A CLINICOPATHOLOGICAL STUDY OF CUTANEOUS SMALL VESSEL VASCULITIS IN A TERTIARY CARE CENTRE FROM NORTH KERALA

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ABSTRACT

BACKGROUND

Cutaneous small vessel vasculitis is a condition with various aetiologies, morphological patterns of presentation and histopathologic types. It can be primary or secondary. Cutaneous lesions being a pointer to the systemic involvement in vasculitis, it requires histology for confirmation of the diagnosis and for long-term follow up. Skin biopsy is the gold standard in diagnosis and helps in guiding further investigations and treatment. The studies regarding the various patterns and histopathological types of cutaneous small vessel vasculitis in Kerala are not well documented so far.

MATERIALS AND METHODS

This is a cross-sectional descriptive study done in patients with a histopathological diagnosis of cutaneous small vessel vasculitis admitted in Dermatology Ward of Government Medical College, Kozhikode, during January 2013 to January 2014. The aim of this study was to delineate the patterns, causes and to assess the clinicopathological correlation of cutaneous small vessel vasculitis. A detailed history, clinical examination of patients and 4 mm skin punch biopsy were done in all selected patients.

RESULTS

66 patients diagnosed with histopathological features of cutaneous vasculitis were included in the study. Palpable purpura was the most common clinical lesion and leukocytoclastic vasculitis represented the most common histopathologic type of cutaneous small vessel vasculitis in the present study. Systemic involvement was observed in half of the patients. An aetiological association could be found in 62.2% of cases out of which drug sensitivity was the commonest cause. Out of the 66 patients, after clinicopathological correlation, 16 cases of Henoch-Schonlein purpura, 5 cases of urticarial vasculitis, 3 cases of connective tissue disease associated vasculitis (2-systemic lupus erythematosus and 1-mixed connective tissue disorder), 2 cases of Churg-Strauss vasculitis, 2 cases of nodular vasculitis, 2 cases of Behcet's disease and 3 cases of vasculitic ulcer were identified. Rest of the 33 patients were offered a diagnosis of idiopathic cutaneous small vessel vasculitis.

CONCLUSION

Definitive diagnosis can be reached with skin biopsy aided with clinical features and relevant investigations including immunofluorescence. Thus, skin biopsy and clinicopathological correlation are important in the diagnosis and treatment of cutaneous small vessel vasculitis.

KEYWORDS

Purpura, Cutaneous Small Vessel Vasculitis, Henoch-Schonlein Purpura, Leukocytoclastic Vasculitis.

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BACKGROUND

Small vessel vasculitis is a histological diagnosis characterised by inflammation of vessel wall predominantly involving post-capillary venules cause destruction of the vessel walls lead to haemorrhage, ischaemia and/or infarction.[1] The histological diagnostic criteria for cutaneous small vessel vasculitis[2] for selection of cases are as following-

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

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

Proposed working classification (updated Gilliam's classification)[3] of small vessel vasculitis include- Cutaneous small vessel vasculitis not further classified, Henoch-Schonlein purpura, essential mixed cryoglobulinemia, Waldenstrom's hypergammaglobulinaemic purpura

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associated with collagen vascular disease, urticarial vasculitis, erythema elevatum diutinum, oeosinophilic vasculitis, rheumatoid nodules, reactive leprosy and septic vasculitis.

Histopathologically, small vessel vasculitis classification is based on composition of infiltrate include neutrophilic/leukocytoclastic, oeosinophilic, lymphocytic and histiocytic/granulomatous.

There are only few studies from South India on cutaneous vasculitis.[1,4] Hence, we undertook this study to evaluate the aetiological factors, morphological patterns and clinicopathological correlation of lesions in patients with histopathological diagnosis of cutaneous small vessel vasculitis in a tertiary care centre in north Kerala.

Aims and Objectives

To identify the causes and to evaluate the clinical, histomorphological features and to assess the clinicopathological correlation of cutaneous small vessel vasculitis.

MATERIALS AND METHODS

The present study is a cross-sectional descriptive study conducted at our tertiary care referral institute. A total of 70 cases with clinical diagnosis of cutaneous vasculitis admitted in Dermatology Ward of Government Medical College, Kozhikode, during January 2013 to January 2014 were considered for the study. Out of these 66 cases with histopathological diagnosis of cutaneous small vessel vasculitis were included. Clinical diagnosis was made by ACR diagnostic (American College of Rheumatology) criteria. Detailed history, physical examination and routine investigations were done. A 4-mm skin punch biopsy taking care to include subcutaneous tissue was taken. Direct immunofluorescence in skin biopsy and serum indirect immunofluorescence for ANA and ANCA were done as indicated in selected cases.

RESULTS

A total of 66 patients with clinical diagnosis of Cutaneous Small Vessel Vasculitis (CSVV) were included in the study.

CSVV was mainly seen in young adults 20-40 years being the commonest age group. Nearly, two thirds of the cases were below 40 years. It was more common in females and the female-to-male ratio- 1.75 to 1.

Clinical Presentation- These were various modes of presentation with palpable purpura being the commonest followed by nodules and ulcers. Lower limbs were the most commonly affected site. The most common lesion was palpable purpura seen in 31 (44.28%) of the patients, followed by nodules in 19 (27.14%) of the patients. Five patients had urticaria, though only 4 had features of urticarial vasculitis. Out of 66 patients, 31 (44.28%) patients had bilaterally symmetrical pitting type of pedal oedema.

Associated Symptoms- The figure 3 shows the most commonly seen associated symptoms. Abdominal pain and dyspnoea topped the most common symptoms.

Aetiologic Associations- The most common associated condition was recurrent drug intake (41.42%), followed by recurrent respiratory tract infection (18.57%) and sore throat and diabetes mellitus (12.85%). One patient had non-Hodgkin's lymphoma.

Laboratory Parameters in Cutaneous Vasculitis- Laboratory parameters are shown in Table 1.

ASO titre was elevated in 10 and ANA was positive in 5 patients. Out of 5 patients with ANCA positivity, all were P-ANCA positive and no one was positive to C-ANCA. Two were associated with Churg-Strauss syndrome and rest were histopathologically diagnosed as leukocytoclastic vasculitis. One was associated with history of treatment with propylthiouracil.

Histopathology- Composition of inflammatory cells in various specimens in this study is shown in Table 8 and the histopathological types of vasculitis in Table 2. The clinicopathological correlation of vasculitis is provided in Table 3 and the aetiologies in various cases in Table 4.

DISCUSSION

Out of 70 patients with clinical diagnosis of cutaneous vasculitis selected, 66 patients were having histopathological features of Cutaneous Small Vessel Vasculitis (CSVV). Leukocytoclastic vasculitis (47 patients) represented the maximum number of patients, which is similar to the earlier studies.[2] Palpable purpura was the most common cutaneous lesion seen in our patients as already been reported.[1,3] Systemic involvement was seen in 50% of our patients as already been reported in other studies. Musculoskeletal involvement was most common feature like other series.[4,5] In this study, renal involvement was seen in only one case, whereas study by Khetan et al observed renal involvement as most common feature. In a recent series from India, 22% of patients had gastrointestinal involvement.[1] In this study, gastrointestinal involvement was seen in 12.8% of patients. Most common laboratory abnormality seen in 34.28% of our patients, but in earlier studies, elevated ESR was the most common laboratory abnormality.

A causal agent or an underlying condition has been reported in 20-85% of the cases with vasculitis.[4,5] The aetiological association was seen in 62.2% of our cases. Infections and CTD are the two most common associated conditions in Europe.[1,6] In our study, drugs were found to be the commonest factor associated with vasculitis, similar to study by Pooja Khethan et al AIIMS, New Delhi.

In Mexico, drugs were implicated in less than 2% of the cases.[3,5] The most commonly implicated drugs in our study were NSAIDs, whereas antibiotics were the most common cause in other studies.[1,7] NSAIDs are easily available over the counter, which might explain its higher frequency of this as a cause. There is no test available that can exactly delineate drugs as the cause of vasculitis. The temporal correlation and effect of withdrawal of drug were considered as method. No difference was observed in the clinical outcome between these patients and those without drug

history. Also, rechallenge was not done and so the definitive causal association could not be established. The overall frequency of infection was 17.1% in our study, 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%).[1,4,7]

Histologically, in skin biopsy of all cases, the inflammatory infiltrate was localised to upper and mid dermis in most cases, though lower dermal and panniculus involvement was also seen. Panniculus involvement was seen in palpable purpura, wheals, nodules, crusted plaques and ulcers. Infiltrate was mostly confined to perivascular and interstitial location and was predominantly neutrophilic in 44 (62.8%) as compared to 76% by Sais et al.[10] Leukocytoclasia and fibrinoid necrosis were present in 85 and 89%, respectively, while others have reported these changes in more than 95% of the cases.[4] RBC extravasation was seen in 90.5% of our cases as compared to 100% in other studies.[8,9]

Most of the patients with LCV and HSP showed SVV with both neutrophilic and oeosinophilic infiltrate. Seven patients showed predominantly lymphocytic vasculitis, which could be explained by advanced age of lesion biopsied.

In patients with CTD, predominantly neutrophilic infiltrate was seen admixed with oeosinophils, which is similar to the observations reported earlier.[10,11] Tissue oeosinophilia was found to be a reliable indicator of drug-induced vasculitis, but here in this study, we did not find any significant difference for tissue oeosinophilia in those patients with and without drug history. Only 2 cases of oeosinophilic vasculitis were observed.

In the present study, out of 5 patients with ANCA positivity, all were p-ANCA positive and were negative to c-ANCA. Two were associated with Churg-Strauss syndrome and rest were histopathologically diagnosed as leukocytoclastic vasculitis. One was associated with history of treatment on propylthiouracil. So, ANCA positivity is not specific for the known ANCA associated vasculitic syndromes. In the study conducted by Sais et al, out of 160 patients, 21% were p-ANCA positive and none had c-ANCA.[8,9]

The direct immunofluorescence study was done only in 21 cases, clinically suspected cases of Henoch-Schonlein purpura. Analysis showed IgA positivity in 6 cases and were IgG negative. But, these findings cannot be correlated with other studies as it is studied only in few patients and not in cases other than HSP. In other studies, as in study of Pooja Khethan et al,[1] DIF analysis revealed presence of at least one of the immunoreactants in 62% of patients. Other studies have reported DIF positivity in 55-92% of cases.[1,2,3] Consistent with the previous reports, the most common immune deposit was C3 followed by IgG, IgA and IgM. However, there was variation in the positivity of different immunoreactants between different studies. Grunwald et al found C3 and IgG as the most common, while IgA as predominant immunoreactant in a study from Kuwait.[1,6] Sanchez et al found IgM, C3 and fibrin as the most common immunoreactants. In concordance with other reports, no specific patterns of DIF results were found in vasculitis with the different aetiologies and types.[10,12] In conclusion, the two most common forms of cutaneous vasculitis were LCV and lymphocytic vasculitis. Histopathologically and clinically, it was HSP.[10] Possible aetiological association was seen in 62.8% of cases. Drugs were probably the most common cause (historically) seen. 37.1% of the cases were idiopathic. Histologically, SVV was the most common pattern. No association was seen between history of drug intake and tissue oeosinophilia and also between histologically severe vasculitis and clinical severity. The presence of direct immunofluorescence done in this study cannot be taken significant here as it was not done in all cases.

Based on the data of this study, workup for patients with cutaneous vasculitis, including clinical history and examination, skin biopsy, haemogram, ANA, routine biochemical profile and urine examination is recommended.

Parameters	Numbers	Percentage
Anaemia	24	34.3
Leucocytosis	10	14.3
Lymphocytosis	10	14.3
Oeosinophilia	12	17.1
Raised ESR	19	27.1
Elevated S. urea	0	0.0
Elevated S. creatinine	1	1.4
Abnormal LFT	0	0.0
Albuminuria	0	0.0
Pyuria	5	7.1
Haematuria	2	2.9
High ASO titre	10	14.3
ANA	5	7.1
P-ANCA	5	7.1
C-ANCA	0	0.0

Table 1. Laboratory Parameters in Cutaneous Vasculitis

Types of Inflammatory Cells	Number	Percentage
Only neutrophils	15	21.4
Neutrophils and oeosinophils	16	22.9
Neutrophils and lymphocytes	13	18.6
Only lymphocytes	33	47.1
Lymphocytes and histiocytes	3	4.3

Table 2. Type of Inflammatory Cells in Cutaneous Vasculitis

Leukocytoclastic vasculitis	47	67.1
Lymphocytic	7	10.0
Urticarial	3	4.3
Oeosinophilic	2	2.9
Granulomatous	2	2.9
Churg-Strauss	2	2.9
Pyoderma gangrenosum	2	2.9
Leukocytoclastic with lobular panniculitis	1	1.4
Papulonecrotic tuberculid	1	1.4

Table 3. Histopathological Types of Vasculitis

Aetiology (Number of Patients)	Histopathology (Number of Patients)
Drugs (15)	Leukocytoclastic vasculitis (8) Oeosinophilic vasculitis (2) Urticarial vasculitis (2) Lymphocytic vasculitis (1) Pyoderma gangrenosum (2)
Infection (12)	Leukocytoclastic vasculitis (5) Lymphocytic vasculitis (6) Leukocytoclastic with lobular panniculitis (1)
Malignancy (1)	Granulomatous vasculitis (1)
Connective tissue disorder associated (2)	Leukocytoclastic vasculitis (2)
Systemic diseases associated (6)	Leukocytoclastic vasculitis (6)
Behcet's (2)	Leukocytoclastic vasculitis (2)
Atopy (5)	Churg-Strauss syndrome (2) Urticarial vasculitis (1) Leukocytoclastic vasculitis (2)
Varicose vein (1)	Leukocytoclastic vasculitis (1)
Not known (26)	Leukocytoclastic vasculitis (25) Granulomatous vasculitis (1)

Table 4. Clinicopathological Correlation

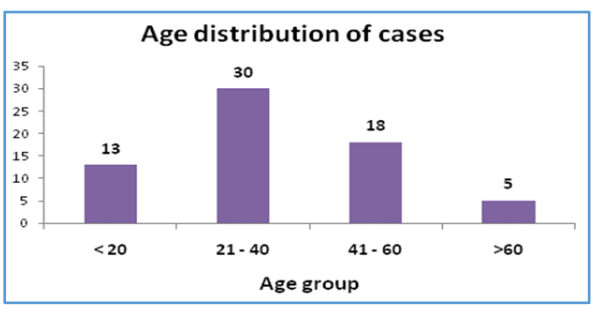

Figure 1. Age Distribution of Cases

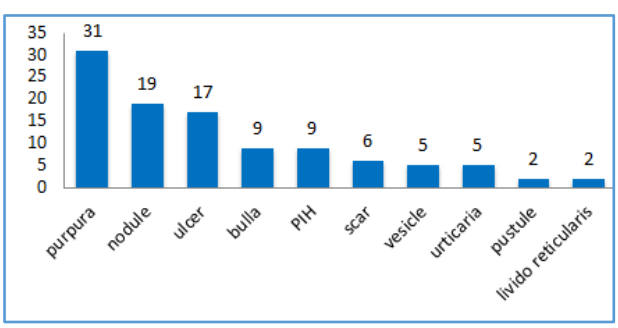

Figure 2. Clinical Presentation

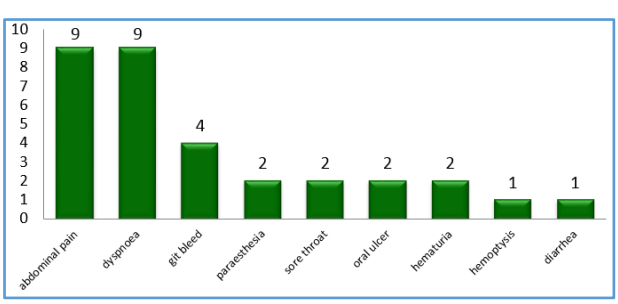

Figure 3. Associated Symptoms

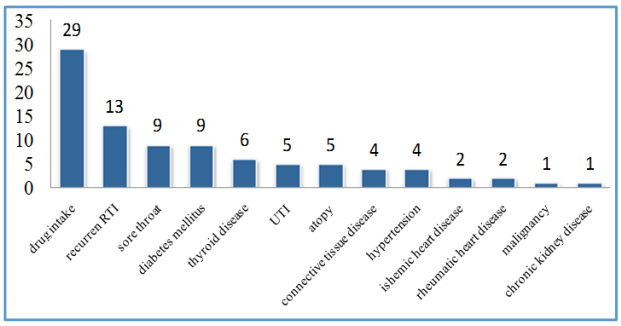

Figure 4. Aetiologic Associations

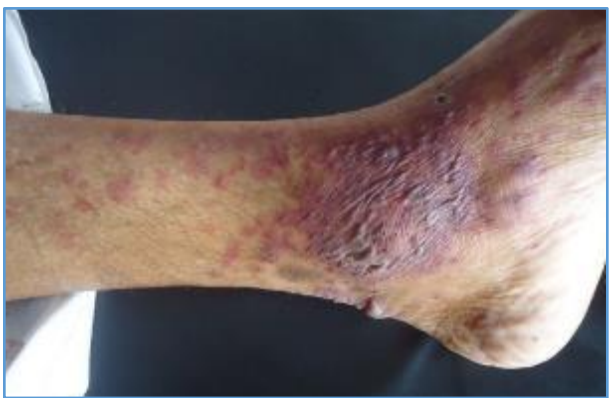

Figure 5. Palpable Purpura and Haemorrhagic Bullae

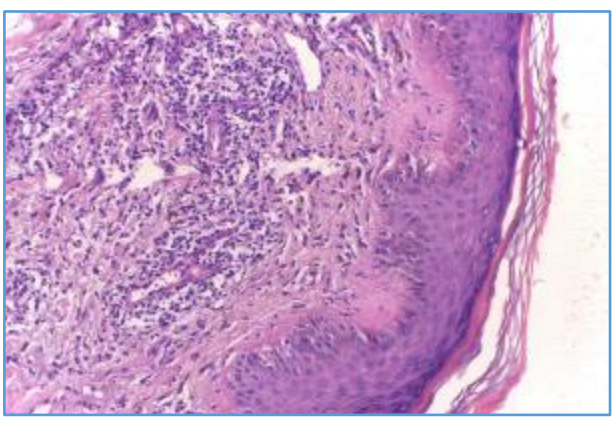

Figure 6. Leukocytoclastic Vasculitis H and E 20x

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Based on the data of this study, workup for patients with cutaneous vasculitis including clinical history and examination, skin biopsy, haemogram, ANA, routine biochemical profile and urine examination is recommended.

CONCLUSION

Cutaneous small vessel vasculitis of no known aetiology is the most common form of vasculitis presenting clinically. The heterogeneity of this group of disorders is well represented in this study. Histologically, the majority had leukocytoclastic vasculitis though other types were also present. To reach an aetiological diagnosis of vasculitis, clinical and pathological features need to be correlated and supplemented by laboratory investigations.

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