacterial infection was 4 days (IQR: 2–6 days). SIRS was observed in all the patients; 21 fulfilled the definitions for sepsis, and 4 met definitions for severe sepsis. The main demographic, clinical and laboratory findings, type of underlying infection, microorganism, and clinical outcome are summarised in the Table I. Eleven patients were receiving antibiotics that had been prescribed by the general practitioners prior to the admission.

Cutaneous lesions were the presenting manifestation in 13 of 27 patients. In the remaining patients the first clinical manifestations were fever (n=6), joint manifestations (n=4), abdominal pain (n=2), pleuritic pain (n=1), and constitutional symptoms (n=1). Nevertheless, all the patients developed cutaneous lesions during the first few days, including palpable purpura (26 patients) and/or maculopapular lesions (8 cases). In all the patients the vasculitic skin lesions were observed at the onset of the clinical syndrome, and in most cases they were located in the lower extremities, although trunk and upper extremities were affected in some of the patients. Twenty-one patients had fever and 5 constitutional symptoms. However, none of them had visceral vasculitic involvement.

The following abnormal laboratory findings were observed in patients with CV associated with severe bacterial infection: leukocytosis (n=27), increased ESR (n=18), anaemia (n=16), mild haematuria (n=8), mild proteinuria (n=9), positive RF (n=6), positive ANA (n=5), serum cryoglobulins (n=3) and low C3 levels (n=2). None of the patients with positive ANA or RF tests had systemic lupus erythematosus, rheumatoid arthritis or any other connective tissue diseases. Serum IgA levels were obtained in 69 patients (4 cases with CV associated with severe bacterial infections and 65 without infection). Levels were found to be elevated in 3 patients with CV associated with severe bacterial infections and in 49 cases with CV unrelated to severe bacterial infection.

Skin punch biopsy was performed in all the 27 pateints with CV associated with severe bacterial infection. All of them showed typical histological findings (Fig. 2). Direct immunofluorescence on skin biopsies was only performed in 21 patients from the whole series of patients with CV. Positive immune deposits for IgG and C1q were found in the only patient with CV associated with severe bacterial infection in whom this technique was performed. No immune deposits positive for IgA were found in this patient. In addition, immune deposits were also found in 10 of 20 cases with CV unrelated to severe bacterial infection.

Table I. Main features of 27 patients presenting with cutaneous vasculitis associated with severe bacterial infection.

Case	Age/ Sex	Main clinical features	Main laboratory data	Delayed diagnosis of bacterial infection / Outcome	Diagnosis	Microorganism
1	40/M	Palpable purpura, fever, arthritis, cough and expectoration	Leukocytosis, elevated ESR, anaemia, positive RF and cryoglobulins	3 days / Resolution	Pneumonia	Unknown
2	64/M	Palpable purpura, cough, expectoration and arthritis	Leukocytosis and elevated ESR	4 days / Resolution	Pneumonia	P. aeruginosa
3	60/F	Palpable purpura, fever and pleuritic chest pain	Leukocytosis and anaemia	2 days / Resolution	Pneumonia plus empyema	Unknown
4	71/M	Palpable purpura, fever, cough, expectoration, abdominal pain and arthralgia	Leukocytosis, elevated ESR, proteinuria and cryoglobulins	1 day / Resolution	Pneumonia	Unknown
5	45/M	Palpable purpura, fever, cough, expectoration and abdominal pain	Leukocytosis, elevated ESR, anaemia, hepatitis C virus, proteinuria, positive ANA and cryoglobulins	4 days / Resolution	Pneumonia	Unknown
6	52/F	Palpable purpura, fever, cough, expectoration and pleuritic chest pain	Leukocytosis	6 days / Resolution	Pneumonia plus empyema	Unknown
7	42/M	Palpable purpura, erythema, cough and expectoration	Leukocytosis, anaemia, hepatitis C virus and HIV	1 day / Death at 14 days	Pneumonia	Unknown
8	51/M	Palpable purpura, erythema, fever, cough and expectoration	Leukocytosis, elevated ESR, anaemia and proteinuria	2 days / Resolution	Pneumonia	Unknown
9	65/M	Palpable purpura, fever, abdominal pain, arthralgia and cardiac murmur	Leukocytosis, elevated ESR, anaemia, haematuria and positive RF	32 days / Resolution after valve prosthesis	Endocarditis	S. viridans
10	55/M	Palpable purpura, fever, back pain, arthralgia and cardiac murmur	Leukocytosis, elevated ESR, anaemia, haematuria, positive RF and decrease of C3	4 days / Resolution	Endocarditis	S. viridans
11	66/M	Palpable purpura, erythema, pleuritic chest pain, arthralgia and cardiac murmur	Leukocytosis, haematuria positive ANA and decrease of C3,	45 days / Resolution after valve prosthesis	Endocarditis	Unknown
12	47/M	Palpable purpura, fever, pleuritic chest pain and cardiac murmur	Leukocytosis and positive RF	7 days / Resolution	Endocarditis	S. viridans
13	66/M	Palpable purpura, fever, constitutional syndrome and arthralgia	Leukocytosis, elevated ESR, anaemia, haematuria, proteinuria and positive ANA	3 days / Resolution	Endocarditis	E. faecium
14	51/F	Erithematous lesions, fever, constitutional syndrome and abdominal pain	Leukocytosis, elevated ESR, haematuria and positive RF	7 days / Resolution	Endocarditis	Unknown
15	56/M	Palpable purpura, erythema, fever, arthritis, headache and vomiting	Leukocytosis and elevated ESR,	6 days / Resolution	Meningitis	N. meningitidis
16	48/M	Palpable purpura, fever, arthritis and headache	Leukocytosis and elevated ESR	7 days / Resolution	Tuberculous meningitis	M. tuberculosis
17	31/F	Palpable purpura, arthritis and headache	Leukocytosis, elevated ESR and positive ANA	4 days / Resolution	Meningitis	Unknown
18	41/M	Palpable purpura, fever, constitutional syndrome, arthritis and headache	Leukocytosis, elevated ESR and positive ANA	5 days / Resolution	Meningitis	N. meningitidis
19	9/M	Palpable purpura, erythema, fever and abdominal pain	Leukocytosis	2 days / Resolution	Abdominal infection	E. coli, P. aeruginosa, B. fragilis
20	78/M	Palpable purpura, fever, abdominal pain, nausea, vomiting, rectal bleeding	Leukocytosis, anaemia, haematuria, proteinuria and positive RF	1 day / Resolution	Abdominal infection	B. fragilis
21	81/M	Palpable purpura, erythema, fever, constitutional syndrome, abdominal pain, nausea and vomiting	Leukocytosis, elevated ESR, anaemia and proteinuria	4 days / Death at 6 days	Abdominal infection in the setting of pancreatitis	CNS, K. pneumoniae
22	70/M	Palpable purpura, fever, arthritis, nausea and vomiting	Leukocytosis, anaemia, and proteinuria	2 days / Resolution	Infectious arthritis of the knee	S. aureus
23	73/M	Palpable purpura and arthritis	Leukocytosis and elevated ESR,	3 days / Resolution	Infectious arthritis of the wrist	S. aureus
24	57/M	Palpable purpura, fever and olecranon bursitis	Leukocytosis and elevated ESR,	6 days / Resolution	Olecranon bursitis	S.aureus
25	34/F	Palpable purpura, erythema, abdominal pain, arthritis, rectal bleeding	Leukocytosis, elevated ESR, haematuria, and proteinuria	1 day / Resolution	Septicaemia	S. viridans
26	9/M	Palpable purpura, fever, constitutional syndrome, arthralgia, nausea and vomiting	Leukocytosis and elevated ESR	2 days / Resolution	Septicaemia	Unknown
27	55/M	Palpable purpura, fever, abdominal pain and arthritis	Leukocytosis, anaemia, haematuria and proteinuria	4 days / Resolution	Urinary tract infection (in a kidney transplant recipient)	P. aeruginosa

M: male; F: female; CNS: Coagulase-negative staphylococci.

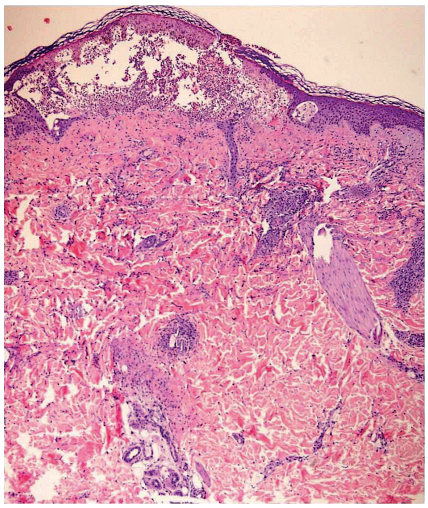

Fig. 2. Skin biopsy of a patient with cutaneous vasculitis associated with meningococcemia presenting with palpable purpura. Leukocytoclastic vasculitis with an intense perivascular neutrophilic infiltrate and pustulosis subepidermal (Haematoxylin-eosin stain¸ original magnification x 25).

Table II. Differences between patients with cutaneous vasculitis (CV) associated with severe bacterial infection and the remaining patients with CV unrelated to severe bacterial infection from the present series.

	CV associated with severe bacterial infection (n=27)	Other CV (n=739)	*p*-value
Demographic data			
- Age (years), mean±SD	53 ± 18	33 ± 28	<0.01
- Sex, n (%)			
- Male, n (%)	22 (81.5%)	398 (53.8%)	<0.01
Clinical manifestations, n (%)			
- Skin lesions			
- Palpable purpura	26 (96.3%)	577 (78.0%)	0.02
- Other skin lesions	8 (29.63%)	177 (23.9%)	0.5
- Duration (days) median (IQR)	15 (10-22)	10 (6-15)	0.7
- Constitutional symptoms	5 (18.5%)	40 (5.4%)	<0.01
- Fever	21 (77.8%)	143 (19.3%)	<0.01
- Joint manifestations	16 (59.3%)	372 (50.3%)	0.36
- Gastrointestinal involvement	12 (44.4%)	281 (38.0%)	0.5
- Nephropathy	13 (48.1%)	232 (31.4%)	0.07
- Focal infectious features†	27 (100%)	3 (0.4%)	<0.01
Routine laboratory findings			
- Haemoglobin (g/dL), mean±SD	10.1 ± 1.6	12.2 ± 2.2	<0.01
- Leukocyte count/mm3, mean±SD	12892 ± 1907	14389 ± 3505	0.03
- Left shift white blood cell count, n (%)	8 (29.6%)	82 (11.1%)	<0.01
- ESR mm 1st hour, mean±SD	60.9 ± 32.6	48.4 ± 28.2	0.07
- Abnormal urynalisis, n (%)	13 (48.1%)	270 (36.5%)	0.2
- Increased serum IgA levels, n (%)*	3/4 tested (75%)	49/65 tested (75%)	0.6
Any cytopenia, n (%)	12 (44.4%)	129 (17.5%)	<0.01
- Anaemia	12 (44.4%)	94 (12.7%)	<0.01
- Leukopenia	0 (0%)	20 (2.7%)	0.4
- Thrombocytopenia	1 (3.7%)	13 (1.7%)	0.5
Hepatitis virus infection, n (%)			
- HBV*	0/12 tested (0%)	15/305 tested (5%)	0.9
- HCV*	2/10 tested (20%)	12/154 tested (7.8%)	0.5
Immunological findings, n (%)			
- Positive ANAs*	5/14 tested (35.7%)	82/317 tested (25.8%)	0.4
- Positive RF*	6/12 tested (50%)	67/331tested (20.2%)	0.01
- Serum cryoglobulins*	3/11 tested (27.3%)	73/273 tested (27.7%)	0.8
- Low C3 and/or C4*	2/15 tested (13.3%)	96/323 tested (29.7%)	0.2
- Positive ANCA*	0/8 tested (0%)	13/157 tested (8.3%)	0.9

IQR: Interquartile range; ESR: erythrocyte sedimentation rate in mm/1st hour; RF: rheumatoid factor; ANA: antinuclear antibodies; C3 and C4 fractions of complement. HBV: hepatitis B virus; HCV: hepatitis C virus.
†Focal infectious features included: cardiac murmur, severe cough, pleuritic chest pain, and meningeal signs. *Expressed as positive/total tested (%).
Leukopenia: leukocyte count <3000/mm^3; Anaemia: haemoglobin <11.0 g/dL.
Increased serum IgA levels: if values were >400 mg/dL.

All the patients received antibiotics, but 7 also required the use of low-dose oral corticosteroids (prednisone 5–15 mg/day) to achieve complete resolution of the cutaneous lesions. It is important to highlight the long diagnostic delay in 2 patients with bacterial endocarditis (32 and 45 days, respectively) (1). One of them developed an acute heart failure and underwent urgent surgery with implantation of a prosthetic mitral valve. The second patient also developed an acute heart failure due to a rupture of the chordae tendineae requiring immediate implantation of a prosthetic mitral valve. However, at the time of admission neither of them had typical signs of infective endocarditis (see Table I). Two of the 27 patients died; a 42-year-old man with severe pneumonia and a history of hepatitis C and HIV infection, and an 81-year-old with acute pancreatitis who developed an abdominal septicaemia.

A comparative study between patients with CV associated with severe bacterial infection and the remaining CV patients is shown in Table II. Noteworthy, patients with severe bacterial infections were older (p<0.01) and more commonly males. Palpable purpura, fever and constitutional symptoms were also more frequent in these patients. They had more commonly focal infectious manifestations (such as cardiac murmur, severe cough, pleuritic chest pain or meningeal signs (p<0.01). Cytopenias (p<0.01), particularly anaemia, were also more common. Of note, while the mean white blood cell count was lower in the group of patients with CV associated with severe bacterial infections, this group had leukocytosis with a left shift more frequently than those with CV unrelated to bacterial infections (p<0.01). Also, a positive RF was more frequently observed in patients with severe bacterial infections than in those with CV not associated with underlying infections (p=0.01). None of the patients with CV associated with severe bacterial infection had relapses, whilst they were observed in 195 patients with other CV (p=0.004).

Discussion

CV includes a wide and heterogeneous group of disorders characterised by predominant involvement of the skin with histopathological findings that share vascular inflammation and blood vessel damage (26, 27). An underlying cause is not found in most cases and the dis-

Table III. Literature review of patients with cutaneous vasculitis due to a severe underlying bacterial infection.

Ref.	Age/Sex	Microorganism	Time between onset of symptoms and diagnosis	Outcome	Final diagnosis
11	68/M	*Streptococcus bovis*	Some days	Resolution	Infective endocarditis
8	64/F	*Staphylococcus aureus*	17 days	Resolution	Infective endocarditis
30	72/M	*Acinetobacter spp.*	4 days	Resolution	Infective endocarditis
30	64/M	*Fusobacterium spp.*	1 month	Resolution after mitral valve replacement	Infective endocarditis
30	21/M	*Enterococcus faecalis*	5 days	Resolution after mitral valve replacement	Infective endocarditis
36	44/M	*Streptococcus bovis*	3 months	NR	Infective endocarditis
13	20/M	*Streptococcus sanguis*	6 weeks	Resolution	infective endocarditis
16	48/F	*Enterococcus faecalis* and CNS	12 days	Resolution after mitral valve replacement	Infective endocarditis
18	64/M	*Abiotropia defective*	NR	NR	Infective endocarditis
14	78/M	*Streptococcus pneumoniae*	NR	Resolution	Pneumonia
15	28/F	*Mycoplasma pneumoniae*	9 days	Resolution	Upper respiratory tract infection
7	45/M	*Chlamydia pneumoniae*	3 weeks	Resolution	Pneumonia and reactive arthritis
12	79/F	*Klebsiella pneumoniae*	NR	Resolution	Bacteremia
6	50/M	Sputum smear microscopy (Ziehl-Neelsen staining positive x3)	24 days	Resolution	Pulmonary tuberculosis
30	38/M	*Neisseria meningitidis*	10 days	Resolution	Meningococcemia
10	16/M	Unknown	3 weeks	Resolution	Meningitis
9	64/M	*Brucella melitensis*	25 days	Death at 28 days of hospitalisation	Peritonitis

M: male; F: female; CNS: Coagulase-negative staphyloccoci; NR: Not reported.

ease is generally self-limited. Nevertheless, CV can be the presenting manifestation of an underlying disease.

CV can be the associated with bacterial infection. The actual frequency of severe bacterial infections in patients presenting with CV is unknown. Current information on CV associated with severe bacterial infections comes from relatively small case series or single case reports (5-17, 28). In our study the overall frequency was 3.5%. This frequency was slightly higher (5.9%) when we specifically assessed adults with CV. This was considerably lower than that shown by Khetan *et al*. who reported a frequency of 11.4% in a population-based study of patients with CV (29). As shown in our series, Khetan *et al*. described a wide range of age (7-64 years) (29) but information on the type of infection was not reported (29). The great variability in the frequency of CV associated with severe bacterial infection may be due to the different criteria used for the diagnosis, including the need of skin biopsy. Therefore, definitions used in our study may explain the lower frequency of CV associated with bacterial infection when compared with previous studies.

Several mechanisms have been proposed as responsible for the development of CV in the setting of infection (4, 30-35). Direct bacterial invasion with endothelial damage is considered the main mechanism in patients with Rickettsial infections (32). However, in most cases vasculitis is the result of an immune response, triggered by an offending infectious agent. Thus, humoral immune response with immune complex formation and deposition, in and around the vessel wall, is thought to be the major mechanism involved in CV associated with infections (34). Molecular mimicry, where a foreign antigen shares sequence or structural similarities with self-antigens, may also lead to the production of autoantibodies and activation of autoreactive lymphocytes (33). Table III shows a literature review of cases with CV due to a severe underlying bacterial infection.

Rheumatic manifestations are frequently observed in the setting of different infectious diseases. Thus, leukocytoclastic vasculitis was found in almost 4% of patients from a population-based study that specifically assessed the frequency and clinical spectrum of rheumatic features in patients with infective endocarditis (36). In keeping with these results, several case reports have linked CV to this type of cardiac infection (8, 11, 13, 16-18, 30), highlighting the frequency and clinical relevance of this association. Therefore, infective endocarditis should be a diagnostic challenge for clinicians. It is particularly true if we consider that typical manifestations of the disease, such a cardiac murmur or typical cutaneous lesions, may be initially absent in some patients. In keeping with that, herein we described two patients with infective endocarditis presenting with CV that at presentation did not exhibit the typical features of this infection, leading to an inappropriate delay to the diagnosis. Low-dose corticosteroids were initially prescribed in both cases to manage the CV. This procedure could have altered the clinical course of the underlying endocarditis, worsening its prognosis. These cases support the claim that vasculitic manifestations may be considered as potential "red flags" for the recognition of patients with severe underlying diseases who require a prompt diagnosis and treatment (8, 30, 36).

Respiratory infections have been associated with CV. Pneumonia was the most frequent disease related to CV in our series. *Streptococcus pneumoniae* (14), *Mycoplasma pneumoniae* **(15)**, *Chlamydia pneumoniae* (7), and *Klebsiella pneumoniae* (12) have been associated with the development of CV. *Mycobacterium tuberculosis* has also been associated with CV (6, 37). How-

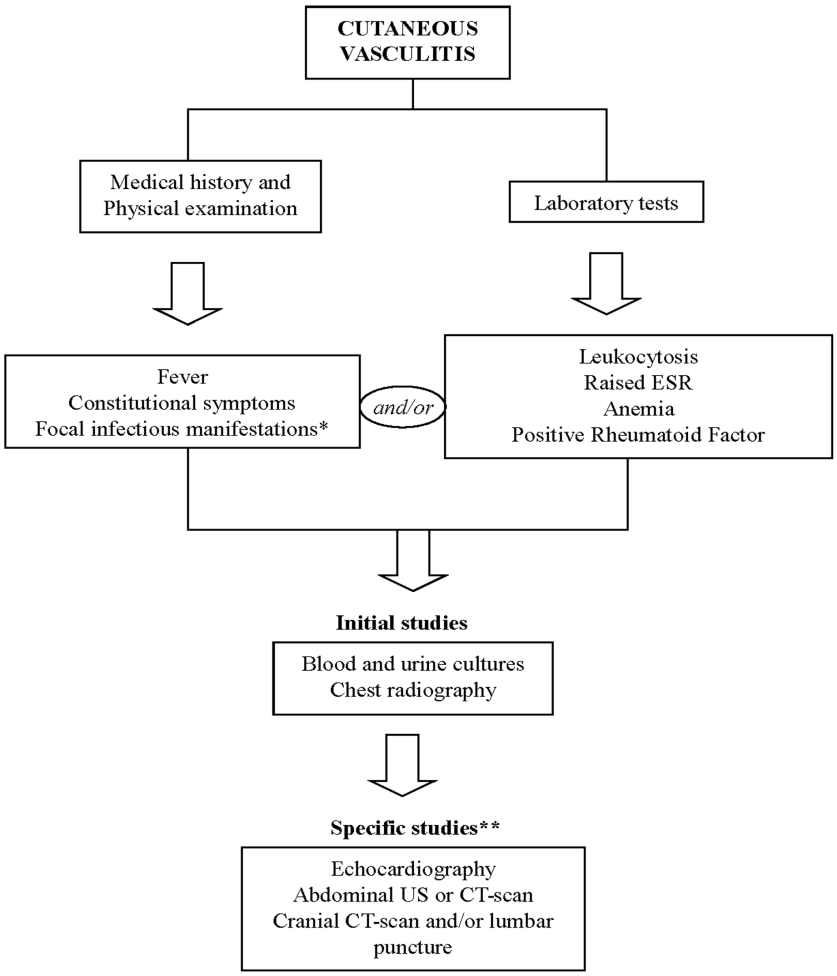

Fig. 3. Work-up in a patient presenting with cutaneous vasculitis to establish the presence of a severe underlying infection. *Focal infectious manifestations include: new cardiac murmur; pleuritic chest pain and cough/expectoration; headache and/or meningeal signs; abdominal pain; dysuria.
** Specific diagnostic studies should be guided by clinical suspicion.

ever, unlike cutaneous tuberculosis, the bacilli are not generally found in the vessel walls. Deposition of immune complexes (composed of antibodies against bacillus antigens) in the vessel wall instead of a direct aggression is the mechanism leading to CV in these cases (6, 37-39).

Intra-abdominal infections are usually the result of the invasion and multiplication of enteric bacteria in the wall of a hollow organ (40). When the infection spreads to the peritoneal cavity or other sterile regions of the abdominal cavity, it is called "complicated intra-abdominal infection" (40-42). However, the potential association of these infections with CV has been scarcely reported in the literature (9).

As emphasised before, CV can be the presenting manifestation of a severe underlying infection. Therefore, in a patient with CV the presence of fever, constitutional symptoms, and focal manifestations of infection (such as heart murmur, severe cough with expectoration, pleuritic chest pain, abdominal pain or meningeal signs) along with some laboratory abnormalities (mainly anaemia, leukocytosis with a left shift, and raised ESR) should be considered as alert signs for the diagnosis of an underlying severe bacterial infection. Based on our data and those retrieved from the literature (43, 44), we propose a simple algorithm that may help clinicians to suspect a severe underlying bacterial infection in patients presenting with CV (Fig. 3).

In summary, CV may be the presenting manifestation of an underlying severe bacterial infection. Early diagnosis is needed to avoid life-threatening complications.

Acknowledgements

We would like to acknowledge the members of the Rheumatology, Internal Medicine, Dermatology, Paediatrics, and Pathology Services of Hospital Universitario Marqués de Valdecilla, Santander, Spain.

References

1. BLANCO R, MARTÍNEZ-TABOADA VM, RODRÍGUEZ-VALVERDE V, GARCÍA-FUENTES M: Cutaneous vasculitis in children and adults: associated diseases and etiologic factors in 303 patients. *Medicine* (Baltimore) 1998; 77: 403-18.
2. GIBSON LE: Cutaneous vasculitis. Approach to diagnosis and systemic associations. *Mayo Clin Proc* 1990; 65: 221-9.
3. GIBSON LE, SU WPD: Cutaneous vasculitis. *Rheum Dis Clin North Am* 1990; 16: 309-24.
4. SOMER T, FINEGOLD SM: Vasculitides associated with infections, immunization, and antimicrobial drugs. *Clin Infect Dis* 1995; 20: 1010-36
5. BENOIT FL: Chronic meningococcemia. Case report and review of the literature. *Am J Med* 1963, 35: 103-12.
6. CARVALHO M, DOMINONI RL, SENCHECHEN D, FERNANDES AF, BURIGO IP, DOUBRAWA E: Cutaneous leukocytoclastic vasculitis accompanied by pulmonary tuberculosis. *J Bras Pneumol* 2008; 34: 745-8.
7. CASCINA A, MARONE BIANCO A, MANGIAROTTI P, MONTECUCCO CM, MELONI F: Cutaneous vasculitis and reactive arthritis following respiratory infection due to Chlamydia pneumoniae: report of a case. *Clin Exp Rheumatol* 2002; 20: 845-7.
8. CONTI T, BARNET B: The diagnostic challenge of infective endocarditis : cutaneous vasculitis leading to the diagnosis of infective endocarditis. *J Am Board Fam Pract* 2001; 14: 451-6.
9. DIZBAY M, HIZEL K, KILIC S, MUTLUAY R, OZKAN Y, KARAKAN T: Brucella peritonitis and leucocytoclastic vasculitis due to Brucella melitensis. *Braz J Infect Dis* 2007; 11: 443-4.
10. KERNÉIS S, MAHÉ E, HEYM B, SIVADON-TARDY V, BOURGEOIS F, HANSLIK T: Chronic meningococcemia in a 16-year-old boy: a case report. *Cases J* 2009; 2: 7103.
11. LÓPEZ GARCÍA F, ENRÍQUEZ R, AMORÓS F, TERUEL A: Acute fenal failure and leukocytoclastic vasculitis as the presenting form of infectious endocarditis caused by Streptococcus bovis. *Nefrologia* 2002; 22: 206-7.
12. LUM PN, WOO PC, WONG SS, YUEN K: Leukocytoclastic vasculitis complicating Klebsiella pneumoniae bacteremia. *Diagn Microbiol Infect Dis* 2000; 37: 275-7.
13. LYON CC, HARRISON PV: Cutaneous vasculitis and collapse. *Postgrad Med J* 1998; 74: 695-6.
14. NAKAMURA S, YANAGIHARA K, IZUMIKAWA K *et al*.: Leukocytoclastic vasculitis after pneumococcal pneumonia in an elderly adult. *Intern Med* 2007; 46: 487-90.
15. PEREZ C, MENDOZA H, HERNANDEZ R,

VALCAYO A, GUARCH R: Leukocytoclastic vasculitis and polyarthritis associated with Mycoplasma pneumoniae infection. *Clin Infect Dis* 1997; 25: 154-5.
16. PIŞKIN N, AKDUMAN D, AYDEMIR H, CELEBI G, OZTOPRAK N, AKTAS E: Infective endocarditis due to high level aminoglycoside resistant Enterococcus faecalis and methicillin resistant coagulase-negative staphylococci presenting with rheumatic manifestations. *Mikrobiyol Bul* 2008; 42: 509-14.
17. PÖSS J, SCHÄFERS HJ, HERRMANN M, VON MÜLLER L, BÖHM M, KILTER H: Leukocytoclastic vasculitis and myocardial infarction as presenting manifestations of infective endocarditis: a case report. *Clin Res Cardiol* 2010; 99: 59-61.
18. SHARIFF N, ROBERTS J, AHMED S: Cutaneous vasculitis rash due to bacterial endocarditis. *Heart* 2009; 95: 106.
19. CALVO-RÍO V, LORICERA J, MARTÍN L *et al*.: Henoch-Schönlein purpura nephritis and IgA nephropathy: a comparative clinical study. *Clin Exp Rheumatol* 2013; 31 (Suppl. 75): S45-51.
20. LORICERA J, CALVO-RÍO V, ORTIZ-SANJUÁN F *et al*.: The spectrum of paraneoplastic cutaneous vasculitis in a defined population. Incidence and clinical features. *Medicine* (Baltimore) 2013; 92: 331-43.
21. ORTIZ-SANJUÁN F, BLANCO R, LORICERA J *et al*.: Reappraisal of the 1990 American College of Rheumatology criteria for the classification of cutaneous vasculitis: an analysis based on 766 patients. *Clin Exp Rheumatol* 2014; 32 (Suppl. 82): S51-4.
22. CALVO-RIO V, LORICERA J, ORTIZ-SANJUÁN F: Revisiting clinical defferences between hypersensitivity vasculitis and Henoch-Schönlein purpura in adults from a defined population. *Clin Exp Rheumatol* 2014; 32 (Suppl. 82): S34-40.
23. AMERICAN COLLEGE OF CHEST PHYSICIANS / SOCIETY OF CRITICAL CARE MEDICINE. AMERICAN COLLEGE OF CHEST PHYSICIANS/SOCIETY OF CRITICAL CARE MEDICINE CONSENSUS CONFERENCE: definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. *Crit Care Med* 1992; 20: 864-74.
24. MICHEL BA, HUNDER GG, BLOCH DA, CALABRESE LH: Hypersensitivity vasculitis and Henoch-Schöenlein purpura: a comparison between the 2 disorders. *J Rheumatol* 1992; 19: 721-8.
25. MILLS JA, MICHEL HA, BLOCH DA *et al*.: The American College of rheumatology 1990 criteria for the classification of Henoch-Schoenlein purpura. *Arthritis Rheum* 1990; 33: 1114-21.
26. CALLEN JP: Cutaneous vasculitis and other neutrophilic dermatoses. *Curr Opin Rheumatol* 1993; 5: 33-40.
27. GONZÁLEZ-GAY MA, GARCÍA-PORRÚA C: Epidemiology of the vasculitides. *Rheum Dis Clin North Am* 2001; 27:729-49.
28. SADANA A, MERRICK-THOMAS D, SCOTT DL: Vasculitis in Reiter's syndrome. *Clin Rheumatol* 1988; 7: 114.
29. KHETAN P, SETHURAMAN G, KHAITAN BK *et al*.: An aetiological & clinicopathological study on cutaneous vasculitis. *Indian J Med Res* 2012; 135: 107-13.
30. GARCÍA-PORRÚA C, GONZÁLEZ-GAY MA: Bacterial infection presenting as cutaneous vasculitis in adults. *Clin Exp Rheumatol* 1999; 17: 471-3.
31. LIE JT: Vasculitis associated with infectious agents. *Curr Opin Rheumatol* 1996; 8: 26-9.
32. MOHAN N, KERR G: Infectious etiology of vasculitis: diagnosis and management. *Curr Rheumatol Rep* 2003; 5: 136-41.
33. OLDSTONE MB: Molecular mimicry and immune-mediated diseases. *FASEB J* 1998; 12: 1255-65.
34. PIPITONE N, SALVARANI C: The role of infectious agents in the pathogenesis of vasculitis. *Best Pract Res Clin Rheumatol* 2008; 22: 897-911.
35. RODRÍGUEZ-PLA A, STONE JH: Vasculitis and systemic infections. *Curr Opin Rheumatol* 2006; 18: 39-47.
36. GONZÁLEZ-JUANATEY C, GONZÁLEZ-GAY MA, LLORCA J *et al*.: Rheumatic manifestations of infective endocarditis in non-addicts. A 12-year study. *Medicine* (Baltimore) 2001; 80: 9-19.
37. PARISH WE, RHODES EL: Bacterial antigens and aggregated gamma globulin in the lesions of nodular vasculitis. *Br J Dermatol* 1967; 79: 131-47.
38. BROSTOFF J, LENZINI L, ROTTOLI P, ROTTOLI L: Immune complexes in the spectrum of tuberculosis. *Tubercle* 1981; 62: 169-73.
39. JOHNSON NM, MCNICOL MW, BURTON-KEE EJ, MOWBRAY JF: Circulating immune complexes in tuberculosis. *Thorax* 1981; 36: 610-7.
40. MAZUSKI JE, SOLOMKIN JS: Intra-abdominal infections. *Surg Clin North Am* 2009; 89: 421-37.
41. BLOT S, DE WAELE JJ: Critical issues in the clinical management of complicated intra-abdominal infections. *Drugs* 2005; 65: 1611-20.
42. MARSHALL JC: Intra-abdominal infections. *Microbes infect* 2004; 6: 1015-25.
43. GONZALEZ-GAY MA, GARCIA-PORRUA C, SALVARANI C, LO SCOCCO G, PUJOL RM: Cutaneous vasculitis: a diagnostic approach. *Clin Exp Rheumatol* 2003; 21 (Suppl. 32): S85-8.
44. GONZALEZ-GAY MA, GARCIA-PORRUA C, PUJOL RM: Clinical approach to cutaneous vasculitis. *Curr Opin Rheumatol* 2005; 17: 56-61.