

THE TELL-TALE SAGA OF PAVING TRANSFIGURATION OF CUTANEOUS VASCULOPATHIES IN CONCORDANCE WITH IMMUNOFLORESCENCE -A THREE -YEAR CLINICOHISTOPATHOLOGICAL STUDY

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ABSTRACT

Introduction: Vasculopathies of cutaneous origin are a complex and incongruous group of inflammatory disorders affecting cutaneous vessels. Several factors such as infections, drugs, connective tissue diseases or malignancies can lead to activation of pathways of vasculopathies.

Aim: The aim of the study was to carry out a histopathological study and classify cutaneous vasculopathies.

Materials And Methods: It was a cross sectional descriptive study done in Armed forces medical services Base Hospital Delhi from June 2014- June 2017) where the cutaneous vasculopathies histopathology analysis with immunofluorescence concordance was done.

Results: Total of 106 cases of clinically suspected vasculopathies were enrolled in the study. In our study the highest frequency of cutaneous vasculopathies was among the patients between the age group of 31- 40 years (n=33) followed by 41-50 years age group (n=25). The most common dermatological manifestations were palpable purpura (n=54, %), followed by petechiae (n=18), plaques, (n=07), ulcers (n= 03), vesicles (n=2), pustules (n=02) and necrosis (n=02). Arthralgia was the most common extracutaneous manifestation in our study followed by pain in the lesions. Pain in abdomen (n=10), fever (n=09), diarrhea (n=03), malena and hemoptysis (02 each) and oral ulcers (01) were seen. ANCA (Anti neutrophil cytoplasmic antibody) was done in 18 patients and only 01 was found to be positive for c-ANC.DIF (Direct immunofluorescence) study was done in 88 patients. 53 patients revealed the presence of at least one of the immune complexes deposited in the vessel walls. 35 repondents showed no deposits. C3 was the most common immunoreactant seen in 36 patients followed by IgA in 25(%) of the cases.

Conclusion: The study showed that Careful clinical examination and correlation with laboratory findings, histopathological findings and immunofluorescence should be done in vasculopathies. If one fails to recognize this, it may result in significant patient morbidity and mortality.

KEYWORDS: Dermat, Vascular morphology, Clinicopathology, Immunofluorescence studies

1-INTRODUCTION

2.1. Cutaneous vasculopathies are a heterogenous group of inflammatory disorders affecting skin blood vessels. They may be triggered by several factors such as infections or drugs or may be related to connective tissue diseases or malignancies. Cutaneous vasculitides are a specific pattern of skin vessel inflammation that is limited to the skin. They may develop at first at the skin level and then proceed to systemic involvement or be a cutaneous manifestation of a systemic vasculitis[1]. Diseases of the blood vessels of the skin are conventionally grouped into six major categories as Non inflammatory purpuras, Vascular occlusive diseases, Urticarias, Vasculitides which are further divided into-Acute vasculitis, Chronic lymphocytic vasculitis, Vasculitis with granulomatosis ,Neutrophilic dermatoses and Miscellaneous[2]. Based on the size of the vessel concerned[3] like large vessel vasculitis which include -Giant cell arteritis[4],Takayasu's arteritis , Medium vessel vasculitis includePolyarteritisnodosa(PAN)[5] and Kawasaki's disease[6] ,lastly Small vessel vasculitis include ANCA associated vasculitis, Wegener's granulomatosis[7] ,Churg Strauss syndrome, Henoch-Schonlein purpura and Cutaneous leucocytoclastic vasculitis and Cryoglobulinaemic vasculitis [8].Histopathological examination is essential in defining these groups as the dermatological manifestation show a considerable overlap. Many entities require the use of ancillary histochemical and fluorescent techniques for further confirmation. Addition of newer techniques along with histopathological study of cutaneous vasculopathies, correlating them with clinical features, provides a critical role in the management of these patients. The main aim of this study was to identify patients with suspected vasculopathies based on clinical preliminary work up and subsequently study the histopathological features of biopsies done in these cases in adjunct with relevant laboratory and ancillary investigations in concordance with immunofluorescence in these patients and correlate them with the findings in order to arrive at a morphological diagnosis.

MATERIALS AND METHODS

It was a cross sectional descriptive study from June 2014- June 2017, conducted in Department of pathology of Base hospital Delhi. The clinical presentation of these patients with specific reference to the involvement of the skin, musculoskeletal system, renal system and central nervous system were recorded in 106 patients. The investigation profile

of all these patients was recorded. Investigations like Complete blood count (CBC), Liver function tests (LFT), urine analysis, Anti Streptolysin O (ASO), Erythrocyte sedimentation rate (ESR), Hepatitis serology, ChestX-Ray were included. Immunofluorescence studies were utilized to delineate these lesions. ANA and ANCA was done in all these patients. The cases evaluated for coagulopathies, metabolic vasculopathy and connective tissue disorders. The histopathological features of all skin biopsies studied in patients as above were correlated with laboratory findings and clinical features.

The prevalence of these vasculopathies in respect to the Indian population will be established. In these 106 patients, presenting to skin OPD of Base Hospital Delhi Cantt with clinical vasculopathies and undergoing skin biopsies for the same were noted.

Calculation of sample size was done assuming that only 30-40% of suspected vasculopathies are confirmed as vasculitis and marginal error of 5% to detect true difference, then sample size formula will be:

$$N = (4PQ)/L^2 \text{ (read it as l square)}$$

-Where P = prevalence, Q= 1- P and L= marginal error.

By using the above mentioned formula the estimated sample size of 96. If we consider at least 10% non response that means have to add 10% of 96 i.e 10 so final sample size of the study was 106.

-Patients with bleeding diathesis, unwilling to give written consent and pregnant females were excluded from the study. Punch biopsy was done in the Dermatology Operation theatre under sterile conditions. 5 mm punch/ surgical biopsy provide an adequate tissue sample for histopathological examination. Round body skin biopsy punches, iris scissors, skin hook, Adson's toothed forceps, suture material (prolene or Mersilk) and a needle holder were required for the biopsy procedure. Two skin biopsies (punch biopsy, 4 mm) were taken in all cases, one each for routine histopathology and direct immunofluorescence (DIF). For histopathology the tissue sample was received in formalin and for immunofluorescence the biopsy was received in normal saline.

Statistical Analysis :The data was analysed by Statistical Package for the Social Sciences, SPSS statistical software (version11.0; SPSS Inc., Chicago, IL, USA). Descriptive statistics were expressed as means and standard deviations and pearsons chi Square test ,p value was applied.

RESULTS

Total 106 cases of clinically suspected vasculopathies in department of pathology were enrolled in the study. Patient were referred from different parts of the country.

1. AGE DISTRIBUTION: The minimum age was 07 years and maximum age was 82 years. 62(56.4%) were males and 48(43.6%) cases were females. In our study, most common site was the lower limbs (n=79) (as shown in table/ fig 1).

Table/Fig1: shows the distribution of lesions.

Site	Frequency	Percent(%)
Abdomen	03	3.6
Chest	03	3.6
lower limb	79	71.9
Upper limb	21	20.9
Total	106	100

The most common aggravating factors was drugs (n=29).The most common offending drugs included NSAIDS (11), antibiotics (07), OCP's (04), anti-diabetics (03), anti-hypertensive (02) and homeopathic medicines (02). Malignancy was not detected in any of our cases. Table/Fig 2 shows the etiological factors.

Table/Fig 2: Etiological factors

Etiological factors	N (%)
Idiopathic	54(51%)
Drugs	29(27%)
Infections	22(21%)
Connective tissue disorders	01(1%)
Total	106(100%)

A wide spectrum of cutaneous lesions was seen ranging from a single type to a combination of two or more types of lesions. The most common presentation was palpable purpura (n=54, %), followed by petechiae (n=18), plaques (n=07), ulcers (n= 03), vesicles (n=2), pustules (n=02) and necrosis (n=02). Systemic involvement that is extracutaneous manifestations was seen in 68 patients. Arthralgia was the most common extracutaneous manifestation in our study followed by pain in the lesions. Pain in abdomen (n=10), fever (n=09), diarrhea (n=03), malena and hemoptysis (02 each) and oral ulcers (01) were seen. P value is significant(<=0.0005) in our study for extracutaneous manifestations as depicted in (Table/Fig 3).

Table/Fig 3 shows laboratory parameters.

LAB PARAMETERS	N(%)
Anemia	24(21.8%)
Leukocytosis	43 (39.1%)
Raised ESR	61(53.6%)
Elevated Serum-urea	03 (2.7%)
Elevated serum - creatinine	03 (2.7%)
Abnormal urine examination	
Albuminuria	19(17.3%)
Haematuria	07(6.4%)
Abnormal chest X -Ray	01(0.9%)
Anti-nuclear antibodies (ANA)	05(4.5%)
C - ANCA	01(0.9%)
ASO titre	08(7.3%)
Montoux test positive	01(0.9%)
HCV positive	03(2.7%)
Elevated CRP	19(17.3%)
HIV	All negative
HbsAg	02 (1.8%)

H & E sections were studied of 106 clinically suspected cutaneous vasculopathies. (Table Fig 4 /Fig 5) shows the frequency and percentage of histological examination in the slides examined.

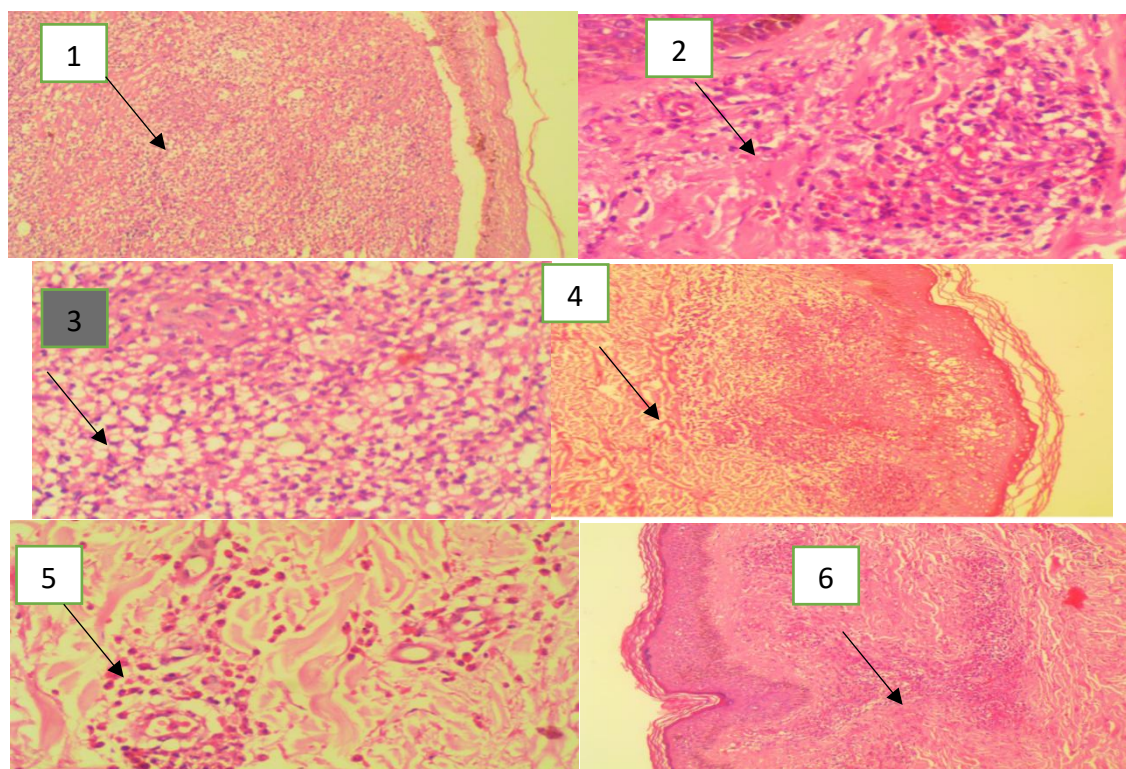
Table /Fig 4 :shows histopathological features in the slides examined.

Histopathological Examination	Frequency	Percent Positive
Positive	89	84.5
Negative	17	15.5
Total	106	100

Table/Fig 5: Frequency and percentage of histological examination in the histopathology slides .

Histopathological features	Frequency
Inflammatory infiltrate	93/106
Leukocytoclasia	70/106
Endothelial swelling	64/106
Dermal oedema	48/106
RBC extravasation	42/106
Fibrinoid necrosis	60/106

Table/Fig 6: Highlights of histopathological images :1.Inflammatory infiltrates(10X) H& E)2.Leukocytoclastic changes- Nuclear debris from infiltrating neutrophils((20X H &E)3.Endothelial Swelling(40X H&E)4.Dermal oedema(10X,H&E) 5.RBC Extravasation (20X H&E)6.Fibrinoid necrosis(scanner view,H&E).



In this study of cutaneous vasculopathies, histopathologically the most common was vasculitis (83) followed by non-inflammatory purpura (02) and chronic urticaria (02) and neutrophilic dermatosis(02), No evidence of vasculitis was seen in (17) patients. Amongst 83 cases of vasculitis, SVV (small vessel vasculitis) was the most common and was seen in 81 cases. MVV (medium vessel vasculitis) was seen in only 02 cases. 81 of the patients with clinically diagnosed SVV showed features of SVV. But only 02 of the 08 patients who were clinically suspected as MVV showed histological features of MVV. Out of 71 cases of leukocytoclastic vasculitis, cutaneous leukocytoclastic angiitis/ HSV(Herpes simplex virus) were seen in 50 cases. Lymphocytic vasculitis was seen in 9 cases, Granulomatous vasculitis was seen in 01 case. MVV (medium vessel vasculitis) was seen in rest 2 cases. The remaining had features of LCV (large cell vasculitis). The most common pattern amongst SVV was Leukocytoclastic vasculitis (71) followed by lymphocytic vasculitis in 09 patients and granulomatous vasculitis in 01 patient. Histopathology was done in all the patients while DIF(direct immunofluorescence) study was done in 88 patients. 53 patients revealed the presence of at least one of the immune complexes deposited in the vessel walls. 35 respondents showed no deposits. C3 was the most common immunoreactant seen in 36(43.3%) patients followed by IgA in 25(%), IgM in 18 and IgG in 14. Extracutaneous manifestations in the form of arthralgia, pain abdomen and pain at the lesions was seen. Out of four clinically suspected urticarias presenting with urticarial wheals, three were found to have feature of urticaria in the form perivascular infiltration of neutrophils, lymphocytes and eosinophils. In our study, one patient was found to have Wegener's granulomatosis. She presented with ulcer in upper limb and haemoptysis. Cytoplasmic antineutrophil cytoplasmic antibodies(C-ANCA)as positive. She had nasal crusting along with breathlessness. Chest X Ray showed solitary nodules both lungs. Renal involvement was seen in the form of haematuria. Histologically leukocytoclastic vasculitis of small vessels was seen along with eosinophils and palisading granulomas. IgG and C3 deposits were seen on DIF. In five patients of clinically suspected septic vasculitis, four of them were young serving soldiers who were referred from field areas with complicated cases of sepsis. One of the them had been referred from Tripura as a case of rickettsial infection and the other from Kargil as a case of fungal infection. These patients presented with plaques, petechiae and one of them as pustules. Systemic features in the form of fever or severe pain at the lesions was present. TLC, ESR, C Reactive Protein was elevated in all the cases. Blood urea and serum creatinine was elevated in one of the cases. The most common laboratory abnormality was elevated ESR found in 59 patients followed by leukocytosis in 43 patients. Elevated CRP was seen in 19 and Raised ASO titre was seen in 08 patients. Anaemia was seen in 24 patients. ANA(Anti nuclear antibodies) was positive for 05 patients. Positive RF was found in 03 patients. ANA was detected in 05 patients. ANCA was done in 18 patients and only 01 was found to be positive for c-ANCA. In our study value of ESR was significant($p < 0.05$). DIF showed no deposits (Table 7/ Fig7 and Table8/ Fig8). Histopathology was done in all 106 patients while DIF was done in 88 patients only. 53/88 revealed presence of atleast one immune complexes deposited in vessel walls. 35/88 Respondents showed no deposits.

Table7/ Fig-7 (showing statistical analysis by pearsons chi Square test ,p value between IF and biopsy ,Out of 106 patients DIF was done in 88/106)

IF	Histopathological Examination	Total	Pearson Chi-Square	p-value
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	Positive	Negative		23.098a	<0,001
Positive	53	0	53		
Negative	22	13	35		
Total	75	13	88		

Table 8/Fig8:Comparitive analysis of clinical diagnosis,with histopathologic diagnosis and DIF.

Clinical diagnosis (No.)	Histological Diagnosis	DIF
Hypersensitivity vasculitis/ Cutaneous LCV(51)	Leukocytoclastic vasculitis: 50 Neutrophilic – 30 Neutrophilic+ eosinophilic – 20	N:48 Neg(16) Pos(32) C3- 8, IgG,C3: 12
Henoch Schonlein purpura(10)	Leukocytoclastic vasculitis : 08 Neutrophilic+ eosinophilic : 05 Neutrophilic :03 NEV: 02	N:09 Neg(01) Pos(08) IgA, C3(02), IgA(04), IgG, IgA, IgM, C3(2)
Urticarial vasculitis (13)	Leukocytoclastic vasculitis : 07 Neutrophilic+ eosinophilic : 07 NEV: 06	N=11 Neg(07) Pos(04) IgA, IgM, C3(03) C3,IgA=01
Septic Vasculitis (05)	Leukocytoclastic vasculitis:05 Vascular damage Occlusive thrombi and fibrinoid change Neutrophils	N=01, Neg (01)
Connective tissue disease (01) Rheumatoid vasculitis (01) Leukocytoclastic vasculitis : 01	Neutrophilic+ eosinophilic : 01 (N>E)	N=01 Pos(01) IgG, C3(1)
Wegener's granulomatosis (01)	Leukocytoclastic vasculitis of small vessels Neutrophilic+ eosinophilic Granuloma	N=01 Pos(01) IgG,C3=01
Lymphocytic Vasculitis(09)	Perivascular infiltration of lymphocytes, endothelial swelling, fibrinoid deposition	N=06 Neg (02)Pos(04) IgM, C3 (04)
Medium vessel Vasculitis(09)	Thrombosis and fibrinoid necrosis of medium vessel, infiltration with neutrophils(02) NEV(01)	LCV(06) N=02 Neg (01)Pos(01) IgM (01) N=05 Neg(04) Pos(01) C3=01
Non Inflammatory purpura(05)	RBC extravasation in upper dermis	NA
Chronic Urticaria(04))	Perivascular infiltration of lymphocytes+ eosinophils+ neutrophils(03) NEV(01)	N=04 Neg(03) Pos=01 IgM=01
Neutrophilic Dermatoses(02) Sweet syndrome(02)	Neutrophils++ Perivascular oedema	NA

DISCUSSION

Cutaneous vasculopathies is a poorly understood entity due to its varied clinical manifestation and its overlap with various infections, connective tissue disorders and malignancies ,confirmation of the same requires several modalities like immunofluorescence and biomarkers are used[9]. In this study we recorded history, clinical features, various laboratory tests were recorded and analysed to reach a clinical diagnosis of cutaneous vasculopathies[10-12]. 89 out of 106 cases were diagnosed as vasculopathy on histopathology as the rest 17 did not fit in the categories of small vessel vasculopathy, Medium vessel vasculopathy and Leucocytoclastic vasculitis.

In this cross sectional study, a total 106 cases of clinically suspected vasculopathies at our institute were screened. The highest frequency of cutaneous vasculopathies was among the patients between the ages 31-40 years(n=36) followed by

41-50 years age group (n=29). Khetan et al [13] revealed that the maximum number of patients was seen in the age group of 16-30 years followed by 31-45 years. In our study 62(56.4%) patients were males and 48(43.6%) patients were females. Similarly Mutairi[14] reported 56% males and 43.9% females who were affected. Rana et al also showed male preponderance [15]. However Leelavathi et al[16] and Chowdhury et al showed [17] equal occurrence among males and females. Palpable purpura (n=54, 58%) is the most common. In our study we found 26.8 % of our cases were drug induced. Similar to our study, NSAIDs was the most common offending drug found in studies by Chowdhury et

al and in study by Swamy and Bhat[18]. 21.5% patients were associated with infections. [M](#)

Mostly upper respiratory infections were seen.

Causes of vasculitis was undefined in 51.6% cases in our study. It is in consistence with studies by Chowdhury et al who found 47% idiopathic, 30% drug induced and 23% associated with infections. Alexander et al[19] however found 78% cases as idiopathic, 4% due to infection, 4% as drug induced and 14% associated with connective tissue disease. Malignancy was not detected in any of our cases. Thus we found that the most common cause of vasculitis is idiopathic. The aggravating factors were found in 58 patients. This was similar to aggravating factors found in a study in Mangalore by Swamy and bhat who claimed drugs followed by exercise as the most common aggravating factors. In our study lower limbs were preferentially affected in 72 % cases followed by upper limb in 21% cases. Similarly in studies by Chowdhury et al and Chintungunta et al, lower limbs were affected the most in 100% and 94.3% respectively[20]. This could be due to sluggish blood flow in the dependant areas which facilitate deposition of immune complexes[16-18].

However Khetan et al [21] showed maximum involvement of upper limbs (52.4%) Systemic involvement was seen in 68 (62%) of the respondents. Chintagunta et al observed systemic involvement in 52.6% and Gupta et al observed in 50% cases. Arthralgia was the most common symptom present in 24.5% cases followed by pain in the lesions in 16 cases. Khetan et al and Gupta et al demonstrated arthralgia as the most common symptom in 31% and 35% cases respectively. However Chowdhury et al found that pain was the most common symptom. In our study, the study population comprised of 106 clinically suspected cases of cutaneous vasculopathies. 93(84.5%) patients showed histopathological evidence of vasculopathies. 17 (15.5%) showed no evidence of vasculopathy. Inflammatory infiltrate was seen in all the cases (100%) followed by leukocytoclasia in 69.8% cases. This was similar to study conducted by Swamy and Bhat who reported 100% cases with inflammatory infiltrate. Khetan et al, showed leukocytoclasia as the most important histological finding followed by endothelial swelling and fibrinoid necrosis.

Among vasculopathies in our study, vasculitides (73.6%) is the most common.

This is also observed by Carlson et al[22]. Amongst the vasculitis, small vessel vasculitis is seen in 97.5% and medium vessel vasculitis is observed in only 2.4% cases. This is in consonance with Khetan et al who observed SVV in 96% and MVV in 4% cases. Low frequency of MVV in our study may be because of the fact that MVV is segmental and patchy process. All the vessels of the same caliber may not be affected. Therefore the biopsy might have missed the involved medium sized vessel leading to sampling bias. Therefore multiple biopsies should be taken at different sites.

Amongst the SVV, the commonest histopathological finding in this study was leukocytoclastic vasculitis. It is seen in maximum cases (88%) cases followed by lymphocytic vasculitis in 09 (11%) cases and granulomatous vasculitis in 01 (1%) case. Similarly Chowdhury et al demonstrated LCV as the most common pattern in 70% patients and lymphocytic vasculitis in 26.7% patients. Gupta et al reported LCV as the most common histological finding followed by lymphocytic vasculitis. Chintagunta et al had noted LCV in 92% cases, lymphocytic vasculitis in 2.6% cases and three showed no evidence of vasculitis. DIF was done in 88 cases and 53 (60%) patients revealed the presence of at least one of the immune complexes deposited in the vessel walls. 35 respondents showed no deposits. Barnadas [et al [23] observed 82% positivity, Khetan et al demonstrated DIF positivity in 62% cases only. Alalwani et al [24] found 70.5% positivity. Nandeesh et al [25] found 39% cases. However Leelavathi et al had found 87% negative DIF. Chowdhury et al found DIF positivity in only 45% cases. Alexander et al found 62% DIF positivity and Gupta et al[26] found 73.9% positive DIF cases. Grunwald et al [27] showed 92% positivity and also demonstrated that DIF is a very sensitive test in the diagnosis of vasculitis and can be used in all stages of vasculitis. P value is significant and is correlating in earlier studies. In our study, the cases which did not show any evidence of vasculopathy on histopathology were DIF negative as well[28-32]. The most important factors that affect the diagnostic yield of DIF are timing of the biopsy and presence of extracutaneous symptoms. It was seen in 85 % of our cases who showed extracutaneous manifestations and DIF positivity. Histopathological findings of our study were similar to that of Chowdhury et al where they found maximum cases of CLA(73.3%) followed by HSP (20%) and UV(3.3%) and Chintagunta et al who observed CLA in 71% cases, HSP in 26% cases and UV in 2.6% cases.

In our study, the cases which did not show any evidence of vasculopathy on histopathology were DIF negative as well. The most important factors that affect the diagnostic yield of DIF are timing of the biopsy and presence of extracutaneous symptoms. It was seen in 85 % of our cases who showed extracutaneous manifestations and DIF positivity. Histopathological examination is essential for the confirmation and identifying the cause, DIF is a robust tool which adds credence to the diagnosis. In our study 20% of the skin biopsies from clinically suspected vasculopathic patients were DIF negative

and were diagnosed only on histopathology. Nandeesh et al also observed substantial number of DIF negative cases in histopathologically confirmed vasculopathic cases. DIF may be falsely negative in case of late lesions or due to improper handling and storage of skin biopsies. Low positivity of DIF in our study may be because most of the patients in our study had their biopsy done after one week of the onset of lesions. Many patients were not aware of the exact duration of their lesions. Many of the patients gave history of drug intake for the lesions which may have affected the DIF positivity.

LIMITATION

The main limitations that we faced in our study was improper sampling error of tissue biopsies which was not freshly procured and poor patient follow up due to floating population in our hospital.

CONCLUSION

Vasculitis shows variable clinical manifestations. The most common causes of cutaneous vasculopathies were drugs followed by infections with innumerable mimics. But in majority of the cases it was idiopathic. This highlights the importance of detailed drug history, rational approach in suspected cases presenting with cutaneous vasculitis. Careful clinical examination and correlation with laboratory findings, histopathological findings and immunofluorescence should be done. Thorough diagnostic workup and a more extensive evaluation to look for extracutaneous involvement is need of the hour, followed by follow up of these patients along with immunofluorescence is important to avoid any serious systemic involvement, with view of important factors that affect the diagnostic yield of DIF and timing of the biopsy and presence of extracutaneous symptoms.

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