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Clinical study on single-organ cutaneous small vessels vasculitis (SoCSVV)

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Abstract

Leukocytoclastic vasculitis (LCV) is a heterogenous group of disorders that may manifest as a mild disease isolated to the skin or be a part of life-threatening systemic vasculitis. According to the 2012 Chapel Hill Consensus Conference nomenclature, patients presenting symptoms of LCV confined only to the skin should be defined as suffering from a single-organ cutaneous small vessel vasculitis (SoCSVV). SoCSVV is a benign disease with a good clinical outcome but with a significant risk of relapse and skin ulcer formation.

The aim of the current study was to characterize SoCSVV and to identify factors that may be associated with the risk of recurrence and skin ulcers.

Medical records of patients with LCV hospitalized at the Department of Dermatology at University Hospital in Cracow in the years 2010 to 2015 were analyzed.

A total of 24 patients fulfilled criteria of SoCSVV. Drugs and preceding infections were identified as precipitating factors in 40% and 20% of cases, respectively. Skin lesions other than palpable purpura (i.e., macules, urticarial vasculitis, or ulcers) were identified in almost half of the patients. Interestingly, the presence of macules independently increased the risk of skin ulcer formation (odds ratio = 16; 95% confidence interval: 1.5–176.6; $P = 0.0075$) in the multivariate logistic regression analysis. One-quarter of patients with SoCSVV experienced relapse during the 6-month follow-up. The greater number of affected skin areas was an independent risk factor of recurrence (odds ratio = 5; 95% confidence interval: 2–45; $P = 0.02$).

SoCSVV was usually associated with drugs and preceding infections. The disease relapses in approximately one-quarter of the patients. The more severe the skin involvement in the course of SoCSVV, the higher is the risk of recurrence.

Abbreviations: CHCC = Chapel Hill Consensus Conference, CRP = C-reactive protein, LCV = leukocytoclastic vasculitis, SoCSVV = single-organ cutaneous small vessel vasculitis.

Keywords: clinical features, single-organ vasculitis, skin, vasculitis

1. Introduction

Leukocytoclastic vasculitis (LCV) is a disorder characterized by skin lesions and typical histological features (i.e., neutrophilic inflammation predominantly limited to the superficial cutaneous venules, leukocytoclasia, fibrinoid necrosis, and erythrocyte extravasation into the vessel wall). The condition can be induced by a variety of causes, including drugs, infections, connective tissue diseases, and malignances.[1] However, in most cases it is idiopathic. LCV shows manifestations ranging from a mild disease isolated to the skin to the symptoms of severe systemic vasculitis.[1]

In 2012, a revised nomenclature of vasculitides was introduced at the International Chapel Hill Consensus Conference (CHCC).[2] One of the changes includes the recognition of a novel entity—"single-organ vasculitis"—for vasculitides affecting the vessels in a single organ with no features suggesting involvement of other organs. When the disease is confined to the skin, the term single-organ cutaneous small vessel vasculitis (SoCSVV) should be used.[2]

Data regarding clinical characteristics, causes, prognosis, and the rate of relapse of SoCSVV are currently lacking. Until now, only 2 studies on the SoCSVV showed that the disease seems to be a mild, self-limiting condition with a good clinical outcome. However, the authors emphasized that the relapse rate seems to be significant, sometimes causing problems in everyday clinical practice.[3,4] Moreover, some patients with palpable purpura may later develop ulcers that significantly lengthen the duration of treatment and may be further complicated by infections or scarring.

The aim of the current study was to clinically characterize the group of patients with SoCSVV, and determine factors that may influence the recurrences and ulcer formation.

2. Patients and methods

2.1. Patient population

Medical records of adult patients (aged >20 years) diagnosed with LCV and hospitalized in the Department of Dermatology at University Hospital in Cracow in the years 2010 to 2015 were

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reviewed. The study has been reviewed and approved by the Cracow University Hospital Institutional Review Board.

2.2. Clinical study and clinical definitions

Full blood cell count, coagulation, liver and renal function tests, urinalysis, erythrocyte sedimentation rate, C-reactive protein (CRP), hepatitis B, C, and HIV serology, antinuclear antibody, antineutrophil cytoplasmic antibodies, complement levels (C3, C4), streptococcal antibodies, chest radiography, abdomen ultrasound examination, stool guaiac tests, and skin biopsy were performed in all patients.

The diagnosis of SoCSVV was based on the presence of typical nonthrombocytopenic palpable purpura; a skin biopsy showing characteristic histological findings such as neutrophilic inflammation, leukocytoclasia, fibrin deposits, and erythrocyte extravasation into the vessel wall; and no signs, symptoms, and laboratory findings consistent with involvement of other than skin organs. Other than palpable purpura lesions on the skin, were diagnosed by the board certified-dermatologist. There were macules (flat, nonpalpable, circumscribed, red lesions), ulcers (a deep defect of the skin, with loss of at least the entire epidermis plus superficial dermis), and urticarial vasculitis (urticarial plaques lasting >24 hours with neutrophils infiltrating vessels' walls in histopathological examination).

A drug or infection process (usually an upper respiratory tract infection) was considered as the probable precipitating event if it was taken or occurred within a week before the onset of the skin lesions. When a patient developed SoCSVV after antibiotic or symptomatic treatment for a mild infection, both the infection and the drug were considered as possible precipitating events.

2.3. Data collection and statistical analysis

Clinical and laboratory data were extracted from patients' clinical records according to a specifically designed protocol, reviewed to confirm the diagnosis, and stored in a computerized file. To minimize entry error, all data were double-checked. Statistical analysis was performed with the STATISTICA 7.1 PL software package (StatSoft Inc, Tulsa, OK). If not stated otherwise, data were expressed as median and minimum–maximum values. Continuous variables were compared with the Mann–Whitney U test. The χ^2 test or the Fisher exact test was used for the dichotomous variables. To identify independent factors, a multivariate logistic regression analysis was used. A P value <0.05 was considered statistically significant.

3. Results

Among 30 patients with LCV, 24 fulfilled criteria of SoCSVV. Palpable purpura was present in all patients. However, other skin lesions were also found: red macules, urticarial vasculitis, and ulcers (Table 1). With regard to potential precipitating factors, a history of drugs and preceding infection was identified in almost half of the patients (Table 1). All patients were negative for hepatitis B, C, and HIV serology. In none of individuals were identified either antinuclear antibodies or antineutrophil cytoplasmic antibodies. In all patients complement levels were in normal range.

The clinical outcome in all patients was good. Symptoms resolved in almost 80% of individuals. Among all the included patients, 9 (37.5%) were treated with systemic steroids. When compared to those with supportive treatment only, they had significantly higher white blood cell count and CRP levels (9 vs. $7.12\times10^3/\mu$L, 11.8 vs. 7.25 mg/dL, respectively; $P<0.05$). Interestingly, there were no significant differences found between group treated and not with systemic steroids with respect to the type of skin lesions, number of affected body skin areas, and other clinical and laboratory results (data not shown).

After a median follow-up of 6 months, relapses occurred in 25% of patients with SoCSVV. Clinical course of relapse was similar to that observed at the first episode (regarding the type and localization of skin lesions and blood laboratory findings). We did not find any association between relapses and the type of treatment (i.e., antibiotics and/or steroids). Interestingly, however, patients with a higher number of affected skin areas at the first episode were at a higher risk of relapse (odds ratio = 5; 95% confidence interval: 2–45; $P=0.02$).

Occurrence of skin ulcers significantly lengthens the hospitalization time ($P<0.05$). Skin ulcers were positively correlated with red macules, higher number of localizations, and longer duration of skin lesions before admission to the hospital ($P<0.05$). The multivariate logistic regression analysis revealed that macules independently increased the risk of skin ulcers (odds ratio = 16; 95% confidence interval: 1.5–176.6; $P=0.0075$).

Table 1

Characteristics of patients with single-organ cutaneous small-vessel vasculitis (SoCSVV; n = 24).

Age, y (minimum–maximum)	50 (18–83)
Women, n (%)	11 (45.8)
Diabetes, n (%)	3 (12.5)
Skin lesions	
Palpable purpura, n (%)	24 (100)
Red macules, n (%)	8 (33.3)
Urticarial vasculitis, n (%)	1 (4.2)
Ulcers, n (%)	4 (16.7)
Localization of skin lesions	
Lower limbs, n (%)	24 (100)
Upper limbs, n (%)	8 (33.3)
Trunk, n (%)	4 (16.7)
Duration, d (minimum–maximum)	21 (1–600)
Blood laboratory findings	
WBC, $\times10^3\,\mu L^{-1}$ (minimum–maximum)	7.2 (3.6–30.7)
Neutrophils, $\times10^3\,\mu L^{-1}$ (minimum–maximum)	4.0 (1.8–22.0)
Lymphocytes, $\times10^3\,\mu L^{-1}$ (minimum–maximum)	2.4 (1.3–5.2)
Eosinophils, $\times10^3\,\mu L^{-1}$ (minimum–maximum)	0.2 (0.07–0.62)
CRP, mg/dL (minimum–maximum)	11.8 (5.0–77.4)
PLT, $\times10^3\,\mu L^{-1}$ (minimum–maximum)	221 (174–413)
aPTT, s (minimum–maximum)	29.6 (22–34.9)
INR (minimum–maximum)	1.1 (1.03–1.3)
Creatinine, μmol/L (minimum–maximum)	72 (48–106)
ALT, IU/L (minimum–maximum)	25 (15–87)
AST, IU/L (minimum–maximum)	27 (13–54)
Cause	
Infection, n (%)	8 (33.3)
Drugs, n (%)	4 (16.7)
Infections + drugs, n (%)	1 (4.2)
Treatment	
GCS, n (%)	9 (37.5)
Antibiotics, n (%)	8 (33.3)
Relapses, n (%)	6 (25)

Data are presented as median (minimum–maximum) or otherwise stated. ALT = alanine aminotransferase, aPTT = activated partial thromboplastin time, AST = aspartate aminotransferase, CRP = C-reactive protein, GCS = glucocorticoids, INR = international normalized ratio, PLT = platelets, WBC = white blood cell count.

4. Discussion

Following the 2012 CHCC definitions, SoCSVV is considered a vasculitis affecting the skin without the involvement of the vessels in any other organ. Therefore, only a few patients with LCV would fulfill the SoCSVV criteria.[2]

SoCSVV is usually a benign disease with a good clinical outcome. However, our observations indicate that it frequently relapses, increasing healthcare costs and patients' concerns. In the current study, we have shown clinical characteristics of patients with SoCSVV with special emphasis on the identification of factors related to their recurrence.

The etiology of SoCSVV is unknown. Recently, it has been shown that drugs and mild infections such as upper respiratory tract infections are responsible for 25% and 10% of SoCSVV, respectively.[3,4] In our study these frequencies were a little different with more infections (33.3%) than drugs (16.7%) as causal agents of SoCSVV.

The main clinical feature of every LCV, including SoCSVV, is palpable purpura. However, other skin lesions, such as red macules, urticaria vasculitis, and ulcers, may be observed.[3,4] In our series, red macules were identified as the second most common clinical finding in patients with SoCSVV. Interestingly, in a multivariate logistic regression analysis, we identified macules as an independent factor of ulcers' occurrence in the course of vasculitis. Further studies are needed to establish whether early and more aggressive treatment (systemic steroids) in individuals with macules and SoCSVV may prevent ulcer formation.

Most SoCSVV patients have a single episode that resolves within a few weeks. However, in some patients relapses occur. In our study, the frequency of recurrence has been assessed at 25%, higher than previously reported (~10%).[3]

In almost all cases of SoCSVV palpable purpura is localized on the lower extremities. In one-third of our patients we found skin lesions also on the upper limbs, and almost one-fifth had them on the trunk. Interestingly, a higher number of affected skin areas were strongly associated with the risk of relapse. We may only hypothesize that the higher number of sites with skin involvement may reflect a more advanced disease with more pronounced levels of circulating immune complexes and antibodies. However, we could not find any correlation between the number of sites involved and the levels of serum inflammatory markers measured.

Finally, we tried to asses factors that may have influenced the method of treatment of SoCSVV (supportive treatment vs. systemic steroids). In both such defined groups, we did not find any differences in clinical features. However, patients treated with steroids had higher white blood cell count and CRP levels. This was certainly not the only reason to opt for systemic steroid therapy. Presumably, the therapeutic decisions were based rather on the individual experience of the physician.

One of the most important limitations of this study is a small number of patients. The incidence of LCV is unknown, but the disorder is presumed to be uncommon. Thus, there is a need for multicentered studies or meta-analysis including small studies (such as ours). Second, according to the study protocol, only hospitalized patients were included in the study. It could cause a selection bias due to the recruitment of mostly more severe cases.

In conclusion, according to the 2012 CHCC definitions, SoCSVV should be differentiated from other LCV. SoCSVV is a benign form of vasculitis confined to the skin. Careful clinical and laboratory assessment is highly recommended in every patient presenting with the skin manifestations of LCV (i.e., palpable purpura) to exclude systemic involvement. In systemic vasculitis prognosis and treatment substantially differ. SoCSVV is commonly associated with drugs and/or infections with a risk of ulcer formation and relapses. The risk of recurrences seems to be correlated with a higher number of affected skin sites. Macules as additional skin findings in patients with SoCSVV may be the prognostic factor of ulcer formation that may occur in the course of vasculitis.

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