"CLINICAL, HISTO-PATHOLOGICAL AND IMMUNOFLUORESCENCE STUDY OF CUTANEOUS VASCULITIS: IN A TERTIARY CARE HOSPITAL"

Submitted by

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M.D.

In

DERMATOLOGY, VENEREOLOGY AND LEPROSY

UNDER THE GUIDANCE OF

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I hereby declare that this dissertation entitled **"CLINICAL, HISTO-PATHOLOGICAL AND IMMUNOFLUORESCENCE STUDY OF CUTANEOUS VASCULITIS: IN A TERTIARY CARE HOSPITAL"** is a bonafide and genuine research work carried out by me under the guidance of **DR. ARUN C. INAMADAR,** Professor and HOD, Department of Dermatology, Venereology and Leprosy at BLDE University's Shri B. M. Patil Medical College Hospital and Research Centre, Vijayapur.

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LIST OF ABBREVIATIONS

1. ACR - American College of Rheumatology
2. ANCA- Anti-neutrophil cytoplasmic antibody
3. CHCC- Chapel Hill Consensus Conference
4. CV-Cutaneous vasculitis
5. CLA- Cutaneous leukocytoclastic angiitis
6. DIF- Direct immunofluorescence
7. EGDP - Eosinophilicgranulomatosis with polyangiitis
8. ESR- Erythrocyte sedimentation rate
9. FITC- Fluorescein isothiocyanate
10. GCA- Giant cell arteritis
11. GPA -Granulomatosis with polyangiitis
12. HSP- Henoch-Schonlein purpura
13. HUV- Hypocomplementemic urticarial vasculitis
14. KD – Kawasaki disease
15. LCV- Leukocytoclastic vasculitis
16. LVV- Large vessel vasculitis
17. MPA- Microscopic polyangiitis
18. MVV- Medium vessel vasculitis
19. PAN- Poly arteritis nodosa
20. NSAIDs- Non steroidal anti-inflammatory drugs
21. SVV- Small vessel vasculitis
22. TAK- Takayasu arteritis
23. VVV- Variable vessel vasculitis
24. WG- Wegener’s granulomatosis

ABSTRACT

Background: Cutaneous vasculitis represents a group of disorders characterized by inflammation of blood vessel wall and it may involve any organ system. Skin biopsy is considered gold standard for the diagnosis and direct immunofluorescence (DIF) aids in categorization. There are very few studies from India which correlate clinical, histopathological as well as DIF findings in patients with cutaneous small vessel vasculitis (CSVV).

Objectives: Objective of this study was to determine the epidemiology of cutaneous vasculitis and its aetiological association, and to study the diagnostic value of histopathological examination and DIF in patients with cutaneous vasculitis.

Materials and method: It was a hospital based cross-sectional study. Fifty consecutive patients attending the Dermatology outpatient department clinically diagnosed as cutaneous vasculitis were included and relevant history was taken. Complete hemogram, urine microscopy and two skin biopsy specimens for histopathology and DIF were taken from all patients. Clinical, histopathological and immunofluorescence findings were analyzed.

Results: Out of 50 patients, 35 (70%) were male and 15 (30%) were females. Males outnumbered females in the ratio of 2.3:1. Adolescents and adults were the common sufferers (n= 44, 88%). Upper respiratory tract infection (n=9, 18%) was the commonest precipitating factor followed by NSAID (n=9,18%). Palpable purpura was the commonest cutaneous manifestation (n=46, 92%) and extracutaneous involvement was noted in 33 (66%) patients i.e., joint pain, abdominal pain and hematuria. Joint

pain was the commonest systemic complaint (n= 35, 70%). On histopathology, the commonest pattern seen was leukocytoclasia and extravasation of Red blood cells (RBC). DIF showed overall positivity 98 % (49) , (n=30, 60%) with IgA , (n=44, 88%) with C3. The importance of IgA deposits in the vessel wall in the diagnosis of cutaneous vasculitis is controversial. In our study, the overall sensitivity of IgA for HSP in children and adults is 83.3% and 65% respectively. Therefore IgA is not very sensitive in adults for HSP.

Conclusion: Direct immunoflourescence in cutaneous vasculitis is a useful ancillary tool provided there is optimal clinicopathological diaganosis. Though IgA positivity does not confirm the diagnosis of HSP, but it can be a supportive finding.

Key Word : CSVV, Vasculitis, HSP, Immunoflourescence**.**

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INTRODUCTION

Vasculitides represent a group of disorders characterized by inflammation of the blood vessel wall and it can involve any organ system.[1] Vasculitis can affect small, medium or large-sized vessels of the arterial and/or venous system. Skin is one of the common organs involved in vasculitis because of its rich vasculature.[2] Cutaneous involvement in vasculitis may be a primary or reflector of a fatal systemic disease. Seldom there may be subtle cutaneous lesions but predominant systemic involvement.[3]

The incidence of cutaneous vasculitis ranges from 15.4-29.4 cases per million per year.[4] The condition affects all ages, slightly less in male than female patients, and adults more often than children.

The clinical manifestations in cutaneous vasculitis are varied and may include petechiae, palpable purpura, urticarial wheals, pustules, vesicles or bullae, nodules, ulcers and digital gangrene, presenting either as a sole feature or in combination. These varied morphologies are a direct reflection of the size of the vessels involved and the extent of vascular bed affected.[5] Palpable purpura is the commonest clinical manifestation.[6]

Vasculitis presents with multitude of clinical manifestations with wide spectrum of clinical disease varying from cutaneous vasculitis to systemic, multi-organ involvement. Primary vasculitis represents vasculitic syndromes for which the exact cause is unknown and the inflammation is directed primarily at the vessels. Secondary vasculitis refers to vasculitic disorders which are additional manifestations of a multi-system disease. Cutaneous vasculitis is idiopathic in 50% cases.[5] However,

evaluation of a patient with suspected vasculitis includes extensive search to identify any treatable underlying cause. Infection (15-20%), systemic disease (15-20%), drugs (10-15%) and malignancies (2-5%) are known precipitating factors for vasculitis.[2]

The challenges include, to classify vasculitis and assessment of the extent of systemic involvement as the range of differential diagnosis of vasculitis is broad. The variation in therapeutic approaches is the main reason for classifying vasculitis as primary and secondary.

The prognosis varies from benign and self-limiting to a progressive disease threatening vital organ functions and patients' life. Therefore, timely diagnosis of these disorders is essential. Hence, the rational approach to these patients is eliciting thorough history, physical examination and appropriate investigations to arrive at a definitive diagnosis.

Vasculitis is a clinico-pathological diagnosis; hence, histopathological evidence of vascular inflammation is confirmatory[4] and in situations where histopathological findings are inconclusive, direct immunofluorescence (DIF) study helps in clinching the diagnosis.[3]

Correlating the histopathological findings with DIF study and pertinent laboratory investigations help in accurate classification of the type of vasculitis, thus helping in most efficacious management andtherapy.

However, in most of the tertiary care hospitals use of immunofluorescence study is limited or absent. Hence, not many studies have been done regarding its diagnostic yield in vasculitis. The most important factor that affects the diagnostic yield of histopathological and DIF study is the timing of biopsy.

There are few studies on cutaneous vaculitis in Indian literature, all of which were conducted in north India.[6,7] Hence, this study has been undertaken to understand the pattern of clinical manifestations, etiological association, diagnostic yields of histopathology and DIF study in patients suffering from cutaneous vasculitis in a tertiary care hospital in South India.

OBJECTIVES OF THE STUDY

1) To study the epidemiology of cutaneous vasculitis and its etiological association.
2) To study the diagnostic value of histopathology and DIF study in patients suffering from cutaneous vasculitis.

REVIEW OF LITERATURE

Definition:

Vasculitis is an inflammatory process directed primarily at blood vessels which results in destruction of the vessel walls leading to hemorrhage, ischemia, and/or infarction and it may affect any organ system of the body.[1] Cutaneous vasculitis (CV) comprises a wide spectrum of diseases that involve predominantly the blood vessels and surrounding tissues of the skin. Cutaneous involvement in vasculitis may be primary, reflect a potentially fatal systemic disease or evidence of association with some other systemic involvement.[5]

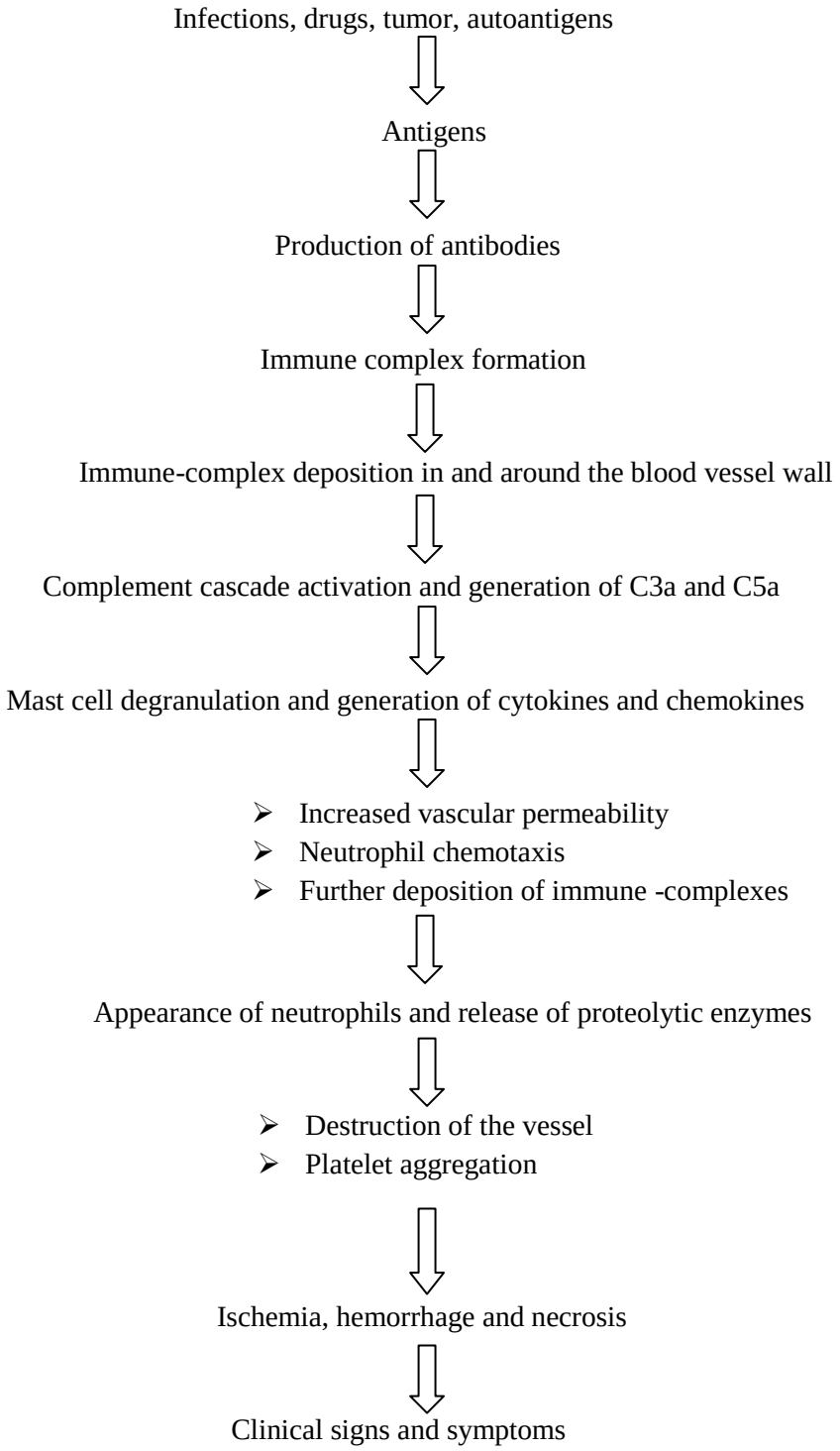
Etiology:

Almost half of all patients presenting with CV have self-limited disease localized to the skin without any known cause, triggering factor, or associated systemic disease; these constitute idiopathic cutaneous leukocytoclastic vasculitis (LCV).[2] The other causes include recent infection (15-20%), systemic disease (15-20%),drug ingestion (10-15%) and malignancy (2-5%).[2] The causes are enlisted in Table 1. About 40% of the patients with CV were found to have etiological association in a study by Khetan *et al*,[7] drugs were found to be the commonest offending agents. Non steroidal anti-inflammatory drugs (NSAIDs) was the most commonly implicated drugs, followed by antibiotics. Pathogenesis of cutaneous vasculitis is been presented in flowchart 1.

Table 1 : Common causes of cutaneous vasculitis[1]:

1.) Medications	NSAIDs
	Antibacterial (penicillins, cephalosporins)
	Sulfa drugs
	Tetracyclines
2.) Infections	*Streptococcus pyogenes*
	Hepatitis B and C virus
	Human immuno deficiency virus
3.) Inflammatory condition	Inflammatory bowel disease
	Cryoglobulinemia
	Anti-neutrophil cytoplasmic antibody (ANCA) associated vasculitis
	Behcet's disease
4.) Connective tissue diseases	Lupus erythematosus
	Rheumathoid arthritis
	Sjogren's syndrome
5) Malignancy	Hematologic: chronic myelomonocytic leukemia, lymphoid malignancy
	Solid organ: lung cancer, gastrointestinal

Flow chart 1- Pathogenesis[8] :



Classification:

Cutaneous vasculitis is mainly classified according to the size and type of blood vessels involved, i.e, small, medium and large vessels of the arterial and/or venous system. Small vessels comprises of arterioles, capillaries and post-capillary venules, which are found in the superficial and mid dermis of the skin. Medium-sized vessels refer to the small arteries and veins those reside within deep dermis or subcutis. Large vessels include the aorta and arteries.

Two commonly used classification systems for vasculitis are the American College of Rheumatology (ACR) classification criteria[9] and the Chapel Hill Consensus Conference (CHCC) nomenclature system.[10] The widely used classification according to the size of the vessel wall involved is the Chapel Hill Consensus Conference nomenclature of vasculitis (CHCC) which has been presented in Table 2.[10]

Table 2: Names for vasculitides adopted by the 2012 International Chapel Hill Consensus Conference on the nomenclature of vasculitides[10]:

Large vessel vasculitis(LVV)
Takayasu arteritis (TAK)
Giant cell arteritis (GCA)
Medium vessel vasculitis (MVV)
Poly arteritis nodosa(PAN)
Kawasaki disease
Small vessel vasculitis (SVV)
Antineutrophil cytoplasmic antibody(ANCA) – associated vasculitis
a. Microscopic polyangiitis (MPA)
b. Granulomatosis with polyangiitis (Wegener's) (GPA)

c. Eosinophilic granulomatosis with polyangiitis (Churg-Strauss) (EGPA)
Immune complex SVV
a. Anti-glomerular basement membrane disease (Anti-GBM)
b. Cryoglobulinemic vasculitis
c. IgA vasculitis (Henoch-Schonlein purpura)
d. Hypocomplementemic urticarial vasculitis (HUV)
Variable vessel vasculitis (VVV)
Behcet's disease
Cogan's syndrome
Single-organ vasculitis
Cutaneous leukocytoclastic angiitis (CLA)
Cutaneous arteritis
Primary central nervous system vasculitis
Isolated aortitis
Others
Vasculitis associated with systemic diseases
Lupus vasculitis
Rheumatoid vasculitis
Sarcoid vasculitis
Others
Vasculitis associated with probable etiology
Hepatitis-C virus associated cryoglobulinemicvasculitis
Hepatitis-B virus asscociatedvasculitis
Syphilis associated aorititis
Drug associated immune -complex vasculitis
Drug associated ANCA-associated vasculitis
Cancer-associated vasculitis

Epidemiology:

The incidence of cutaneous vasculitis ranges from 15.4-29.4 cases per million per year.[2] The condition affects all ages, slightly less in male than female patients, and adults more often than children.[2] Children are the common sufferers of Henoch-Schonlein purpura (HSP)[11] with an estimated annual incidence of 3.0- 26.7 cases per million children,[9] which comprises about 10% of vasculitis and is the most common cause of vasculitis in children (90%).[3] The mean age of onset of vasculitis in adults and children is 47 and 7 years respectively.[4] Specific data regarding incidence of CV in Indian population is scarce.

Clinical features:

Cutaneous findings of vasculitis depend upon which vessels are primarily involved. The clinical hallmark of cutaneous vasculitis is palpable purpura.[5] The hemorrhagic papules are bright red in color and range in size from one millimetre to several centimetre in diameter. These may start as macular erythema and progress to become papules, nodules, vesicles or bullae, pustules, annular lesions or necrotic ulcers and heal with post-inflammatory hyperpigmentation. The typical locations are the dependent areas, usually the lower extremities or under the tight-fitting garments and are symmetrically distributed. The intertriginous areas are usually spared.

Upper extremity, trunk and head and neck involvement is infrequent and often signals the presence of more severe disease or co-existing systemic vasculitis.[2] HSP is commonly associated with systemic involvement of the gastrointestinal tract, joints and kidneys. Renal disease is the principal cause of morbidity and mortality in children with HSP, and about 1-3% progress to end-stage renal disease.[4] Raynaud's phenomenon and peripheral cyanosis are common in CV.[2] Pale, cold extremities are

seen in giant cell arteritis in association with asymmetric pulses. Digital gangrene is a common presentation of large vessels like polyarteritis nodosa. Mucosa may be involved in the form of persistent oral and nasal mucosal ulcers in Wegener's granulomatosis (WG) and nasal polyps are seen in Churg-Strauss syndrome.[1] Cutaneous involvement is exclusive of vasculitis involving small and medium-sized arteries. In general, small-vessel (post-capillary venules) disease gives rise to palpable purpura and urticarial lesions; small-artery disease manifests as subcutaneous nodules; medium-sized arterial involvement presents with necrosis of major organs, livedo reticularis, and large-vessel disease presents with symptoms of claudication and necrosis. Cutaneous manifestation depending on the size of the vessel wall have been tabulated in Table 3.

Table 3:Cutaneous and systemic presentation of vasculitis depending on the size of vessel wall[1]

Blood vessel size	Cutaneous manifestation
Small vessel	Purpuric macules, palpable purpura, urticarial lesion, nodules, superficial ulcer, vesico-bullous lesion.
Medium vessel	Subcutaneous nodules, livedo reticularis deep ulcers, infraction, digital gangrene

The constitutional symptoms accompany all cutaneous vasculitic syndromes, and these include fever, malaise, weight loss, arthritis, and/or arthralgia.Systemic features of cutaneous vasculitis has been presented in Table 4.

The onset of vasculitis after exposure to a trigger such as drug or infection occurs after 7 to 10 days. An interval of weeks, months or years may exist between the onset of symptoms and signs of systemic disease and the onset of secondary cutaneous vasculitis. Three patterns of disease evolution occur in cutaneous vasculitis[1]:

1) A single acute, self-limited episode (resolved in < 6 months) of vasculitis often associated with a drug or infectious trigger.
2) A relapsing disease with symptom-free periods usually found in patients with HSP and associated vasculitis.
3) A chronic, unremitting disease often associated with cryglobulinemia, hypergammaglobulinemia and malignancy.[2]

The duration of vasculitis may range from less than a week to years, but in half of the cases it resolves by 4 months.[4]

Khetan *et al*[7] found palpable purpura to be the commonest cutaneous lesion which was seen in the 43 (70.9%) patients. Crusted plaques, ulcers, wheals and hemorrhagic vesicles were the other cutaneous lesions noted. Clinical presence of deep seated nodules, ulcers or gangrene was seen in 14 patients. Thirty two patients had involvement of the upper limbs, trunk or face along with involvement of lower limbs. Gupta *et al*,[5] also had similar finding of palpable purpura as the commonest cutaneous presentation in 43 (86%) patients. Purpurae were commonly found on the legs and ankles followed by thighs, buttocks, forearm, abdomen, back and chest. Plaques, ulcers, bullae, vesicles, gangrene of toes, urticarial and atypical lesions were the other cutaneous lesions seen.

Table 4: Systemic findings in cutaneous vasculitis[12]:

ORGAN SYSTEM	SYMPTOMS	SIGNS
Constitutional	Chills, weight loss, night sweats, fatigue	Fever
Cardiovascular	Chest pain, breathlessness, dyspsnea	Cardiac rub, gallop, edema
Renal	Hematuria, swelling of lower limbs	Hypertension, edema
Gastrointestional	Abdominal pain, nausea/vomiting, melena	Abdominal tenderness, hepatosplenomegaly
Respiratory	Shortness of breath, cough, hemoptysis, wheezing	Crepitus, wheeze, rhonchi
Musculoskeletal	Arthralgias, weakness, myalgias	Arthritis
Neurological	Paresthesia, numbness, weakness	Foot/wrist drop, abnormal reflexes/ sensation.
Head & otorhinolaryngological	Dryness, sinusitis	Iritis, sinus tenderness, otitis media, lymphadenopathy

Diagnosis:

Usually history and clinical examination of the patient help in the initial presumptive clinical diagnosis. Histopathological information coupled with direct immunofluorescence, anti-neutrophil cytoplasmic antibody (ANCA) and pertinent laboratory investigation enables more accurate and precise diagnosis of CV. Following investigations are required for confirmation of diagnosis:

1) **Skin Biopsy :** Vasculitis is a clinico-pathological diagnosis and microscopic evidence of vascular inflammation is confirmatory.[4] Skin being the most accessible organ, is most frequently sampled for this purpose. A deep punch /

incisional biopsy is taken from a lesion of appropriate stage. Optimum timing for this purpose is within 18-48 hours of the onset of the lesion.[4] In case of cutaneous small vessel vasculitis (CSVV), the most recent lesion from the uppermost part of the limb is chosen. In case of nodular lesions, a biopsy extending to subcutis is taken from the most tender, reddish lesional skin. Skin biopsy includes a lesional specimen for light microscopy and direct immunofluorescence (DIF). Ideally, separate biopsy samples for histopathology and DIF study should be obtained.[1]

a) Histolopathological examination :

Histopathological pattern of cutaneous vasculitis is dynamic. A lesion should be biopsied within 18-48 hours of development, for bestdiagnostic yield.[2] Biopsy obtained from the purpuric lesion in the first 24 hours is characterized by fibrin deposits within the vessel wall accompanied by neutrophilic infiltration of the vessel wall and surrounding hemorrhage and nuclear debris.[13]After 48 hours, histopathology is usually non specific, showing an inflammatory reaction with a predominance of mononuclear cells rather than neutrophils.[4] Deeper, elliptical, incision biopsy is required when the lesions are suggestive of large vessel involvement, e.g., presence of nodules.

Fibrinoid necrosis is a common histopathological feature of nearly all early vasculitic lesions and is due to the accumulation of plasma proteins and coagulation factors which are converted to fibrin. The diagnosis of vasculitis can be unequivocally made if there are inflammatory infiltrates within and around the wall of vessels accompanied by fibrin deposition as

the media of vessel is not the site of inflammatory diapedesis. These changes commonly coexist with signs of endothelial damage in the form of endothelial swelling and extravasation of RBCs.

Other histopathological findings may help to determine the appropriate subtype of CSVV and identify its cause. CSVV involving small and medium-sized vessels may suggest vasculitis associated with ANCA or connective tissue disease (CTD). In patients with urticarial lesions suggestive of urticarial vasculitis, a dermal interstitial neutrophilic infiltrate may indicate hypocomplementemic urticarial vasculitis, which is more commonly associated with systemic lupus erythematosus.[1] Tissue eosinophilia may indicate drug induced CSVV. Absence of eosinophils may predict the risk of renal disease in adult patients with IgA vasculitis, which may be a useful renal risk stratification tool.[2] The combination of leukocytoclastic vasculitis without eosinophils in patients older than 40 years with HSP has been associated with a 75 % rate of renal disease, a risk nearly three times greater than for other adult patients with HSP.[2]

Nandeesh *et al* [3] in their study took biopsies between less than 3 days (<72 hours) and 6 months after the onset of lesions. Lower extremity (*n*= 117, 47%) was the commonest site followed by upper extremity (*n* = 59, 29.79 %). Histopathology revealed leukocytoclastic vasculitis (66%) to be the commonest diagnosis followed by lymphocytic vasculitis in 18%. Perivascular inflammation was noted in 16%.

In a study conducted by Khetan *et al*[7] they observed small vessel involvement in 96% patients and medium vessel involvement in only 4 %

of the patients. Most of the cases had upper and mid-dermal infiltration, lower dermal and involvement of panniculus was also seen. Clinically the lesion which presented as palpable purpura, wheals, nodules, crusted plaques and ulcers had involvement of panniculus. Infiltrate which was predominantly neutrophilic (50%) and was confined to perivascular and interstitial location. Leukocytoclasia and fibrinoid necrosis were present in 85 and 89% of patients respectively. Extravasation of red blood cells (RBCs) was seen in 90.5% of the cases. Most of the patients with HSV and HSP showed small vessel vasculitis (SVV) which comprised of both neutrophilic andeosinophilic infiltrate. Threepatients showed predominantly lymphocytic vasculitis. In patients with Connective tissue disease, predominantly neutrophilic infiltrate admixed with eosinophilic infiltrate was also noted.

b) Direct Immunofluorescence study :

For DIF study, the skin sampling should be done from a fresh, most tender and most proximal lesion. Biopsy from a dependent area, e.g., lower leg may demonstrate non-specific fluorescence resulting from hydrostatic extravasation of immune-complex.[14]About 100% of the biopsies illustrate immunoglobulins within the first 48 hours, 70% will be positive at 48-72 hours and immunoglobulins are not detectable after 72 hours.[4] However, complement can still be detected in more than 50% of vasculitic lesion even after 72 hours.[2] The ideal time frame for obtaining a biopsy sample for DIF is less than 48 hours after the onset of lesion because immune complexes may dissipate within 48 hours.[4] The foremost role of DIF is to

identify major immunoreactants.[1] The most common immunoreactant found in the vessels by DIF is C3 followed by IgM, IgA and IgG.[15]The type of immunoglobulins and the pattern of their deposition in DIF examinations havediagnosticvalue and also help in categorizing vasculitis.

Nandeesh *et al*,[3] in their study found an overall DIF positivity in 79 (39%) patients with C3 in 52 (26%) and IgA in 46 (23%) patients. The timing of biopsy ranged from less than 3 days to 6 months, with 110 (56%) cases being biopsied within 7 days of onset of lesions (25% being within 72 hours). Among the biopsies which were performed within 7 days of the onset of lesions 85% turned out to be positive. Forty six out of 66 patients (70%) with extracutaneous features showed immune deposits. Forty three out of 48 (90%) suspected cases of HSP showed positive staining for IgA, and 60% of them showed C3 deposits as well. About 4 (2%) cases also showed immune deposits at the epidermal basement membrane zone in addition to blood vessels and these patients had positive antinuclear antibodies. Overall, positive antinuclear antibodies were detected in 28% of cases. Among 15% of the cases which were tested for ANCA, all of the cases turned out to be negative.

Takatu *et al*[16] conducted a retrospective study on 282 patients, DIF was positive in 235 (70.21%) patients and the most common immune deposit was C3. Deposition of IgA was seen in younger age and absence of autoimmune/inflammatory disorders. IgM deposition was seen more in females, autoimmune/inflammatory disorders, and low levels of C3 and

C4. IgG was seen in older age and positive ANCA patients and C3 deposition was related to hematuria and renal involvement.

2) Laboratory Evaluation:

The main goals of laboratory evaluation are to search for an underlying cause and to exclude systemic involvement. The laboratory evaluations performed differ greatly with respect to whether the disease has a clear inciting factor or cause, shows systemic involvement, or is recurrent.[5] The other purpose is to screen for the involvement of underlying organ and to identify the risk factors which may modify the therapeutic approach. A battery of investigations are needed which have been mentioned in Table 5.

Table 5: Laboratory tests for patients with cutaneous vasculitis[2,17,18]

Type of evaluation	Laboratory tests
Baseline	Complete blood count with differential Urine analysis Serum creatinine Liver function tests
Additional	Anti-streptolysin O titers C-reactive protein Hepatitis B and C serology Streptococcal antibodies Human immunodeficiency virus antibody Serum complement levels (C3, C4, total) Antinuclear antibody Extractable nuclear antigen Rheumatoid factor Chest radiography Stool guaiac test Cryoglobulins Serum monoclonal protein study (protein electrophoresis and immunofixation) Antineutrophil cytoplasmic antibodies Other tests for specific organ involvement, malignancy, etc.

Treatment

General measures:

In the active stage of the disease, the basic instructions include avoiding stress, bed rest, foot end elevation, loosely fitted garments& keeping the extremities warm. Symptomatic treatment in the form of antihistamines and NSAIDs are administered to relieve symptoms like pruritus and joint pain.

Specific therapy:

It is aimed at reducing acute symptoms and preventing complications. If vasculitis presents with an underlying disorder it usually resolves with control of the infection, withdrawal of the causative drug or removal of the tumor. In many cases, a chronic course presents a difficult situation; hence an effective but least toxic therapeutic regimen is preferred. The treatment options for cutaneous vasculitis have been outlined in Table 6.

Table 6: Treatment for cutaneous vasculitis[2, 18, 19]

Category	Treatment
General measures	Remove inciting cause (if any identified)
	Bed rest
	Leg elevation
	Compression stocking
	Avoid cold and tight-fitting clothing
	Symptom alleviation: Antihistaminics for pruritus and NSAIDs for joint pain.

Mild, limited skin involvement	Dapsone 100-200mg (CLA, HSP, UV)
	Colchicine 0.6 mg 2–3 times daily (CLA, HSP, UV)
	Dapsone 100-200mg and colchicine 0.6mg 2-3times daily
	Pentoxyphylline 400mg 3 times daily (CPAN)
Moderate to severe skin involvement (above waist lesion, vesicobullous, ulceronecrotic lesion, nodules)	Systemic steriod: Injectable/Oral.
	Azathioprine 2-2.5mg/kg/day
	Methotrexate 5-20mg/ week
	Hydroxychloroquine400mg TID/day (HUV)
	Cyclosporine 2.5-5mg/kg/day
	Cyclophosphamide 100mg-2gm/day
	Mycophenolatemofetil2g/day (HUV, WG, MPA)
Systemic vasculitis	Prednisolone 1-1.5mg/kg ± cyclophosphamide/azathioprine / mycophenolatemofetil
	IV methyl prednisolone 1g/day for 3days then prednisolone 1-1.5mg /kg/day
	Rituximab 2mg/kg/day
Refractory (unresponsive to above treatment)	Hydroxychloroquine (400 mg daily; only for urticarial vasculitis) Intravenous immunoglobulin (2 g/kg monthly, divided over 2–4 days) Rituximab (1 g intravenous, on days 1 and 15) Cyclosporine (2.5–5 mg/kg daily, in divided doses; short-term use in severe disease)

From the review of literature on cutaneous vasculitis, it is evident that, the work-up of the patients with suspected vasculitis starts with a detailed history, probing into the possible etiological factors like drugs, recent infection and the presence of other pre-existing symptoms suggesting any underlying disease. A careful correlation of medical history and the clinical, serological and imaging findings can

help to clinch the correct diagnosis. In all patients with CV, skin biopsy and DIF are must for final diagnosis and accurate classification of vasculitis. However, these investigations should be done at an appropriate stage of evolution of the disease, so as to avoid missing important diagnostic evidence despite strong clinical suspicion. Since cutaneous involvement is almost universal in all types of vasculitis, dermatologists play a crucial role in diagnosing vasculitic disorders, predicting the extent of underlying systemic involvement and prognosis.

METHODOLOGY

SOURCE OF DATA:

A hospital-based, cross-sectional study to determine the clinical, histopathological and direct immunofluorescence findings in patients diagnosed with cutaneous vasculitis attending the outpatient section of the department of Dermatology, Venereology and Leprosy of B.L.D.E.U's Shri. B.M. Patil Medical College Hospital and Research Centre, Vijayapur. Fifty patients with vasculitis were enrolled in the study. The study was conducted between the period of November 2014 to August 2016.

METHOD OF COLLECTION OF DATA:

Inclusion criteria:

Patients attending the dermatology OPD presenting with palpable purpura, papules, plaques, nodules, vesicles, bullae, ulcers and other cutaneous finding like urticaria, livedo reticularis were included in the study irrespective of age, sex and duration of the disease.

Methods:

- Detailed history and clinical examination was recorded in proforma. History of drug exposure was considered significant if exposure was within 4 weeks of appearance of lesion. Based on clinical feature, attempt was made to categorize the disease of individual patients according to the Chapel Hill Consensus Conference classification.

LABORATORY INVESTIGATIONS:

- Following baseline investigations were carried out for all the patients
  - Complete haemogram
  - Erythrocyte sedimentation rate (ESR)
  - Serum urea and creatinine levels
  - Liver function test
  - Urine analysis
- Following specific test were done whenever indicated:
    - Hepatitis B and C serology
    - Streptococcal antibodies
    - Human immunodeficiency virus antibody
    - Antinuclear antibody
    - Extractable nuclear antigen
    - Rheumatoid factor
    - Complement levels (C3, C4, total)
    - Cryoglobulins
    - Serum monoclonal protein study
    - Peripheral blood smear
    - Antineutrophil cytoplasmic antibodies
    - Chest radiography
    - Stool guaiac test

Two skin biopsies were taken and sent for histopathological examination and direct immunofluorescence. Biopsy was taken in strict aseptic condition, using 3mm disposable skin punch. For light microscopy sections were formalin fixed, paraffin embedded and stained with hematoxylin and eosin stain.

As facility for immunofluorescence study was not available in this institution, the biopsy specimen for DIF was transported in Michel's transport media to Kasturba Hospital, Manipal. All biopsies were frozen in a cryostat and sectioned at 4 μm.

Sections were incubated with fluorescein isothiocyanate (FITC) conjugated, Fc-specific F (ab) 2 antisera directed against IgG (1:30 diluted), IgA (1:30 diluted), IgM (1:30 diluted), and complement C3 (1:30) (Dako), respectively. A specimen was considered to be positive if granular deposits of one or more immunoreactants were found in the walls of vessel. The DIF findings from the skin biopsy were compared with duration of illness and clinical manifestations.

STATISTICAL ANALYSIS:

The observations pertaining to the parameters under study group was expressed as percentage.

The quantitative variables such as age was expressed as mean ± SD. Pattern of clinical features and etiological association with histopathological features and DIF findings were tested using Chi-square test.

ETHICAL CLEARANCE:

Institutional ethical committee clearance was undertaken for the study.

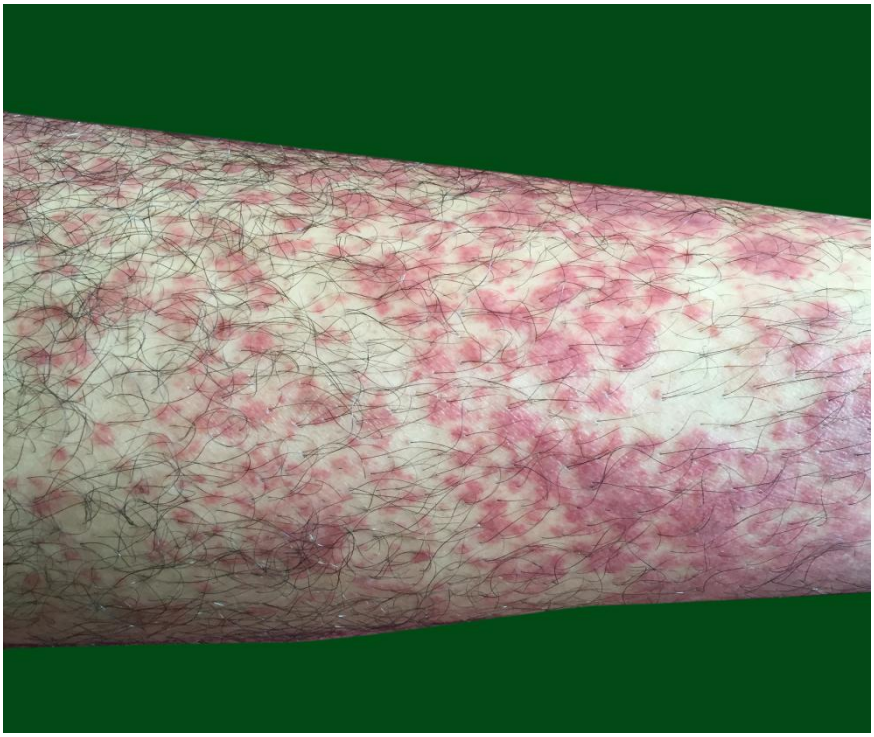


Figure 1: Palpable purpurae

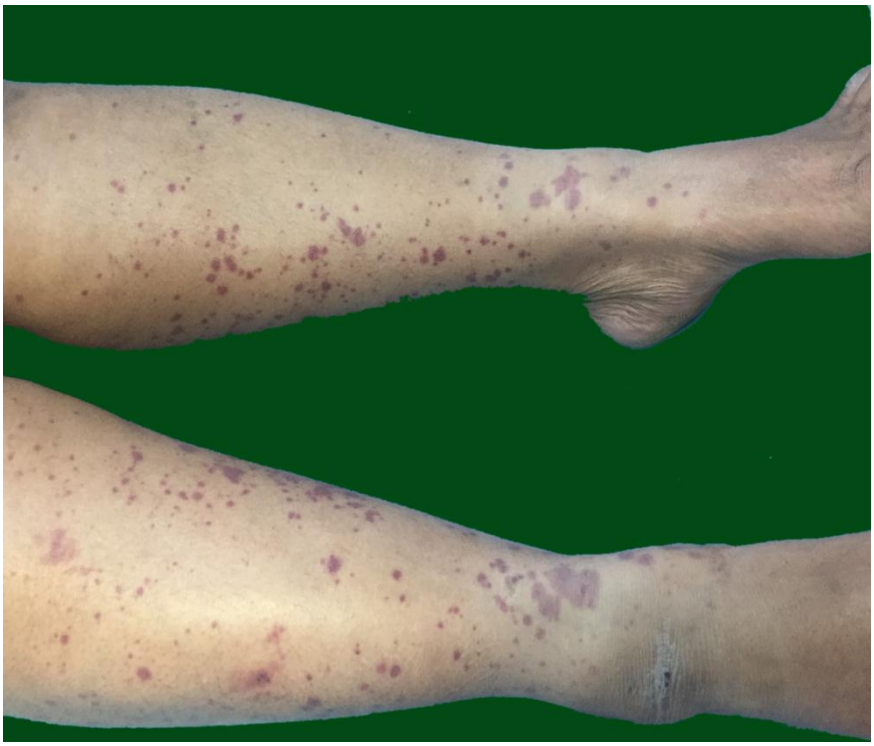


Figure 2: Multiple palpable purpura present bilaterally symmetrical over the lower limbs

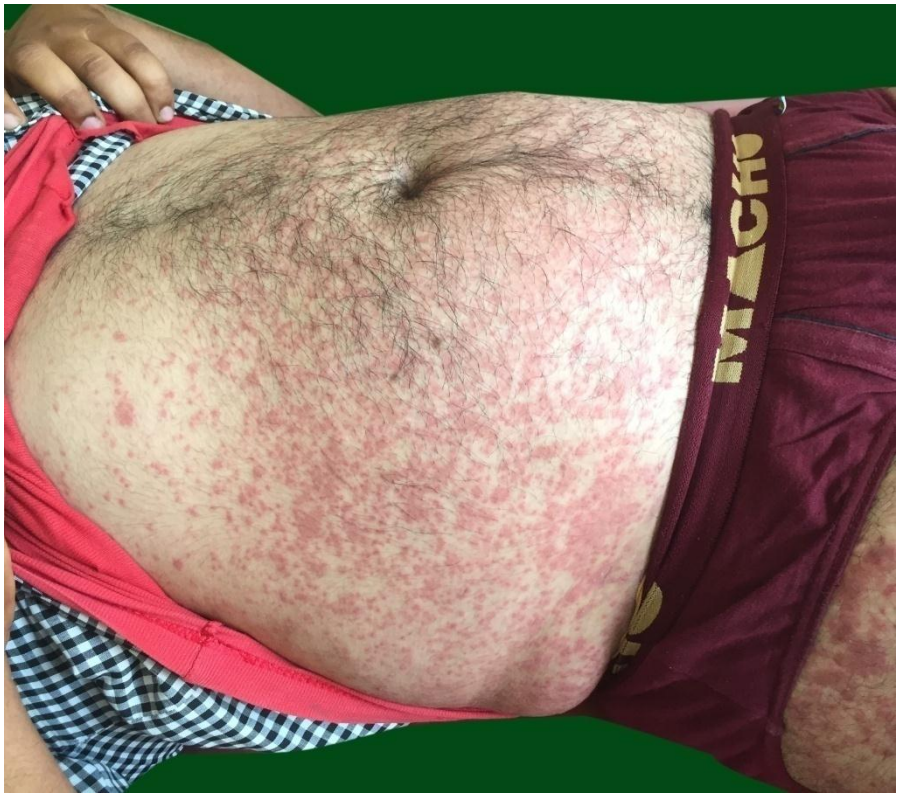


Figure 3: Multiple palpable purpura over the abdomen (above waist involvement)

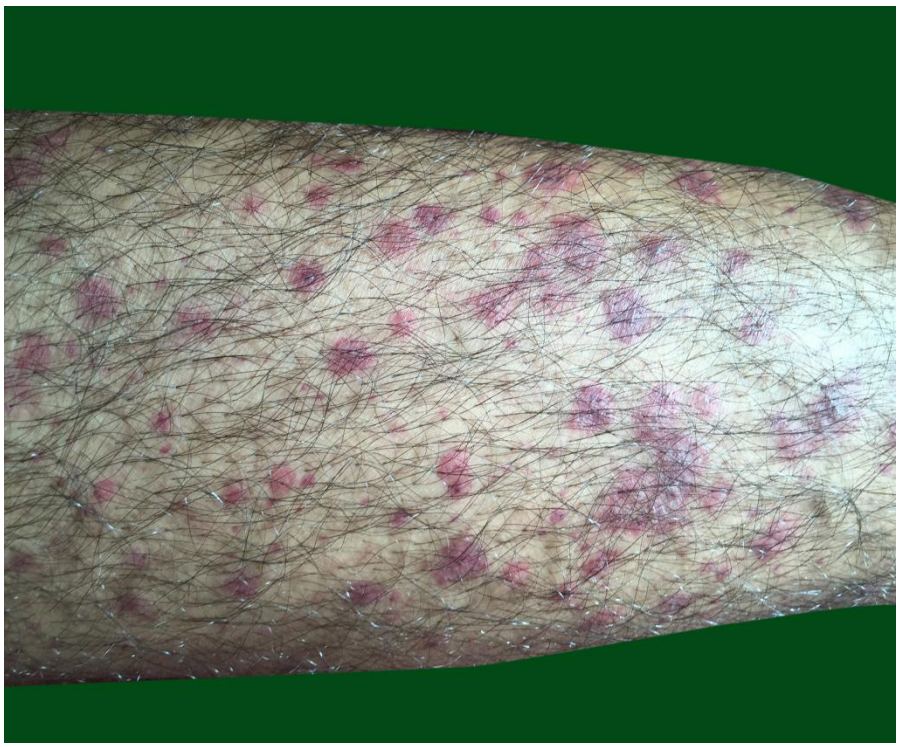


Figure 4: Multiple vesicular lesions

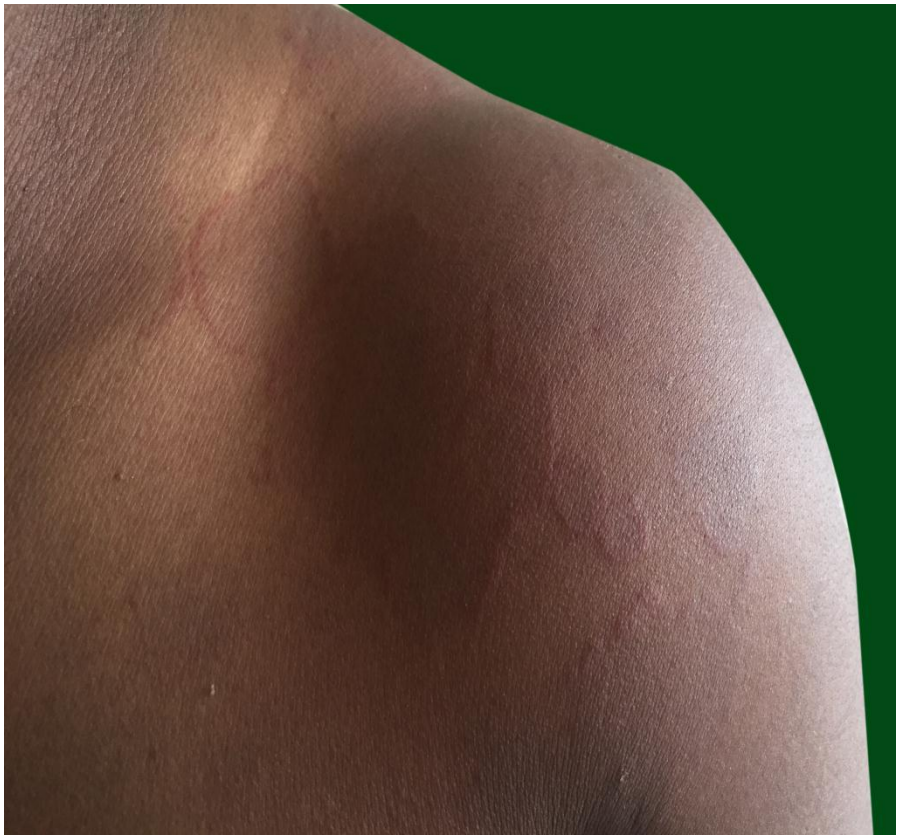


Figure 5: Multiple annular plaques of urticarial vasculitis

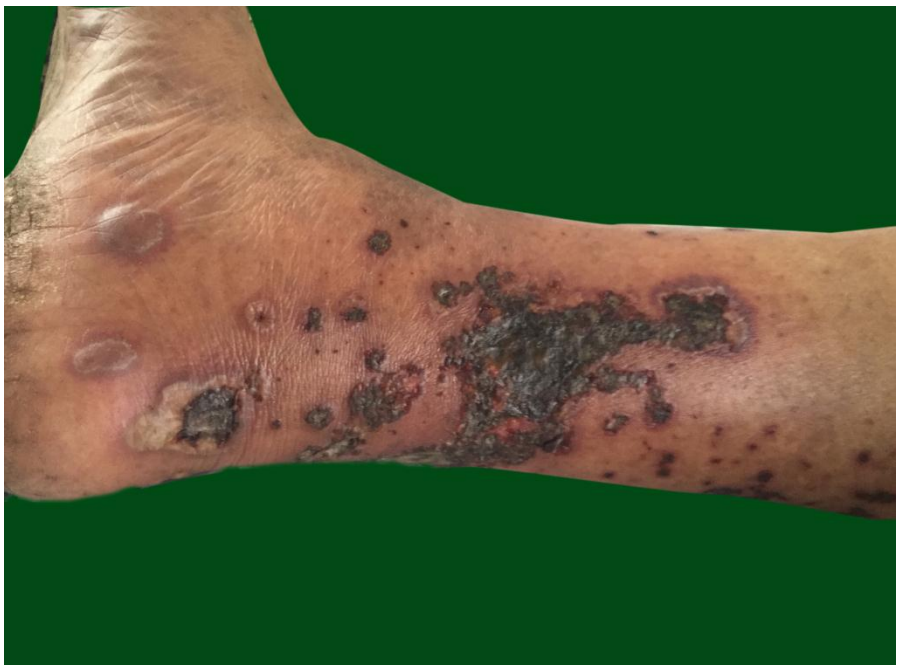


Figure 6: Multiple necrotic plaques with few bullous lesions

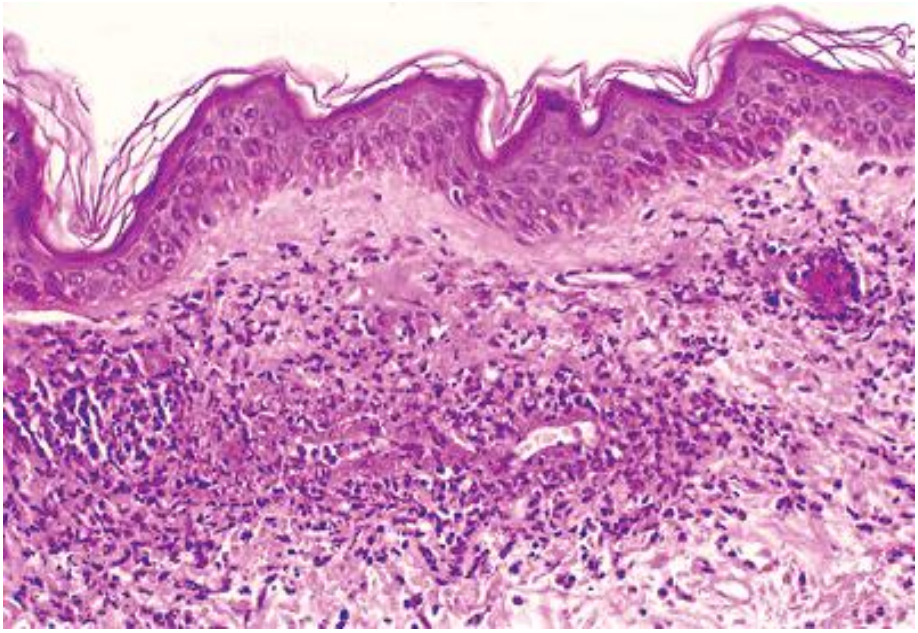


Figure 7: Leukocytoclasticvasculitis showing predominant neutrophilic infiltration around the vessel wall with nuclear dust, fibrin deposits and extravasation of RBCs(H and E 100X)

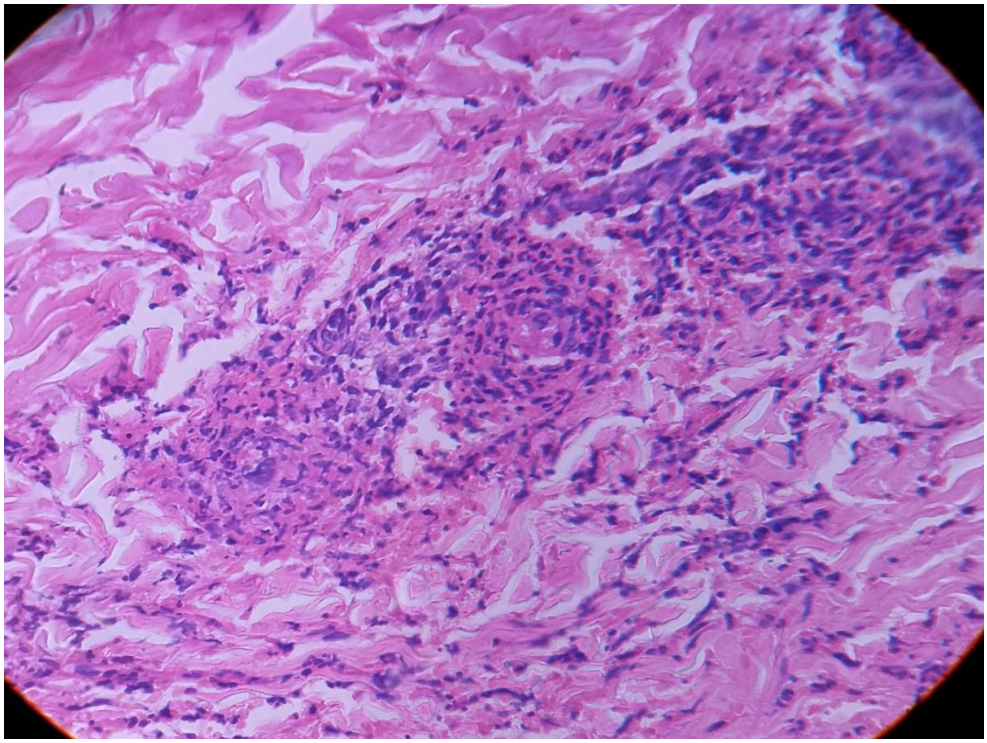


Figure 8: Lymphocytic infiltration around the vessel wall with extravasation of RBCs (H and E 100x)

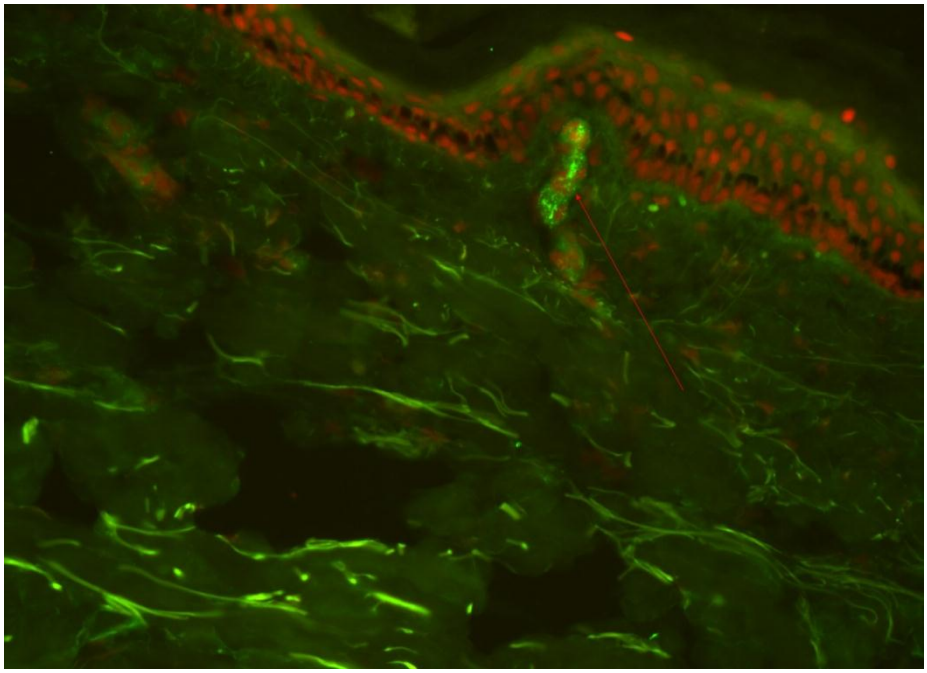


Figure 9: Showing granular blood vessel wall staining with IgA,C3 and fibrinogen on DIF

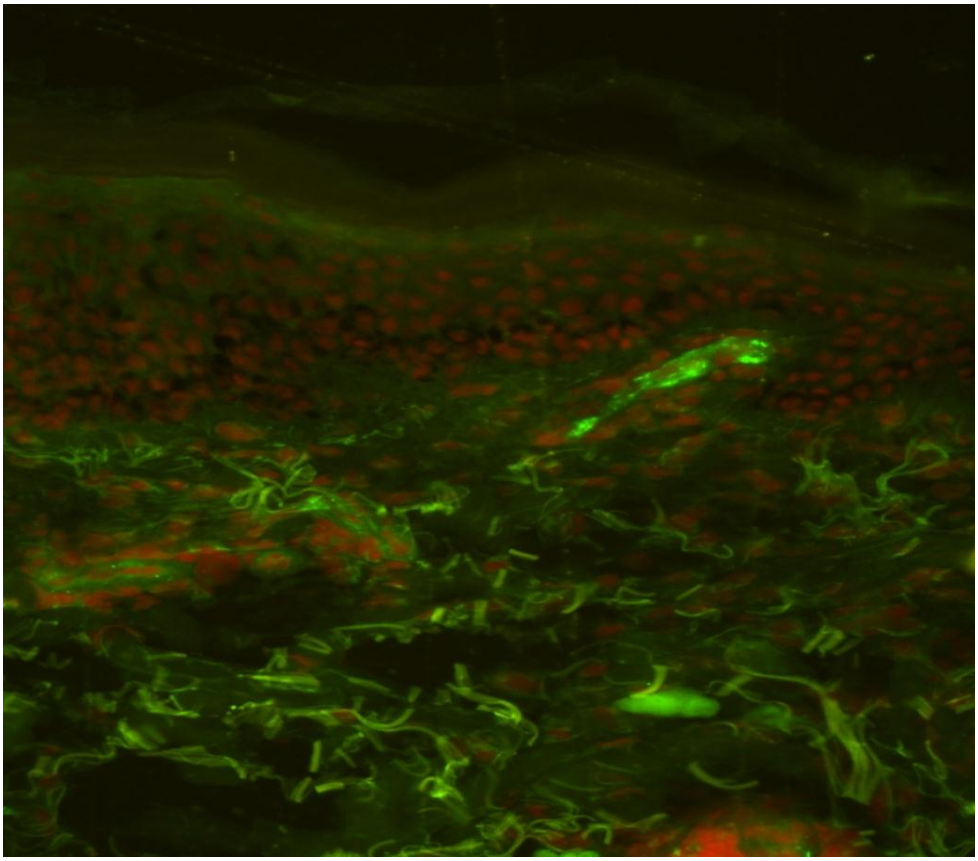


Figure 10: Showing C3 and fibrinogen deposition in the blood vessel wall on DIF

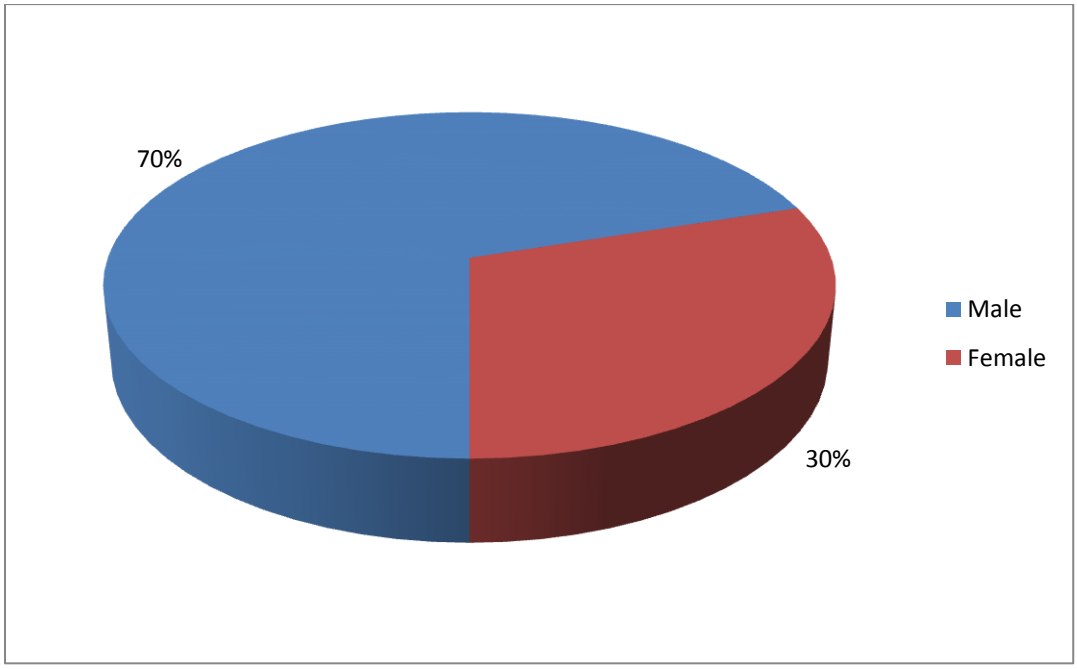
RESULTS

A hospital based cross-sectional study was conducted from November 2014 to August 2016. A total of 50 patients with cutaneous vasculitis were included in the present study.

Gender distribution:

Among 50 patients, 35 (70%) were males and 15 (30%) were females. Males outnumbered females in a ratio of 2.3:1. There was no statistically significant difference in the gender distribution of cutaneous vasculitis. Figure 11 presents the gender distribution of the patients with cutaneous vasculitis included in the study.

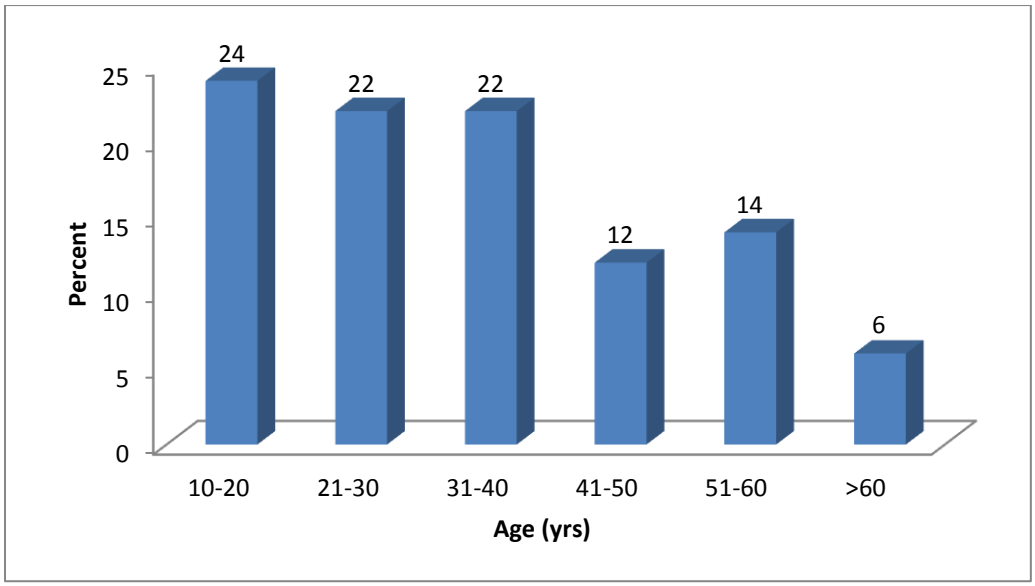
Figure 11: Gender distribution of patients with cutaneous vasculitis



Age distribution:

The age of the patients enrolled in the study ranged from 10 years to 66 years with a mean age of 34.6±15.8years. Figure 12 presents the age distribution of the patients included in the study. Adolescent and adult population constituted the majority of study population with maximum of 12 (24%) patients in the age group of 10-20 years followed by 21-30 years and 31-40 years with 11(22%) patients in each group.

Figure 12: Age distribution of patients with cutaneous vasculitis



Aetiological association:

Probable aetiological association was seen in 23 (46%) patients. Infections followed by drugs were commonest causal factors. History with preceding infections was seen in a total of 11(42%) patients which constituted upper respiratory tract infections URTIs in 9 (18%), cellulitis and scrofuloderma in 1 patient each. Drug intake up to one month prior to the onset of cutaneous lesions was considered relevant. Such association was present in 12 (24%) of the study population. NSAIDs were the commonest implicated drugs in 9 (18%) followed by antibiotics in 2 (4%) and clopidogrel in 1 (2%). Figures 13a and 13b present the distribution of patients with infections and causative drug.

Figure 13a: Distribution of patients with preceding history of infection

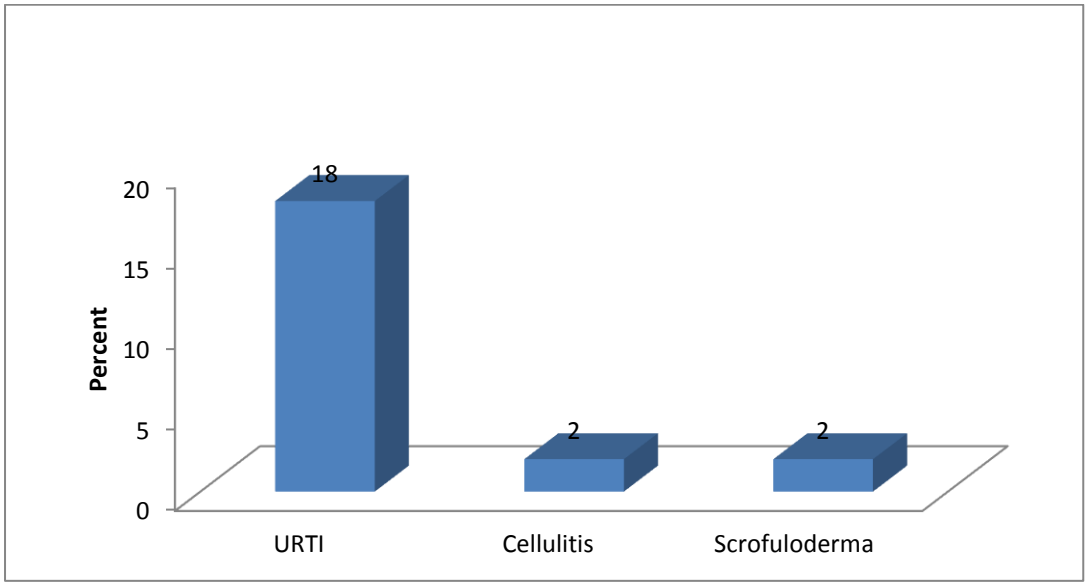
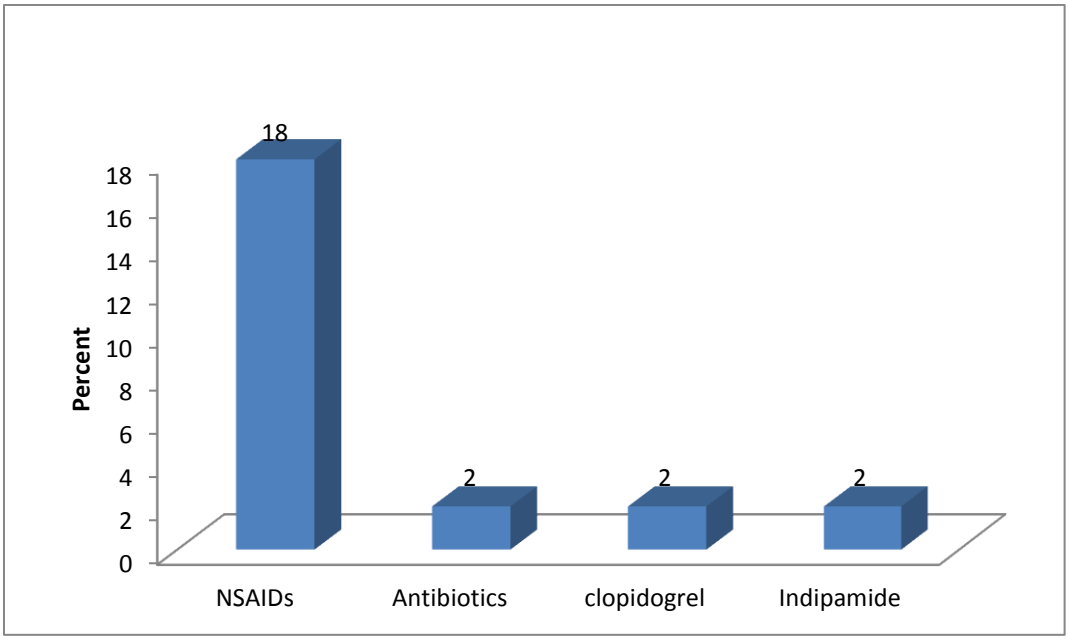


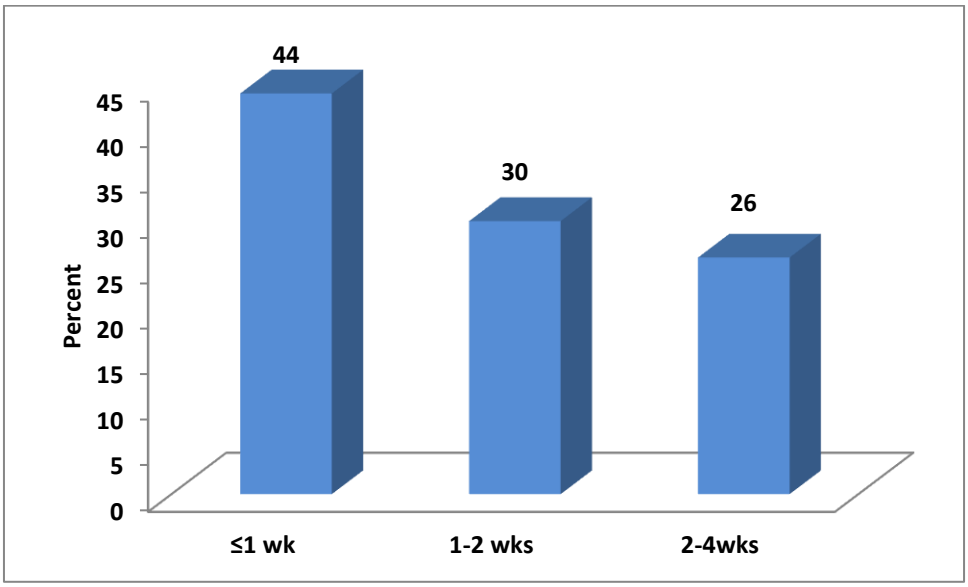
Figure 13b: Distribution of patients with causative drug



Duration of onset:

Out of 50 study subjects of 37 (64%) patients presented within the first 2 weeks of onset of cutaneous lesion and 13 (26%) patients presented 2-4 weeks after the onset. The percentage distribution of patients based on duration of onset of lesin has been presented in figure 14.

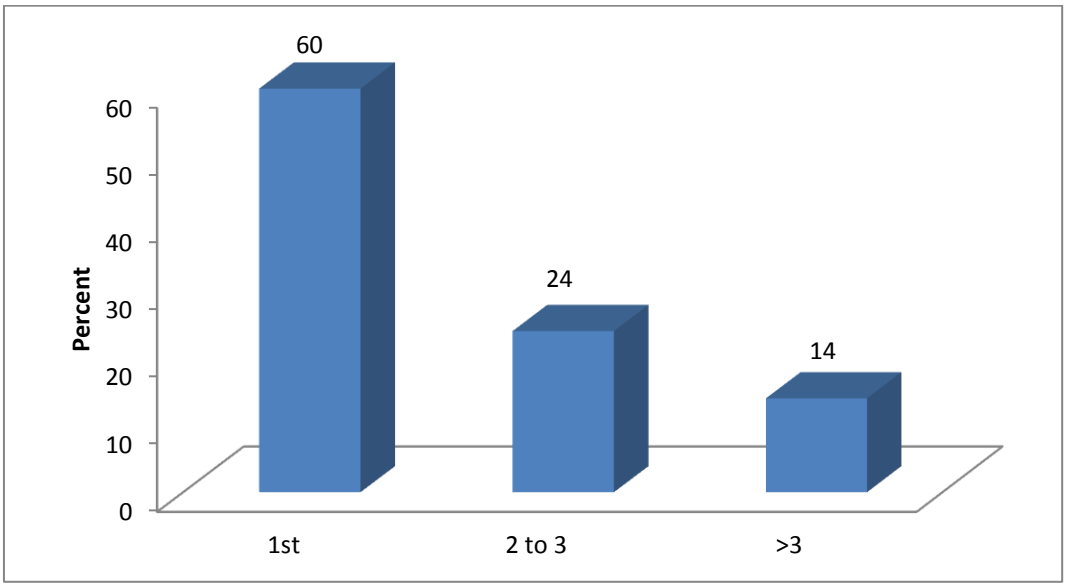
Figure 14: Distribution of patients according to duration of onset



Frequency of cutaneous vasculitis:

In a total of 50 study patients, majority of patients 30 (60%) had cutaneous vasculitis for the very first time and 20 (40%) patients had more than two episodes in the past. The percentage distribution of frequency of cutaneous vasculitis has been presented in the figure 15.

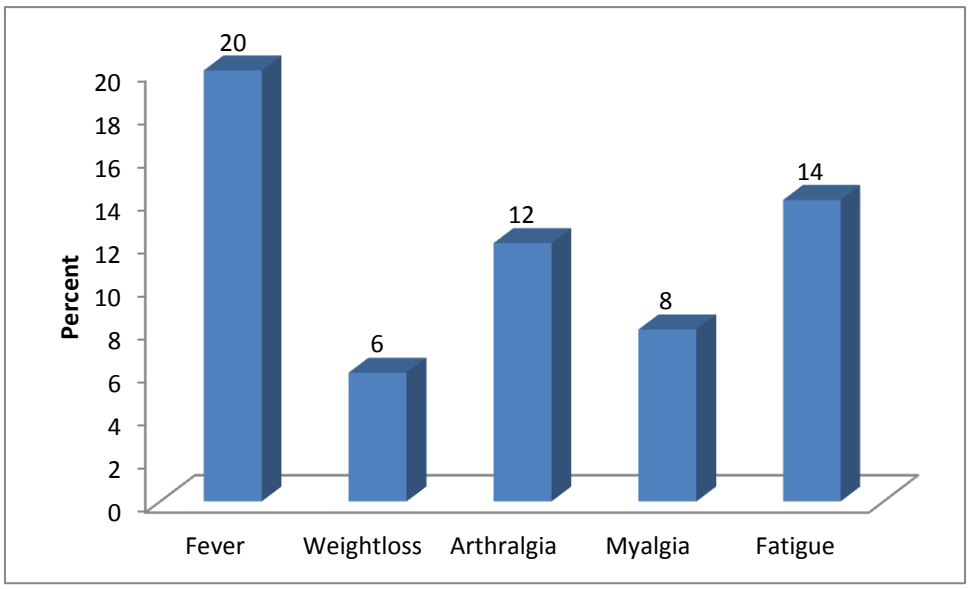
Figure 15: Distribution of patients according to frequency of vasculitic episode



Constitutional symptoms

Constitutional symptoms were present in 15 (30%) patients in the study group. Fever being the commonest symptom in 10 (20%) followed by fatigue in 7 (14%), arthralgia in 6 (12%), myalgia in 4 (8%) and weightloss. Figure 16 presents percent distribution of constitutional symptoms in patients with cutaneous vasculitis.

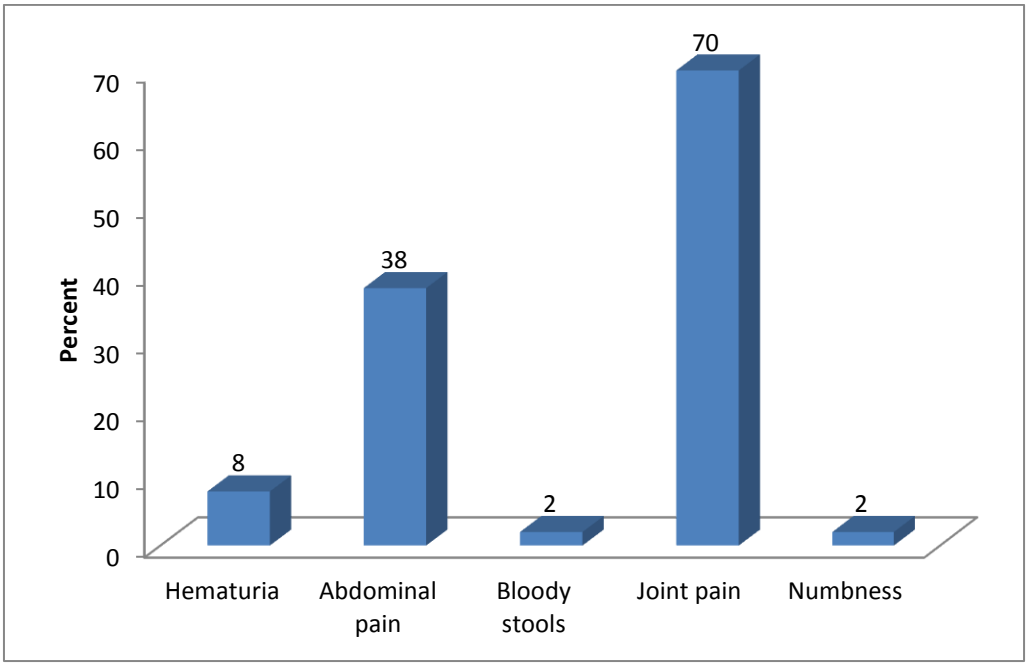
Figure 16: Distribution of constitutional symptoms in patients with cutaneous vasculitis



Extracutaneous manifestation:

Extracutaneous manifestations were seen in 38 (76%) patients. Joint pain was seen in 35 (70%), abdominal pain in 19 (38%), hematuria in 4 (8%), malena in 1 (2%) and parasthesia in 1 (2%). Nine (18%) patients had prior history of hypertension and 4 (8%) patients had diabetes mellitus. Two patients were diagnosed with hypertension at admission and they also had both hematuria and proteinuria on urine analysis. Figure 17 represents distribution in patients with extracutaneous manifestations.

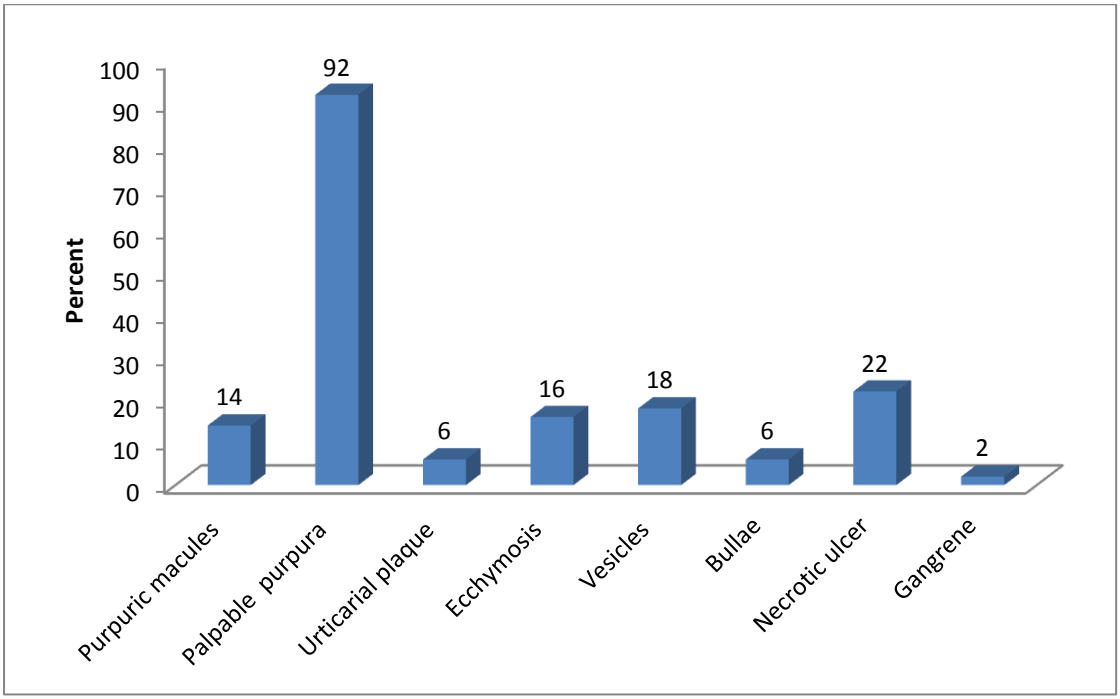
Figure 17: Distribution of extracutaneousmanifesations in patients



Cutaneous manifestations:

Palpable purpura was seen as the hallmark cutaneous finding in 46 (92%) patients followed by necrotic ulcers in 11 (22%), vesicles in 9 (18%), ecchymotic lesions in 8 (16%), purpuric macules in 7 (14%), bullae and urticarial plaques in 3 (6%) in each and gangrene in 1 (2%). The percentage distribution of cutaneous lesion has been presented in figure 18.

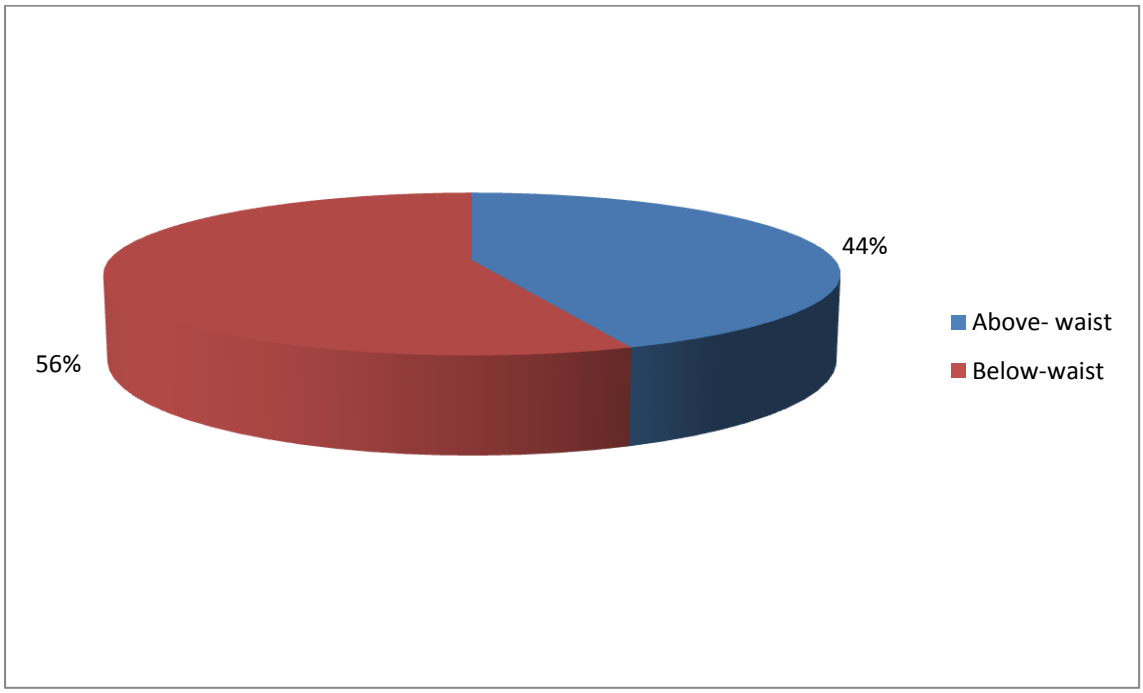
Figure 18: Distribution of cutaneous lesions in patients with cutaneous vasculitis



Distribution of the lesions:

Among 50 patients with cutaneous vasculitis, 28patients (56%) had involvement of only lower extremities and 22 (44%) patients had involvement of upper limbs and/ or trunk in addition to lower extremities. Site of involvement in the patients which has been presented in figure 19.

Figure 19: Distribution of patients by involvement of body



Laboratory parameters:

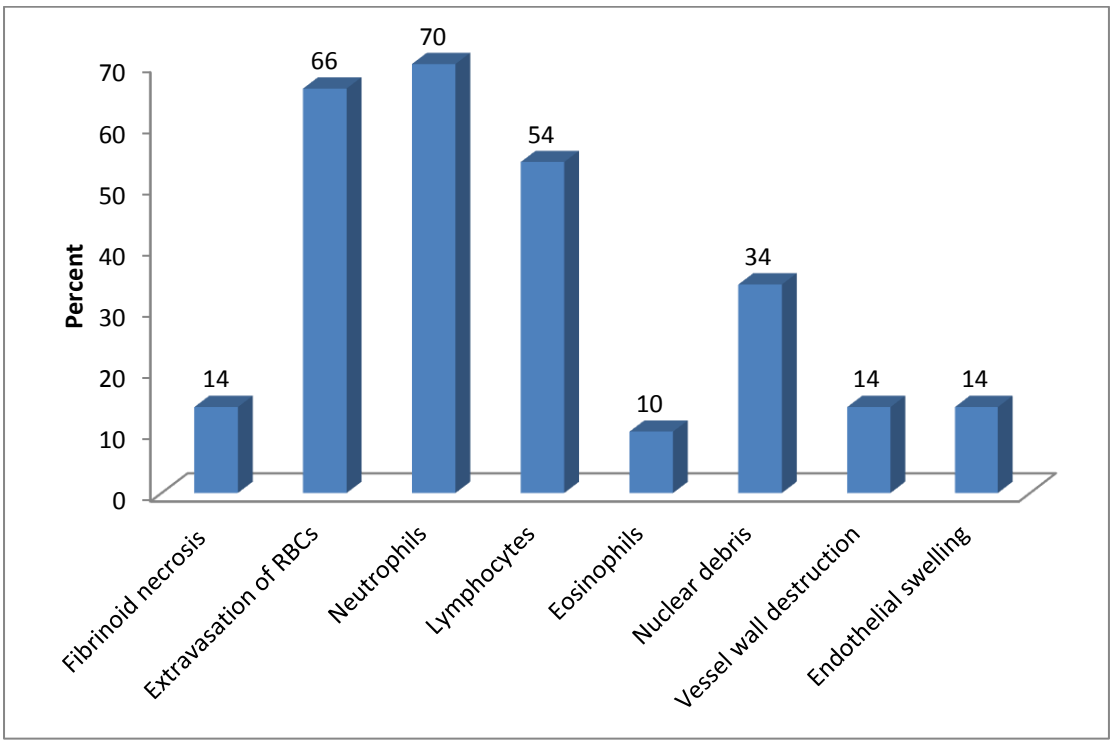
The most common laboratory abnormality was elevated ESR in 31 (62%). Urine analysis showed RBCs and albumin in 9 (18%) patient each. Out of these 5 (10%) had both RBCs and albumin in the urine. Other test done in selected patients showed, ANA positivity in 1(2%) patient, CRP was done in 3 patients and it was raised in 2 (4%) patients and ASLO titre assay was done in 3 patients with one patient having increased titre.

Histopathological findings:

Based on histopathological findings, 40 (80%) of the cases were suggestive of diagnosis of cutaneous vasculitis, 6 (12%) were diagnosed as lymphocytic vasculitis and 4 (8%) did not show any evidence of vasculitis.

On histopathological examination, neutrophilic infiltration was noted in 35 (70%), only lymphocytic infiltration in 13 (26%), eosinophilic infiltration in 5 (10%), mixed infiltration in 14 (28%), extravasation of RBCs in 33 (66%), nuclear debris in 17 (34%) and fibrinoid necrosis, vessel wall destruction and endothelial swelling in 7 (14%) patients each. There was no association between drug intake and tissue eosinophilia.The percentage distribution of histopathological findings has been presented in figure 20.

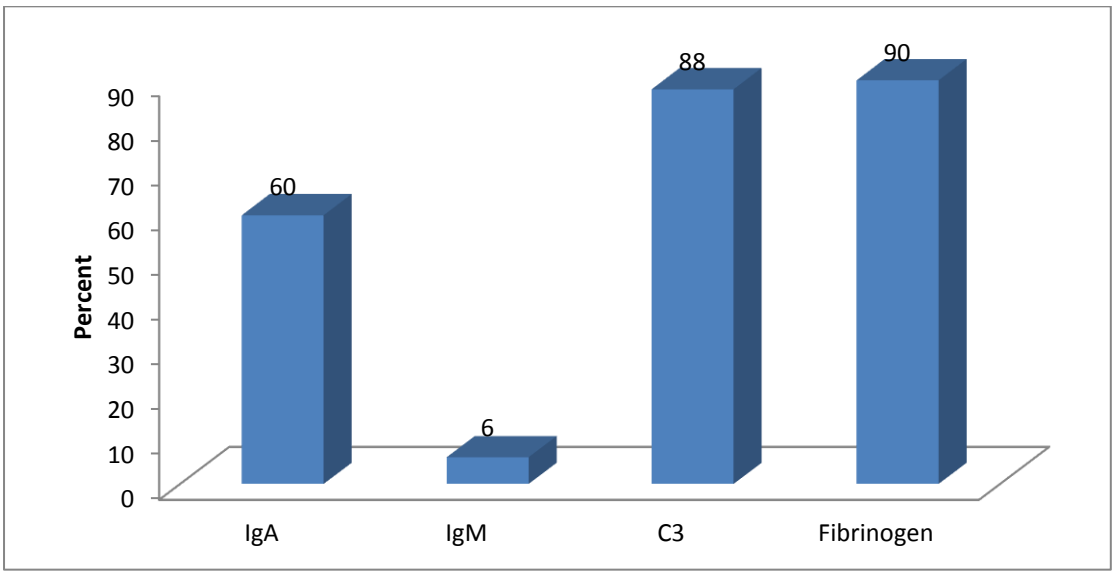
Figure 20: Distribution of histopathological findings



Direct immunofluorescence findings:

Ninety eight per cent patients (n=48) had positivity for at least one immunoreactant on direct immunofluorescence examination. Majority 45 (90%) showed positivity to fibrinogen followed by C3 in 44 (88%) patients, IgA in 30 (60%) patients, IgM in 3(6%) and two patients showed positivity for both IgA and IgM. The percentage distribution of immunoreactants has been presented in figure 21.

Figure 21: Distribution positive immunoreactants on DIF



Ten patients under the age group of 18 years suspected of having HSP according to ACR criteria had 100% positivity for IgA. Twenty patients above the age group of 18 years fulfilled the criteria HSP, only 13 patients had positivity. Seven patient inspite of not fulfilling the criteria had IgA positivity. Presented in table 7

Table 7: Association of IgA with ACR criteria for HSP

Age	**Met the ACR criteria**		**Not met the ACR criteria**	
	Age ≤ 18 years	Age>18 years	Age ≤ 18 years	Age>18 years
Met ACR criteria	12	20	-	18
IgA positivity	10	13	-	07
IgA negativity	02	07	-	11

DISCUSSION

Cutaneous vasculitis is an inflammatory disorder involving the blood vessels of skin and other organ system. It commonly presents clinically as palpable purpura though the presentation can be varied depending upon the size of the blood vessel wall involved. It can be benign and self limiting involving only the skin or can involve other organ system causing life threatening complications.[3] Therefore timely diagnosis is crucial.

While histopathological examination is essential for confirmation of the diagnosis, DIF adds to its credence and helps in further categorization.[4] Not many studies have been done in understanding the diagnostic yield of DIF in cutaneous vasculitis in this part of South India. This study analyzed the clinical features, relevant past history, laboratory, histopathology and DIF findings to confirm the diagnosis.

In this cross-sectional study, we report findings in 50 consecutive patients with cutaneous vasculitis. HSP contributed to the maximum number of patients followed by hypersensitive vasculitis, which was similar to other studies.[6,7,20] Among 50 patients, 35 (70%) were males and 15 (30%)were females. Males outnumbered females in a ratio of 2.3:1. The age of the patients enrolled in this study ranged from 10 years to 66 years with a mean age of 34.6 years. Adolescent and adult population constituted the majority of study population with maximum of 12 (24%) patients in the age group of 10-20 years followed by 21-30 years and 31-40 years with 11 (22%) patients in each group, which was comparable to the study done by Khetan *et al*,[7] comprising of 61 patients, there were 35 males (57.4%) and 26 females (42.6%) aged between 7 and 64 years. The mean age was 29.4 and 35.5 years for males and females

respectively. Maximum number of patients i.e, 20 (36%) were seen in the age group of 16-30 years followed by 31-45 years i.e, 20 (32.7%).

An aetiological association was seen in 24 (48%) of the study subjects, which was comparable to the findings by Gupta *et al*[6] and Sais *et al*[15] who found aetiological association in 40% and 67% of their study subjects. Drugs and infection were the commonest implicating factors in 12 (24%) and 11 (22%) respectively which was in comparison to study done by Gupta et al.[6] The majorly implicated drugs in our study were NSAIDs which was similar to the study done by Khetan *et al* [7] and Gupta *et al*.[6] NSAIDs are easily available over the counter and their indiscriminate use might explain, NSAIDs as commonest aetiological agent. Preceding infections which were present in 11 (22%) patients, URTIs were the commonest cause in 9 (18%), which was similar to reports given by Khetan *et al*[7] (11%) and Al Mutairi (14%).[21]

Table 8: Probable aetiological association in cutaneous vasculiltis

Sl. NO			**Present study**	**Gupta *et al* [6]**	**Khetan *et al* [7]**	**Sais *et al*[15]**
	Probable aetiological cause		48%	40%	39.3%	67%
	1.	Drugs	24%	50%	19.7%	9.6%
	2.	Infection	22%	8%	11%	28%
	3.	Connective tissue disorders	-	-	6.5%	8.4%

History of recurrent lesion was seen in 14% of our patients which was comparable to the studies done by Gupta *et al* [6] (18%), and Ekenstam and Callen[22] (16%) which could be due to the relapsing nature of the HSP which constituted half of our patients. Constitutional symptoms were present in 20% of the study population which was lesser than the findings noted in a study done by Khetan *et al*[7] in which they found constitutional symptoms in 39% of the patients. Fever was the commonest constitutional symptoms in 10 patients followed by fatigue in 7 (14%) patients, arthralgia in 6 (12%) patients and myalgia in 4 (8%) patients which was contrary to the findings seen by Khetan *et al* [7] in which they observed arthralgia in 19 (31.1%) patients, myalgia in 11 (18%) and fever in 6 (9.8%) patients.

Seventy per cent of the study subjects had extracutaneous manifestation. Joint pain accounting for the majority of the symptoms in 35 (70%) patients followed by pain abdomen in 20 (40%) patients and hematuria in 9 (18%) patients which was comparatively higher than the findings noted by Khetan *et al* [7] in which they found extracutaneous manifestation only in 37.7% of the patients in the form of joint pain in 17 (27.9%) patients, pain abdomen and melena in 5 (8.2%) each and hematuria in 3 (6%). Sais *et al*[10] and Gupta *et al*[4] also noted slightly lesser extracutaneous involvement compared to our study in only 51% and 50% of their study population. Henoch Schonlien purpura is characterized by systemic manifestation in the form of articular, gastrointestinal and renal system involvement. The higher frequency of systemic manifestation in our study population could be due to increased number of patients affected with HSP.

Henoch Schonlien purpura was diagnosed based on the American College of rheumatology criteria.[9] The criteria includes a) palpable purpura, b) age $\leq$ 20 years at disease onset, c) bowel angina and, d) wall granulocytes on biopsy. Patients should at

least fulfill two criteria to be diagnosed as HSP. Twelve patients under the age group of 18 years and twenty patients more than 18 years fulfilled the criteria for HSP.

Palpable purpura was the main cutaneous lesion seen in almost all of the patients (n = 46, 92%) followed by necrotic ulcers (n = 12, 24%) which was comparable with studies done by Gupta *et al*[6] 86% and 12% and Sais *et al* [15] 87% and 20% respectively. Involvement of the lower extremities was seen in 66% of the patients in our study which was similar to the study done by Nandeesh[6] and Bouiller *et al* [23]were they observed lower limb involvement in 47% and 70% of their patients. Predominant involvement of lower extremities is likely to be related to the increased gravitational stasis in the lower extremities.

Consistent with the earlier studies,[6,7] elevated ESR was the most common laboratory abnormality seen in nearly two-third of our patients, which could denote the on-going chronic inflammatory process. Eighteen patients (36%) had urinary abnormalities of which 5 (10%) patients had both hematuria and proteinuria both and 4 (8%) patients had hematuria or proteinuria alone which was lesser than the study done by Khetan *et al* [7] in which they observed urinary abnormalities in only 18 (29.5%) of the study population.

Based on the histopathological findings, predominant neutrophilic infiltration mostly confined to perivascular and interstitial location seen in 70% of the patient s as compared to 76% in a study by Sais *et al*.[15] Extravasation of RBCs was seen in 66% of the cases which was lesser compared to 90.5% and 100% in studies done by Gupta *et al*[6] and Sais *et al*[15] respectively. Leukocytoclasia and fibrinoid necrosis were present in 34% and 14% of the patients which was significantly lower than the findings observed by Gupta *et al*,[6] 85% and 89% respectively. Twelve (24%) patients

showed predominantly lymphocytic vasculitis. No association between tissue eosinophilia and drug intake was seen as it was noted in other studies by Bahrami *et al.*[24,25] In a recent study by Johnson *et al,* [26] which comprised of 51 pediatric patients of HSP, showed arteriole involvement in 33 (97%) patients, extravasation of RBCs in 32 (94%), papillary dermal inflammation in 32 (94%), endothelial swelling in 30 (80%), neutrophilic infiltration in the vessel wall in 29 (85%), nuclear debris in 29 (85%) and fibrinoid necrosis in 27 (79%) patients.

Histopathological findings of vasculitis are dependent on the timing of the biopsy. Purpuric lesions obtained in the first hour are characterized by fibrin deposits within the vessel wall accompanied by neutrophilic infiltration of the wall and surrounding hemorrhage and nuclear debris. After 24 hours, neutrophils begin to be replaced by lymphocytes and macrophages. Thus, biopsy done after 48 hours, regardless of the underlying cause may show lymphocytic infiltration. This could explain the variations in the histopathological findings in our study. Comparison of histopathological findings with other studies is presented in table 9.

Table 9: Comparison of histopathological findings with other studies

Sl. No	**Histopathological finding**	**Present study**	**Khetan *et al* [7]**	**Sais *et al* [15]**
1.	Neutrophilic infiltration	70%	50%	76%
2	Lymphocytic infiltration	10%	06%	03%
3	Extravasation of RBCs	66%	90.5%	100%
4.	Leukocytoclasia	34%	85%	95%
5.	Fibrinoid necrosis	14%	89%	90%

DIF analysis revealed presence of at least one immunoreactants in 98% of the patients. Other studies have reported DIF positivity in 39-86 per cent of cases.[3,7, 15, 16, 27] One of the important reason for high DIF positivity in the present study is timing of the biopsy. The importance of timing of biopsy in DIF is paramount and should ideally be done in less than 48 hours.[28] In the present study, biopsy was done in less than 48 hours of onset of the lesion in majority of the study population. The most common immunoreactant was fibrinogen followed by C3, IgA and IgM, which is variable from the study done by Nandeesh,[3] where the common immune deposit was C3 followed by IgG, IgA and IgM. And another report by Sanchez *et al* [29] found IgM, C3 and fibrin as the common immunoreactant. It was observed that variation in the positivity of different immunoreactants between different studies exist.[3,15,16, 27] In concordance with other studies,[15,16] no specific pattern of DIF results was found in vasculitis with different aetiologies and types. Comparison of DIF findings with other studies has been presented in table 10.

Table 10: Comparison of DIF findings with other studies

Sl No.	DIF finding	Present study	Sais *et al* [15]	Nandeesh[3]	Takatu *et al* [16]
1	Positivity	98%	86%	39%	70.2%
2	C3	88%	80.4%	26%	-
3	IgA	60%	64.7%	23%	-
4	IgM	04%	49%	07%	-
5	IgG	0	-	10%	-

The importance of IgA deposits in the vessel wall in the diagnosis of cutaneous vasculitis is controversial, some authors believe it as confirmatory finding[10] while others do not.[30,31] In our study, the overall sensitivity and specificity of IgA for HSP is 71.8% and 61.1% respectively which was lower than reported by Allison *et al,*[30] where the sensitivity and specificity were 86% and 84% respectively. This could be due the fact that ACR criteria[9] was used in this study rather than the EULAR criteria used by Alison *et al*.[30,32]

We also assessed the sensitivity, specificity, positive predictive value, negative predictive value and accuracy between the pediatric and adult population as presented in the table 7. We found the values to be comparatively higher in the children. Therefore, IgA is not very sensitive in adults for HSP which was concurrent with other studies.[(30, 31)]

Table 11: Sensitivity, specificity, positive predictive value, negative predictive value and accuracy between the pediatric and adult population

Characteristics	**Pediatric population (Age ≤ 18years)**	**Adult population (Age > 18 years)**
Sensitivity	83.3%	63%
Specificity	NA	61%
Positive predictive value	100%	65%
Negative predictive value	0	61%
Accuracy	83.3%	63%

CONCLUSION

Cutaneous vasculitis is a poorly understood inflammatory condition due to multitude of manifestations and its association with various infection, drugs, connective tissue disorders and malignancies. In this study, we analyzed clinical features, relevant past history and laboratory parameters to reach a clinical diagnosis of cutaneous vasculitis. Patients were accordingly categorized into the Chapel Hill Consensus Classification. Further histo-pathological examination and DIF was done to confirm the diagnosis. This study confirms various established facts and also throws light on new findings.

The following conclusions were drawn from the study:

1. Adolescent and adults were the commonest age group affected.
2. Preceding infection and drug intake were the major aetiological associations; NSAIDs were the commonest implicated drugs.
3. Palpable purpura was the hallmark cutaneous finding followed by necrotic ulceration.
4. Lower extremities were predominant site involved.
5. Histo-pathological findings were time dependent and the earliest lesions showed neutrophilic infiltration and the older lesions showed lymphocytic infiltration.
6. Drug intake was not associated with tissue eosinophilia.
7. IgA positivity was less sensitive in adults than children for HSP.
8. Systemic involvement was seen in patients with IgA positivity.

Direct immunoflourescence in cutaneous vasculitis is a useful ancillary tool provided there is optimal clinicopathological diagnosis. IgA positivity does not necessarily confirm diagnosis of HSP, but it can be a supportive finding. This study demonstrates that the diagnosis of vasculitis should be interpreted along with clinical, laboratory and hispathological findings, supported by DIF study.

SUMMARY

A hospital based, cross-sectional study was conducted between November 2014 to August 2016 to determine the clinical, histopathological and direct immunofluorescence findings in cutaneous vasculitis. Detailed history was taken from all the study subjects with emphasis upon the relevant preceding history of infection and drug intake prior to the onset.

With the aid of laboratory tests screening for underlying organ involvement was done. Vasculitis is a clinico-pathological diagnosis and microscopic evidence of vascular inflammation is confirmatory. DIF helps in categorization.

Following are the salient findings of this study:

- Adolescents and adults were the common sufferers of cutaneous vasculitis with male preponderance.
- Infection and drugs were the commonest implicated cause in cutaneous vasculitis.
- Systemic involvement in the form of joint pain was the commonest finding.
- Histopathological finding was time dependent and perivascular neutrophilic infiltration and extravasation of RBCs were commonly seen.
- IgA positivity on DIF was not sensitive for HSP in adults.

In the setting of adequate clinicopathological diagnosis and timely biopsy of DIF. DIF helps in categorizing cutaneous vascultis. Though IgA positivity does not confirm the diagnosis of HSP, but it can be a supportive finding.

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ANNEXURES

ETHICAL CLEARANCE CERTIFICATE

Institutional Ethical Committee BIJAPUR-586 103. OUTWARD No. 54/14 Date 24/11/14 BLDE's Shri B.M. Patil Medical College,

B.L.D.E. UNIVERSITY'S
SHRI.B.M.PATIL MEDICAL COLLEGE, BIJAPUR-586 103
INSTITUTIONAL ETHICAL COMMITTEE

INSTITUTIONAL ETHICAL CLEARANCE CERTIFICATE

The Ethical Committee of this college met on 22-11-2014 *at* 3-30pm *to scrutinize the Synopsis of Postgraduate Students of this college from Ethical Clearance point of view. After scrutiny the following original/corrected & revised version synopsis of the Thesis has been accorded Ethical Clearance.*

Title clinical, Histo-pathological and Immunofluo-rescence, Study of cutaneous vasculitis: In a tertiary care hospital.

Name of P.G. student Dr Ayushi, Dept of Dermatology

Name of Guide/Co-investigator Dr Arun. C. Inamadar, Prof & HOD. Dept of Dermatology

for

DR.TEJASWINI. VALLABHA
CHAIRMAN
INSTITUTIONAL ETHICAL COMMITTEE
BLDEU'S, SHRI.B.M.PATIL
MEDICAL COLLEGE, BIJAPUR.

Following documents were placed before E.C. for Scrutinization
1) Copy of Synopsis/Research project.
2) Copy of informed consent form
3) Any other relevant documents.

CONSENT FORM

B.L.D.E.U.'s SHRI B.M.PATIL MEDICAL COLLEGE HOSPITAL AND RESEARCH CENTER, VIJAYAPUR-586103

INFORMED CONSENT FOR PARTICIPATION IN DISSERTATION/RESEARCH

I, the undersigned,_____ , S/O D/O W/O _____, aged ____years, ordinarily resident of _____ do hereby state/declare that Dr. Ayushi of Shri. B. M. Patil Medical College Hospital and Research Centre has examined me thoroughly on _____ at _____ (place) and it has been explained to me in my own language that I am suffering from _____ disease (condition) and this disease/condition mimic following diseases. Further Dr. Ayushi informed me that he/she is conducting dissertation/research titled "Clinical, Histo-Pathological And Immunofluorescence Study Of Cutaneous Vasculitis: In A Tertiary Care Hospital" under the guidance of Dr. Arun. C. Inamadar requesting my participation in the study. Apart from routine treatment procedure, the pre-operative, operative, post-operative and follow-up observations will be utilized for the study as reference data.

Doctor has also informed me that during conduct of this procedure like adverse results may be encountered. Among the above complications most of them are treatable but are not anticipated hence there is chance of aggravation of my condition and in rare circumstances it may prove fatal in spite of anticipated diagnosis and best treatment made available. Further Doctor has informed me that my participation in this study help in evaluation of the results of the study which is useful

reference to treatment of other similar cases in near future, and also I may be benefited in getting relieved of suffering or cure of the disease I am suffering.

The Doctor has also informed me that information given by me, observations made/ photographs/ video graphs taken upon me by the investigator will be kept secret and not assessed by the person other than me or my legal hirer except for academic purposes.

The Doctor did inform me that though my participation is purely voluntary, based on information given by me, I can ask any clarification during the course of treatment / study related to diagnosis, procedure of treatment, result of treatment or prognosis. At the same time I have been informed that I can withdraw from my participation in this study at any time if I want or the investigator can terminate me from the study at any time from the study but not the procedure of treatment and follow-up unless I request to be discharged.

After understanding the nature of dissertation or research, diagnosis made, mode of treatment, I the undersigned Shri/Smt _____ under my full conscious state of mind agree to participate in the said research/dissertation.

Signature of patient:

Signature of doctor:

Witness: 1.

2.

Date:

Place

PROFORMA

Department of Dermatology, Venereology and Leprosy

Serial no:

Ip/op no:

Date:

Name:

Age & sex:

Occupation:

Address & contact no :

Presenting features :

H/o any preceding infection:

H/o any drug intake before the onset of lesions:

H/o recurrent episodes:

Cutaneous lesions:

Other systemic involvement:

Constitutional: fever, weight loss, fatigue.

Musculocutaneous: arthralgias, myalgias.

Renal: hematuria.

Gastroentrologic: abdominal pain, bloody stools.

Neurologic: numbness, paresthesias, weakness.

Cardiopulmonary: shortness of breath, chest pain, cough, hemoptysis.

Ear/nose/throat: sinusitis.

Joint pain

Scrotal pain

Hypertension/ headache:

Provisional diagnosis :

Investigations done :

Haemogram :

ESR:

Urine routine & microscopy:

Histopathology:

Immunofluorencence findings:

Final diagnosis

KEY TO MASTER CHART

ANA	- Anti nuclear antibody
AW	- Above waist
BW	- Below waist
ESR	- Erythrocyte sedimentation rate
C	- Clopidogrel
CRP	- C-Reactive protein
I	- Indipamide
NSAIDs	- Non steroidal anti inflammatory drugs
n	- Normal
UTI	- Upper respiratory tract infection