Spectrum of Cutaneous Vasculitis in Adult Patients from the Farwaniya Region of Kuwait

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Key Words

Cutaneous vasculitis, adults • Kuwait

Abstract

Objective: To determine the clinical profile, etiologic factors, disease associations, and the laboratory profile of adult patients with cutaneous leukocytoclastic vasculitis (LV) presenting to the Dermatology Department at Farwaniya Hospital, Kuwait. **Subjects and Methods:** The medical records of 57 adult patients (>18 years) with biopsy-proven cutaneous LV from January 2004 to June 2006 at Farwaniya Hospital were reviewed. **Results:** Of the 57 patients studied, 21 (36.8%) were classified as having primary cutaneous small vessel vasculitis. The most common type of skin lesions found was palpable purpura seen in 29 (50.9%) patients. No possible cause for the cutaneous vasculitis could be identified in 21 patients. Extracutaneous involvement was seen in 32 (56.1%) patients of which 29 had joint involvement. The most frequent laboratory abnormality was an elevated erythrocyte sedimentation rate (ESR). Altered laboratory evaluation in the form of leukocytosis, raised antistreptolysin O titers and urine abnormalities were found in association with systemic vasculitis. IgA deposits were present in 33 patients. Risk factors for chronicity of cutaneous LV were female sex, advanced age, unidentified etiology, absence of fever and presence of joint involvement. **Conclusion:** The commonest type of LV in Kuwait is primary cutaneous small vessel vasculitis. The most frequent laboratory abnormality associated with LV was increased ESR.

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Introduction

Vasculitis can range in severity from a self-limited single-organ disorder to a life-threatening disease with the prospect of multiple-organ failure [1]. The skin is commonly involved in vasculitic disorders reflecting systemic disease states as well as in the context of hypersensitivity disorders in which disease expression is largely confined to the skin. In the skin, the most frequent form of vasculitis is leukocytoclastic vasculitis (LV) [1]. Cutaneous LV is characterized histopathologically by segmental areas of transmural infiltration and disruption of the vessel architecture by neutrophils with fibrinoid necrosis [1]. The clinical hallmark is palpable purpura due to the infiltrate and hemorrhage. This condition may be localized to the skin alone or, less commonly, may be a manifestation of a systemic vasculitic syndrome with multiple extracutaneous end-organ involvement. Cutaneous LV is commonly associated with a wide spectrum of systemic inflammatory conditions, malignancies, infections, or drug hypersensitivities [2–4]. The natural course of the cutaneous lesions is unpredictable [2–4]. Risk factors to distinguish patients with a poor prognosis from those with a benign course have not been identified, and a rational therapy has not been standardized in this disorder [5, 6]. To date there has been no study on cutaneous LV in Kuwait. Hence, the aim of this study was to retrospectively analyze the medical records of adult patients with histopathologically proven cutaneous LV.

Subjects and Methods

The records of all adult patients from 2003 to 2006 with suspected cutaneous vasculitis and histopathologically proven cutaneous LV at the Department of Dermatology, Farwaniya Hospital, Kuwait, were reviewed. Age, sex, clinical history, possible etiological factors, associated conditions and examination details of all the patients were recorded. A detailed perusal of the recorded history was done regarding the duration of vasculitis, constitutional and systemic symptoms, infections, drug intake, food allergy, malignancy, collagen vascular disease and any other coexisting systemic disorder.

The investigative profile of each patient was noted as shown in table 1. The lesions selected for biopsy were those with less than 48-hour duration. For all cases, the biopsies were taken using deep punch biopsy method. The diagnosis of cutaneous LV was confirmed in all patients by the presence of an inflammatory infiltrate predominantly constituted by neutrophils, nuclear fragmentation, extravasation of erythrocytes, and necrosis of dermal vessel walls.

The clinical course was divided into acute (single episode of less than 3 months' duration) and chronic (prolonged course of over 3 months or at least two recurrent episodes over a period exceeding 3 months).

Patients were considered as having extracutaneous involvement as observed from the clinical assessment, biochemistry, radiology or histology. Renal involvement was defined as the presence of persistent glomerular hematuria and/or proteinuria.

Biostatistical Analysis

The χ^2 test was done to compare observed and expected frequencies in primary and secondary types of cutaneous (localized) vasculitis and systemic vasculitis; frequencies in distribution of palpable purpura in various organs; frequencies for age, gender, etiology, constitutional symptoms, lesion distribution and morphology of lesions in the group of patients showing acute course versus the group showing chronicity/recurrences.

Results

From a total of 86 patients clinically suspected as having cutaneous LV, 57 were histopathologically proven cutaneous LV that were analyzed in this study. Of these 57 patients, 32 (56.1%) were males and 25 (43.9%) females, mean age 42.5 years, range 22–76 years.

Various etiologies and/or other associated conditions associated with my cases are shown in table 2. Just over a third of the patients (21 patients or 36.8%) were classified as having primary cutaneous small vessel vasculitis, mostly the idiopathic limited cutaneous manifestation.

The spectrum of cutaneous manifestations of vasculitis observed in the patients is shown in table 3. The most common type was palpable purpura seen in 29 (50.9%) patients, and of these 19 (33.3%) were seen in the lower limbs. The χ^2 analysis of the observed and expected fre-

Table 1. Laboratory evaluation for LV

Complete blood count with differential
ESR
Urine analysis, gross and microscopic
Liver function tests
Renal function tests
Chest X-ray
Infectious serology/cultures (blood, urine, swabs)
Hepatitis B and C
Cutaneous biopsy
Hematoxylin and eosin
Direct immunofluorescence
Any other special staining procedure as the case warrants
Stool guaiac
Cryoglobulins
Complement (CH50, C3, C4)
Rheumatoid factor
Antinuclear antibody
Antineutrophil cytoplasmic antibodies

Table 2. Etiologies and/or conditions associated with cutaneous LV in the 57 patients

Entity	Patients
Primary cutaneous (localized) vasculitis	
Idiopathic	21 (36.8)
Urticarial vasculitis	3 (5.3)
Secondary cutaneous vasculitis	
Drug-induced	10 (17.5)
Infection-induced	8 (14.0)
Primary systemic vasculitis	
Polyarteritis nodosa	1 (1.7)
Henoch-Schönlein purpura	5 (8.8)
Erythema elevatum diutinum	1 (1.7)
Secondary systemic vasculitis	
Connective tissue disease	
Systemic lupus erythematosus	1 (1.7)
Rheumatoid arthritis	1 (1.7)
Sjögren's syndrome	1 (1.7)
Malignancy	1 (1.7)
Other disorders	
Cryoglobulinemia (essential mixed)	4 (7.0)

Figures in parentheses are percentages. $p = 0.5$ for observed compared to expected frequencies in primary and secondary types of cutaneous (localized) vasculitis and systemic vasculitis.

quencies in distribution of palpable purpura in different body areas led to the inference that palpable purpura is not influenced by types of vasculitis ($p > 0.05$).

Extracutaneous involvement (table 4) was seen in 32 patients (56.1%). Joint involvement, arthralgias in 21 and

Table 3. Cutaneous manifestations of LV in the 57 patients

Cutaneous manifestation	Patients	Localized vasculitis	Systemic vasculitis
Palpable purpura	29 (50.9)		
Lower extremity	19 (33.3)	17 (29.8)	2 (3.5)
Above waist line	6 (10.5)	5 (8.8)	1 (1.8)
Generalized	4 (7.0)	3 (5.3)	1 (1.8)
Urticarial lesions	4 (7.0)		
Lower extremity	3 (5.3)	3 (5.3)	
Above waist line	1 (1.8)		1 (1.8)
Generalized	0		
Ulcers	6 (10.5)		
Lower extremity	3 (5.3)	3 (5.3)	
Above waist line	1 (1.8)		1 (1.8)
Generalized	2 (3.5)	1 (5.3)	1 (1.8)
Nonpalpable purpura	6 (10.5)		
Lower extremity	4 (7.0)	3 (5.3)	1 (1.8)
Above waist line	0		
Generalized	2 (3.5)	1 (1.8)	1 (1.8)
Vesiculobullous lesions	4 (7.0)		
Lower extremity	3 (5.3)	2 (3.5)	1 (1.8)
Above waist line	0		
Generalized	1 (1.8)		1 (1.8)
Livedo reticularis	2 (3.5)		
Lower extremity	2 (3.5)	2 (3.5)	
Above waist line	0		
Generalized	0		
Nodules	6 (10.5)		
Lower extremity	5 (8.8)	5 (8.8)	
Above waist line	0		
Generalized	1 (1.8)		1 (1.8)

Figures in parentheses are percentages. $p = 0.07$ for observed compared to expected frequencies in distribution of palpable purpura in different body areas.

arthritis in 8 patients (mostly involving the knee), was seen in 29 cases.

The most frequent laboratory abnormality (table 5) was an elevated erythrocyte sedimentation rate (ESR) found in 29 patients. Altered laboratory evaluation in the form of leukocytosis (42.1%), raised antistreptolysin O titers (28%) and urine abnormalities (19.3%) were found in association with systemic vasculitis. Eleven cases had urine abnormalities of which 6 had microscopic hematuria and proteinuria, and 5 had isolated proteinuria.

Direct immunofluorescence study showed IgA deposition in the dermal vessels in 33 (57.9%) patients; of these, 5 were cases of Henoch-Schönlein purpura (HSP), 7 drug-induced vasculitis, 1 rheumatoid arthritis and 20 were idiopathic. The results of direct immunofluorescence were negative for other immunoreactants tested except

Table 4. Extracutaneous associations of cutaneous LV in our patients

System involvement	Patients
Fever	18
Cutaneous vasculitis	6 (6/18, 33.3%)
Systemic vasculitis	12 (12/18, 66.7%)
Joint involvement	29
Cutaneous vasculitis	4 (4/29, 13.8%)
Systemic vasculitis	25 (25/29, 86.2%)
Gastrointestinal	8
Renal	16
Pulmonary	7
Neurological	0

Table 5. Laboratory evaluation for LV

Test	Cutaneous	Systemic
Complete blood count with differential		
Raised TLC	3	21
ESR		
Raised	9	20
Urine analysis, gross and microscopic		
Abnormal	1	10
Liver function tests WNL in all		
Renal function tests WNL in all		
Chest X-ray, NAD in all		
Infectious serology/cultures (blood, urine, swabs)		
ASO titer		
Raised	6	10
Hepatitis B and C		
Positive serology for hepatitis C virus		1
Cutaneous biopsy		
Hematoxylin and eosin, in all		
Direct immunofluorescence, in all		
Any other special staining procedure as the case warrants		
Stool guaiac		4
Cryoglobulins		4
Complement (CH50, C3, C4)		
Decreased		1
Rheumatoid factor		1
Antinuclear antibody		1
Antineutrophil cytoplasmic antibodies	0	0

TLC = Total leukocyte count; WNL = within normal limits; NAD = no abnormal diagnosis; ASO = antistreptolysin O.

the deposition of IgG at the basement membrane in the case with systemic lupus.

The course of the disorder was acute in 34 cases (59.6%) and chronic in 23 (40.4%) as given in table 6. Results of

Table 6. Clinical characteristics of 34 cases showing an acute course versus 23 cases showing chronicity/recurrences

Parameter	Acute course	Chronicity/recurrences
Age group*		
22–40	26	7
>40–76	8	16
Sex**		
Males	22	8
Females	12	15
Etiology		
Identified	29	7
Idiopathic	5	16
Constitutional symptoms		
Fever	16	2
Joint involvement	6	19
Lesion distribution		
Lower extremities	23	20
Lower extremities and above the waist	5	3
Morphology of lesions		
One type	25	20
Multiple types	9	
Ulcers	3	1
Livedo	1	1

* p = 0.0006; ** p = 0.0264.

χ^2 tests for various parameters showed that cases showing acute course and chronicity/recurrences are influenced by age ($p \leq 0.001$), gender ($p \leq 0.05$), etiology ($p \leq 0.001$) and constitutional symptoms ($p \leq 0.001$), but not by lesion distribution ($p > 0.05$) and morphology of lesions ($p > 0.05$).

A standard therapeutic pattern for the management of patients with cutaneous LV is shown in table 7. The patients showing chronicity or recurrences too could be effectively managed with a combination of various systemic agents.

Discussion

In this study primary cutaneous small vessel vasculitis represents the majority of patients (36.8%) with cutaneous LV, which is similar to the 40.7% incidence reported by Blanco et al. [1]. Tai et al. [7] reported an incidence of 61.3%, which is higher compared to the present study. This might be explained by the fact that different researchers may use varying definitions of the vasculitic syndromes for classifying patients in different categories, such as the American College of Rheumatology criteria and the

Table 7. Therapeutic approach to the patients with cutaneous LV

Category	Findings	Treatment
General measures	most cases of cutaneous LV representing a self-limited short-lived episode	confirm diagnosis exclude systemic disease remove triggers leg elevation avoid tight clothing avoid cold exposure antihistamines, aspirin, NSAIDS
Mild to limited skin disease	persistent/recurrent disease	dapsone and/or colchicine others: pentoxifylline
Moderate to severe skin disease	extensive skin disease with vesicles, ulcers, and/or nodules	methotrexate, azathioprine, and/or prednisolone others: hydroxychloroquine, cyclosporine, cyclophosphamide
Systemic vasculitis present	skin and other organ disease with risk of death/permanent damage	prednisolone $\pm$ cyclophosphamide or azathioprine or cyclosporine or mycophenolate mofetil

Chapel Hill Congress Conference definitions, which identify different patients [5, 6, 8–11]. Equally important is the absence of any underlying cause or association that could be identified for this group of patients, consistent with recent reports in which about 40–60% of all cases of cutaneous vasculitis are idiopathic [5–12]. The low incidence of HSP in this study is reflective of the fact that HSP mainly involves children [5] in accordance with other studies [1, 5, 7]. Drugs and infections contributed to cutaneous vasculitis in 31.6% of our patients, which is consistent with a previous report by Carlson et al. [5]. Antibiotics were the commonest cause of drug-induced vasculitis as reported previously by García-Porrúa et al. [13].

Palpable purpura constituted the most common manifestation of cutaneous LV in this study, mirroring other studies [14–16], and it has been identified as the most sensitive diagnostic sign for cutaneous LV [17].

The natural history of LV depends on the degree of systemic involvement [1, 5]. Multisystem organ involvement has been reported in up to 50% of patients, most commonly in the small vessels of the kidneys, gastrointestinal tract, joints, muscles, lungs, and peripheral nerves [18], similar to the present findings.

The incidence of IgA deposits in skin lesions (57.9%) in this study is comparable to the 40% [19] and 17% [20] reported in other studies. In a recent report [21], IgA was the immunoglobulin most frequently detected in blood vessels of both skin lesion (82%) and perilesion (68%), thereby leading to the suggestion that the presence of IgA, in involved and uninvolved skin, although not pathognomonic, can be considered as highly sensitive and specific for the diagnosis of cutaneous LV, indepen-

dent of the existence of extracutaneous involvement [21].

Certain parameters showed a remarkable contrast in the two groups of patients, one showing an acute course and the other showing a chronic course or a course marked by recurrences. Risk factors for chronicity were female sex, advanced age, unidentified etiology, absence of fever and presence of joint involvement in my patients. Presence of arthralgia and absence of fever have already been identified as predictive factors for chronicity of cutaneous LV [22].

The treatment of cutaneous LV is by and large empiric in nature as few randomized control trials have been performed. The treatment has to be tailored to disease severity and the risk for permanent organ damage [5].

Conclusion

Although the relatively benign condition of primary cutaneous small vessel vasculitis is the commonest type encountered in adults, a wide spectrum of clinical associations and laboratory anomalies have been observed. Risk factors for chronicity are female sex, advanced age, unidentified etiology, absence of fever and presence of joint involvement. As the patient's management and prognosis depend on the presence or absence of an underlying disease or association, adults need a thorough diagnostic workup and a more extensive evaluation to look for possible extracutaneous involvement. Failure to recognize this may result in significant patient morbidity and mortality.

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