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Original Article

A study analyzing the clinical, histopathological and immunological profile of patients with cutaneous vasculitis: IgA vasculitis and IgA-negative vasculitis

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Abstract

Background Skin is frequently involved in small-vessel vasculitis. Based on immunofluorescence studies, it can be IgA type (Henoch-Schoenlein purpura) or IgA-negative type i.e. leukocytoclastic vasculitis. Clinically, palpable purpura is the hallmark of the disease. Both subtypes can be associated with variable systemic involvement.

Objective To compare the clinical, histopathological and immunological profile of patients with IgA and IgA-negative vasculitis with special reference to renal involvement.

Methods Seventy-five patients presenting to the outpatient clinic of a tertiary care hospital with a clinical diagnosis of palpable purpura were enrolled in the study. All patients had a thorough clinical examination and detailed history, and results were documented on a pre-made proforma.

Results On direct immunofluorescence findings, 40 patients had IgA vasculitis and 35 IgA-negative vasculitis. The mean age of presentation was 38.8 years in IgA vasculitis and 54.3 years in IgA-negative vasculitis. IgA vasculitis presented with frequent cutaneous (n=27, 67.5%, itching or pain) and systemic symptoms (n=18, 45%, abdominal and joints) seventeen (42.5%) as compared to IgA-negative subgroup (25.4% and 11.4%, respectively). Morphologically, palpable purpura was seen in both groups, but 11.4% patients in IgA-negative vasculitis group presented with ulcerated lesions. Patients of both groups had vessel wall fibrin deposition and necrosis, inflammatory infiltrate in the vessel wall, erythrocyte extravasation, unclear dust and endothelial swelling in descending frequencies. Complement 3 (C3) was the commonest immunoreactant (n=71; 94.7%) followed by fibrinogen (n=59; 78.7%) and immunoglobulin A (IgA) [n=40; 53.3%]. Abnormal urine microscopy findings were detected in (n=28; 70%) patients with IgA vasculitis and in (n=2; 5.7%) with IgA-negative vasculitis. Serum creatinine was raised in 12 (30%) patients with IgA vasculitis and 7 (20%) patients with IgA-negative vasculitis. Other laboratory tests had similar frequency in two groups.

Conclusion IgA vasculitis was seen in a relatively younger age group in comparison to IgA-negative vasculitis. C3 was the commonest immunoreactant staining the blood vessel wall followed by fibrinogen and IgA. Renal involvement occurred more frequently in the IgA vasculitis.

Key words
Vasculitis; IgA vasculitis; IgA-negative vasculitis; Purpura; Leukocytoclastic vasculitis.

Introduction

Vasculitis is clinically and histopathologically a heterogeneous group of pathologies that is characterized by inflammation of, small, medium or large, blood vessels. Due to the large vascular system of the skin open to cold temperatures, and due to frequent stasis, the skin

is involved in various vasculitic syndromes ranging from localized, self-limiting to generalized, multiorgan, life-threatening disease.[1,2] Cutaneous small-vessel vasculitis (CSVV), affects typically the postcapillary venules of the dermal vasculature.

Pathologically, CSVV results from antigen-antibody complexes, vasodilatation, endothelial swelling, and leukocytoclasia. Etiologically, CSVV may be associated with infections, inflammatory diseases (systemic lupus erythematosus, rheumatoid arthritis etc.), drugs, food additives and preservatives.[1,2] However, it can be either IgA-mediated or non-IgA-mediated, as determined by immunofluorescence studies. Henoch-Schönlein purpura, is a typical prototype of IgA-mediated CSVV with systemic involvement. Palpable purpura, edema, stomach discomfort, joint pain, and renal symptoms are the hallmarks of HSP.[3] It mostly affects the children. IgA-negative CSVV shows many similar clinical, pathological and laboratory features.[4]

The present study was undertaken to compare the demographic characteristics and clinical profile of patients with IgA vasculitis with that of IgA-negative vasculitis and the systemic manifestations in these two groups with special reference to renal involvement.

Materials and methods

Patients attending dermatology outpatient department of Hamdard Institute of Medical Sciences and Research, Delhi, India between June 2020 and April 2023 with a clinical diagnosis of cutaneous vasculitis were enrolled in the study. Detailed history and clinical examination were undertaken in all patients and findings were recorded in a pre-designed proforma. All patients with a clinical diagnosis of cutaneous vasculitis/palpable purpura and who consented for biopsy were included. Following investigations were done in all the patients: complete hemogram, urine protein and microscopy, renal function tests and liver function tests. Other optional investigations depended upon associated symptoms e.g. skin biopsy from new lesion for histopathology and direct immunofluorescence, anti-nuclear antibody tests (ANA), antineutrophil cytoplasmic antibodies (ANCA), microalbuminuria and 24-hour urinary proteins, hepatitis work-up and cryoglobulin levels.

IBM SPSS statistics version 25.0 (IBM corporation) was used for doing statistical analysis.

Results

Seventy-five patients, 36 (48%) males and 39 (52%) females were enrolled in the study. On the basis of direct immunofluorescence studies (details described later,), IgA vasculitis was diagnosed in 40 (53.3%) patients and 35 (46.7%) suffered from IgA-negative vasculitis. **Table 1-3** show the comparison of demographic, clinical, laboratory features in IgA and IgA-negative vasculitis groups. Mean age of patients was 47.60 years (range 7 to 69 years). The duration of disease ranged between 15 days to 45 days

Table 1 Age distribution in the study population, IgA and IgA-negative vasculitis.

Age (years)	*IgA vasculitis (n=40)*	*IgA-negative vasculitis (n=35)*
0-14	9 (22.5%)	1 (2.8%)
15-29	8 (20%)	5 (14.3%)
30-44	11 (27.5%)	8 (22.9%
>45 years	12(30%)	21 (60%)
Mean age (years)	38.8	54.3

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Table 2 Clinical features in the study population, IgA and IgA-negative vasculitis.

	IgA vasculitis (n=40)	*IgA-negative vasculitis (n=35)*
Associated cutaneous symptoms		
Itching	24 (60%)	5 (14.3%)
Pain	3 (7.5%)	4 (11.4%)
Asymptomatic	13 (32.5%)	26 (74.3%)
Associated systemic complaints		
Joint pain	7 (17.5%)	4 (11.4%)
Abdominal pain	2 (5%)	0
Both abdominal & joint pain	9(22.5%)	0
No complaint	22 (55%)	31 (88.6%)
Morphology of cutaneous lesions		
Palpable purpura	40 (100%)	35 (100%)
Ulcer	0	4 (11.4%)
Precipitating factors		
Drug intake	8 (20%)	0
Upper respiratory tract infection	9 (22.5%)	1 (2.8%)

(mean 28.26 days). IgA vasculitis presented in relatively younger patients (38.8 year vs. 54.3 year, P <0.05).

Regarding symptomatology, 24 (32%) patients complained of itching over the lesions, and 11 (14.7%) had associated pain. Rests were asymptomatic. Out of 75, 9 (12%) patients had complaints of both abdominal and joint pains, 11 (14.7%) had only joint pains and 2 (2.7%) patients had abdominal pain only. None of the patients presented with urinary complaints e.g. hematuria or oliguria. IgA vasculitis patients presented with itching or pain (27, 67.5%) whereas majority of the patients in IgA-negative vasculitis were asymptomatic (26, 74.3%).

History was suggestive of preceding infection in 11 (14.7%) patients. Out of these, 10 (13.3%) had a history of upper respiratory tract infection (URTI), and 1 (1.3%) had symptoms of urinary tract infection (UTI). Eight (10.7%) patients had a history of drug intake prior to the onset of cutaneous rash. However, nature of the drug intake could not be elicited.

Table 3 Comparison of different biochemical, hematological, immunological and histopathological parameters in IgA and IgA-negative vasculitis.

	IgA vasculitis (n=40)	*IgA-negative vasculitis (n=35)*
Urinalysis		
Granular casts	11 (27.5%)	2 (5.7%)
Proteinuria	10 (25%)	0
Granular casts and proteinuria	7 (17.5%)	0
Normal	12 (30%)	33 (94.3%)
Serum creatinine		
1.5-2 mg/dl	7 (17.5%)	5 (14.3%)
2-4 mg/dl	3 (7.5%)	1 (2.8%)
>4mg/dl	2 (5%)	1 (2.85%)
Complete blood count		
ESR	6 (15%)	1 (2.8%)
↑ESR, platelet & WBC count	4 (10%)	6 (17.1%)
↑ Platelet & WBC count	5 (12.5%)	2 (5.7%)
↑ C-reactive protein	5 (12.5%)	4 (11.4%)
ANA Profile		
Anti-SSA/Ro	6 (7.3%)	2 (5.7%)
Anti-Ro-52	6 (7.3%)	2 (5.7%)
Anti-SSB/La	2 (5.0%)	0
Anti-histone	2 (5%)	0
Anti-RNP	1 (2.5%)	1 (2.8%)
ANA Global		
Homogeneous	1 (2.5%)	0
Speckled	1 (2.5%)	0
Granular	5 (12.5%)	6 (17.1%)
Antineutrophil cytoplasmic antibodies (ANCA)		
c-ANCA	4 (10%)	6 (17.1%)
p-ANCA	2 (5%)	3 (8.6%)
Histopathology		
Fibrinoid necrosis	17 (42.5%)	5 (14.3%)
Inflammatory infiltrate	16 (40%)	10 (28.6%)
Extravasation of RBCs	15 (37.5%)	5 (14.3%)
Nuclear dust	11 (27.5%)	11 (31.4%)
Endothelial swelling	9 (22.5%)	0

Morphology of cutaneous lesions showed that all (75, 100%) patients included in the study presented with palpable purpura while 4 (5.3%) had associated ulcers. All (75, 100%) patients showed lesions on lower limbs while 15 (20%) showed additional involvement of upper limbs and 13 (17.3%) patients that of the trunk.

Laboratory Investigations Urinalysis showed abnormal urinary microscopy in 30 (40%) patients. Among these, 10 (13.3%) had proteinuria only, 13 (17.3%) patients had granular casts, and 7 (9.3%) patients had both granular casts and proteinuria. Forty-five (60%) patients were normal. Regarding hematological investigations, abnormal results were detected in 24 (32%) patients. Out of these, raised erythrocytes sedimentation rate (ESR) was found in 7 (9.3%) patients, 10 (13.3%) patients had elevated ESR, thrombocytosis, and leukocytosis, while 7 (9.3%) had thrombocytosis, and leukocytosis. Regarding renal function tests, a total of 19 (25.3%) patients had abnormal serum creatinine values (>1.5mg/dl); out of these, 12 (16%) patients had values between 1.5-2mg/dl, 4 (5.3%) had values between 2-4mg/dl, and 3 (4%) patients had serum creatinine values >4mg/dl. Amongst other tests, C-reactive protein (CRP) levels were elevated in 7 (9.3%) and antistreptolysin (ASO) levels in only 1 (1.3%) patient.

Anti-nuclear antibodies profile (ANA profile) Eleven (14.7%) patients tested positive, and the commonest antibodies found were anti-Ro (SS-A) and anti-Ro-52 in 6 (8%) patients each, followed by anti-histone in 3 (4%) patients, and La (SS-B) in 2 (2.7%) patients. Anti-RNP antibodies were positive in 2 (2.7%) patients, anti-ds-DNA in one (1.3%), and anti-nucleosome in one (1.3%) patient.

Antinuclear Antibody Global (ANA Global) The test was positive in 11 (14.7%) patients. Nine (12%) patients showed granular pattern while 1 (1.3%) patient each showed homogenous or speckled patterns.

Antineutrophil cytoplasmic antibodies (ANCA) Four (5.3%) patients tested positive for c-ANCA and 2 (2.7%) for p-ANCA, while it was negative in the remaining patients.

Histopathology Twenty-two (29.3%) patients had vessel wall fibrin deposition and necrosis, 26 (34.7%) inflammatory infiltrate in the vessel wall, 22 (29.3%) nuclear dust, 20 (26.7%) patients had erythrocyte extravasation, and only 9 (12%) had endothelial swelling.

Direct Immunofluorescence (DIF) It was done from the newly developed purpuric lesion in all patients. Complement 3 (C3) was the commonest immunoreactant detected in 71 (94.7%) patients followed by fibrinogen in 59 (78.7%) and immunoglobulin A (IgA) in 40 (53.3%) patients. Nine (12%) patients had one (IgE or C3), 23 (31%) two, 28 (37%) three and 15 (20%) patients had four immunoreactants. Multiple immunoreactants ($\geq$3) were found in 43 (57.3%) patients. Based on the immunofluorescence results, patients were further divided into IgA-positive and IgA-negative subgroups for further analysis. Forty (53.3%) patients in the study group had IgA deposits in the blood vessel wall while 35 (46.7%) patients did not show IgA deposition (IgA-negative vasculitis).

Discussion

Cutaneous vasculitis (CV) refers to a group of diseases characterized clinically by the spectrum of changes ranging from erythema, urticaria to purpura, ischemia, necrosis, and infarction.[1,4] Immunopathogenic mechanisms are known to be the cause of lesions in all cases of CV. Sams *et al*.[5] proposed that the antigen which may be a drug, streptococcus, hepatitis B antigen, or any unknown antigen, stimulates antibody production leading to antigen-antibody complex formation, which gets lodged in damaged vessels having gaps due to vasoactive factors released by aggregated platelets. Complement activation and vasoactive amines attract polymorphs (PMNL) which release lysozymes causing necrosis of vessel wall that leads to CV.[1] Deposition of immunoglobulins and

complement has been demonstrated in the vessel walls. Deposition of complement 3 (C3) frequently in association with IgG or IgA has also been demonstrated.[3,5] It has been reported that the types of immunoglobulins present in circulating immune complexes and in vasculitic lesions are identical.[6]

We investigated the clinical and immunofluorescence findings of 75 patients (40 with IgA vasculitis and 35 IgA-negative vasculitis) who presented with palpable purpura to the outpatient department of dermatology. There were 39 (52%) females and 36 (48%) males. The age of presentation ranged from 7 to 69 years with the mean age being 46.60 years. The mean age of presentation was relatively younger in IgA subgroup as compared to IgA-negative subgroup (38.8 years vs. 54.3 years). CV is known to occur in all age groups with equal frequency in both genders. When compared with the previous studies, our observations proved the same **(Table 4)**. Sais *et al*.[7] examined 160 cases of leukocytoclastic vasculitis and found 55.6% male and 44.4% females. The mean age was 51 years. Van Hale *et al*.[8] studied 20 patients with Henoch-Schonlein purpura out of which 55% were males and 45% were females. Barnadas *et al*.[9] studied 50 patients out of which 52% were males and 48% were females. The mean age was 60.3 years which was higher than our study. In contrast, Grunwald *et al.*[10] did a study in 40 patients, and that showed a clear female preponderance with 62.5%. The average age was 41 years in their study.

Clinically, palpable purpura is described as the hallmark of CV. Though various morphological pattern, ranging from erythematous macules to bullae and ulceration can be seen but palpable purpura is the commonest manifestation of cutaneous vasculitis. Lesions are mostly asymptomatic, although can be associated with pain. Skin lesions mostly occur in lower limbs but can also involve upper limbs and generalized distribution of lesions is seen on rare occasions. Face and mucous membranes are always spared. In our study, all patients showed lesions on lower limbs, while 20% of the patients showed additional involvement of the upper limbs and 17.3% of that of trunk. All patients in IgA subgroup had purpuric lesions whereas 4 (11.4%) patents had ulcerated lesions in addition to purpuric lesions. Majority of patients with IgA vasculitis in our study presented with symptoms of itching (60%) or pain (7.5%) whereas IgA-negative subgroup were asymptomatic (65%). About 45% of IgA vasculitis patients had Systemic complaints were more frequent in IgA (45%) patients than IgA-negative (11.4%) patients in our study.

CV is frequently known to be precipitated infections, drugs or other disorders. 14.7% of our patients had infection, 10.7% had history of drug intake and 74.7% had no cause. Results of our study are no way different from other studies **(Table 5)**.

Renal involvement is a known association of cutaneous vasculitis, especially the IgA vasculitis (Henoch-Schoenlein purpura). In our study, 10 (13.3%) patients demonstrated proteinuria and 19 (25.3%) patients had raised serum creatinine. Renal involvement was more frequent in IgA vasculitis (70%) than in IgA-negative subgroup 5.7%).

Table 4 Comparison of mean age of presentation gender distribution in patients of cutaneous vasculitis.

	Our study	*Sais et al.[7]*	*Van Hales et al.[8]*	*Barnadas et al.[9]*	*Grunwald et al.[10]*
Number of cases	75	160	20	50	40
Mean age (years)	38.96	51	22	60.3	41
Males	48%	55.6%	55%	52%	37.5%
Females	52%	44.4%	45%	48%	62.5%

Table 5 Frequency of precipitating factors in different studies.

	Our study (n=75)	*Eaf et al.[12] (n=160)*	*Hodge et al.[13] (n=61)*	*Sais et al.[7] (n=40)*
Idiopathic	74.6%	54%	63%	-
Drugs	10.7%	10%	11.1%	-
Infection	14.7%	13%	-	19%
Malignancy	-	-	1.9%	7.4%
Others	-	2%	7.4%	-

Abnormal urine microscopy findings were detected in (n=28; 70%) patients with IgA vasculitis and in (n=2; 5.7%) with IgA-negative vasculitis. Similarly, serum creatinine was raised in 12 (30%) patients with IgA vasculitis and 7 (20%) patients with IgA-negative vasculitis. The study conducted by Sais *et al*.[7] showed similar results with 19% and 13% of patients showing proteinuria and creatinine, respectively and no incidence of hematuria. Barnadas *et al*.[9] in their study showed a higher incidence of abnormal urine parameters; 42% had hematuria and 60% had proteinuria **(Table 6)**. Van Hales *et al*.[8] 38 documented a total of 65% of patients with hematuria, proteinuria, or renal casts.

High levels of antistreptolysin were detected only in 1 (1.3%) of our patients which is a very low proposition compared to 2 of 50 patients as documented by Barnadas *et al*.[8] 39 Antinuclear antibody was detected in 22 (29.3%) of our patients. Both IgA and IgA-negative subgroups had similar positive frequency. None of the 13 patients studied by Grunwald *et al*.[9] 40 showed positive antinuclear antibody, whereas 28.5% of patients in the study by Sais *et al.* had positive ANA.

In the present study, histopathological examination revealed that 69 (97.2%) patients had a perivascular predominantly neutrophilic infiltrate and 2 (2.8%) showed lymphocytic infiltrate. Other studies also showed similar results. Neutrophil predominance was reported in 35 (70%), 10 (66.6%) and 121 (76%) patients by Barnadas *et al*;[9] Van Hale *et al*.[8] Sias *et al*.[7] respectively. The rest showed lymphocytic infiltrate. Regarding the inflammatory infiltrate seen in CV, the infiltrate changes as the lesion ages. Serologic reactivity, manifested as hypocomplementemia, anti-Ro antibodies, antinuclear antibodies, hyperglobulinemia, and a positive rheumatoid factor, determines the type of inflammatory infiltrate. Zax *et al*.[11] in a serial histopathologic evaluation on a single patient of leukocytoclastic vasculitis found a temporal transition from a neutrophilic to a mononuclear infiltrate supporting the dynamic theory.

Regarding direct immunofluorescence findings, the results of our study were concordant with previous studies (**Table 7**) except for the one done by Van Hale *et al*.[8] who noticed IgA to be the most commonly encountered immunoreactant. This can be explained by the fact that the patients included in their study were suffering from Henoch-Schonlein purpura (HSP), in contrast to our study which included all patients of CV. However, Sams *et al*.[5] detected the same proposition of IgA and IgM.

Table 6 Comparison of abnormal renal parameters across various studies.

	Our study (n=75)	*Barnadas et al.[9] (n=50)*	*Sais et al. [7] (n=160)*
Hematuria	-	42%	-
Proteinuria	13.3%	60%	19%
Increased serum creatinine	25.3%	-	13%

Table 7 Comparison of proportions of immunoreactants in different studies.

Immunoreactant	*Our study*	*Barnadas et al[9]*	*Sais et al.[7]*	*Sams et al.[5]*	*Van Hale et al. [8]*
Complement 3	94.7%	92%	80.4%	69.2%	50%
Fibrinogen	78.7%	100%	-	38.5%	67.5%
IgA	53.3%	41%	64.7%	30.8%	75%
IgM	18%	28%	49%	30.8%	25%
IgG	20%	10%	42.2%	-	-

Conclusion

In the present study, IgA vasculitis was seen in a relatively younger age group compared to IgA-negative vasculitis. History of previous drug intake or preceding infection, abdominal pain, and joint pain was seen more frequently in IgA vasculitis, however, leg ulcer was associated more with IgA-negative vasculitis. Abnormal urine microscopy was more frequently encountered in IgA vasculitis. This subgroup also showed raised serum creatinine. Antinuclear antibodies were found more frequently in IgA vasculitis as compared to IgA-negative vasculitis. In this study, C3 was the commonest immunoreactant staining the blood vessel wall followed by fibrinogen and IgA.

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