Journal of Pakistan Association of Dermatologists. 2020; **30(3)**: 441-448.

Original Article

A clinico-pathological study of cutaneous vasculitis in a tertiary hospital of North India

Jaspriya Sandhu, Sunil Kumar Gupta, Bhavna Garg, Neena Sood

Department of Dermatology, Venereology & Leprosy, Dayanand Medical College & Hospital Ludhiana, Punjab, India.

Abstract

Objective Cutaneous vasculitis is often seen in dermatological practice. The etiology maybe infections, drugs, connective tissue disease among others. The objective of this study was to study the clinico-pathological features in patients of cutaneous vasculitis who underwent biopsy.

Methods In this retrospective study, data of patients diagnosed with Cutaneous Vasculitis who underwent biopsy over a 3-year-period, between January 2016 and December 2018 was taken.

Results There were 53 patients, with slight female preponderance [(F=27 (50.9%), M=26 (49.1%). Mean age= 32.15 years]. The most common cutaneous presentation was palpable purpura seen in 36 patients (67.8%).The most common form was Cutaneous small vessel vasculitis (CSVV) seen in 29 patients (54.7%), followed by Urticarial vasculitis (UV) in 13.2%. Prior drug intake (9.4%) appeared to be the most common eliciting factor. Direct immunofluorescence was done in 10 patients, where it was found to be negative..

Conclusion The most commonly seen vasculitis were CSVV and UV. An eliciting factor was found in 22.6% of our patients. Among the histopathological features, there was a statistically significant correlation between the presence of endothelial swelling and HSP, and urticarial infiltrate with UV. No association of drug history with tissue eosinophilia was found. DIF was negative in all 10 patients.

Key words
Cutaneous vasculitis, clinico-pathological features of vasculitis.

Introduction

Cutaneous vasculitis is a fairly common diagnosis made in the dermatological practice. Most forms, barring large vessel disease, manifest in the skin and it is usually the cutaneous features that bring the patient to the doctor's office. The most common forms seen are leukocytoclastic vasculitis (LCV), the incidence rate for which estimated was 4.5 per 100,000 person-years in a 10-year retrospective population study from the USA (1996-2010).[1]

The common etiology may be drugs, infections, connective tissue diseases among others. But most often turn out to be idiopathic even with robust investigations. A punch biopsy should be performed preferably in the first 24 to 48 hours of lesion onset when the diagnostic yield of the biopsy is greatest. A DIF further adds to the diagnostic accuracy. Hypersensitivity vasculitis was previously a clinical diagnosis given to small vessel vasculitis with histological features of Leukocytoclasia i.e. nuclear dust from the degenerated neutrophilic infiltrate. Though standard battery of tests or "vasculitis screen"

Address for correspondence
Dr. Jaspriya Sandhu
Department of Dermatology, Venereology & Leprosy, Dayanand Medical College & Hospital, Ludhiana, Punjab, India.
Email: sandhu.jaspriya@gmail.com

maybe a useful approach for the less experienced, a thorough history and physical examination usually point towards the diagnosis, decreasing the resources spent on tests and their interpretation.

In previous studies, vasculitis was classified using the ACR criteria (American College of Rheumatology), but most authors now favor the Chapel Hill Consensus of 2012 which discourages the use of eponyms while describing vasculitis.[2,3]

Both clinical as well as pathological features aid in accurate diagnosis, the prognosis varying widely. To date there have been very few studies published on cutaneous vasculitis from India.[4,5]

Materials and Methods

A retrospective study was conducted, and data of patients diagnosed with Cutaneous Vasculitis who underwent biopsy over a 3-year-period, between January 2016 and December 2018, was collected from the hospital database in the Dermatology and Pathology Departments. A detailed pro forma was used to collect relevant data. Each patient's medical record was reviewed in relation to age, sex, clinical history and examination, presence of systemic symptoms, possible etiological factors and laboratory results. Detailed histological and DIF findings were noted (**Table 1**).

The final diagnosis was made after clinico-pathological correlation. The patients were classified using Modified Chapel Hill Consensus of Vasculitis Nomenclature 2012 (**Table 2**).[3]

Statistical analysis Statistical analysis was done using SPSS version 21. Quantitative results were calculated in percentages, and association was analyzed using Pearson's Chi square test. P value <0.05 was considered significant.

Table 1 Pathological findings & DIF noted in patients in study

Epidermis
Hyperkeratosis
Acanthosis
Ulceration
Neutrophilic exudate
Dermis
Perivascular infiltrate
Vessel wall infiltration
Neutrophils/Eosinophils/Plasma cells/Lymphocytes
Leukocytoclasia
Fibrinoid necrosis
Endothelial swelling
RBC extravasation
DIF
IgA
IgM
IgG
C3
Fibrinogen

Table 2 Definitions &Classification of vasculitis in this study [Modified Chapel Hill Consensus 2012][3]

Small vessel vasculitis (Skin only)
Cutaneous small vessel vasculitis (CSSV)
Urticarial vasculitis
Erythema elevatum diutinum
Acute hemorrhagic oedema of infancy
Granuloma faciale
Small vessel vasculitis (Immune complex)
Henoch Schoenlein purpura
Cryoglobulinemic vasculitis
Hypocomplementemic urticarial vasculitis
Anti-GBM Vasculitis
Small vessel vasculitis ANCA associated
Microscopic polyangiitis
Granulomatosis with polyangiitis (Wegener's granulomatosis)
Eosinophilic granulomatosis with polyangiitis (Churgh Strauss vasculitis)
Vasculitis associated with systemic disease/variable vessel size
Lupus vasculitis
Rheumatoid vasculitis
Bechet's vasculitis
Sarcoid vasculitis
Medium vessel vasculitis (MVV)
Polyarteritis nodosa
Kawasaki disease
Large vessel vasculitis
Giant cell arteritis
Takayasu vasculitis

Table 3 Associated features among patient in the study (n=53)

Associated H/O	N (%)
Prior drug history	5 (9.4%)
UTI/URI/AGE (preceding)	4 (7.5%)
CTD (known)	3 (5.7%)
Diabetes type I/II	2 (3.8%)
Thyroid disorder	1 (1.9%)
Psoriasis	1 (1.9%)
CKD	1 (1.9%)
Associated symptom	
Pruritus	12 (22.6%)
Pain abdomen	3 (5.7%)
Joint pain	3 (5.7%)
Oedema	1 (1.9%)
Other	3 (5.7%)

Table 4 Cutaneous manifestation of vasculitis

Morphology of lesions	*N (%)*
Palpable purpura	36 (67.9%)
Ulcer/nodulo-ulcerative	7 (13.2%)
Urticarial weals	7 (13.2%)
Large purpuric plaques	4 (7.5%)
Ulceration/gangrene of digits	1 (1.9%)
Other	1 (1.9%)

Results

There were 53 patients, with slight female preponderance (F=27 (50.9%), M=26 (49.1%). The age varied from 2 years to 70 years (Mean age= 32.15 years). The duration of the disease was less than 7 days in 24 patients (45.3%). The most common presenting complaints were: Red raised lesions followed by painful ulcers {n=5 (9.4%)}[6], painful wheals {n=5 (9.4)}f and others in 2 patients (3.8%). Prior drug intake {n=5(9.4%)} appeared to be the most common eliciting factor followed by acute infectious illness (UTI/URI/AGE) {n=4(7.5%)}[7,8] and associated connective tissue disease was seen in three patients (5.7%) (**Table 3**).

The morphological features of vasculitis were palpable purpura (**Figure 1**), ulcers/nodulo-ulcerative lesion (**Figure 2**), urticarial weals (**Figure 3**), large purpuric plaques (**Figure 4)** and ulceration/gangrene of digits (**Table 4**). The most common cutaneous presentation was palpable purpura seen in 36 patients (67.8%). The distribution of the lesions was most commonly on the lower limbs seen in 46 (86.6%) patients. Other sites were digits/toes, buttocks, trunk and upper extremities. A provisional differential diagnosis was made before biopsy, LCV (64.2%) was kept as the most common diagnosis followed by Polyarteritis nodosa (PAN, 15.1%), Lupus vasculitis (LV,15.1%), Urticarial vasculitis (13.2%) (Henoch Schoenlein purpura (HSP,

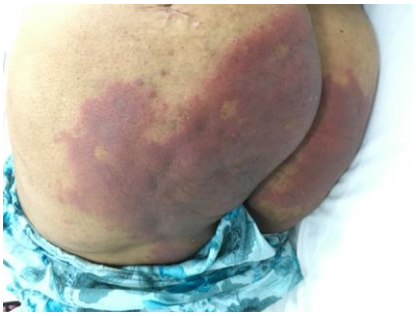

Figure 1 Palpable purpura present over the lower limb of a patient with cutaneous small vessel vasculitis (CSVV).

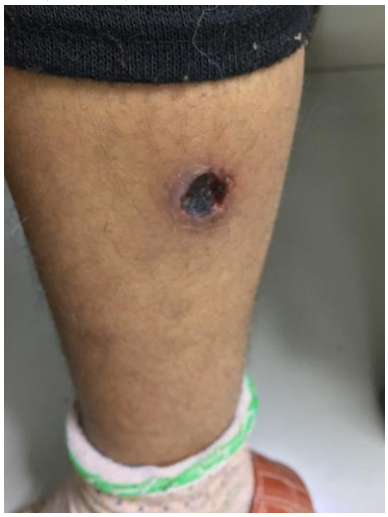

Figure 2 An ulcerated nodule seen over the leg of a young girl with known SLE, black eschar is seen over the floor of the ulcer.

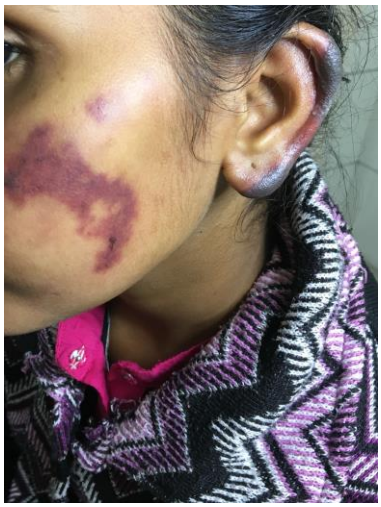

Figure 3 Urticarial vasculitis: A boy with annular erythematous urticarial plaques present over the trunk.

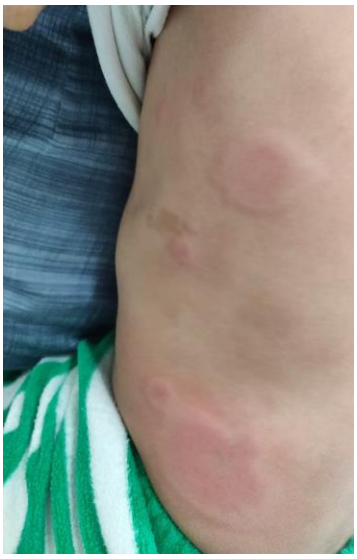

Figure 4 Adult Henoch Schoenlein Purpura (HSP): A woman with large purpuric plaques coalescing to cover the buttocks. There were no lesions elsewhere, few palpable purpura were seen over the thighs.

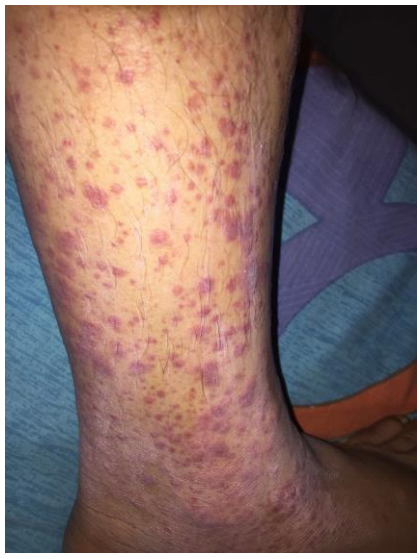

Figure 5 Acute hemorrhagic oedema of infancy: large purpuric plaques seen over cheek and ear.
Bulla formation is seen over the pinna, cockade-like purpura seen over the cheek.

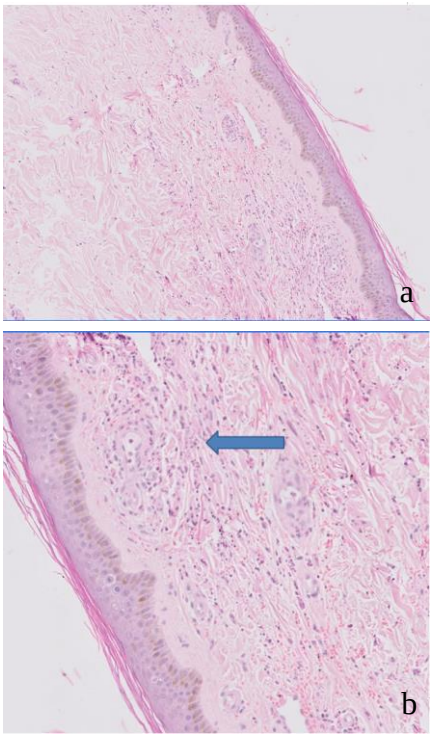

Figure 6 Microphotograph showing Leukocytoclastic vasculitisA. 100xB 400x.

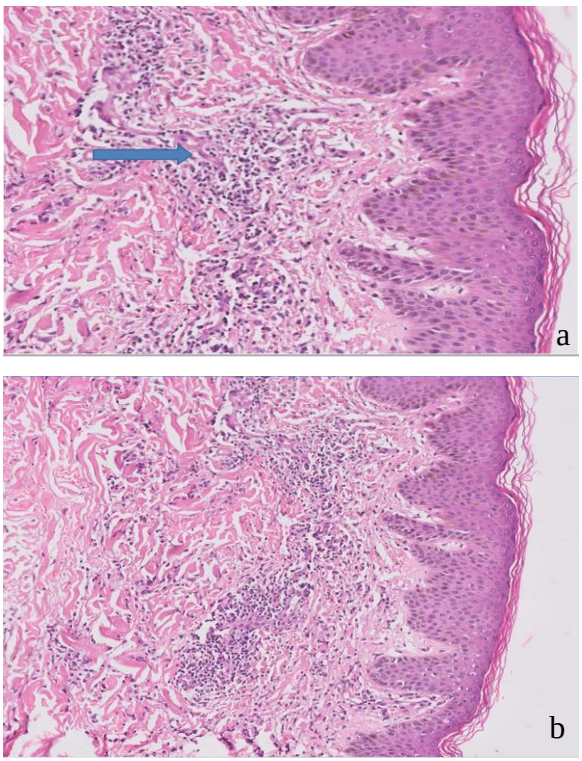

Figure 7 Microphotograph showing perivascular inflammation, endothelial cell swelling, RBC extravasationA. 100xB. 400x

11.3%) and Pyoderma gangrenosum respectively (7.6%).

The histopathology was done in all 53 patients whereas direct immunofluorescence was done in 10 of these patients. Out of the 53 biopsies, epidermal changes seen were; acanthosis (11.3%), hyperkeratosis (30.2%), ulceration (7.5%) and neutrophilic exudate (7.5%).

In the dermis, perivascular infiltration was seen in all biopsies (n=53, 100%) (**Figure 6a&7a**).

Table 5 Composition of inflammatory infiltrate in specimens examined (n=53)

Inflammatory infiltrate	*N (%)*
Neutrophils only	3 (5.7%)
Lymphocyte only	10 (18.9%)
Neutrophils + Lymphocyte	25 (47.2%)
Neutrophils + Lymphocyte + Eosinophils	8 (15.1%)
Neutrophils + Lymphocyte + Eosinophils + Plasma cells	2 (3.8%)
Lymphocyte + Eosinophils	5 (9.4%)

The infiltrate most commonly had lymphocytes (94.3%) followed by neutrophils (71.7%), eosinophils (28.3%) and plasma cells were seen in 3 biopsies (3.8%). Only neutrophils were seen in 3 cases, only lymphocytic infiltrate was seen in 10 cases and the rest had a mixed infiltrate (**Table 5)**.

Table 6 Clinical, histological and immunofluorescence features (n=53)

Final diagnosis	*%age*	*Histological features seen*		*DIF (IgA, IgG, IgM, C3, fibrinogen)*
CSVV (n=29)	54.7%	Perivascular infiltrate	100% (29)	Negative=6 ND*=23
		Neutrophils	72.4% (21)	
		Lymphocyte	89.6% (26)	
		Eosinophils	27.5% (8)	
		Plasma cells	3.4% (1)	
		RBC extravasation	68.9% (20)	
		Fibrinoid necrosis	17.2% (5)	
		Vessel wall infiltration	96.5% (28)	
		Leukocytoclasia	37.9% (11)	
		Endothelial swelling	68.9% (20)	
Lupus Vasculitis, AHOI (1)	1.9%	Perivascular infiltrate	present	ND
		Neutrophils	present	
		Lymphocyte	present	
		RBC extravasation	present	
		Vessel wall infiltration	present	
		Endothelial swelling	present	
HSP (6)	11.3%	Perivascular infiltrate	100% (6)	Negative=2 ND=4
		Neutrophils	100% (6)	
		Lymphocyte	100% (6)	
		Eosinophils	33.3% (2)	
		Plasma cells	16.6% (1)	
		RBC extravasation	100% (6)	
		Vessel wall infiltration	100% (6)	
		Leukocytoclasia	50% (3)	
		Endothelial swelling	100% (6)	
MVV-PAN (10)	18.9%	Perivascular infiltrate	100% (10)	ND
		Neutrophils	70% (7)	
		Lymphocyte	100% (10)	
		RBC extravasation	60% (6)	
		Fibrinoid necrosis	40% (4)	
		Vessel wall infiltration	100% (10)	
		Leukocytoclasia	10% (1)	
		Endothelial swelling	60% (6)	
Urticarial Vasculitis (7)	13.2%	Perivascular infiltrate	100% (7)	Negative=2 ND=5
		Neutrophils	45% (3)	
		Lymphocyte	100% (7)	
		Eosinophils	71.4% (5)	
		RBC extravasation	45% (3)	
		Vessel wall infiltration	85.7% (6)	
		Leukocytoclasia	45% (3)	
		Endothelial swelling	28.5 % (2)	
Total n=53	100.0%			Negative=10 ND=43 n=53

*ND=not done

Fibrinoid necrosis of vessel was seen in 9 biopsies (17%) whereas wall infiltration was seen in 51 (96.2%).

Endothelial swelling was present in 35 patient biopsies (66%) (**Figure 7b**). Leukocytoclasia was seen in 18(34%) (**Figure 6b**), RBC extravasation was seen in 36 (67.9%) of the biopsies (**Figure 7b**).

The most common final diagnosis after HPE and DIF study was Cutaneous small vessel vasculitis(CSVV), seen in 29 patients (54.7%) (**Table 6**). One patient was diagnosed as Lupus vasculitis; a female child with nephrotic syndrome secondary to connective tissue disease, the morphological variant being Acute hemorrhagic oedema of infancy (AHOI) (**Figure 5**). Urticarial vasculitis was seen in 7 patients (13.2%) (**Figure 2)**.

Out of the six patients of Henoch Schoenlein purpura (HSP), three had preceding history of pain abdomen, joint pain along with the cutaneous lesions (p value= 0.001). Acute infectious illness (URI/UTI/AGE) was seen in 2 patients of CSSV (n=29), one patient of HSP (n=6) and one patient of urticarial vasculitis (n=7). There was no statistically significant correlation of infection with occurrence of vasculitis (p value=0.720). There was no statistically significant correlation between preceding drug history and presence of eosinophilic infiltrate (p value=0.54).

Table 7 Studies on cutaneous Vasculitis by various authors

Author	*n*	*Study type*	*Prominent findings*	*Remarks*
Johnson et al 2017[13]	56	Retrospective	Leukocytoclastic Vasculitis, Pediatric patients only	Only pediatric population taken
Latha et al 2017[7]	275	Retrospective	Focus on etiology and presentation, Idiopathic Vasculitis most common, palpable purpura most common morphological presentation. Both adult &pediatric population.	Etiology studied; International Nomenclature not used to classify disease.
Khetan et al 2012[4]	61	Prospective	Small vessel Vasculitis most common, followed by Henoch Schönlein purpura. Drugs most common implicating factor. DIF done for all patients, positive for at least one immune-reactant in 60% cases. Both adult & pediatric population.	Modified American College of rheumatology criteria used.
Gupta et al 2009[14]	50	Prospective	LCV most common type. HPE done in all, DIF done in 23 patients only.	Modified Gilliam's classification of Vasculitis used. Emphasis on follow up of patients.
Al-Mutairi 2008[15]	57	Retrospective	Leukocytoclastic Vasculitis, Adult patients only.	Primary cutaneous type most common, no cause elicited in 21 patients.
Tai et al 2006[9]	95	Retrospective	Only Leukocytoclastic Vasculitis, Adult population only	Chapel Hill consensus of 1994 used for classifying Vasculitis.
Blanco et al 1998[8]	303 (Adults =172 Children = 131)	Retrospective	Of the 131 children, 130 had primary CV: Henoch-Schönlein purpura (HSP) in 116 and hypersensitivity vasculitis (HV) in 14. In contrast, of the 172 adults, only 120 had primary CV: HSP in 39, HV in 70, and essential mixed cryoglobulinemia in 11.	Authors suggest a less detailed work up in case of children, where disease whereas in adults the work up should rule out all the possible causes as well as systematic involvement.
Present study	53	Retrospective	Most commonly seen vasculitis were CSSV and UV. An eliciting factor was found in 22.6% of our patients.	Statistically correlation between the presence of endothelial swelling and HSP, and eosinophilic infiltrate with UV.

Discussion

A modification of the Chapel Hill consensus 2012 was used to classify the patients of this study. Majority of the patients (54.7%) in the study had CSSV. This would correspond to the hypersensitivity vasculitis (37.7%) seen in study by Khetan et al.[4] Since their study used the ACR criteria, hypersensitivity vasculitis (37.7%) and unspecified small vessel vasculitis (14.7%) were classified separately.

A known etiology that triggers vasculitis in various studies has varied from 20 % to 80%.[4,9] In this study, a known trigger was seen in 22.6% of the patients, most common being drug (9.4%). Among the CSSV group, Leukocytoclasia was seen in 37.9% patients compared to 50 % in the HSP group. The CSSV-LCV group had neutrophils in 72.4% biopsies, whereas neutrophils were seen in 100 % of the HSP cases. This could be attributed to the fact that the patients with HSP has a more rapid and dramatic onset of symptoms, and so the biopsies were done from early lesions. Fifty percent of the patients with HSP had the classical triad of abdominal pain, joint pain and vasculitis (p=0.001).

Fibrinoid necrosis featured more prominently in the MVV-PAN, seen in 40% of patients compared to 17.2% cases of small vessel vasculitis. Though a classical feature of histopathology in vasculitis, fibrinoid necrosis was seen in only 17% of the biopsies.

Endothelial swelling was seen in 100% of the HSP biopsies *vs*.68.9% of the CSVV; this would be expected since HSP is an immune complex mediated small vessel vasculitis. The endothelial cells in affected individuals have been shown to demonstrate membrane attack complex of complement (MAC) which sets off the immune mediated reaction, this manifests as endothelial swelling.[10] Endothelial cell swelling may even be demonstrated in uninvolved skin of patients of immune complex mediated vasculitis.

There was a statistically significant correlation between the diagnosis of HSP and endothelial swelling (p value=0.03).

Eosinophils were most commonly seen in urticarial vasculitis (UV) (71.4%), whereas no eosinophils were seen in the MVV-PAN group. There was a statistically significant correlation between the presence of eosinophils and the diagnosis of urticarial vasculitis (p value=0.006).

Tissue eosinophilia may be a manifestation of drug-induced vasculitis[11], however there was no statistically significant correlation between history of drug intake and eosinophilic infiltrate in this study. Fibrinoid deposits were not a consistent feature of urticarial vasculitis[12] and none of patients in this study with UV had any fibrinoid necrosis in their biopsies.

One of the limitations of this study was that DIF was not done in all patients, but of the 10 patients where it was done the results were negative. A brief summary and comparison of studies by various authors on cutaneous vasculitis is presented in **Table 7**.[4,7,9,13-15]

In conclusion, the most commonly seen vasculitis were CSSV and UV. An eliciting factor was found in 22.6% of our patients. Among the histopathological features, there was a statistically significant correlation between the presence of endothelial swelling and HSP, and eosinophilic infiltrate with UV. No association of drug history with tissue eosinophilia was found. DIF was negative in all 10 patients.

References

1. Arora A, Wetter DA, Gonzalez-Santiago TM, Davis MD, Lohse CM. Incidence of leukocytoclastic vasculitis, 1996 to 2010: a population-based study in Olmsted County, Minnesota. *Mayo Clin Proc*. 2014;**89(11)**:1515-24.
2. Hunder GG, Arend WP, Bloch DA, Calabrese LH, Fauci AS, Fries JF, et al. The American College of Rheumatology 1990 criteria for the classification of vasculitis. Introduction. *Arthritis Rheum*. 1990;**33(8)**:1065-7.
3. Jennette JC. Overview of the 2012 revised International Chapel Hill Consensus Conference nomenclature of vasculitides. *Clin Exp Nephrol*. 2013;**17(5)**:603-6.
4. Khetan P, Sethuraman G, Khaitan B, Sharma V, Gupta R, Dinda A, et al. An aetiological & clinicopathological study on cutaneous vasculitis. *Indian J Med Res.* 2012;**135(1)**:107-13.
5. Poornimambaa M, Asokan N, Augustine J. Utility of direct immunofluorescence in the diagnosis of small vessel vasculitis of the skin: A cross-sectional study. *Indian Dermatol Online J.* 2017;**8(6)**:515-7.
6. Nandeesh B, Tirumalae R. Direct immunofluorescence in cutaneous vasculitis: Experience from a referral hospital in India. *Indian J Dermatol*. 2013;**58(1)**:22-5.
7. Latha S, Choon SE, Tey KE, Chee YN. Clinical features and prognostic factors of cutaneous vasculitis among dermatology patients in Johor Bahru, Malaysia. *Med J Malaysia*. 2017;**72(6)**:345-9.
8. Blanco R, Martinez-Taboada VM, Rodriguez-Valverde V, Garcia-Fuentes M. Cutaneous vasculitis in children and adults. Associated diseases and etiologic factors in 303 patients. *Medicine*. 1998;**77(6)**:403-18.
9. Tai YJ, Chong AH, Williams RA, Cumming S, Kelly RI. Retrospective analysis of adult patients with cutaneous leukocytoclastic vasculitis. *Australas J Dermatol*. 2006;**47(2)**:92-6.
10. Boom BW, Mommaas M, Daha MR, Vermeer BJ. Complement-mediated endothelial cell damage in immune complex vasculitis of the skin: ultrastructural localization of the membrane attack complex. *J Invest Dermatol*. 1989;**93(2)**:68s-72s.
11. Bahrami S, Malone JC, Webb KG, Callen JP. Tissue Eosinophilia as an Indicator of Drug-Induced Cutaneous Small-Vessel Vasculitis. *JAMA Dermatol*. 2006;**142(2)**:155-61.
12. Davis MD, Brewer JD. Urticarial vasculitis and hypocomplementemic urticarial vasculitis syndrome. *Immunology and allergy clinics of North America*. 2004;**24(2)**:183-213, vi.
13. Johnson EF, Wetter DA, Lehman JS, Hand JL, Davis DM, Tollefson MM. Leukocytoclastic vasculitis in children: clinical characteristics, subtypes, causes and direct immunofluorescence findings of 56 biopsy-confirmed cases. *J Eur Acad Dermatol Venereol* 2017;**31(3)**:544-9.
14. Gupta S, Handa S, Kanwar AJ, Radotra BD, Minz RW. Cutaneous vasculitides: clinico-pathological correlation. *Indian J Dermatol Venereol Leprol*. 2009;**75(4)**:356-62.
15. Al-Mutairi N. Spectrum of cutaneous vasculitis in adult patients from the Farwaniya region of Kuwait. *Med Princ Pract*; 2008;**17(1)**:43-8.