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CUTANEOUS VASCULITIS: A RETROSPECTIVE STUDY OF THE HISTOPATHOLOGICAL PATTERNS AT A TERTIARY CARE CENTER

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ABSTRACT

Background: Cutaneous vasculitisis a condition with various aetiologies, morphological and histopathologic patterns. Skin biopsy is the gold standard in diagnosis and helps in guiding further investigations and treatment. Based on the type of vessel disrupted by inflammation (small and/or medium), the distribution of vasculitis in the dermis and subcutis, and the predominate inflammatory cell-type mediating vessel wall damage, a list of relevant differential diagnoses can be generated. This study aimed to analyzed the spectrum of histopathological patterns and to determine the correlation with morphology. **Material & methods:** Histopathologically proven last 5 year 100 slides of cutaneous vasculitis were analyzed retrospectively at the tertiary care center, after ethical clearance. Clinical data from the records and detailed histopathologic patterns were recorded. **Results:** Out of 100, 43 were females and 57 were males. Most common morphology was palpable purpura seen in 40% of the patients. Legs were most commonly involved in all age groups. Most common epidermal pattern was spongiosis(52%). Small vessel vasculitis was the commonest type of vasculitis presented, only one case involved medium sized blood vessel. Infiltration of vessel wall was seen in 92% of cases, whereas vessel wall destruction was seen in 71 cases. Leukocytoclasia was noted in 88 cases with 50% having moderate density. Fibrin deposition was seen in 84% of patients; and the most common location of fibrin deposition was within the vessel wall(80%).RBC extravasation was seen in all cases. **Conclusion:** Skin biopsy is the gold standard for the diagnosis of cutaneous vasculitis. Our study confirms that amount of leukocytoclaisa and fibrinoid necrosis correlates with clinical severity and the absence of fibrin deposition doesn't rule out cutaneous vasculitis.

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Key words: Cutaneous vasculitis, Small vessel vasculitis, Medium vessel vasculitis, fibrinoid necrosis, Leukocytoclasia

INTRODUCTION

Cutaneous vasculitis presents with a mosaic of clinical, histopathological, and immunofluorescence findings with various pathogenic mechanisms and clinical manifestations.[1] The histological diagnostic criteria for cutaneous small vessel vasculitis[2,3] are as follows-

Dermal small vessels (venules and arterioles) (2 of 3 criteria needed)-

1. Angiocentric and/or angioinvasive inflammatory infiltrates.
2. Disruption and/or destruction of the vessel wall by inflammatory infiltrates.
3. Intramural and/or intraluminal fibrin deposition (fibrinoid necrosis).

Skin biopsy is the gold standard for the diagnosis of cutaneous vasculitis.[4] The diagnostic yield of a biopsy depends on the timing, type, and site and the location chosen to biopsy.[5] In skin hematoxylin and eosin-stained sections, separating vasculitic disorders first by vessel size and extent of involvement then by the predominant inflammatory cellular component allows for quick classification and determination of a relevant differential diagnosis.

There are only a few studies on histopathological patterns of cutaneous vasculitis. Hence we undertook this study to evaluate histopathological patterns, correlation with morphological lesions, level of vessel involvement and stage of cutaneous vasculitis as detection of early vasculitis and prompt treatment will be helpful to patients.

MATERIAL AND METHODS-

This hospital-based, retrospective study was conducted at the Department of Dermatology, Seth G.S. Medical college, Mumbai. Histopathologically proven last 5 year 100 slides of cutaneous vasculitis were analysed in the study. The study was carried out after obtaining the requisite Ethics Committee permission. A detailed perusal of the recorded history including age, sex, clinical history, possible etiologic factors, associated conditions and examination details of all the patients were recorded. The investigative profile of each patient was noted. The preserved biopsy specimen as paraffin blocks and haematoxylin and eosin stained slides were reviewed and all the histopathologic findings were analysed in the depth.

The diagnosis of cutaneous leukocytoclasticvasculitis was confirmed in the patients by the presence of an inflammatory infiltrate predominantly constituted by neutrophils, nuclear fragmentation, extravasation of RBCs and necrosis of dermal vessel walls. Inflammatory infiltrate, leukocytoclasia, fibrinoid deposition and RBC extravasation was evaluated as mild (1), moderate (2), and dense (3) according to the intensity. Vessel wall destruction was noted as - preserved, partial destruction and complete destruction.

After data collection, data analysis was done with the help of appropriate statistical software. Study characteristics were described using Descriptive statistics. Qualitative data was presented with the help of frequency and percentage table. Descriptive statistics wherever required were presented with the help of proportion, standard error of proportion, etc. Association among various study parameter within the study group was assessed with the help of chi square test. P value <0.05 was taken as a level of significance.

RESULT

Out of 100, 43 were females and 57 were males. Most common age group was 20-40 years. Age distribution of the patients showed that minimum age was 3 years and maximum age

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was70 years with mean age of 29.97 ±15.4 years.The commonest site involved was leg in 65 patients followed by foot (15), arm/forearm (15) and thigh (4).Legs were most commonly involved in all age groups. (Table 1)

Table 1: Site of the lesion

Site	Frequency	Percent
Leg	65	65.0
Thigh	4	4.0
Foot	15	15.0
Arm &forearm	15	15.0
Back	1	1.0
Total	100	100.0

Most common morphology was palpable purpura seen in 40% of the patients followed by papules in 18%, nodules in 11%, vesicles in 9%, and ulcers in 9% patients. Five patients had petechiae and only 4 had plaque.

The time of biopsy from the onset of lesions varied from 1 day to 30 days.Mean duration from appearance of morphological lesions to biopsy was 11.74 days with a standard deviation of +/- 7.78. There was a history of recurrence in 25% of patients. Out of 100, 46 patients had associated symptoms. Joint pain was the commonest associated finding in 16 patients with the knee joint being the most commonly involved joint. There was a history of fever in 8 patients, abdominal pain and pedal edema in 6 patients each and upper respiratory tract infection in 5 patients. (Table 2)

Table 2: Associated clinical symptoms

Associated clinical symptoms	Frequency	Percent
Fever	**8**	**8.0**
Joint pain	16	16.0
Pedal edema	6	6.0
Abdominal pain	6	6.0
URTI	5	5.0
Malena	2	2.0
Frothy urine	2	2.0
Conjunctivitis	1	1.0

Three – three patients each had history of essential hypertension, diabetes mellitus and tuberculosis. Leprosy, systemic lupus erythematosus, chronic kidney disease and septicemia was present in two patients each. One patient had liver cirrhosis with hepatitis B virus infection (HBV), and one had malignancy. No significant past history was elicited in rest of the 81 patient.

On analyzing the histopathological patterns-

A) Epidermal pattern- The most common epidermal pattern was spongiosis seen in 52% of patients. Out of them, neutrophilicspongiosis was seen in 14 patients. Papillary microabscesses(Figure 1) were observed in 6% patients.(Table 3) On correlating epidermal changes with morphology, necrosis of epidermis (focal or complete) (Figure 2) was significantly associated with papular, nodular, vesicular and ulcerated lesions as compared to

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purpuric and macular lesions(Table 4), but no significant association was observed between the epidermal changes and duration of the lesions.

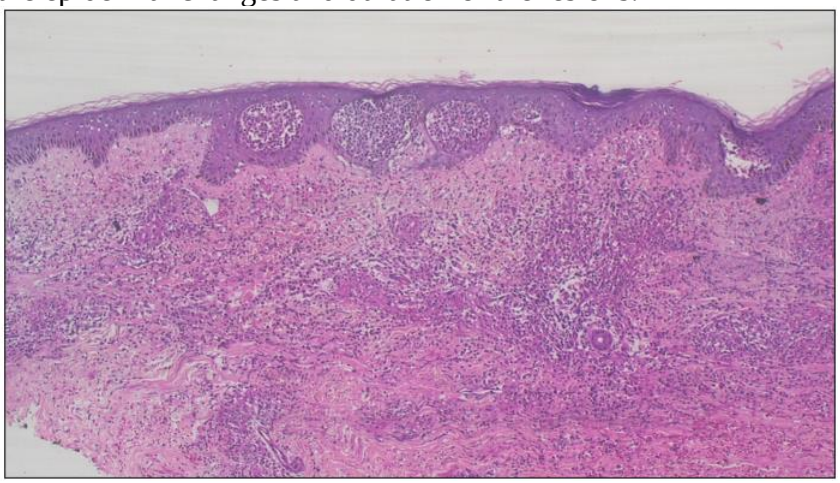

Figure 1: Papillary microabsess of neutrophils with underlying dermis showing leucocytoclasia and fibrin deposition around blood vessels (H & E, 10X)

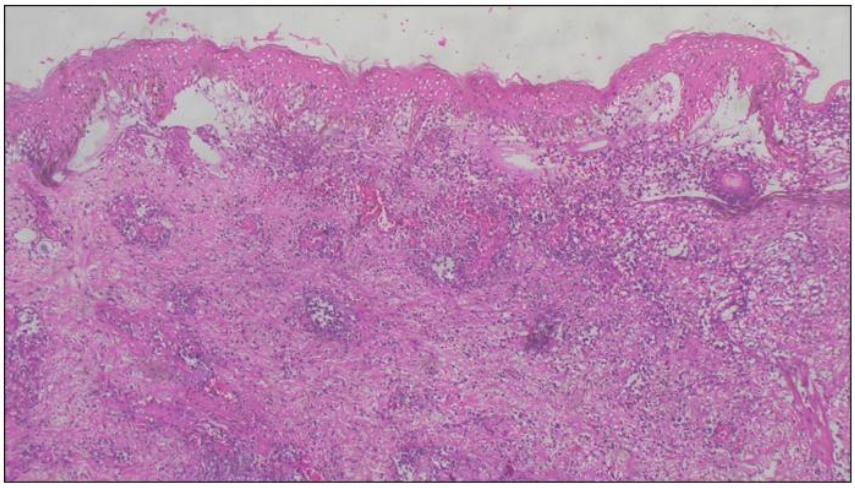

Figure 2: Confluent necrosis of epidermis with underlying dermis showing extensive leucocytoclasia and fibrin deposition around blood vessels (H & E, 10X)

Table 3: Epidermal patterns in cutaneous vasculitis

Epidermal pattern	Frequency	Percent
Spongiosis	38	38
Neutrophilicspongiosis	14	14
Acanthosis	14	14
Flattening of rete ridges	16	16
Necrosis	15	15
Papillary edema	4	4
Papillary abscess	6	6
Intra &subepidermal split	6	6

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Table 4: Epidermal changes & morphology correlation

Morphology category	Epidermal change			Total	
	Spongiosis, neutrophilicspongiosis, acanthosis	Flattening of rete ridges	Necrosis of epidermis		
Purpura, erythematous macule, petechiae	35	12	2	49	p value = 0.004
Nodule, erythematous papule, plaque, vesicle, ulcer	35	4	12	51	
Total	70	16	14	100	

Chi square value :11.107, Degrees of freedom : 2

B) Blood vessel involved-Small blood vessel (Figure 3) was involved in all cases and only one case also involved a medium sized blood vessel (Figure 4).

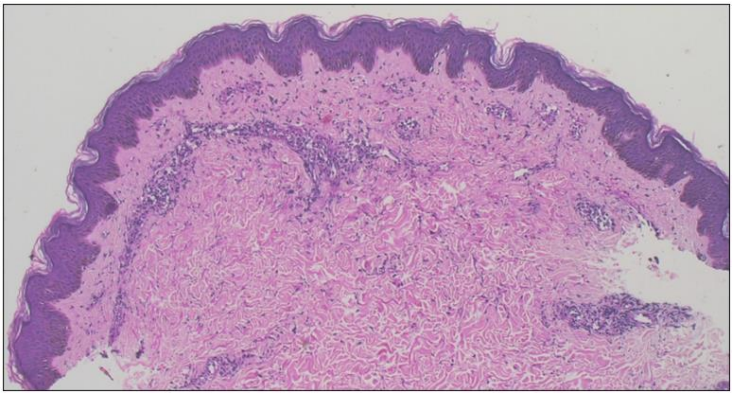

Figure 3: Small vessel vasculitis (H & E, 4X)

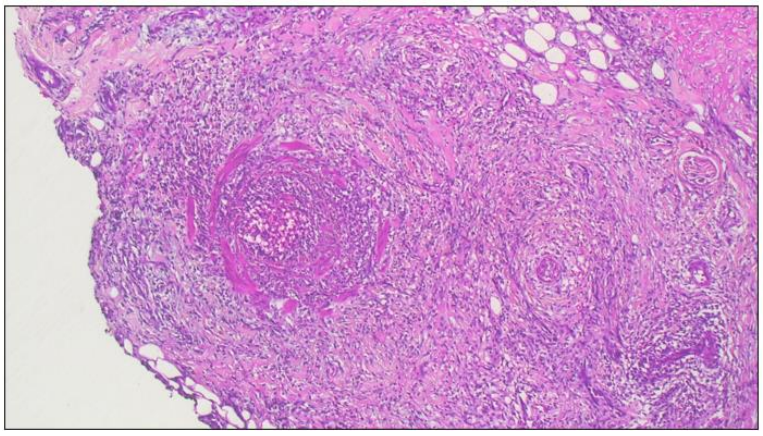

Figure 4: Arterial inflammation with fibroplasia (H & E, 10X)

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C) Blood vessel site involved-The most common location of involved blood vessel was upper dermis (36%) followed by upper & deep dermis (30%). Involvement of panniculus was seen in 6 patients, which was noted in nodular lesions. Upper dermis involvement was statistically significant as compared to deeper involvement in purpuric and macular lesions, whereas deep dermis and subcutaneous involvement was more common in papular, nodular and ulcerated lesions; on correlating the blood vessel location with morphology.

D)Perivascular infiltrates–Out of 100, predominant neutrophilic infiltrate was in 49% patients; whereas with admixture of lymphocytes and eosinophils in 21% and 23% cases respectively. Granulomatous changes were noticed in 7 cases. Most of the cases had moderate density of neutrophilic infiltration. (Table 5)

Table 5: Perivascular infiltrates

Type of inflammatory cell	Number	Percent
Predominant neutrophils	49	49
Neutrophils &eosinophils	23	23
Neutrophils & Lymphocytes	21	21
Granuloma	7	7

Nodule, vesicle and ulcerated lesions commonly showed moderate to dense neutrophilic infiltrate as compared to macular lesions; but this association was statistically insignificant. Perivascular neutrophilic infiltration severity also didn't show any association with the duration.

E) Vessel-wall infiltration - Infiltration of the vessel wall was seen in 92% of cases.

F) Leukocytoclasia-Leukocytoclasia (Figure 5) was noted in 88 cases with 50% having moderate density (Table 6). The statistical analysis demonstrated a significant association between leukocytoclasia severity and morphology. Absent to mild leukocytoclasia was more common in purpuric and macular lesions, whereas nodular, vesicular and ulcerated lesions had moderate to dense leukocytoclasia(Table 7). But leukocytoclasia density didn't correlate with the duration of the lesions.

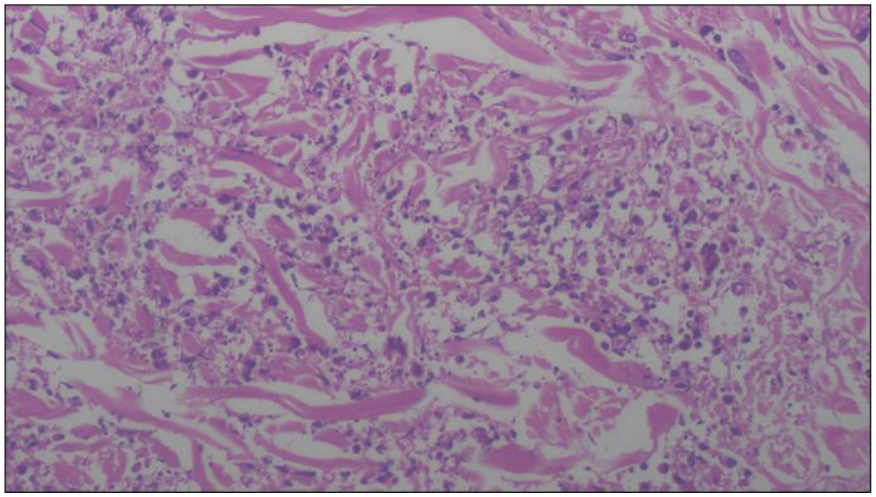

Figure 5: Leukocytoclasia (H & E, 10X)

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Table 6: Grading of leukocytoclasia

Leukocytoclasia	Frequency	Percent
Absent	12	12.0
Mild	33	33.0
Moderate	44	44.0
Dense	11	11.0
Total	100	100.0

Table 7: Grading of leukocytoclasia and morphology correlation

Morphology category	Leukocytoclasia		Total	
	Absent& mild	Moderate & dense		
Purpura, macule, petechiae	27	22	49	
Nodule, papule, plaque, vesicle, ulcer	18	33	51	**p value = 0.047**
Total	45	55	100	

Chi square value 3.962, Degrees of freedom: 2

G) Vessel wall destruction-Vessel wall destruction was seen in 71 cases. Out of them, partial destruction (Figure 6) and complete destruction (Figure 7) was seen in 26% and 22% cases respectively. Combination of partial and complete destruction was observed in 23% of cases(Table 8).

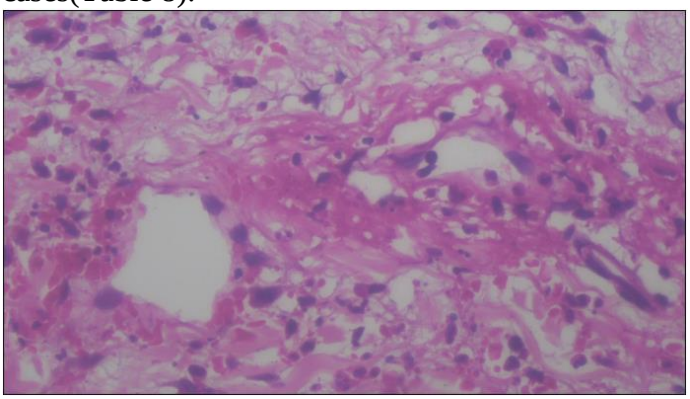

Figure 6: Partial destruction of vessel wall (H & E, 40X)

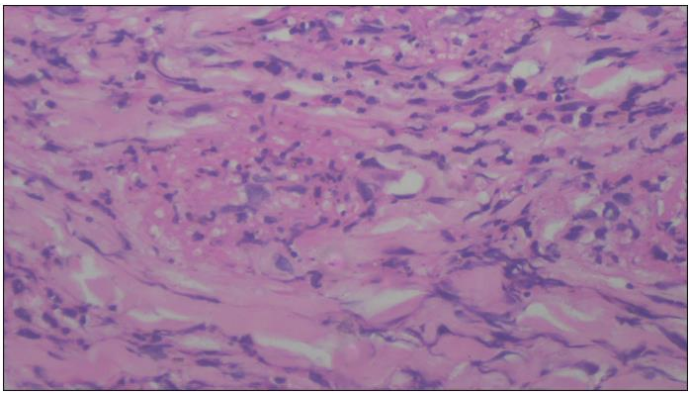

Figure 7: Complete destruction of vessel wall (H & E, 40X)

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Table 8: Vessel wall destruction

Vessel wall destruction	Frequency	Percent
Preserved	29	29.0
Partial destruction	26	26.0
Complete destruction	22	22.0
Partial & complete destruction	23	23.0
Total	100	100.0

H) Fibrinoid deposition - Fibrin deposition (Figure 8) was seen in 84% of patients. Out of them, mild to moderate was more common, seen in 71% cases(Table 9). Fibrinoid deposition grades had a statistically significant correlation with morphology. Denser deposition being more common inpapular, nodular and ulcerated lesions, and no fibrin deposition in purpuric and macular lesions (Table 10). Whereas no significant association between duration and the amount of fibrinoid deposition was observed. Blood vessels of upper dermis were commonly observed to have absent or mild deposition of fibrin, whereas it was moderate to dense in deep dermis and subcutaneous blood vessel involvement. These correlations were statistically significant. (Table 11)

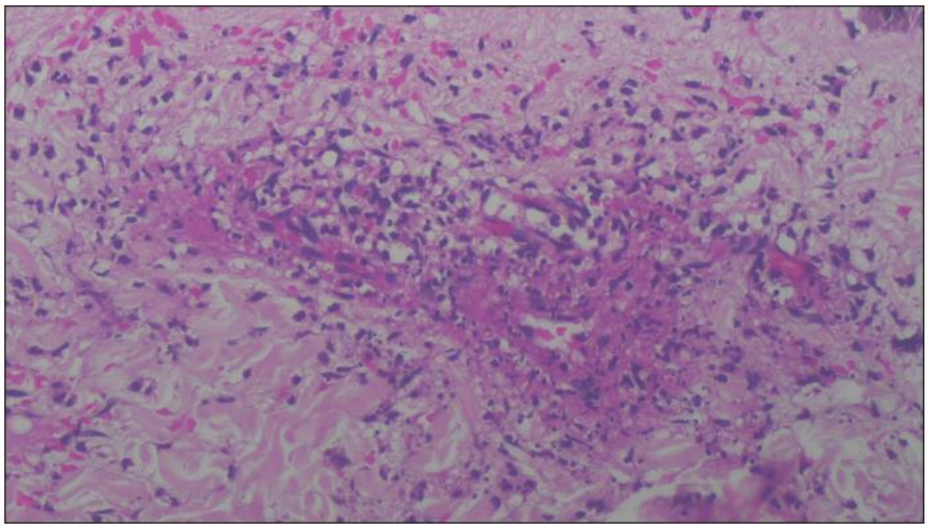

Figure 8: Fibrin deposition within the vessel wall with neutrophilic infiltration of vessel wall and extravasation of RBCs (H & E, 20X)

Table 9: Grading of fibrinoid deposition

Grading of fibrinoid deposition	Frequency	Percent
Absent	16	16.0
Mild	33	33.0
Moderate	38	38.0
Dense	13	13.0
Total	**100**	**100.0**

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Table 10: Grading of fibrinoid deposition and morphology correlation

Fibrinoid deposition	Morphological category		Total	
	Purpura, macule, petechiae	Nodule, papule, plaque, vesicle, ulcer		
Absent	14	2	16	p value = 0.001
Mild	15	18	33	
Moderate	18	20	38	
Dense	2	11	13	
Total	49	51	100	

Table 11: Blood vessel site and fibrin amount correlation

Fibrin amount category	BVsite category			Total
	Upper dermis	Upper & mid dermis	Mid, deep, upper & deep, upper &subcutis	
Absent & mild	26	10	13	49
Moderate & dense	10	18	23	51
Total	36	28	36	100

Chi square value = 12.139, p value = 0.002

I)Extravasation of RBCs- Most common grade of RBC extravasation (Figure 9) was moderate extravasation, seen in 58% of cases (Table 12). Extravasation of RBCs alsodidn't show any correlation with morphology.

Table 12: Grading of extravasation of RBCs

Extravasation of RBC	Frequency	Percent
Mild	35	35.0
Moderate	58	58.0
Severe	7	7.0
Total	100	100.0

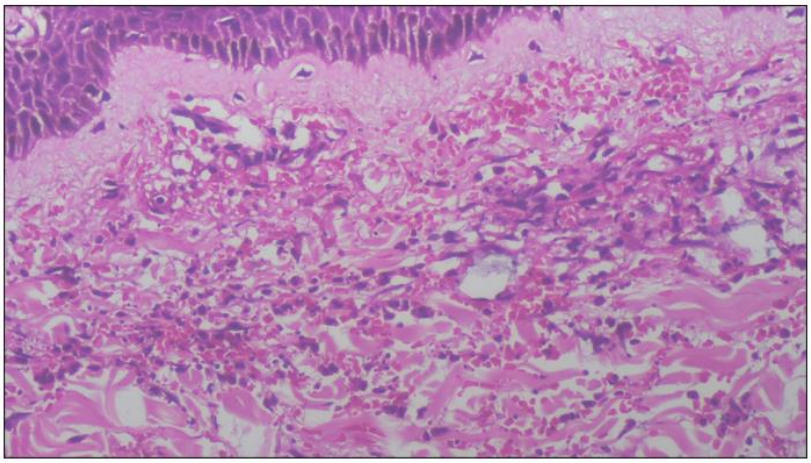

Figure 9: Extravasation of RBCs (H & E, 20X)

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DISCUSSION

Cutaneous vasculitis is a poorly understood entity due to its varied clinical manifestation and its overlap with various infections, connective tissue disorders and malignancies. In this study, clinical features, duration and histopathological changes were recorded and analyzed retrospectively. An attempt was also made to demonstrate the histopathology spectrum, and its correlation with morphology and duration of cutaneous vasculitis. Our study confirms various established histopathologic facts regarding cutaneous vasculitis.

In this study, 100 slides histopathologically reported as vasculitis were analyzed. Out of 100, 43 were females and 57 were males with male to female ratio 1.5:1. Age distribution of the patients showed that minimum age was 3 years and maximum age was70 years with mean age of 29.97 ±15.4 years. All these results were similar to other studies.[3,6,7]Most common age group in our study was 20-40 years. Cutaneous vasculitis can affect at any age, adults more often than children.[5,8]

In our study, palpable purpura was the most common cutaneous manifestation, similar to other studies.[2,3,6,7] The second most common type was nodules observed in 11% of patients similar to Swapna et al.[2]Whereas vesicle and ulceration was noted in 9% patients each.

Chintagunta *et al.* and Gupta *et al.* observed that cutaneous vasculitis mostly affects legs, with 94.73% and 86% of cases involved, respectively.[6,7] Following a similar pattern, most common site involved in our study was legs in 65 patients of all age groups.

Mean duration of biopsy from the appearance of morphological lesions was 11.74 days with a standard deviation of ± 7.78. Minimum duration was 1 day and maximum duration was 30 days. As this was a retrospective study, we didn't have detail about the duration of the biopsied lesion which varies. Maximum duration in our study was 30 days, but the patient might get recurrent lesions during this period.

Systemic involvement was observed in 46 (46%) patients with joint pains being the commonest presenting manifestation(15 patients) similar to other studies.[2,9]Fever was seen in only 8% of our patients while it was seen in 39.47% patients by Chintaguntа*et al*.[6]

History of recurrence was observed in 25% of patients of our study, whereas Hodge et al study noted recurrence and chronicity in 30% of cases.[10]

Histopathology patterns-

After analyzing histopathology, most common epidermal pattern observed was spongiosis, seen in 52% patients followed by flattening of rete ridges(16%), and acanthosis(14%). Epidermal necrosis (focal or complete) was observed in 15% cases.

After cross-evaluating the epidermal patterns with morphology, we found that spongiosis and neutrophilicspongiosis were commonly noted in all morphological variant. Flattening of rete ridges was significantly more common in purpuric and macular lesions; whereas focal or complete necrosis of the epidermis was significantly more associated with papular, nodular, vesicular and ulcerated lesions as compared to purpuric and macular lesions. Epidermal changes had no significant correlation with duration, we couldn't find any study showing similar correlation.

We observed involvement of small vessels in all the cases whereas only one case reported medium sized vessel involvement similar to Khetan P et al study in which small vessel vasculitis was observed in 96% patients and medium vessel vasculitis in 4%.[3]Sais *et al* reported SVV and MVV in 60 and 40 per cent respectively.[11] The low frequency of MVV in our study may be due to the fact that MVV is a segmental and patchy process and all the vessels of the same caliber may not be affected and thus the biopsy may not have picked up the

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involved medium sized vessel leading to sampling bias. Multiple skin biopsies could have been taken at different times.

The commonest location of blood vessel involvement was upper dermis, seen in 36% cases, followed by involvement of upper and deep dermis together noticed in 30%, whereas isolated deep dermis and subcutaneous involvement was seen in 4% cases; in contrast to Khetan P et al and Hodge et al where most common was upper and mid dermis.[3,10]

After cross-evaluating the involved blood vessel site with morphology, we found that upper dermis involvement was statistically significant as compared to deeper involvement in purpuric and macular lesions, whereas deep dermis and subcutaneous involvement was more common in papular, nodular and ulcerated lesions. These findings were similar to the literature.[5,12]

Perivascular infiltrate was predominantly constituted by neutrophils in 49% cases as compared to 50% by Khetan P et al and 76% by Sais *et al.*[3,11] Sais et al had a prospective study design and biopsy was done within 4 days of the onset of lesions.[11]

We observed no association of morphology and duration with the perivascular neutrophilic infiltration severity. This may be attributed to the retrospective study design with duration of the lesions extending from zero to 30 days and no information of duration of the biopsied lesion.

In this study, leukocytoclasia was noted in 88 cases with 50% having moderate density, which was similar to Khetan *et al.* study.[3] Hodge et al study had reported leukocytoclasia in more than 95% of the cases with moderate to dense involvement in 72% cases.[10] Hodge et alwase a prospective study in which the duration of biopsied lesion was within 48 hours.[10]

Leukocytoclasia severity showed a statistically significant relation with the morphology but not with duration. Absent to mild leukocytoclasia was more common in purpuric and macular lesions, whereas nodular, vesicular and ulcerated lesions had moderate to dense leukocytoclasia. In Hodge et al study clinical severity was statistically predicted by the amount of leukocytoclasia, similar to our study.[10]

In this study, vessel wall was preserved in 29 cases, whereas partial destruction and complete destruction was seen in 26% and 22% cases respectively. Combination of partial and complete destruction was observed in 23% cases. Evidence of vascular injury is a major component of vasculitis. In our study, fibrinoid necrosis was seen in 84% cases, this was comparable with earlier studies by Khetan P *et al.* and Hodge et al in 89% and 72% respectively.[3,10]The most common location of fibrin deposition was within the vessel wall, seen in 29% cases. Deposition of fibrinoid material is considered as a primary evidence of true vasculitis.

Fibrinoid deposition grades had a statistically significant correlation with morphology in this study. Denser deposition being more common in popular, nodular and ulcerated lesions, and no or mild fibrin deposition in purpuric and macular lesions. In Hodge et al study, clinical severity was statistically predicted by the severity of fibrinoid necrosis, similar to our study.[10] Vascular damage and occlusion due to fibrinoid material deposition within the lumen and vessel wall may lead to ischemic damage resulting in increased clinical severity.

In this study, blood vessels of upper dermis were commonly observed to have absent or mild deposition of fibrin, whereas it was moderate and dense in deep dermis and subcutaneous blood vessel involvement. These correlations were statistically significant. This indirectly correlates with the independent association of these two variables with the morphology of the lesion.

RBC extravasation was seen in all cases similar to other studies.[10,11]RBC extravasation denotes the evidence of vessel wall leakiness; criteria for vascular injury.

There were several weaknesses in our study. Being a retrospective study design, clinical data was collected from requisition forms and not prospectively; so, certain data may be incomplete.

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Studied slides were diagnosed based on clinical and histopathological findings without immunofluorescence study confirmation, which is a major drawback. Grading of histopathological findings to evaluate results was not quantitative but based on the senior authors cumulative observation, which is subjective and may have affected results. Moreover the sample size is small, longer study with large sample size is required.

Conclusion –Skin biopsy is the gold standard for the diagnosis of cutaneous vasculitis, allowing differentiation from vasculitis mimics such as vaso-occlusive disorders, and should be performed in all suspected cases of vasculitis. This study was conducted to observe the histopathological patterns of cutaneous vasculitis and its relation with the morphology and duration. To conclude, amount of leukocytoclaisa and fibrinoid necrosis correlates with clinical severity, and clinical severity favours deep vessel involvement. We couldn't find any correlation between histopathologic findings and duration. This study demonstrated that purpuric and macular lesions can present with absent fibrin; stating that the absence of fibrin deposition doesn't rule out cutaneous vasculitis.

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