EVALUATION OF CLINICOPATHOLOGICAL CHARACTERISTICS IN SINGLE-ORGAN CUTANEOUS SMALL VESSEL VASCULITIS
SINGLE-ORGAN CUTANEOUS SMALL VESSEL VASCULITIS

TEK-ORGAN KUTANÖZ KÜÇÜK DAMAR VASKÜLİTİNİN KLİNİKOPATOLOJİK ÖZELLİKLERİNİN DEĞERLENDİRİLMESİ
TEK-ORGAN KUTANÖZ KÜÇÜK DAMAR VASKÜLİTİ

Erkan DAVARCI[1], Fatma Sule AVSAR[2], Nuket OZKAVRUK ELIYATKIN[*3]

[1]Izmir Katip Celebi University, Izmir Atatürk Training and Research Hospital, Dermatology Department, Izmir, Türkiye. e-mail: drerkandavarci@gmail.com
[2]Izmir Katip Celebi University, Izmir Atatürk Training and Research Hospital, Dermatology Department, Izmir, Türkiye. e-mail: suleafsar@hotmail.com
[*3] Izmir Katip Celebi University, Faculty of Medicine, Izmir Atatürk Training and Research Hospital, Pathology Department, Izmir, Türkiye. e-mail: nuket.ozkavruk.eliyatkin@ikcu.edu.tr

ORCID ID: ED: 0000-0002-7156-0406 **FSA:** 0000-0002-9103-2782 **NOE:** 0000-0002-7784-5699

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ABSTRACT

Objective: Cutaneous vasculitis includes a wide and heterogeneous spectrum of vasculitic syndromes characterized by inflammation of skin blood vessels. When the disease is confined to the skin, the term single-organ cutaneous small vessel vasculitis is used. Data regarding this entity is limited. This study aims to retrospectively evaluate the clinicopathological characteristics of patients who were diagnosed with single-organ cutaneous small vessel vasculitis retrospectively.

Material and Methods: One hundred eight patients were included in the study. Demographic characteristics, clinical features, laboratory findings, etiological factors, treatment modalities, and prognoses of 108 patients were evaluated. Biopsy specimens of patients were re-evaluated histopathologically.

Results: Most frequently acral involvement, and palpable purpura were observed in 82.4% of the patients. Clinical presentation was acute in 80 (74.1%) patients and relapse was seen in 24 (23.1%) patients. Relapse and ulcerative lesions were observed more frequently in chronic patients. The mean age was found to be lower in relapsing patients. Etiology was idiopathic in 75% of the patients. The elevation of CRP was significant in patients with severe fibrinoid necrosis and subcutaneous tissue involvement. Treatment option with topical corticosteroids and nonsteroidal anti-inflammatory drugs (54,3%) was the most common type. The clinical and histopathological features were found to have no effect on relapse, but treatment type was associated with relapse.

Conclusion: There are few studies on single organ cutaneous small vessel vasculitis. Results were similar to the features of the other studies. Further studies in which clinical and histopathological features will be evaluated together are needed.

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ÖZET

Amaç: Kutanöz vaskülit, deri kan damarlarının enflamasyonu ile karakterize geniş ve heterojen bir vaskülitik sendrom spektrumunu içerir. Hastalık deriyle sınırlı olduğunda, tek organlı kutanöz küçük damar vasküliti terimi kullanılır. Bu antiteye ilişkin veriler sınırlıdır. Bu çalışmada tek organlı kutanöz küçük damar vasküliti tanısı alan hastaların klinikopatolojik özelliklerinin retrospektif olarak değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntemler: Yüz sekiz hasta çalışmaya dahil edildi. Hastaların demografik özellikleri, klinik özellikleri, laboratuvar bulguları, etiyolojik faktörleri, tedavi modaliteleri ve prognozları değerlendirildi. Hastaların biyopsi örnekleri histopatolojik olarak yeniden değerlendirildi.

Bulgular: Hastaların %82,4'ünde akral tutulum mevcuttu. Palpabl purpura (%82,4) en sık görülen deri lezyonuydu. Klinik prezentasyon 80 (%74,1) hastada akut iken, 24 (%23,1) hastada nüks görüldü. Kronik hastalarda nüks ve ülseratif lezyonlar daha sık gözlendi. Nüks eden hastalarda yaş ortalaması daha düşük bulundu. Hastaların %75'inde etiyoloji idiyopatikti. CRP yüksekliği şiddetli fibrinoid nekroz ve subkutan doku tutulumu olan hastalarda anlamlıydı. Topikal kortikosteroidler ve nonsteroid antiinflamatuvar ilaçlarla tedavi seçeneği (%54,3) en yaygın tipti. Klinik ve histopatolojik özelliklerin nüks üzerinde etkisi olmadığı, ancak tedavi tipinin nüks ile ilişkili olduğu bulunmuştur.

Sonuç: Tek organ kutanöz küçük damar vasküliti ile ilgili az sayıda çalışma vardır. Sonuçlar diğer çalışmaların özelliklerine benzerdi. Klinik ve histopatolojik özelliklerin birlikte değerlendirileceği ileri çalışmalara ihtiyaç vardır.

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Correspondence to: Nuket Ozkavruk Eliyatkin Izmir Katip Celebi University, Faculty of Medicine, Department of Pathology, Izmir, Turkey
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Ethical Approval: The study was approved by the Ethics Committee of Izmir Ataturk Training and Research Hospital and adhered to the principles of the Declaration of Helsinki (2020GOKAE-0374) on 17 September 2020

Introduction

Cutaneous vasculitis is an inflammatory disease affecting the dermal blood vessel walls. The skin, as the organ primarily involved in vasculitis, facilitates physical examination and safe biopsy, thus allowing accurate identification of inflammatory lesions of the cutaneous vasculature. Cutaneous vasculitis may present clinically as cutaneous component of vasculitis, the cutaneous limited component of systemic vasculitis or the cutaneous predominant expression or single organ vasculitis alone. Multiple and polymorphic vasculitis lesions have a wide spectrum of clinical manifestations depending on the location and size of the blood vessels involved. The type of inflammatory infiltration is also a key finding in the diagnosis of cutaneous vasculitis (1).

In 2012, the International Chapel Hill Consensus Conference (CHCC) defined single-organ vasculitis affecting arteries or veins of any size in only a single organ without systemic involvement. If the vasculitis is limited to the skin, the term single-organ cutaneous small vessel vasculitis (SoCSVV) was adopted. The presence of characteristic leukocytoclastic vasculitis (LCV) on biopsy and vasculitis confined to the skin were stated as the diagnostic criteria for (SoCSVV) (2).

There are limited number of studies on SoCSVV in the literature (3-5). Although the disease is a self-limiting condition with good clinical outcomes, significantly higher relapse rates and challenges in its treatment may be experienced due to complications encountered during daily clinical practice (6). In our study, we aimed to screen and clinicopathologically evaluate patients diagnosed with cutaneous vasculitis in terms of additional systemic involvement and to investigate clinical and histopathologic features, etiologic factors, treatment modalities and prognosis of the patients who fulfilled the diagnostic criteria of SoCSVV.

Materials and Methods

Patient population

In this study, patients diagnosed with vasculitis based on histopathological examination of their skin biopsy specimens in the Dermatology Clinic of IKCU Atatürk Training and Research Hospital between 2006 and 2020 were analyzed. Clinical and laboratory data of the patients were retrieved retrospectively from patient files and electronic medical records.

Skin biopsy specimens of these patients stored in the pathology archive were re-evaluated by a pathologist, and patients diagnosed with LCV were evaluated once more in terms of clinical features and systemic involvement elaborated below. LCV was defined as neutrophil infiltration in the vessel wall, swelling of endothelial cells, erythrocyte extravasation and fibrinoid necrosis and nuclear dust (dust), which are characteristic findings in skin biopsy (7). In 2012, patients in the group defined as SoCSVV without other organ involvement, which was accepted in CHCC, constituted the population of the study.

Clinical and laboratory definitions

A total of 108 patients diagnosed with SoCSVV were evaluated in terms of age, gender, type of skin lesions (palpable purpura, ulcerative lesion, palpable purpura+non-palpable purpura, palpable purpura+vesicle/bulla), area involved (acral, generalized), clinical presentation (acute, chronic), etiological factors (idiopathic, drug, infection, drug+infection), treatment modalities and prognosis (complete remission, relapse). Single episodes lasting less than three months were considered acute, prolonged disease course lasting longer than three

months or recurrent episodes at least twice in a period exceeding three months were considered chronic SoCSVV. Relapses were defined as recurrence of vasculitis symptoms following a remission period of more than one month.

Complete blood counts, results of liver, kidney function, fecal occult blood tests, hepatitis B, hepatitis C and HIV serologies, levels of antinuclear antibody (ANA), serum complement, anti-neutrophil cytoplasmic antibodes (p-ANCA, and c-ANCA), rheumatoid factor (RF), and chest X-ray findings of the patients were re-evaluated in terms of the presence of systemic involvement. Inflammation markers of patients diagnosed with SoCSVV as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were also evaluated.

Skin biopsy specimens were evaluated histopathologically for the presence of neutrophilic infiltration in the vessel wall, swelling of endothelial cells, erythrocyte extravasation and fibrinoid necrosis (fibrin deposition in the vessel wall), nuclear dust, leukocytoclasia, perivascular cell infiltration, ulcer-necrosis, granuloma, endothelial change and subcutaneous tissue involvement which are characteristic diagnostic features of LCV (7).

Statistical analysis

Statistical analysis of the data was performed using SPSS 22.0 program. Chi-square test was used to reveal the differences between nominal and ordinal variables, Mann-Whitney U and Wilcoxon tests were used to examine the differences between independent variables, and Student-t test was used to evaluate numerical variables with normal distribution characteristics. Logistic regression test was used for prognostic and predictive factors. P values of 0.05 and below were considered statistically significant.

Results

A total of 108 patients with a mean age of 52.21±19.98 years including 58 (53.7%) female, and 50 (46.3%) male cases (female/male: 1.16) among 728 patients diagnosed with vasculitis based on their clinical features and histopathological examination findings of their skin biopsy specimens archived between 2006 and 2020 and re-evaluated according to International CHCC criteria, received the diagnosis of SoCSVV. The flow chart of the study is shown in Figure 1.

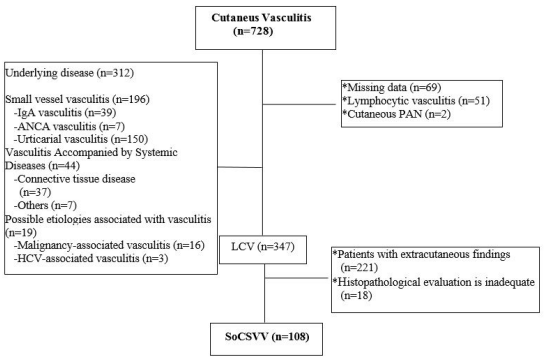

Figure 1. *The flow chart of the study.*

The distribution of the patients in terms of involved area, skin lesions, clinical presentation and prognosis is shown in Table 1.

Table 1. *Distribution of patients with SoCSVV in terms of affected area, skin lesions, clinical presentation and prognosis.*

	n	%
Affected area	108	100
Acral	89	82,4
Generalized	19	17,6
Skin lesions	108	100
Palpable purpura	89	82,4
Ulcerative lesion	10	9,3
Palpable purpura + non-palpable purpura	5	4,6
Palpable purpura + vesicle/bulla	4	3,7
Clinical presentation	108	100
Acute	80	74,1
Chronic	28	25,9
Prognosis	104	100
Relapse	24	23,1
Complete remission	80	76,9

Biopsy specimens of 108 patients diagnosed with SoCSSV were evaluated for histopathologic features of LCV such as neutrophils in the vessel wall, fibrinoid necrosis (Figure 2), nuclear dust (Figure 3), erythrocyte extravasation (Figure 4) and severity of these features. In addition, perivascular cell infiltration (Figure 5), ulcer-necrosis, granuloma, endothelial change (Figure 2), and involvement of subcutaneous tissue (Figure 6) were included in the histopathologic evaluation. Granuloma was not detected in any patient.

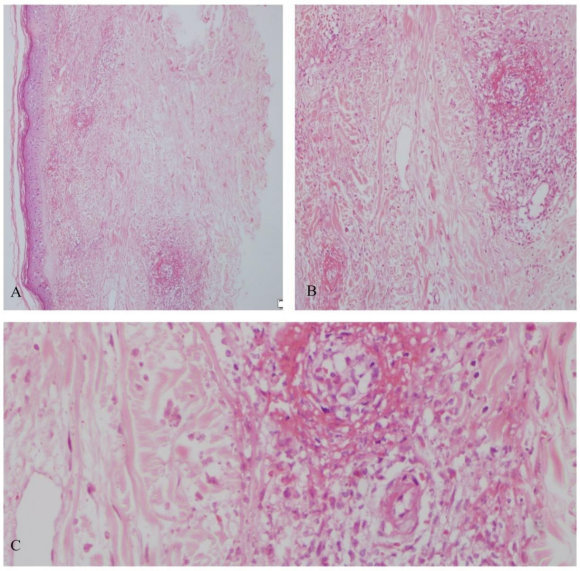

Figure 2. *(A) Fibrinoid necrosis (Hematoxylin-Eosin x 100), (B) Fibrinoid necrosis (Hematoxylin-Eosin x 200), (C) Fibrinoid necrosis and endothelial shedding and swelling (Hematoxylin-Eosin x 400).*

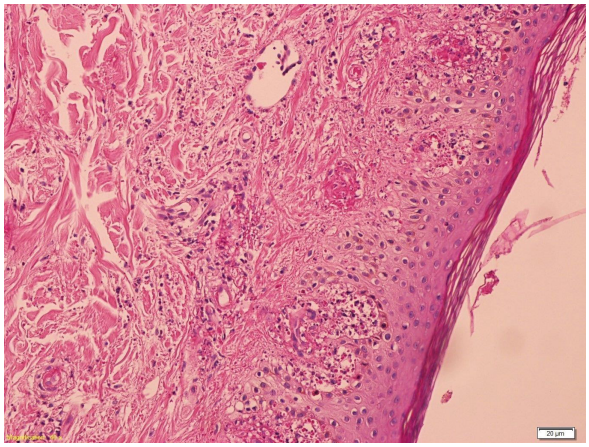

Figure 3. *Fibrinoid necrosis and nuclear dust (Hematoxylin-Eosin x 200).*

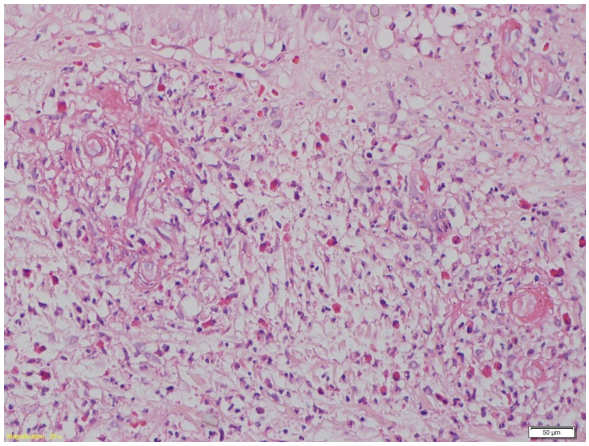

Figure 4. *Erythrocyte extravasation, neutrophil+eosinophil infiltration and fibrinoid necrosis (Hematoxylin-Eosin x 400).*

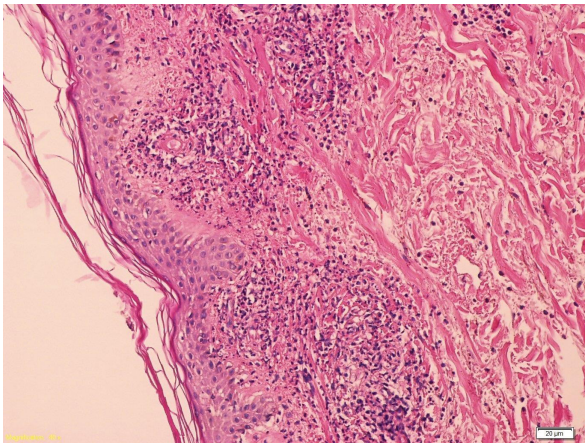

Figure 5. *Perivascular cell infiltration and nuclear dust (Hematoxylin-Eosin x 200).*

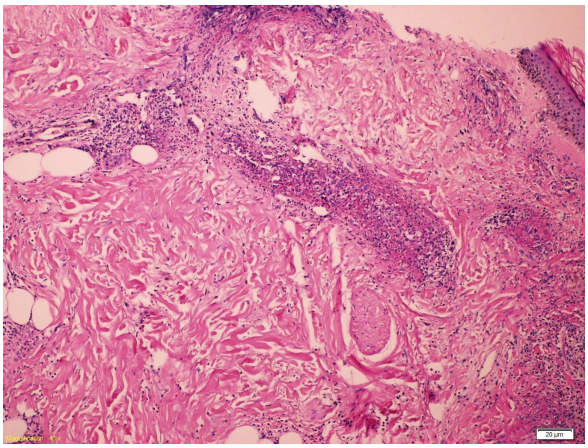

Figure 6. *Polymorphonuclear cell infiltration and fibrinoid necrosis including subcutaneous tissue involvement (Hematoxylin-Eosin x 100).*

The comparison of clinical and histopathologic features according to acute and chronic presentation of vasculitis in 108 patients with SoCSSV is shown in table 2. Clinical characteristics (gender, area involved, type of skin lesions, etiologic factors, prognosis) and histopathologic features (neutrophil infiltration in the vessel wall, fibrinoid necrosis, nuclear dust, erythrocyte extravasation, perivascular cell infiltration, endothelial change, level of involvement) in terms of acute and chronic presentation of vasculitis, a statistically significant difference was found between acute and chronic cases in terms of type of skin lesions and prognosis ($p<0.05$). While ulcerative lesions were less common in acute cases compared to chronic cases, complete remission rates were significantly higher than chronic cases. No statistically significant difference was found between the other groups compared.

Table 2. *Comparison of clinical and histopathological features in patients with SoCSSV according to acute and chronic presentation of vasculitis.*

		Clinical presentation				χ2	p
		Acute		Chronic			
		n	%	n	%		
Gender	Female	45	56,3	13	46,4	0,805	0,370
	Male	35	43,8	15	53,6		
Affected area	Acral	65	81,3	24	85,7	0,285	0,775
	Generalized	15	18,8	4	14,3		
Skin lesions	Palpable purpura	69	86,3	20	71,4		
	Ulcerative lesion	3	3,8	7	25,0		
	Palpable purpura + Non-palpable purpura	4	5,0	1	3,6	10,021	0,009
	Palpable purpura + vesicle/bulla	4	5,0	-	-		
Palpable purpura	No	11	13,8	8	28,6	3,143	0,089
	Yes	69	86,3	20	71,4		
Ulcerative lesion	No	77	96,3	21	75,0	11,147	0,003
	Yes	3	3,8	7	25,0		
Palpable purpura + non-palpable purpura	No	76	95,0	27	96,4	0,096	1,000
	Yes	4	5,0	1	3,6		
Palpable purpura + vesicle/bulla	No	76	95,0	28	100,0	1,454	0,571
	Yes	4	5,0	-	-		
Etiology	Idiopathic	57	71,3	24	85,7		
	Drug	14	17,5	2	7,1	2,440	0,568
	Infection	4	5,0	1	3,6		
	Drug&infection	5	6,3	1	3,6		
Prognosis	Complete remission	76	97,4	4	15,4	73,956	<0,001
	Relapse	2	2,6	22	84,6		
Neutrophils in the vascular wall	Mild-Moderate	40	50,0	12	42,9	0,424	0,515
	Severe	40	50,0	16	57,1		
Fibrinoid necrosis	Mild-Moderate	40	50,0	12	42,9	0,424	0,515
	Severe	40	50,0	16	57,1		
Nuclear dust	Mild-Moderate	32	40,0	13	46,4	0,353	0,553
	Severe	48	60,0	15	53,6		
Erythrocyte extravasation	Mild-Moderate	48	60,0	14	50,0	0,848	0,357
	Severe	32	40,0	14	50,0		
Perivascular cell infiltration	Neutrophil+less eosinophil or neutrophil+eosinophil	18	22,5	6	21,4		
	Neutrophil or eosinophil or lymphocyte or neutrophil+lymphocyte or mixt	62	77,5	22	78,6	0,014	0,907
Endothelial change	No	11	13,8	4	14,3		
	Shedding	7	8,8	2	7,1		
	Swelling	34	42,5	14	50,0	3,854	0,399
	Shedding+Swelling	27	33,8	6	21,4		
	Uncertain	1	1,3	2	7,1		
Involvement of the subcutaneous tissue	No	29	47,5	10	47,6	<0,001	0,995
	Yes	32	52,5	11	52,4		

Pearson Chi-Square, Fisher's Exact test

The comparison of clinical features, treatment modalities and histopathological features in 108 patients with SoCSSV in terms of CRP elevation is shown in table 3. When the mean age distribution of the patients evaluated as SoCSVV was statistically compared in terms of gender, clinical presentation, area of involvement, type of skin lesions and etiologic factors, the age of patients with complete remission according to prognosis was significantly higher than the age of patients with relapse ($p<0.05$). No statistically significant difference was found between the other groups compared. CRP elevation among inflammatory markers, clinical features of SoCSVV (gender, clinical presentation, area involved, type of skin lesions, etiologic factors, prognosis), preferred treatment modalities and histopathologic features (neutrophil infiltration in the vessel wall, fibrinoid necrosis, nuclear dust, erythrocyte extravasation, perivascular cell infiltration, endothelial change, involvement level), there was a statistically significant difference between treatment modalities and histopathologic features of fibrinoid necrosis and involvement level ($p<0.05$). When treatment modalities were compared in pairs, CRP elevation was statistically significant in colchicine and systemic corticosteroid treatment, topical corticosteroid and NSAID treatment and topical corticosteroid and systemic corticosteroid treatment. In patients with histopathologically severe fibrinoid necrosis, there was a statistically significant CRP elevation compared to those with moderate to mild fibrinoid necrosis. CRP elevation was statistically significant in patients with subcutaneous tissue involvement compared to patients without subcutaneous tissue involvement. No statistically significant difference was found between the other groups compared (Table 3).

Table 3. *Comparison of clinical features, treatment modalities and histopathological features in patients with SoCSSV in terms of CRP elevation.*

		CRP				χ^2	p
		Normal		High			
		n	%		%		
Gender	Female	17	53,1	36	54,5	0,018	0,895
	Male	15	46,9	30	45,5		
Clinical presentation	Acute	22	68,8	51	77,3	0,824	0,364
	Kronik	10	31,3	15	22,7		
Affected area	Akral	29	90,6	54	81,8	1,289	0,256
	Generalize	3	9,4	12	18,2		
Skin lesions	Palpable purpura	30	93,8	55	83,3		
	Ulcerative Lesion	1	3,1	6	9,1	3,205	0,355
	Palpable purpura + Non-palpable purpura	1	3,1	1	1,5		
	Palpable purpura + Vesicle/bulla	0	0,0	4	6,1		
Etiology	Idiopathic	24	75,0	50	75,8		
	Drug	4	12,5	9	13,6	0,456	1,000
	Infection	2	6,3	3	4,5		
	Drug&Infection	2	6,3	4	6,1		
Treatment	Topical Corticosteroid + NSAID	17	54,8	38	57,6		
	Topical Corticosteroid + Colchicine	3	9,7	3	4,5		
	Topical Corticosteroid + Systemic Corticosteroid	5	16,1	23	34,8	9,732	0,013
	Colchicine + Systemic Corticosteroid	6	19,4	2	3,0		

Paired Matching in Treatment	Topical Corticosteroid + NSAID *vs* Topical Corticosteroid +Colchicine						0,384
	Topical Corticosteroid+NSAID *vs* Topical Corticosteroid+Systemic Corticosteroid						0,294
	Colchicine+Systemic Corticosteroid						0,043
	Topical Corticosteroid + Colchicine vs Topical Corticosteroid + Systemic Corticosteroid						0,126
	Topical Corticosteroid + Colchicine vs Colchicine+Systemic Corticosteroid						0,0580
	Topical Corticosteroid + Systemic Corticosteroid vs Colchicine + Systemic Corticosteroid						0,005
Prognosis	Complete remission	22	71,0	52	81,3	1,282	0,257
	Relapse	9	29,0	12	18,8		
Neutrophils in the vascular wall	Mild-Moderate	13	40,6	31	47,0	0,351	0,554
	Severe	19	59,4	35	53,0		
Fibrinoid necrosis	Mild-Moderate	20	62,5	26	39,4	4,620	0,032
	Severe	12	37,5	40	60,6		
Nuclear dust	Mild-Moderate	12	37,5	27	40,9	0,105	0,746
	Severe	20	62,5	39	59,1		
Erythrocyte extravasation	Mild-Moderate	18	56,3	36	54,5	0,025	0,874
	Severe	14	43,8	30	45,5		
Perivascular cell infiltration	Neutrophil+less osinophil or neutrophil+ eosinophil	10	31,3	13	19,7	1,601	0,206
	Neutrophil or eosinophil or lymphocyte or neutrophil+lymphocyte or mixt	22	68,8	53	80,3		
Endotelial change	No	4	12,5	8	12,1		
	Shedding	1	3,1	6	9,1		
	Swelling	17	53,1	29	43,9	1,599	0,866
	Shedding+Swelling	9	28,1	21	31,8		
	Uncertain	1	3,1	2	3		
Involvement of the subcutaneous tissue	No	15	62,5	18	36,7	4,317	0,038
	Yes	9	37,5	31	63,3		

Pearson Chi-Square, Fisher's Exact test

For direct immunofluorescence (DIF) examination, 38 (35.1%) of one hundred and eight patients were sampled and only 5 (13.1%) of them were positive. Two (40%) patients had isolated IgG positivity, one (20%) patient had isolated C3 positivity, and two (40%) patients had IgG and C3 positivity.

Since cutaneous biopsy specimens of twenty-six (24.08%) patients did not include subcutaneous tissue, when the relationship between subcutaneous tissue involvement and area of involvement, type of skin lesions, etiologic factors and prognosis was investigated in 82 (75.92%) SoCSVV patients, a statistically significant difference was found in terms of the type of skin lesions ($p<0.05$). Histopathologically, the frequency of ulcerative lesions in patients with subcutaneous tissue involvement was statistically significantly higher than in patients without subcutaneous tissue involvement, while the frequency of palpable purpura in patients without subcutaneous tissue involvement was statistically significantly higher than in patients with subcutaneous tissue involvement. No statistically significant difference was found between the other groups compared (Table 4).

Table 4. *Relationship between subcutaneous tissue involvement and the area of involvement, type of skin lesions, etiological factors and prognosis in patients with SoCSVV.*

		Involvement of the subcutaneous tissue				X^2	p
		No		Yes			
		n	%	n	%		
Affected area	Acral	30	76,9	38	88,4	1,893	0,169
	Generalized	9	23,1	5	11,6		
Skin lesion	Palpable purpura	36	92,3	32	74,4		
	Ulcerative lesion	-	-	8	18,6		
	Palpable purpura + non- palpable purpura	3	7,7	1	2,3	11,169	0,003
	Palpable purpura + vesicle/bulla	-	-	2	4,7		
Palpable purpura	No	3	7,7	11	25,6	4,623	0,032
	Yes	36	92,3	32	74,4		
Ulcerative lesion	No	39	100,0	35	81,4	8,040	0,006
	Yes	-	-	8	18,6		
Palpable purpura + non-palpable purpura	No	36	92,3	42	97,7	1,269	0,342
	Yes	3	7,7	1	2,3		
Palpable purpura + vesicle/bulla	No	39	100,0	41	95,3	1,859	0,495
	Yes	-	-	2	4,7		
Etiology	Idiopathic	26	66,7	35	81,4		
	Drug	10	25,6	3	7,0	5,497	0,126
	Infection	2	5,1	3	7,0		
	Drug&infection	1	2,6	2	4,7		
Prognosis	Complete remission	27	73,0	33	80,5	0,619	0,432
	Relapse	10	27,0	8	19,5		

Pearson Chi-Square, Fisher's Exact test

When the relationship between the type of skin lesions in patients with SoCSVV and gender, etiologic factors, treatment options and prognosis was investigated, no statistically significant difference was found between the groups. One hundred and eight patients with SoCSVV were treated in 105 patients (97.2%). When the treatment modalities of the treated patients were compared in terms of area of involvement, type of skin lesions, etiologic factors and clinical presentation of vasculitis, a statistically significant difference was found between the treatment modalities in terms of clinical presentation ($p<0.05$). The rate of chronic presentation was significantly higher in patients given topical corticosteroids and NSAIDs than in patients given topical corticosteroids and colchicine, topical corticosteroids and systemic corticosteroids, and colchicine and systemic corticosteroids. No statistically significant difference was found between the other groups compared (Table 5). When gender, area of involvement, type of skin lesions, etiologic factors, ESR elevation, CRP elevation, treatment modalities and histopathologic features that may affect prognosis in patients with SoCSVV were evaluated by single logistic regression analysis, topical corticosteroids and NSAIDs, topical corticosteroids and colchicine, and colchicine and systemic corticosteroids were found to be statistically significant for relapse ($p<0.05$).

Table 5. *Comparison of treatment modalities in patients with SoCSVV in terms of area of involvement, type of skin lesions, etiological factors and clinical presentation.*

		Treatment								X^2	p
		Topical Corticosteroid + NSAID		Topical Corticosteroid + Colchicine		Topical Corticosteroid +Systemic Corticosteroid		Colchicine +Systemic Corticosteroid			
		n	%	n	%	n	%	n	%		
Affected area	Acral	50	87,7	6	85,7	25	75,8	6	75	2,856	0,390
	Generalized	7	12,3	1	14,3	8	24,2	2	25		
Skin lesions	Palpable purpura	49	86	4	57,1	26	78,8	8	100		
	Ulcerative lesion	2	3,5	2	28,6	6	18,2	-	-		
	Palpable purpura + non-palpable purpura	2	3,5	1	14,3	1	3	-	-	13,214	0,071
	Palpable purpura + vesicle/bulla	4	7	-	-	-	-	-	-		
Etiology	Idiopathic	39	68,4	6	85,7	25	75,8	8	100		
	Drug	10	17,5	1	14,3	5	15,2	-	-	3,694	0,937
	Infection	3	5,3	-	-	2	6,1	-	-		
	Drug&infection	5	8,8	-	-	1	3	-	-		
Clinical presentation of vasculitis	Acute	50	87,7	3	42,9	23	69,7	3	37,5	14,702	0,001
	Chronic	7	12,3	4	57,1	10	30,3	5	62,5		
	Acute	50	87,7	3	42,9					0,014	
	Chronic	7	12,3	4	57,1						
	Acute	50	87,7	10		23	69,7			0,035	
	Chronic	7	12,3			30,3					
	Acute	50	87,7			5	62,5	3	37,5	0,004	
	Chronic	7	12,3								
	Acute	4		3	42,9	23	69,7			0,214	
	Chronic			57,1	10	30,3					
	Acute	4		3	42,9	5	62,5	3	37,5	1,000	
	Chronic			57,1							
	Acute			10	30,3	23	69,7	3	37,5	0,117	
	Chronic					5	62,5				

Fisher's exact test

Discussion

Defined in the 2012 CHCC, SoCSVV is considered a vasculitis affecting the skin without involvement of vessels in any other organ. Therefore, few patients with LCV may fulfill the SoCSVV criteria (2). SoCSVV usually presents with a good clinical picture and the prognosis is mild. Although less frequent, the fact that the disease may progress with relapses may lead to increased costs and patient concerns (6).

Since SoCSVV has been defined relatively recently, epidemiologic and clinical data are limited. In our retrospective study, the mean age of patients with SoCSVV was 52.21±19.98 years and a slight female predominance was found. In studies conducted with patients with SoCSVV, the mean age was found to be 66.9, 50 and 56 years, with a slight female predominance in only one study (6, 8-9). In a study on LCV including 75 patients in Türkiye, the mean age was found to be 43.5 years (10). In a more

comprehensive review, the mean age in cutaneous vasculitis was reported to be 47 years (11). In a study in which patients with SoCSVV were compared with the LCV patient group, the mean age of the patient group with SoCSVV was found to be higher (9). When evaluated together with the clinical characteristics, the mean age of the patients who were found to have complete remission in our study was higher than the patients who showed relapse and it was thought that the possibility of relapse was higher in younger patients with SoCSVV.

When the distribution of skin lesions was examined, nearly all patients had lower extremity involvement. Consistent with our study, Bouiller et al. reported acral involvement in 79.3% of patients with SoCSVV (9), and Pastuszczak et al. reported acral involvement in 83.3% of patients with SoCSVV (6). The most common clinical manifestation of LCV is palpable purpura, which occurs mostly on the feet and lower extremities. Lesions can also occur on the forearms and hands. may be observed, but it is not frequently observed in the upper part of the trunk. Similar to previous studies, palpable purpura was observed in 90.7% of patients in our study, ulcerative lesions were present in 9.3%. In other studies conducted with patients with SoCSVV, ulcer rates were found to be 17.2% and 16.7%, which are slightly higher than our study (6, 9).

According to the anamnesis at the time of presentation, 80 (74.1%) of the patients in our study had an acute course and 28 (25.9%) had a chronic course. In the few studies conducted with SoCSVV, there was no information on whether the patients presented with acute or chronic symptoms. In the study by Bouiller et al, it was reported that skin lesions persisted for one month or more in 27.6% of twenty-nine SoCSVV patients (9). In a study involving 82 patients with LCV, it was reported that 56.09% of the patients presented with acute clinic (12). In another study on cutaneous vasculitis, chronic presentation was found to be approximately 20% (11).

Known etiologic causes of cutaneous vasculitis include infections, connective connective tissue diseases, drug reactions and malignancies (13). In our study, 75% of the patients with SoCSVV were evaluated as idiopathic. This rate was found to be 45.8% and 46.7% in two other studies conducted with patients with SoCSVV. In the same two studies, drug etiology was reported as 16.7% and 25%, respectively (6, 8). In our study, the rate of drugs among etiologic factors was 14.8%. The high rate of idiopathic etiology in our study may be explained by the fact that the study was retrospective and did not have sufficient anamnesis data. In a review including studies on CSVV, the rate of patients with drugs in the etiology was reported as 10-15%, similar to our study (14).

Among the 108 patients with SoCSVV included in our study, 105 were treated. In a study involving sixty SoCSVV patients, it was reported that 33.3% of the patients received treatment and 13.3% of these patients received NSAIDs, 15% received systemic corticosteroids, 3.3% received antihistamines and 1.7% received colchicine (8). In a study including 29 patients with SoCSVV, it was reported that only 17.2% of the patients received a specific treatment and this treatment was prednisone treatment (9). In another study involving twenty-four patients with SoCSVV, it was reported that 70.8% of the patients received treatment, 37.5% of all patients received systemic corticosteroid treatment and 33.3% received systemic antibiotic treatment (6). Although there is not enough data for treatment recommendations for SoCSVV, it has been reported that systemic treatment is not needed for LCV unless there are hemorrhagic bullae

suggestive of necrosis or ulceration or systemic involvement (15). However, the fact that systemic treatment was given to all but three of the patients included in our study shows that conservative treatment approach is not preferred in cases where vasculitis is limited to the skin. It is noteworthy that systemic treatment was given to all those for whom drugs were considered in the etiology.

Elevated CRP was found in 90.7% of patients with inflammation and tissue damage, and elevated ESR, which is used to determine inflammatory activity, was investigated in 91.6% of patients and found to be elevated in 67.3% and 61.6%, respectively. In a study conducted with patients with SoCSVV, CRP elevation was found in 78.6% of patients and ESR elevation was found in 86.4% of patients, and these rates were slightly higher compared to our study (9). In another study including patients with SoCSVV, it was reported that one of the most common laboratory findings was elevated ESR, but the rate was not specified (8). In a study investigating patients with LCV, CRP values of 196 patients were examined and CRP values were found to be elevated in 70.91% of the patients (16). In a retrospective study of 275 patients with cutaneous vasculitis, it was reported that 49.1% had elevated CRP and 72.9% had elevated ESR (17).

When evaluated together with histopathologic features, CRP elevation was found to be significant in cases with severe fibrinoid necrosis and in cases with subcutaneous tissue involvement. Colchicine and systemic corticosteroid treatment was preferred in patients with high CRP values. However, no correlation was found between clinical and histopathologic features and ESR elevation in our study. There is insufficient data on the relationship between inflammatory markers and histopathologic features of vasculitis. In a study one hundred and seventy patients with cutaneous vasculitis, no significant relationship was found between ESR elevation and clinicopathologic features (17).

In our study, involvement in subcutaneous tissue was observed in about half of the patients with subcutaneous tissue in the biopsy samples of patients with SoCSVV. Histopathologic features were not mentioned in detail in the limited number of studies conducted with patients with SoCSVV, and only one study reported involvement in subcutaneous tissue in 53% of patients, which is compatible with our study (6,8-9). Ulcer-necrosis was observed in 12.03% of the patients. Granuloma formation was not observed in any patient. In a study including 56 patients in which cutaneous vasculitis was evaluated, it was reported that 75% of patients had LCV, 17.8% had lymphocytic vasculitis, 1.78% had eosinophilic vasculitis and 1.78% had granulomatous vasculitis. As a result of this evaluation, inflammatory cell infiltration was observed in all cases, followed by leukocytoclasia (nuclear dust) in 53.5%, endothelial cell swelling in 50%, and dermal edema in 46.4%. Fibrin deposition was found in only 16% of the patients (19). In another study involving fifty-three patients with cutaneous vasculitis, leukocytoclasia (nuclear dust) was reported in 84.9%, fibrinoid necrosis in 88.6%, erythrocyte extravasation in 90.5% and dermal edema in 84.9% (20).

In our study, it was observed that DIF examination could be performed in only a minority of patients. Bouiller et al. reported that samples were taken for DIF in 26 of 29 SoCSVV patients (89.65%) and DIF findings were positive in 69% of these patients (9). In our study, the relationship between clinical features and DIF findings could not be evaluated due to both the low rate of DIF examination in patients and the low rate of positivity in the analyzed samples.

When we evaluated patients with SoCSVV as acute and chronic, we observed that the frequency of ulcerative lesions was low and the frequency of complete remission was high in acute cases. In a study conducted by Tai et al. with 93 cutaneous LCV patients, it was reported that the incidence of ulcerative lesions was higher in chronic cases, which is consistent with our study (21). However, in a retrospective study by Selvarajah et al. with 275 patients with cutaneous vasculitis, it was reported that there was no difference between acute and chronic cases in terms of age and ulcer (17).

The factor affecting the treatment selection in patients with SoCSVV was the predominance of topical corticosteroid and NSAID combination use in patients presenting with acute presentation. In a similar study, 37.5% of the patients were treated with systemic steroids. When these patients were compared with those treated conservatively, significant leukocytosis and CRP elevation were found in the group treated with systemic steroids. The same study reported that there was no significant difference between the groups treated with and without systemic steroids in terms of the type of skin lesions, the area involved, and other clinical and laboratory results (6). There are few studies on the factors determining relapse in patients with LCV (12, 22). While relapse was seen in 23.1% of our study, no significant relationship was found with other characteristics other than treatment choices as a result of the analysis performed for the clinical and histopathological features thought to be effective in the occurrence of relapse. The frequency of relapse in patients using topical corticosteroids and NSAIDs, topical corticosteroids and colchicine, and colchicine and systemic steroids was significant compared to patients using the other treatment option, topical corticosteroids and systemic corticosteroids. It can be suggested that the combined use of topical and systemic corticosteroids may be effective in preventing relapse in SoCSVV. In a study of 29 SoCSVV patients, it was suggested that no relapse was observed in any SoCSVV patient, on the contrary, SoCSVV itself was a protective factor (135). In the study conducted by Pastuszczak et al., relapse was observed in 25% of 24 SoCSVV patients, no relationship was found between relapse and treatment modalities, but it was reported that patients with more affected body areas in the first attack had a higher risk of relapse (6).

In the study conducted by Loricera et al., it was stated that relapse was observed in 8.3% of 60 SoCSVV patients, and the factors related to relapse were not investigated (8).

Conclusion

In conclusion, although it is suggested that SoCSVV, defined according to the 2012 CHCC criteria, is a benign form of vasculitis, there is limited data on this yet. When the results of this study, in which we investigated the clinicopathological features of SoCSVV, are supported by larger patient groups and prospective studies, this relatively newly defined vasculitis will be better understood.

Limitations

The strength of our study is the relatively high number of patients and the re-evaluation of cutaneous vasculitis biopsy samples by the same pathologist. Its retrospective nature is a limitation. On the other hand, DIF evaluation could not be evaluated in all patients.

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