IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 21, Issue 6 Ser.1 (June. 2022), PP 11-17
www.iosrjournals.org

A clinico-etiological study of cutaneous vasculitis in a Tertiary Care Centre

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Background
Vasculitis is a group of disorders characterized by inflammation of vessel walls. Because of the rich vasculature the skin is prone to be frequently affected in vasculitis. Cutaneous involvement in vasculitis may be primary or reflector of a fatal systemic disease or evidence of association with some other systemic diseases. The purpose of our study was to assess the clinical profile and etiology of cutaneous vasculitis. Besides the study also illustrated treatment modalities. Such type of studies are rare in the literature.

Methods
This hospital-based cross-sectional study included 50 patients of cutaneous vasculitis of either sex and all age groups. The clinical, laboratory, histopathological findings, treatment and outcome were discussed in this studied.

Results
In our study palpable purpura (84 %) was the most common type of cutaneous lesion. Hypersensitivity vasculitis (HSV) 68 % was the most common form. Systemic involvement was seen in 24 % patients. Drugs were implicated in 20 % patients, infections in 10 % patients. Histologically leukocytoclastic vasculitis was the most common pattern. Direct immunofluorescence showed positivity for at least one immunoreactant in 42 per cent of the patients and the most common deposit was IgM & C3.

Conclusion
Although majority of our patients with cutaneous vasculitis are idiopathic thorough examination of patients with cutaneous vasculitis should include detailed history, clinical examination and investigations to rule out multisystem involvement.

Keywords: *Vasculitis, Purpura, Hypersensitivity vasculitis, Drugs, Histopathology.*

Date of Submission: 20-05-2022 Date of Acceptance: 03-06-2022

I. Introduction

Vasculitis is a term referring to inflammation of blood vessels; these may be arteries, veins or both, and can affect any part of the body [1] [2].When vasculitis affects small or medium sized blood vessels in the skin, it is known as cutaneous vasculitis .Cutaneous vasculitis presents as a tessellation of clinical and histological findings. It offers a window to diagnosis and a ready source of accessible tissue for histopathologic examination. A definitive diagnosis of vasculitis requires histological confirmation in almost all cases [3],[4]. Occasionally cutaneous vasculitis can be a sign of inflammation occurring in other organs (systemic vasculitis) and further investigation may be required for a proper diagnosis. Many times it becomes challenging to diagnose and treat the condition.

II. Aims And Objectives

To evaluates demographic profile, clinical features, etiology of cutaneous vasculitis and to evaluate the clinical diagnosis with histopathological confirmation and treatment outcome.

III. Methodology

This cross-sectional study was conducted between January 2019 and December 2019 (12months) at a tertiary care teaching hospital located in Southern India. 50 successive cutaneous vasculitis patients of all ages were included in the study. Study patients were enlisted from dermatology outpatient clinics and referrals from other departments and convenience sampling was followed. The patients with thrombocytopenia (< 50, 000/mm^3) and disorders of coagulation, patients on warfarin/heparin, patients with lesions more than 48 hrs, pregnant and lactating women were excluded from the study. A written informed consent was procured from all the patients. All patients were evaluated with detailed history and complete physical examination. Clinical diagnosis of cutaneous vasculitis was made on the basis of morphology of cutaneous lesions and associated signs and symptoms.

Cases presenting with palpable purpura in association with joint pains, abdominal pain, hematuria and melena recorded as Henoch-schonlein purpura. Patients presenting with urticarial wheals which lasted for more than 24 hours associated with purpuric lesions along with constitutional symptoms like fever, joint pains were taken as urticarial vasculitis. Painful erythematous tender nodules on lower legs were recorded as erythema nodosum. Drug induced vasculitis was considered significant if the drug intake was within 4 weeks of appearance of the lesions. A history of infections both acute and chronic and their treatments were recorded .The patients with cutaneous vasculitis that gave clues for systemic diseases were weight loss, fatigue, fever**,** ear pain**,** oral/nasal ulcers**,** chest pain/dyspnea**,** abdominal pain, blood in faeces , blackouts, seizures.

All patients were subjected to baseline investigations consisting of complete hemogram, renal function tests, liver function tests, chest X-ray, urine (routine and microscopic) examination, ASO titer, hepatitis B and C antibody profile. Specific investigations such as ANA and RA tests were done in 26 and 18 patients, respectively. Histopathological examination of lesional skin biopsy from all patients was done while direct immunofluorescence (DIF) test was done in 21 patients only. We have also recorded the data concerning management, outcome, relapses and complications when available.

Statistical Analysis

The findings were recorded on a specially designed master chart and statistical tests were done using Epi info software version 7.2.2.6 and analyses were done at a 5 % level of significance and a P-value of < 0.05 was considered significant. Chi-square test was applied to obtain the P-value.

IV. Results

Demography

The mean age of onset was 32.9 ± 3.35 years with the age of the patients ranging from 10 to 69 years. The majority of the patients belonged to the age group of 30 - 39 years (22 cases) (44 %) and a minimum number of patients in 60 - 69 years group (2 cases) (4 %). There were 18 males (36 %) and 32 females (54 %) with a male to female ratio being 0.56:1 showing female preponderance.

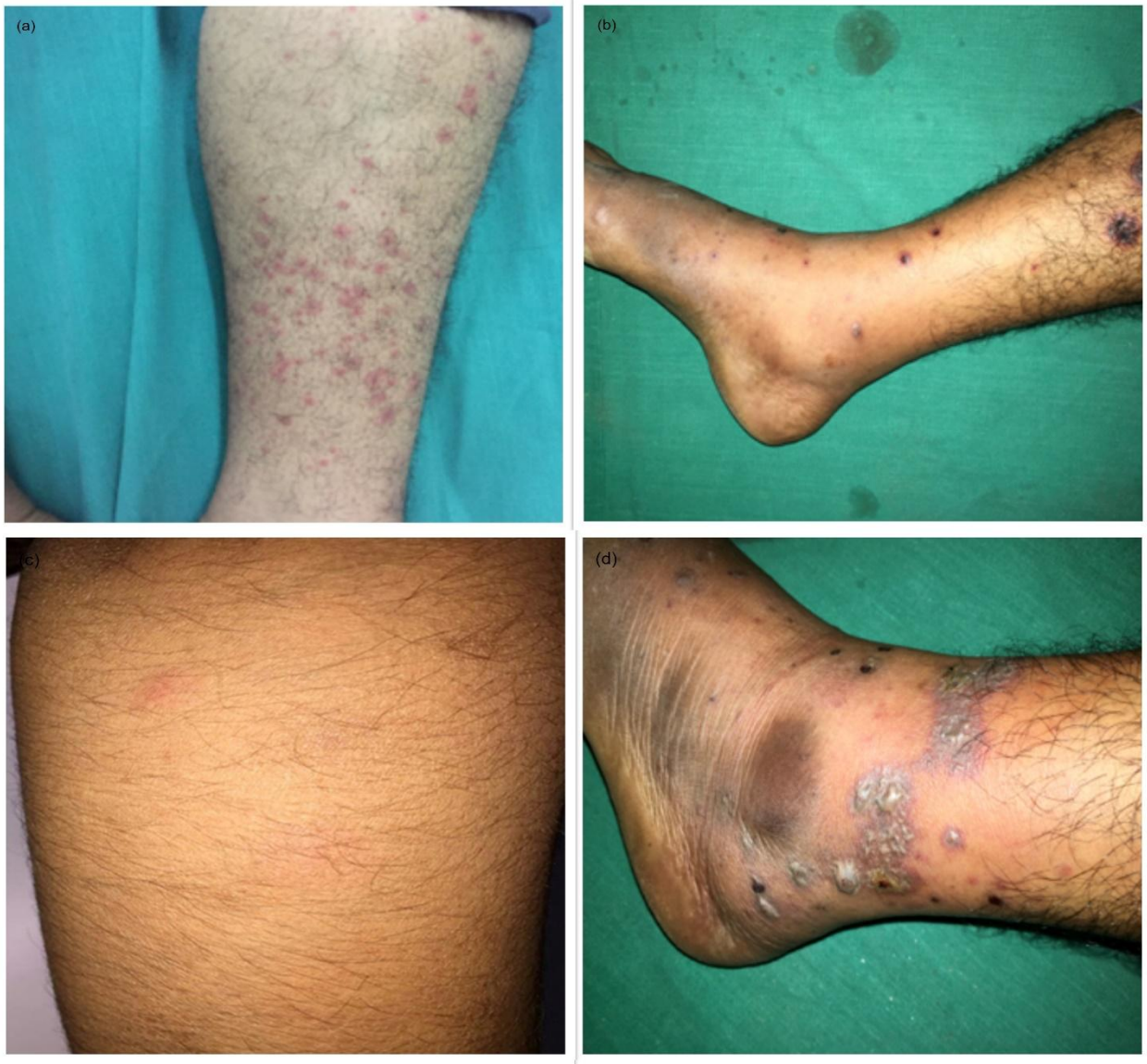
In the study comorbidities were recorded in 18patients (36 %). The most common comorbidities documented were hypertension (5 patients), diabetes (4 patients), tuberculosis (2 patients), epilepsy (2 patients), rheumatoid arthritis (5 patients)

Clinical features

The mean duration of onset of symptoms were 5 days (median = 8 days) (range: 1– 30 days). Progression of the disease was in less than 3 days in 39 patients (78 %); where as 11 (22 %) patients showing gradual progression within 1 week.

Palpable purpura was the most common type of cutaneous lesions seen in 42 (84 %) patients. The most common combination of lesions were purpura and petechiae which was seen in 42 patients (84%). Clinical presence of deep seated nodules/ulcers/gangrene (suggestive of Medium vessel vasculitis) was seen in 11 (22 %) patients**.** The lower extremities were the most common site involved seen in 50 (100 %) patients.The cutaneous lesions which were seen in the study are depicted in Figure 1

Figure 1 Presenting lesions (a) Palpable purpura (b) Necrotic lesions (c) Urticarial wheals (d) Vesicobullous lesions



Constitutional features were present in 28 (56 %) patients and systemic symptoms were seen in 12 patients (24 %). The presenting complaints of the patients are illustrated in Table no.1

Table 1: The presenting complaints of patients with cutaneous vasculitis

Clinical feature	**Percentage of patients**
Presenting symptoms	
Pain over the lesions	12 (24 %)
Arthralgia	10 (20 %)
Fever	8 (16 %)
Itching	20 (40 %)
Systemic symptoms	
Abdominal pain	8 (16 %)
Hematuria	3 (6 %)
Melena	2(4 %)
Morphology of lesions	
Palpable purpura	42 (84 %)
Petechia	30 (60 %)
Plaques	12(24 %)
Papules	12(24 %)
Urticarial wheals	3 (6 %)
Ulcers/nodules/necrosis	11(22 %)

Distribution of lesions	
Lower limbs	50 (100 %)
Upper limbs	5 (10 %)
Trunk	10 (20 %)
Head and neck	2 (4 %)

Laboratory investigations

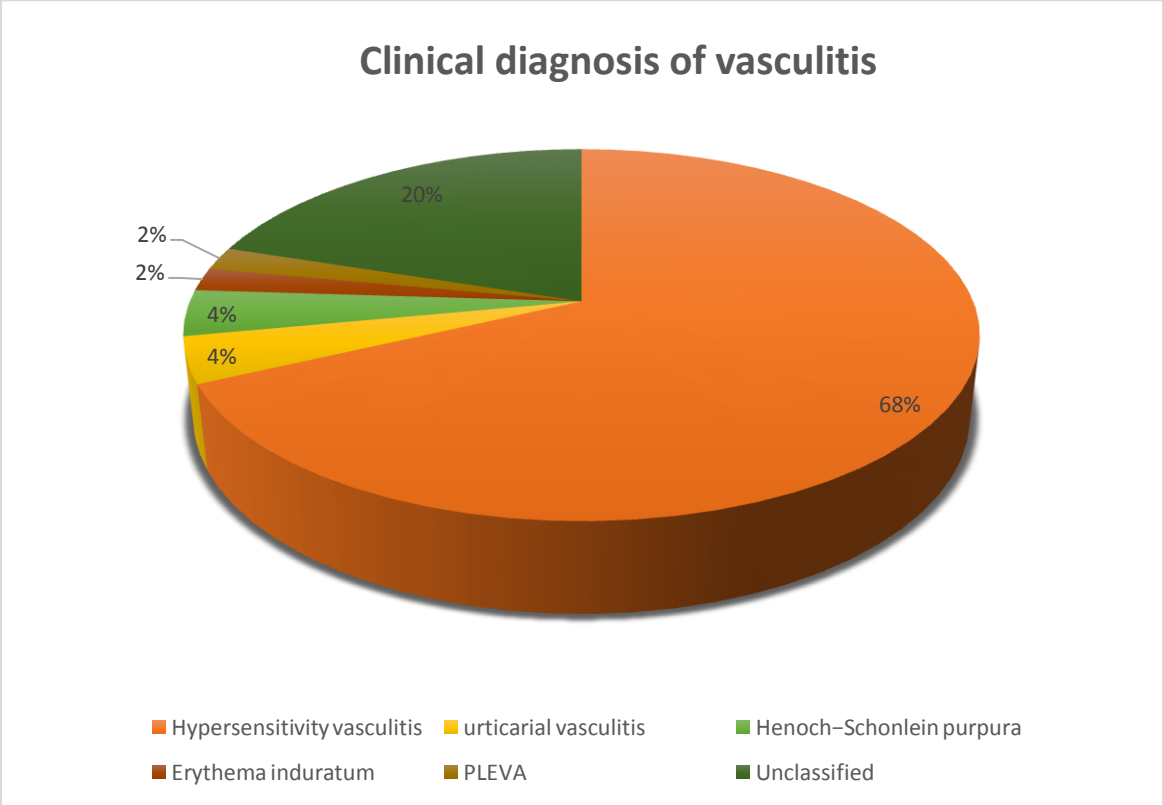
The hematological and biochemical evaluation revealed anemia in 6 patients (12 %), leukocytosis in 7 patients (14 %), elevated ESR in 10 patients (20%), raised serum-urea in two (4%) and raised creatinine levels in one patient (2%). Routine urine examination showed albuminuria in 5 patients (10%), while urine microscopy demonstrated red blood cells in 6 patients (12%) and pus cells and bacilli in 3 patients each (6 %). Anti-nuclear antibody and rheumatoid factor were positive in three patients each (6%). ASO titer was also raised in 3 patients (6 %), while Mantoux was positive in 3 patients (6%).

Etiology

Clinically 34 (68 %) patients were offered a diagnosis of Hypersensitivity vasculitis 2 (4 %) patients each of urticarial vasculitis and Henoch−Schonlein purpura (HSP). Erythema induratum and pityriasis lichenoides et varioliformis acuta (PLEVA) were diagnosed in one (2%) patient each. Nine patients (18%) did not qualify for any group despite having features of vasculitis and were labelled as unclassified vasculitis.

Drug intake up to 4 weeks prior to onset of cutaneous lesions was considered relevant. Such association was present in 10 patients (20 %). Suspected drugs were phenytoin in 2 patients, Non-steroidal anti-inflammatory drugs (NSAIDs) in 5 patients followed by indigenous drugs in 3 patients. The other etiological factors are infections in 5 patients (10%), ANA profile was positive in 3 (6 %) patients though no overt collagen vascular disease was detected in any of these patients. Malignancy was not detected in any of our cases and 32 patients (64 %) were found to be idiopathic. The results are depicted in Figure 2

Figure 2:Pie diagram depicting the clinical diagnosis of vasculitis

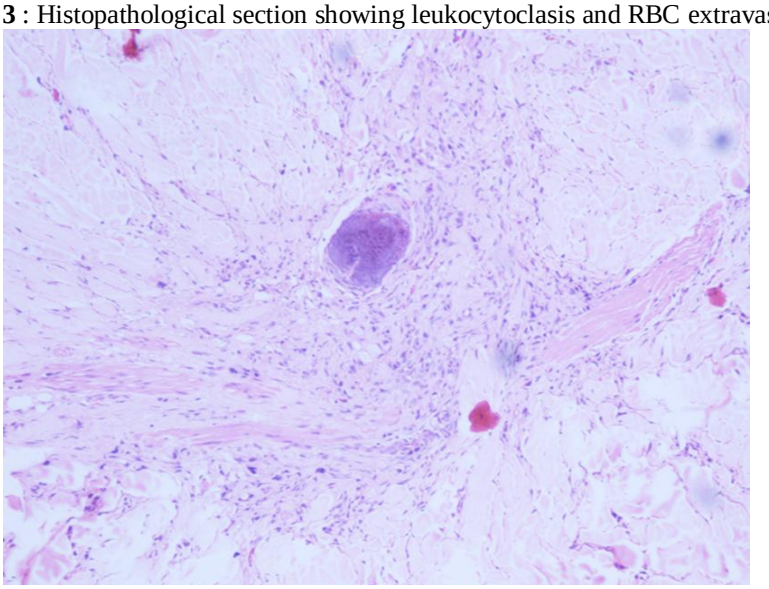


Histopathology and immunofluorescence examination

In our study diagnosis was made with correlating clinical features and pathological reports. Skin biopsy was obtained in all the 50 patients. Three of them had two biopsies a total of 53 biopsies. 13 (26%) patients did not show any evidence of vasculitis histopathologically were as skin biopsy showed typical features of

endothelial swelling, fibrinoid necrosis, extravasation of RBC and leukocytoclasis suggestive of small vessel vasculitis were seen in 34 (68 %) patients illustrated in Figure 3.

Figure 3 : Histopathological section showing leukocytoclasis and RBC extravasation



Direct immunofluorescence examination results were available for 21 patients (42%) only. Out of which 16 (32 %) were found positive for vasculitis. IgM and complement C3 were the commonest deposits in 12 (24 %) patients. IgA was seen in 4 (8 %) patients .The correlation between clinical and histological diagnosis is shown in Table no.2

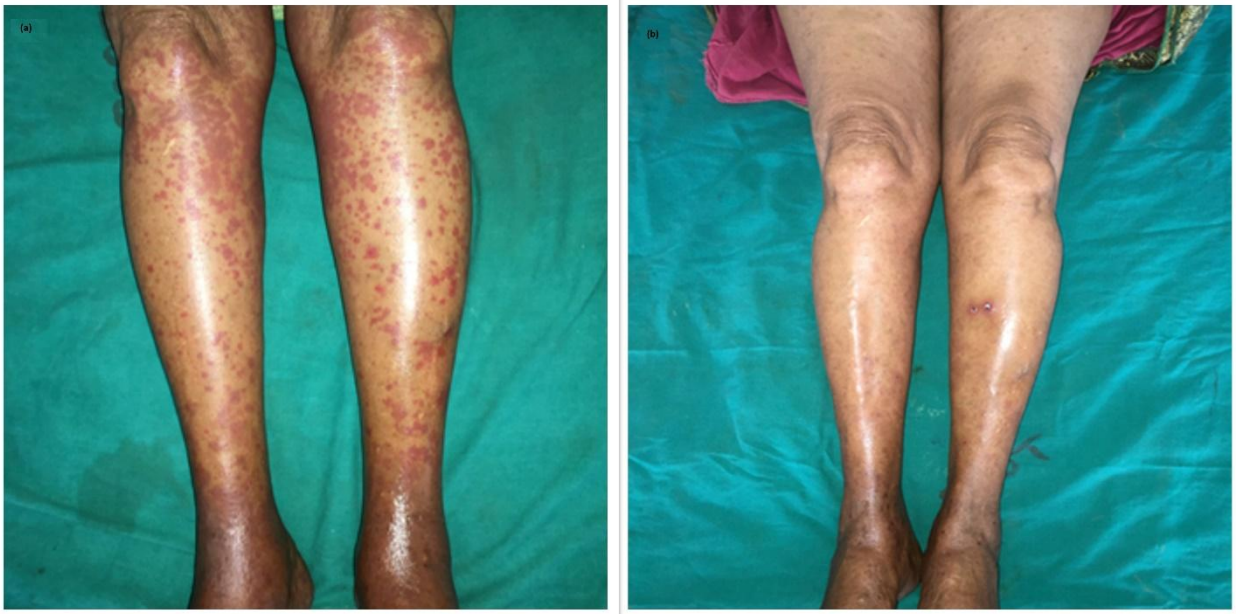
Table 2 :shows the correlation between clinical and histological diagnosis

Clinical Diagnosis (No.)	**Number of Biopsies**	**Histopathological Diagnosis**	**DIF**
Hypersensitivity vasculitis (34)	35	Leukocytoclastic vasculitis: 22 Neutrophilic vasculitis: 2 Eosinophilic vasculitis: 2 Unclassified:9	N-13 Neg (2), IgM (7) IgM+C3(2) IgA (2),
Urticarial vasculitis (2)	2	Leukocytoclastic vasculitis:2	N-2 IgM+C3(2)
Henoch−Schonlein purpura (2)	2	Leukocytoclastic vasculitis: 1 Neutrophilic vasculitis: 1	N-2 Neg (1) Ig A (1)
Erythema induratum (1)	1	Leukocytoclastic vasculitis: 1	N-1 IgM (1)
PLEVA (1)	1	Leukocytoclastic vasculitis: 1	N-1 IgM (1)
Unclassified (10)	13	Leukocytoclastic vasculitis: 7 Unclassified:4	N-2 Neg (2)

Treatment

All the patients were advised to take complete bed rest, plenty of fluids and keep their foot end of bed elevated. 36 patients (72 %) responded with this line of management in 1 week. In the remaining 14 patients (28 %) lesions persisted even after 4 weeks of the above treatment. These 14 patients were started on colchicine 0.6 mg twice daily. Satisfactory clinical response was seen in 12/14 patients in 3 weeks. Because of persistent lesions even with 4 weeks of colchicine in the remaining 2 patients were started on azathioprine who responded well in 3 weeks. Patients are being followed up for recurrences.The treatment response to colchicine is depicted in Figure 4

Figure 4: (a),(b) Improvement in lesions before and after colchicine therapy



V. Discussion

Vasculitis is usually a multisystem disorder that presents in a myriad of ways. Diagnosis is based on a detailed history and thorough clinical examination. Patients may present to different specialties and their care should be led by a multidisciplinary team involving physicians with a special interest in vasculitis.

In our study a total of 50 patients were analyzed. Their age was from 10 to 69 years and mean age was 32.9 year and about 44 % patients were within 30-39 year age group. Male to female ratio being 0.56:1, showing female preponderance. A similar type of study was conducted by Suruchi Gupta et al [5] on 50 patients. They found the age range 5-67 years and mean age was 41.1 years for males and 35.9 years for females.. There were 20 male and 30 female patients with age range of 5-67 years which correlates with our study results.

The mean duration of lesions at the time of presentation was found to be 5 days within a range of 1-30 days. This is in contrast to the study conducted by Chowdhury et al [6] where in mean duration was 28.2 with a range of 5-120 days. In our study progression of disease was rapid in 39 (78 %) patients and slow in rest of the cases which is similar to that observed in study by Chowdhary et al [6] .

In our study itching over the lesions was the most common presenting symptom. 40 % of the patients presented with the itching, 24 % had pain , 20 % arthralgia and 16 % abdominal pain. Sais et al [7] carried out a study on 50 patients and found 30% patients presented with pain at the site of the lesions, 41.4% with pruritus, 36.7% with arthralgia and 9.5% with abdominal pain. They found pruritus as most common symptoms which is similar to our study.

Various types of cutaneous lesions were found in our study. Palpable purpuric lesions were seen in 84 % of patients which is similar to that seen in the earlier studies.[7],[8],[9],[10]

Ulcers/nodules/necrosis were seen in 14 % patients in our study while in the study of Chowdhury et al [6] it was 23.3%. In our study all the 50 patients (100%) had lesions over lower extremities. Involvement of upper limbs were found in 10 % of the cases. Other sites were trunk 20 % and head and neck 4 %. Alexander et al.[11] found the most common affected sites were lower limbs (38%). The other affected sites were upper limb, trunk, face in that order of frequency either alone or in combination. Results of their study support our results in this regards .

Systemic involvement was observed in 12 (24 %) patients with abdominal pain being the commonest presenting manifestation in 16 % of the patients. This was in contrast with the systemic involvement observed by Ekenstam et al. [12]. in 51% of the patients where as musculoskeletal system was most commonly involved system in 43% of the patients. However Sais et al. [7] observed systemic involvement only in 20% of the cases with joint involvement in 36.7% of the cases. Amongst patients who had systemic disease, cutaneous lesions were painless in 5 patients; necrotic and ulcerated in 7 patients consistent with the earlier studies.

Elevated ESR was the most common laboratory abnormality seen in 10 (20%) patients.[7],[10],[12]

Histopathology revealed leukocytoclastic vasculitis in 34 (68 %) cases with predominant cell was neutrophil with nuclear debris while others have reported these changes in more than 95 per cent of the cases [7],[13] . Histopathology was inconclusive in 13 (26%) patients probably due to the biopsy of the lesion at a late stage in the disease evolution.

DIF analysis revealed presence of at least one of the immune reactants in 32 per cent of patients. Other studies have reported DIF positivity in 55-92 per cent of cases [13],[14],[15] . The low DIF positivity in our study could be attributed to the inability to perform DIF in all our patients.(owing to the cost to perform the investigation).

In our study diagnosis was made with correlating clinical features and pathological reports. HSV (68 %) a represented the maximum number of patients, which is similar to earlier studies[8] Our study was designed to search etiological factors of vasculitis. Causes of vasculitis were undefined in 32 (64 %) patients. In spite of thorough evaluation we found that most common cause of vasculitis is idiopathic. In those cases where etiology was identified drugs were found to be the commonest factor seen in 10 (20%) of our patients. The most common implicated drugs in our study were NSAIDs whereas antibiotics were the most common cause in other studies [8],[10],[12],[14]. NSAIDs are easily available over the counter which might explain its higher frequency. There is no test available that can exactly delineate drugs as the cause of vasculitis except for the temporal correlation, effect of withdrawal of drug and rechallenging.

Five(10 %) patients were associated with infections. Streptococcal infection was evidenced in 3 cases which is slightly higher than that observed in reports from Belgium (9.5%) and Mexico (6.8%) while higher frequency has also been reported from Australia (26%), Spain (19.8%) and Kuwait (14%) [8],[9],[10],[14],[16]. Three patients (6 %) were associated with collagen vascular diseases.

VI. Conclusion

The cutaneous and systemic features of vasculitis are not pathognomonic in most of the cases. A careful correlation of the medical history and the clinical, serological and imaging findings can help reach a correct diagnosis. The disease is often self limiting. Evaluation of a patient with suspected vasculitis includes intensive search to find out any treatable underlying cause . If a triggering agent is identified, such as a drug or infections it should be removed or treated. The evidence for efficacy of therapy is derived from clinical experience rather than controlled trials. In our experience, in case the lesions do not resolve spontaneously in 4 weeks, colchicine has been proved to be most effective initial agent for treatment of cutaneous vasculitis in the absence of evidence of systemic involvement. In our study colchicine was started in acute episode of the disease and response is observed within two weeks.

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