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Original Article

Pathology Section

Clinicopathological Features of Cutaneous Vasculitis: A Cross-sectional Study from a Tertiary Care Centre in Karnataka, India

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ABSTRACT

Introduction: Cutaneous vasculitis is an inflammatory disease of the dermal blood vessels with varying clinical presentations. It is not a single disease but a spectrum of entities that present as cutaneous vasculitis. Hence, histopathological evaluation is essential to confirm the diagnosis and determine the type of vasculitis. Direct Immunofluorescence (DIF) studies add credibility to the diagnosis.

Aim: To investigate the spectrum of cutaneous vasculitis, its aetiological factors, and the clinicopathological features.

Materials and Methods: This cross-sectional study was conducted over a three-year period (February 2015-January 2018). All cases of biopsy-proven cutaneous vasculitis diagnosed in the Department of Pathology, Kasturba Medical College, Manipal, Karnataka, India were included in the study. The clinical data, along with laboratory investigations including skin biopsy and DIF, were analysed.

Results: A total of 137 cases of cutaneous vasculitis were diagnosed during the study period. The age of the patients ranged from 1-73 years. The peak incidence of cutaneous vasculitis was observed in the fourth decade 31 (22.6%), with no significant gender preponderance. Palpable purpura over the lower extremities was the most common skin lesion at the time of presentation seen in 47 (34.3%). Most cases of vasculitis were primary cutaneous vasculitis, while 11 cases showed evidence of systemic vasculitis such as Wegener's granulomatosis, Polyarteritis Nodosa (PAN), and Churg-Strauss syndrome. No underlying aetiology was identified in the majority of cases 82 (59.9%), while a possible underlying aetiology like connective tissue disorder, drug intake, infections, etc., could be identified in 55 (40.1%) cases. Small vessel vasculitis was the most frequent, with leukocytoclastic vasculitis being the predominant type seen in 89 (65%) cases. DIF positivity was sensitive, with positivity around the blood vessel wall observed in89 (87.3%) of cases (N=102).

Conclusion: Vasculitis is a broad, poorly defined category of diseases and can manifest with a variety of clinical presentations. Therefore, compiling clinical, laboratory, and pathological findings is essential for formulating the diagnosis.

Keywords: Direct immunofluorescence, Inflammatory disease, Skin biopsy

INTRODUCTION

Cutaneous vasculitis refers to inflammation of the vessels in the skin, which compromises or destroys the vessel wall, leading to haemorrhagic and/or ischaemic events [1]. It may be a primary cutaneous disorder or a sign of systemic vasculitis like Wegener's Granulomatosis (WG), PAN, Churg-Strauss syndrome, etc., or it can be secondary to infections, inflammatory diseases, drugs, malignancies, and connective tissue disorders [2]. Approximately 50% of cases are idiopathic and self-limited. Histologically, cutaneous vasculitis can be classified into small vessel, medium vessel, or mixed types based on the size of the cutaneous vessels involved [3]. Clinical manifestations of cutaneous vasculitis vary with the type of vessel affected, with small vessel vasculitis presenting as palpable purpura, urticaria, blisters, and targetoid lesions, while Medium Vessel Vasculitis (MVV) usually presents as subcutaneous nodules, livedo reticularis, ulcers, infarcts, and gangrene [4].

Cutaneous vasculitis has an incidence ranging from 15.4 to 29.7 cases per million per year [5]. Although it may affect any age group, ranging from 1-90 years, it is seen more often in adults than children, with a slight female predominance [5]. Skin biopsy is performed as a first-line investigation in the assessment of patients with a clinical diagnosis of vasculitis. A definitive diagnosis of vasculitis requires histologic confirmation by both light microscopy and DIF, and ideally, two biopsy samples are recommended, as the typical clinical, radiographic, and/or laboratory findings are observed in very few cases [6-8]. However, a diagnosis based solely on biopsy remains incomplete without detailed clinical history, physical examination, and laboratory results [9]. This study was designed to analyse the clinical, laboratory, and histopathological parameters of cutaneous vasculitis, to study the aetiological factors, and explore its clinicopathological features, including DIF study findings.

MATERIALS AND METHODS

This was a cross-sectional study conducted in the Department of Pathology, Kasturba Medical College, Manipal, Karnataka, over a period of three years (February 2015-January 2018). The study was approved bt Institutional Ethical Committee (IEC) with number IEC 529/2015.

Inclusion criteria: A total of 137 skin biopsies with a histological diagnosis of cutaneous vasculitis were included in the study.

Exclusion criteria: Cases with inadequate clinical data and associated thrombocytopenia were excluded from the study.

In the present study, out of a total of 3,061 skin biopsy specimens received and studied during this time period, 150 cases were diagnosed as cutaneous vasculitis while 13 were excluded.

Clinical data included age, sex, duration of disease, history of drug intake, systemic complaints, etc. Clinical examination was performed, and details including the type of skin lesions, their site, and number were recorded. History of other co-morbidities such as Systemic Lupus Erythematosus (SLE), diabetes mellitus, hypertension, malignancies, infections, other connective tissue disorders, and medical renal diseases was documented.

Recorded laboratory investigations included Erythrocyte Sedimentation Rate (ESR), Haemoglobin (Hb), Total Leukocyte Count (TLC), Absolute Eosinophil Count (AEC), serum urea, creatinine, total bilirubin, Aspartate transaminase (AST), urine analysis for proteinuria and microscopic haematuria, wherever available. Anaemia was defined as Hb levels

<12 g/dL for females and 13 g/dL for males. Raised ESR was defined as ESR >20 mm/hr, leukocytosis was defined as White Blood Cell (WBC) count >11×10^3/µL, eosinophilia was defined as Absolute Eosinophil Count (AEC) >0.4×10^3/µL. Abnormal renal function test was defined as serum urea levels >40 mg/dL, serum creatinine levels >1.4 mg/dL. Abnormal liver function test was defined as total bilirubin levels >1.2 mg/dL and AST levels >40 IU/L. Proteinuria was defined as urinary protein levels >20 mg/dL and microscopic haematuria >3 Red Blood Cells (RBCs)/high power field (hpf) [10].

Serological parameters recorded were C-Reactive Protein (CRP), Antistreptolysin O (ASO) titre, cryoglobulins, Antinuclear Antibodies (ANA), Antineutrophilic Cytoplasmic Antibodies (ANCA), Rheumatoid Factor (RF), Lupus Anticoagulant (LA), anticardiolipin antibody (IgG and IgM), complement levels (C3 and C4), and markers for Hepatitis B and C. Normal C3 levels were 80-178 mg/dL, and C4 levels were 12-42 mg/dL.

Skin biopsy was evaluated for the size of the vessel affected and the type of inflammatory infiltrate. The predominant vessel involved-small/medium/mixed-small and medium size was noted. Evidence of vessel damage such as fibrin deposition, fibrinoid necrosis of the vessel wall, extravasation of RBCs, and other secondary changes associated with vasculitis were noted. The type of immune deposit (IgG/IgM/IgA, C3, and fibrinogen) and pattern of deposits on DIF study were documented.

STATISTICAL ANALYSIS

All the variables were analysed using descriptive statistics. Quantitative variables such as age were expressed as the mean, and the results of qualitative variables were expressed as a percentage. Each laboratory data was dichotomised according to a predetermined cut-off value.

RESULTS

In the present study, a total of 137 cases of cutaneous vasculitis were included and studied. The patients' age ranged from 1 to 73 years. The peak incidence of cutaneous vasculitis was observed in the fourth decade 31 (22.6%) with a mean age of 37.15 years [Table/Fig-1]. Out of the total, 73 patients were males (53.3%) and 64 were females (46.7%), showing a slight male predominance (1.1:1).

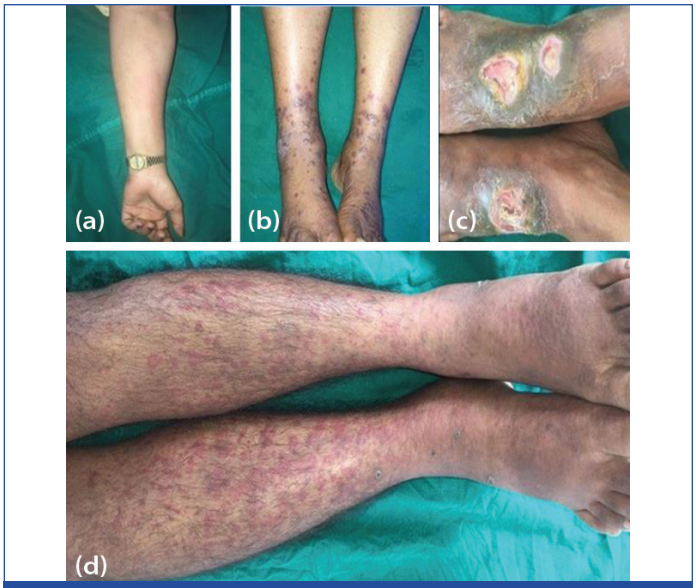
Age group (years)	n (%)
0-10	12 (8.8)
11-20	14 (10.2)
21-30	23 (16.8)
31-40	31 (22.6)
41-50	23 (16.8)
51-60	25 (18.2)
61-70	6 (4.4)
71-80	3 (2.2)
Total	137 (100)

[Table/Fig-1]: Age distribution of patients.

The majority of the patients had multiple lesions 105 (76.6%), predominantly seen on the lower extremities 104 (75.9%). Small vessel vasculitis was the most frequent type of involvement 118 (86.1%), followed by mixed small and medium vessel vasculitis 15 (11%), and medium vessel vasculitis 4 (2.9%).

Histologically, Leukocytoclastic Vasculitis (LCV) was the most common type of vasculitis 83 (64.9%), followed by Urticarial Vasculitis (UV) 19 (13.8%). Palpable purpura was the most common type of skin lesion observed in 47 (34.3%) cases. Other types of skin lesions observed included urticarial lesions, papules, and plaques [Table/Fig-2a-c]. Lesions such as deep-seated nodules, ulcers, and gangrene were more frequently seen with MVV [Table/Fig-2d].

LCV, Henoch-Schönlein Purpura (HSP), UV, and lymphocytic vasculitis showed small vessel involvement, while PAN and



[Table/Fig-2]: a) Urticarial wheal over the forearm; b) Erythematous palpable purpuric lesions over the legs; c) Ulcerated lesions over the legs; d) Hyperpigmented maculopapular rashes over the legs and feet.

Erythema nodosum showed predominantly medium-sized vessel vasculitis. Wegener's granulomatosis and Churg-Strauss showed mixed vessel involvement.

The majority of the cases were primary cutaneous vasculitis, while in 11 cases (8.02%), cutaneous vasculitis occurred as a component of systemic vasculitis, such as Wegener's granulomatosis, PAN, and Churg-Strauss Syndrome.

Systemic involvement was observed in 79 cases (57.7%), with the musculoskeletal system being predominantly affected (49.6%), followed by the renal and gastrointestinal tract. At the time of presentation, most of the patients had complaints of arthralgia 54 (39.4%), followed by fever 53 (38.7%) and abdominal pain 36 (26.3%). [Table/Fig-3] shows the constitutional symptoms in patients with cutaneous vasculitis.

Constitutional symptoms	n (%)
Arthralgia	54 (39.4)
Fever	53 (38.7)
Abdominal pain	36 (26.3)
Myalgia	19 (13.9)
Loose stools+vomiting	10 (7.3)
Malena	4 (2.9)
Photosensitivity	4 (2.9)
Oral ulcers	2 (1.5)
Haematuria	1 (0.7)
Angiooedema	4 (2.9)

[Table/Fig-3]: Distribution of cases based on constitutional symptoms.

Underlying co-morbidities seen in the patients included diabetes mellitus (22.6%) in 30 cases followed by hypertension (18.2%) in 25 cases. In 59.9% of cases (N=82), no underlying aetiology was identified. Fourteen cases (10.2%) had a history of drug intake, with non-steroidal anti-inflammatory drugs being the most common. A history of bronchial asthma was observed in 11 cases (8%), but only two cases showed evidence of eosinophilic vasculitis on skin biopsy and blood eosinophilia, suggesting a diagnosis of "Churg-Strauss syndrome". Among the six cases with underlying SLE/connective tissue disease, two showed features of connective tissue vasculitis, one showed features of eosinophilic vasculitis, and three showed features of LCV. [Table/Fig-4] displays the underlying aetiology in cutaneous vasculitis.

DIF studies were performed in 102 patients, with positive results in 89 cases (87.3%). The most common deposits in the vessel wall

Underlying aetiology	n (%)
Idiopathic	82 (59.9)
History of drug intake	14 (10.2)
Bronchial asthma	11 (8.0)
Autoimmune	
Systemic lupus erythematosus	6 (4.4)
Undifferentiated seronegative arthritis	2 (1.5)
Sjogren's syndrome	1 (0.7)
Rheumatoid arthritis	1 (0.7)
Crohn's disease	1 (0.7)
Psoriasis	1 (0.7)
Malignancy	
Multiple myeloma	2 (1.5)
Colon adenocarcinoma on oxaliplatin	2 (1.5)
Non-Hodgkin lymphoma	1 (0.7)
Infections	
Tuberculosis	2 (1.5)
Rheumatic heart disease	2 (1.5)
Leprosy	1 (0.7)
Hepatitis B	1 (0.7)
Retroviral disease	1 (0.7)
Renal	
Renal failure	2 (1.5)
IgA nephropathy	4 (2.9)

[Table/Fig-4]: Underlying aetiologies and their prevalence.

were C3 and fibrinogen, each accounting for 58.4%, followed by IgA in 33.5% and IgM in 10.9%. Additionally, five cases (3.6%) with underlying connective tissue disorder showed positivity for DIF at the dermoepidermal junction, with IgG being the most common deposit identified. Results of other laboratory investigations are summarised in [Table/Fig-5]. Out of the 87 cases in which ANA was done, 33 showed positive results (37.9%). cANCA was performed in 52 cases, out of which seven were positive (13.5%), and only one case showed histologic features suggestive of Wegener's granulomatosis. Complement reports were available for nine cases of UV, of which eight cases showed normal levels, while one case showed hypocomplementemia.

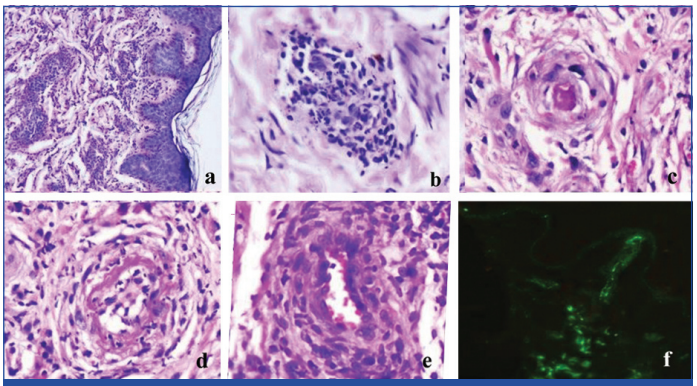
Investigations	n (%)
Raised ESR (>20 mm/ hr)	80 (58.4)
Anaemia	59 (43.1)
Leukocytosis (>11×10^3/µL)	57 (41.6)
Microscopic haematuria (>3 RBCs/hpf.)	33 (24.1)
Proteinuria (>20 mg/dL)	33 (24.1)
Positive ANA	33 (24.1)
Raised CRP (>6 mg/L)	24 (17.5)
Abnormal liver function test	16 (11.7)
Abnormal renal function test	15 (10.9)
Raised complement	14 (10.2)
Eosinophilia (AEC >0.4×10^3/µL)	11 (8)
Reduced complement	09 (6.6)
Positive cANCA	07 (5.1)
Positive pANCA	06 (4.4)
Raised IgE (>150 IU/mL)	05 (3.6)
Lupus Anticoagulant (LA)	03 (2.2)
Raised IgA (>3 g/L)	02 (1.5)
Anti Ro Ab	02 (1.5)
Reduced IgM (<0.4 g/L)	02 (1.5)
HBsAg	01 (0.7)
Rheumatoid Factor (RF)	01 (0.7)
HLAB27	01 (0.7)
Positive Mantoux test	01 (90.7)

[Table/Fig-5]: Laboratory parameters of the patients.
ESR: Erythrocyte sedimentation rate; ANA: Antinuclear antibody; CRP: C- reactive protein; AEC: Absolute eosinophil count; cANCA: Antineutrophil cytoplasmic antibody; cytoplasmic, pANCA: Perinuclear antineutophil cytoplasmic antibody; IgE: Immunoglobulin E; IgA: Immunoglobulin A; IgM: Immunoglobulin M; HBsAg: Hepatitis B surface antigen

[Table/Fig-6] displays the various histological diagnosis of vasculitis compared to the clinical diagnosis. LCV was the most common type of vasculitis, characterised by angiocentric infiltration with predominantly neutrophils, leukocytoclasia involving small vessels in all 89 cases, endothelial cell swelling in 74 cases (83.14%), RBC extravasation in 62 cases (69.66%), and fibrinoid necrosis in 47 cases (52.8%) [Table/Fig-7]. Fifteen cases of LCV occurred as a component of HSP. The morphological features and DIF findings of both LCV and HSP were similar.

Clinical diagnosis	Number (n)	Histological diagnosis	Number (n)
Primary vasculitis=118			
Small vessel vasculitis	76	Leukocytoclastic vasculitis	71
		Lymphocytic vasculitis	05
Henoch Schonlein Purpura (HSP)	16	Leukocytoclastic vasculitis	15
		Lymphocytic vasculitis	01
Urticarial Vasculitis (UV)	19	Urticarial Vasculitis (UV)	19
Erythema nodosum	07	Nodular vasculitis Sweet's like neutrophilic dermatoses	07
Systemic vasculitis=8			
Wegener's Granulomatosis (WG)	02	Wegener's Granulomatosis (WG)	02
Churg-strauss syndrome	02	Eosinophilic vasculitis, consistent with Churg-strauss syndrome	02
Polyarteritis Nodosa (PAN)	04	Polyarteritis Nodosa (PAN)	04
Underlying predisposing condition (n=11)			
Lupus erythematosus	06	Connective tissue disease vasculitis	02
		Leukocytoclastic vasculitis	02
		Eosinophilic vasculitis	02
Drug induced vasculitis	03	Drug induced vasculitis	02
		Leukocytoclastic vasculitis	01
Septic vasculitis	02	Septic vasculitis	02

[Table/Fig-6]: Clinicopathological concordance of patients.

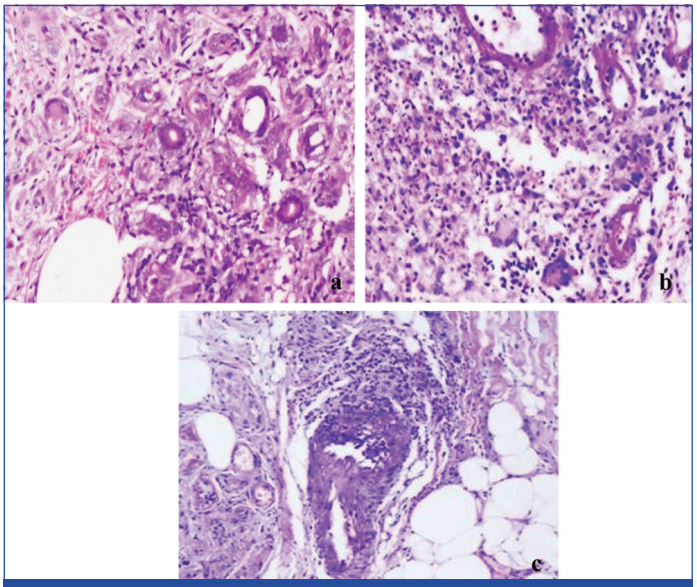


[Table/Fig-7]: a) Dermis showing small sized blood vessel with angiocentric neutrophilic infiltrate (H&E X100). b-e) Nuclear dust, Intraluminal fibrin, Intramural fibrin and Endothelial swelling respectively (H&E X400); f) C3 deposit along blood vessel wall on DIF (X 200).

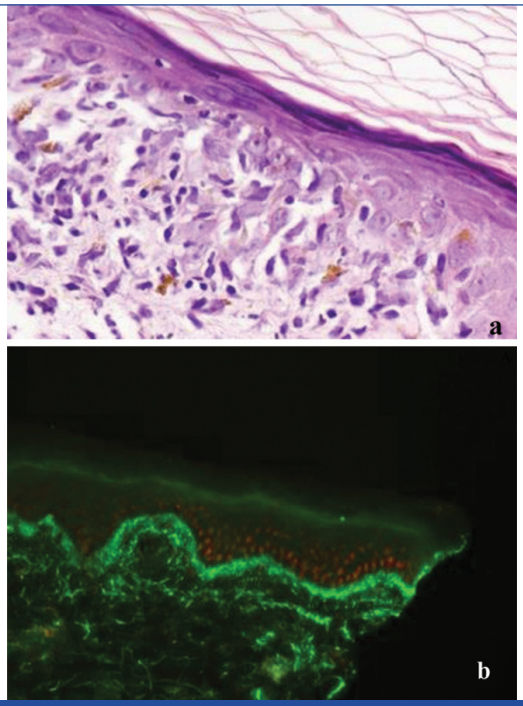
All cases of UV involved small vessels, clinically presenting with wheals, and histologically showing features similar to LCV. However, there was more pronounced dermal oedema and interstitial eosinophilic

infiltrate. Only one case showed hypocomplementemia, while normal complement levels were seen in others. Five cases of lymphocytic vasculitis were reported in patients with suspected SVV.

Two cases of eosinophilic vasculitis were seen as a component of Churg-Strauss syndrome in association with bronchial asthma and eosinophilia, while two were seen in SLE patients. All five cases of nodular vasculitis diagnosed presented with tender subcutaneous nodules on the lower extremities in middle-aged women and were clinically diagnosed as Erythema Nodosum. All cases showed involvement of small and medium-sised vessels, panniculitis, and granulomas [Table/Fig-8]. All four cases of PAN showed medium-sized vasculitis in the deep dermis and subcutis without evidence of panniculitis, and had systemic involvement. Septic vasculitis showed widespread fibrin thrombi within vessels with neutrophils, with less dermal neutrophilic infiltrate/leukocytoclasia. The cases with underlying lupus erythematosus also had characteristic histologic findings, including basal vacuolar degeneration and Civatte bodies, as well as a lupus band at the dermoepidermal junction [Table/Fig-9].



[Table/Fig-8]: a) Erythema Nodosum: small and medium-sized vessel involvement and perivascular Langhans giant cells (H&E, X200); b) Wegner's granulomatosis: Perivascular necrotising granulomas with Langhans giant cells (H&E, X200); c) Polyarteritis Nodosa: Medium-sized vessel showing lymphocytic infiltrate (H&E, X400).



[Table/Fig-9]: a) Connective tissue disease vasculitis: Epidermis showing basal vacuolar degeneration and Civatte bodies (H&E X400); b) Direct Immunofluorescence: lupus band at the dermoepidermal junction (X200).

DISCUSSION

In present study, small vessel vasculitis was seen in 97.1% of cases, while MVV was seen in 2.9% of cases, which was similar to the study by Khetan P et al., In their published study, SVV was the most common pattern, seen in all clinically diagnosed patients with SVV (47) and in 12 of the 14 clinically diagnosed patients with MVV [9]. LCV and UV represented the maximum number of patients, followed by HSP. In a study by Kumar A et al., the majority were LCV and HSP, and UV was less frequent [7].

The mean age of the patients included in this study was 37.15 years, with the most frequent occurrence in the age group of 31-40 years, similar to other studies [6,7]. Although it is reported to be more frequently seen in females, present study observed a slight male preponderance. The most common site of involvement in this study was the lower extremities (75.9%), followed by generalised distribution (15.3%), comparable to earlier studies by Sais G et al., [11]. Crops of palpable purpura was seen as the only lesion (34.3%) and in combination with other types of lesions (25.5%) were the most common clinical presentation, followed by urticarial lesions in the form of papules (12.4%) and in combination (24.8%). Other lesions that were seen included ulcers (16.1%). Present study findings were similar to those of Tai YJ et al., [12]. In this study, the most common clinical presentation in small vessel vasculitis was palpable purpura, while in MVV, it was nodules, similar to Khetan P et al., [9].

Systemic involvement was seen in 57.7%, which was similar to what has been reported in the literature, with the musculoskeletal system being the most commonly involved. The most common constitutional symptom observed in this study was arthralgia (39.4%), followed by fever (38.7%) and abdominal pain (26.3%). In the literature, an underlying aetiology has been reported in 20-85% of cases with vasculitis. An aetiological association was seen in 59.9% of present study cases. In present study study, drugs were found to be the most common factor associated with vasculitis, similar to studies by Khetan P et al., and Al Mutairi N [9,13]. The most commonly implicated drugs in present study were non-steroidal anti-inflammatory drugs, similar to previous studies by Khetan P et al., [9]. Infections were the most common associated conditions according to Tai YJ et al., [12].

DIF analysis revealed the presence of atleast one of the immunoreactants in 87.3% of the patients. Other studies have reported DIF positivity in 62-92% of cases [14,15]. The most common laboratory abnormality was elevated ESR (58.4%), which was comparable to previous studies [12,13].

Microscopically, LCV was the most common type of small vessel vasculitis, characterised by angiocentric neutrophilic infiltrate, leukocytoclasia in all 89 cases (100%), endothelial cell swelling in 74 cases (83.14%), RBC extravasation in 62 cases (69.66%), and fibrinoid necrosis in 47 cases (52.8%). In present study, leukocytoclasia and fibrinoid necrosis were present in 85% and 89% of cases, respectively, which was consistent with other studies [16]. UV showed features similar to LCV, as seen in other studies, with a clinical presentation of wheals. However, in present study, authors observed the presence of scattered eosinophils and dermal oedema in addition to the features of LCV. An increased number of eosinophils was also reported in the Mehregan series, similar to present study [17]. Five cases of lymphocytic vasculitis were reported in patients with suspected SVV. This likely represents LCV in its late stage, as the clinical presentation and immunofluorescence pattern resembled LCV. Khetan P et al., suggested that biopsy of an advanced lesion of LCV could be the cause of lymphocytic vasculitis in their study [9].

Two cases of eosinophilic vasculitis were observed in SLE patients in present study. Chen KR et al., described eight cases of eosinophilic vasculitis in connective tissue disorders [18].

Both nodular vasculitis and PAN showed medium vessel involvement, but nodular vasculitis showed the absence of panniculitis and the presence of granulomas, as described in the literature.

For early diagnosis of any type of skin lesion, it is recommended to perform two separate skin biopsies, one for routine evaluation with a light microscope and the other for DIF. Vasculitis is a dynamic process, and the type of inflammatory infiltrates can change over time. Therefore, the timing of the skin biopsy is critical, and a deep punch biopsy or excisional biopsy reaching the subcutis is recommended. As a result, small- and medium-sized vessel vasculitides of the skin can only be properly evaluated with an appropriate biopsy [19-21].

Limitation(s)

DIF was not done on all the cases studied and was available for only 102 cases, which constituted 74.4%.

CONCLUSION(S)

Clinical association is essential in arriving at a histological diagnosis as there is considerable overlap in clinical findings. A complete work-up of a patient is recommended, including clinical history and examination, haematological, biochemical, and serological investigations, along with both histological assessment and DIF studies of skin biopsies, to formulate an accurate diagnosis and plan management.

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- Manual Googling: Oct 02, 2023
- iThenticate Software: Oct 24, 2023 (13%)

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