Concise report

Single-organ cutaneous small-vessel vasculitis according to the 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides: a study of 60 patients from a series of 766 cutaneous vasculitis cases

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Abstract

Objective. Cutaneous vasculitis (CV) encompasses a wide group of entities characterized by inflammation of skin blood vessels. The term single-organ vasculitis was recently coined by the 2012 Chapel Hill Consensus Conference (CHCC) to define vasculitis affecting a single organ. To our knowledge there are no published reports on single-organ cutaneous small vessel vasculitis (SoCSVV). Our aim was to characterize this entity from a wide series of patients with CV.

Methods. We analysed cases of SoCSVV from a series of 766 patients with CV from a single university referral centre. According to 2012 CHCC, the following conditions were required to define SoCSVV: (i) skin biopsy showing characteristic leucocytoclastic vasculitis and (ii) vasculitis limited to skin.

Results. We included 60 patients (26 women and 34 men) with a mean age of 56 years. The main precipitating factors for SoCSVV were drugs [26 patients (52%)] and previous infection [17 patients (34%)]. The main clinical manifestations were palpable purpura (81.7%) and fever (18.3%). The most frequent laboratory findings were leucocytosis and elevated ESR. Nearly one-quarter of patients with SoCSVV required pharmacological therapy. Corticosteroids (15%) and NSAIDs (13.3%) were the main agents prescribed. After a median follow-up of 4 months, complete recovery was observed in all the patients, although relapses occurred in 8% of patients.

Conclusion. SoCSVV defined according to the 2012 CHCC may be considered a benign disease usually associated with drugs and/or a previous infection.

Key words: cutaneous vasculitis, single cutaneous small vessel vasculitis, single-organ vasculitis, cutaneous leucocytoclastic angiitis, Chapel Hill Consensus Conference.

Introduction

Cutaneous vasculitis (CV) encompasses a wide and heterogeneous group of disorders characterized by the presence of necrotizing inflammatory lesions in the cutaneous blood vessels [1]. They may range from an isolated CV to a severe, life-threatening syndrome, including ANCA-associated vasculitis.

The 2012 revised International Chapel Hill Consensus Conference (CHCC) Nomenclature of Vasculitides defines...
single-organ vasculitis [2] as a vasculitis affecting arteries or veins of any size in a single organ, with no features suggesting limited expression of a systemic vasculitis. When confined to the skin, the term single-organ cutaneous small vessel vasculitis (SoCSVV) is used. This entity is equivalent to the previous cutaneous leukocytoclastic angiitis defined by the 1994 CHCC [3]. In contrast, in 1990 a committee of the ACR for the classification of vasculitis proposed the term hypersensitivity vasculitis (HV). Unlike SoCSVV, extracutaneous involvement may occur in the context of HV and it is of note that confirmation by skin biopsy was not required [4].

Several studies have been published on the clinical characterization of HV [1, 5–7]. However, to the best of our knowledge there are no reports on SoCSVV. Therefore our purpose was to characterize SoCSVV as a distinct entity according to the 2012 CHCC Nomenclature of Vasculitides, based on a wide and unselected series of CV from a single centre.

Patients and methods

Patient population

We reviewed the medical records of patients diagnosed with CV at a university tertiary care teaching hospital between January 1976 and December 2011. Regardless of the initial attending physician, in our institution the vast majority of patients with CV, either with or without systemic involvement (that is to say, both patients who fulfilled definitions for SoCSVV and those with extracutaneous involvement), are evaluated by dermatologists and rheumatologists. This procedure reduces the possibility of selection bias.

Full blood cell count, coagulation, liver and renal function tests, ESR and urinalysis were performed at the time of diagnosis in most patients. According to clinical findings, an immunological profile, chest radiograph and electrocardiogram were performed in most adults, but in only a minority of children [1, 8–11]. The diagnosis of CV was based on (i) a skin biopsy showing characteristic histological findings of vasculitis (neutrophilic infiltration, leucocytoclasis, fibrinoid necrosis or erythrocyte extravasation into the vessel wall) and/or (ii) the presence of typical non-thrombocytopenic palpable purpura. Based on these definitions, 766 patients were diagnosed with CV.

Patients with CV due to underlying diseases were excluded: CTDs (n = 35), major infections (n = 27), malignancies (n = 16), essential mixed cryoglobulinaemia (n = 13), microscopic polyangiitis (n = 4), granulomatosis with polyangiitis (n = 3), Churg–Strauss syndrome (n = 3) and polyarteritis nodosa (n = 3). The remaining 662 patients were considered to have primary CV.

HV and Henoch–Schönlein purpura (HSP) were defined using the criteria proposed by Michel et al. [12] based on the ACR database. Thus patients with primary CV were classified as having HV (n = 250) if they had two or fewer criteria or HSP (n = 392) if they fulfilled three or more criteria from the following six criteria: cutaneous palpable purpura, bowel angina, gastrointestinal bleeding, gross haematuria or microhaematuria, age at disease onset ≤ 20 years and no history of drug intake.

SoCSVV is a more restricted entity than HV since it is confined to skin without involvement of vessels in any other organs and it always requires histological confirmation [2, 3]. Taking these considerations into account, 155 patients with HV and extracutaneous involvement were also excluded.

The remaining 95 patients had CV limited to skin. Skin biopsy was not performed in 35 of these patients and thus they were excluded from the category of SoCSVV. Therefore only 60 patients in whom a biopsy was performed met the definitions for SoCSVV. Fig. 1 shows the flow chart for the present study.

Clinical and laboratory definitions

As previously proposed, patients > 20 years of age were considered adults [12, 13]. Precipitating factors included whether there was a history of drug therapy or infection before the onset of vasculitis. To reinforce the causal relationship between these factors and the development of SoCSVV, infections must have occurred and drugs must have been taken within 1 week before onset of the disease. Fever was an axillary temperature > 37.7 °C. Joint manifestations included arthralgia and/or joint effusion. Gastrointestinal manifestations included bowel angina (diffuse abdominal pain worsening after meals),

FIG. 1 Flow chart showing the distribution of 766 patients with CV

CV: cutaneous vasculitis; HSP: Henoch–Schönlein purpura; UV: urticarial vasculitis; HV: hypersensitivity vasculitis; SoCSVV: single-organ cutaneous small vessel vasculitis.
gastrointestinal bleeding (melena, haematochezia or positive stool guaiac test), nausea and/or vomiting. Nephropathy was categorized as mild or severe. Mild nephropathy was the presence of microhaematuria [≥5 red cells/high-power field (hpf)] without fulfilling the criteria for nephritic syndrome (see below) and/or non-nephrotic proteinuria. Severe nephropathy was the presence of nephrotic syndrome (plasma albumin levels ≤25 g/l and either 1 g of proteinuria/day/m² 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 level and oliguria). Renal insufficiency was defined as serum creatinine level above 125% of the upper limit of normal. Anaemia was a haemoglobin level ≤11 g/dl. Leucocytosis was a white blood cell count ≥11 000/mm³. ESR was considered elevated when it was >15 or 20 mm/first hour for men or women, respectively. Relapse was a new flare of cutaneous lesions in a patient asymptomatic for at least 1 month.

Data collection
Data on clinical, laboratory and histopathological features, aetiology, treatment and outcome were retrieved from the clinical charts and stored in a computerized database. To minimize entry error, all data were double checked and reviewed for diagnosis confirmation. The immunological profile included RF, ANA, serum C3 and C4 and cryoglobulins. ANCA has only been assessed since 1990. Other tests, such as anti-nDNA antibodies; blood cultures; stool guaiac test; hepatitis B or C or HIV infection serology; bone marrow biopsy and chest radiographs were performed based on the judgement of the attending physician.

Statistical analysis
Normally distributed variables were expressed as the mean (s.d.) and those not normally distributed as the median [interquartile range (IQR)]. Continuous variables were compared with the two-tailed Student’s t-test or Mann–Whitney U-test. Dichotomous variables were analysed by chi-square test or Fisher’s exact test. A P-value <0.05 was considered statistically significant. Analysis was performed with the STATISTICA software package (StatSoft, Tulsa, OK, USA).

This was a retrospective review. No specific request was made to our local ethics committee for that purpose. Nevertheless, ethics committee approval and informed patient consent was obtained to perform genetic studies in patients with CV.

Results
Between January 1976 and December 2011, 60 patients (26 women and 34 men) with a mean age of 56 years (s.d. 16) were diagnosed with SoCSVV. In the same period, 250 patients met definitions for HV according to the 1990 ACR criteria. Table 1 summarizes the main characteristics of patients with SoCSVV and HV.

Patients with SoCSVV were older (P = 0.001) and less frequently had anaemia (P = 0.04) and leucocytosis (P = 0.0003) than those with HV. A trend towards lower ESR values in SoCSVV than in HV patients was also observed (P = 0.07). No other significant differences were found.

With regard to potential precipitating factors, a history of drugs, mainly antibiotics and NSAIDs, was found in 53.3% of SoCSVV patients.

Palpable purpura was the typical cutaneous lesion in most patients with SoCSVV and HV (Table 1). The distribution of skin lesions in SoCSVV patients was as follows: lower limbs (60 patients, 100%), trunk (17 patients, 28.3%) and upper limbs (17 patients, 28.3%). The median duration of these lesions was 10 days, which was not different from that found in the HV group (9 days).

Apart from cutaneous lesions, fever was present in 11 of 60 SoCSVV patients.

The frequency of positive ANA or serum cryoglobulins was similar in the SoCSVV and HV groups. However, positive RF was more commonly observed in SoCSVV than in HV patients (P = 0.004).

The outcome of SoCSVV was good. Symptoms resolved in 73% of the patients with bed rest. Nevertheless, one-quarter of these received drugs, mainly corticosteroids or NSAIDs. The use of NSAIDs was more commonly observed in HV patients.

After a median follow-up of 4 months (IQR 2–13), relapses characterized by the presence of new flares of skin lesions occurred in only five (8.3%) patients with SoCSVV. Although relapses were more commonly observed in HV patients (12.8%), differences were not statistically significant when compared with SoCSVV patients.

Discussion
Following the 2012 CHCC definitions, SoCSVV is considered a specific entity. In this study we describe for the first time the clinical spectrum of patients with SoCSVV. We also compared SoCSVV with HV defined following the criteria proposed by Michel et al. [12], which were based on the 1990 ACR classification criteria.

In a former study on systemic vasculitis, some patients classified as having polyarteritis nodosa, HV or HSP according to the 1990 ACR classification criteria also fulfilled definitions for microscopic polyangiitis when the 1994 CHCC definitions were applied [14]. In our series, the 60 patients diagnosed with SoCSVV according to the 2012 CHCC definitions also fulfilled the 1994 CHCC definitions for cutaneous leucocytoclastic angiitis and the 1990 ACR classification criteria for HV.

CV includes a wide and heterogeneous spectrum of vasculitic syndromes characterized by predominantly but not exclusively cutaneous involvement. Histologically it is characterized by a leucocytoclastic vasculitis. The term cutaneous leucocytoclastic angiitis was proposed in 1994 by the CHCC to define vasculitis affecting the skin.
without involvement of vessels in any other organs. According to the 2012 CHCC, cutaneous leucocytoclastic angiitis is included under the heading of single-organ vasculitis. This is an important issue since, due to the restrictive 2012 CHCC definitions, only a few patients with HV would fulfill the criteria to be included in the category SoCSVV.

As described for HV, the aetiology of SoCSVV is frequently unknown. Upper respiratory tract infections and drugs are the most common causes. Khetan et al. [15] reported association with drugs and infections in 20% and 11% of patients with CV, respectively. Although eventually any drug may trigger the disease, antibiotics (especially β-lactams), NSAIDs, anticonvulsants, hydralazine and allopurinol have been the most common drugs associated with CV [16]. Clinical onset after drug exposure may be abrupt, but usually ranges from 7 to 21 days. The main clinical feature of any CV, including SoCSVV, is palpable purpura. Other skin lesions such as urticaria, ulcers, nodules, vesicles, bullae or pustules may be observed.

In our series, abnormality of haematological parameters was less common in SoCSVV than in HV. This fact may reflect the absence of involvement of other organs, such as the kidneys, heart, or central nervous system.

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TABLE 1 Main features of a series of patients with SoCSVV and hypersensitivity vasculitis

<table>
<thead>
<tr>
<th></th>
<th>SoCSVV (n = 60)</th>
<th>HV (n = 250)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (s.d.), years</td>
<td>56 (16)</td>
<td>47 (25)</td>
<td>0.001</td>
</tr>
<tr>
<td>Women/men, n/n</td>
<td>26/34</td>
<td>107/143</td>
<td>0.9</td>
</tr>
</tbody>
</table>

**Aetiological agents, n (%)**

- Only infection: 6 (10) vs. 26 (10.4)
- Only drugs: 15 (25) vs. 67 (26.8)
- Infection + drug: 11 (18.3) vs. 73 (29.2)
- Unknown: 28 (46.7) vs. 84 (33.6)

**Clinical findings, n (%)**

- Skin lesions: 60 (100) vs. 250 (100)
- Palpable purpura: 49 (81.7) vs. 187 (74.8)
- Other skin lesions*: 17 (28.3) vs. 63 (25.2)
- Duration, median (IQR), days: 10 (7–20) vs. 9 (6–15)
- Joint manifestations: — vs. 102 (40.8)
- Fever: 11 (18.3) vs. 46 (18.4)
- Gastrointestinal involvement: — vs. 19 (7.6)

**Laboratory findings, n (%)**

- Urinalysis
  - Haematuria: — vs. 18 (7.2)
  - Proteinuria: — vs. 9 (3.6)
  - Haematuria + proteinuria: — vs. 23 (9.2)
  - Renal insufficiency: — vs. 19 (7.6)
- Haemoglobin, mean (s.d.), g/dl: 13.4 (2.1) vs. 12.8 (2.1)
- Leucocytes, mean (s.d.), mm³: 13009 (1082) vs. 13913 (3164)
- ESR, mean (s.d.), mm/first hour: 40.2 (22.7) vs. 46.7 (25.6)

**Immunological test, % (n cases/n tested)**

- Positive ANA: 23.9 (11/46) vs. 23.2 (39/168)
- Positive RF: 10.9 (5/46) vs. 1.2 (2/169)
- Low C3 and/ or C4: 3.7 (1/27) vs. 13.8 (15/109)
- Cryoglobulins: 18.9 (7/37) vs. 22.8 (29/127)
- Positive ANCA: 11.1 (2/18) vs. 4 (3/75)

**Treatment, n (%)**

- NSAIDs: 8 (13.3) vs. 53 (21.2)
- Corticosteroids: 9 (15) vs. 43 (17.2)
- Antihistaminic drugs: 2 (3.3) vs. 8 (3.2)
- Colchicine: 1 (1.7) vs. 4 (1.6)
- AZA: 0 (0.0) vs. 2 (0.8)
- CYC: 0 (0.0) vs. 2 (0.8)
- Relapses, n (%): 5 (8.3) vs. 32 (12.8)

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*aIncluding ulcers, blisters and maculopapular rash. bANA titres were ≤1/80 showing a homogeneous pattern on immunofluorescence. Anti-ENA and anti-DNA were negative in all the cases. cANCA were positive in only two cases. Titres were ≤1/40 by immunofluorescence. In both cases, ANCA specificity remained undetermined. SoCSVV: single-organ cutaneous small vessel vasculitis; HV: hypersensitivity vasculitis; IQR: interquartile range.
as the joints or gastrointestinal tract, in SoCSVV. Immunological tests can be negative or positive at low titres, with no differences between CV subtypes. Nevertheless, we found that positive RF was more common in patients with SoCSVV than in those with HV. This was somewhat unexpected considering its limited involvement restricted to the skin.

Skin biopsy is required to confirm the diagnosis of SoCSVV according to the 2012 CHCC definitions. Since CV may evolve quickly, it is important to perform the biopsy within the first 24 h after the onset of cutaneous lesions. Obviously, when a drug is suspected as causative agent, it should be discontinued. In most cases bed rest is sufficient to resolve the disease, although when skin lesions are extensive, low-dose corticosteroids may be necessary. NSAIDs may also be useful in some cases. As with other vasculitic syndromes, other therapies such as antihistaminic drugs, pentoxyfilline, dapsone or colchicine may be used. However, their therapeutic efficacy remains controversial. Cytotoxic agents are not usually needed in SoCSVV. Nevertheless, El-Reshaid et al. [17] recently reported two patients with cutaneous leucocytoclastic angiitis who relapsed after treatment with high-dose corticosteroids and CYC, and one of them even after taking MMF. In both cases, rituximab led to clinical improvement [17]. Although our study covered a long period of time, there was no important change in the management of SoCSVV over the period of study, as vasculitis was limited to skin and treatment was based on bed rest and corticosteroids or NSAIDs regardless of the time of diagnosis. Most SoCSVV patients have a single episode that resolves without complications within a few weeks. Only ~10% will have relapses.

In conclusion, SoCSVV according to the 2012 CHCC definitions may be considered a benign disease, generally presenting as palpable purpura and often associated with drugs and/or infections.

Rheumatology key messages

- Single-organ cutaneous small vessel vasculitis is a benign disease.
- The main clinical manifestation of cutaneous small vessel vasculitis is palpable purpura.
- Upper respiratory tract infections and the use of medication were the most common conditions associated with cutaneous small vessel vasculitis.

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