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An aetiological & clinicopathological study on cutaneous vasculitis

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***Background & objectives*: Cutaneous vasculitis has protean clinical manifestations. It may be idiopathic or associated with a spectrum of conditions such as infections, drugs, *etc*. Skin is involved in both small vessel vasculitis (SVV) and medium vessel vasculitis (MVV). Overlapping features are seen between SVV and MVV. The histopathological features may not always relate with the clinical lesions. The aim of the present study was to evaluate the aetiological factors and clinicopathological association in patients with cutaneous vasculitis.**

***Methods*: In this cross-sectional study, detailed history and clinical examination were done on patients with biopsy proven cutaneous vasculitis. Two skin biopsies were taken from each patient for routine histopathology and direct immunofluorescence.**

***Results*: Of the 61 patients studied, hypersensitivity vasculitis (HSV) [23 (37.7%)] and Henoch Schonlein purpura (HSP) [16 (26.2%)] were the two most common forms. Systemic involvement was seen in 32 (52.45%) patients. Drugs were implicated in 12 (19.7%) cases, infections in 7 (11.4%) and connective tissue disorders in 4 (6.5%) cases. Histologically SVV was the most common pattern, seen in all the clinically diagnosed patients with SVV (47), and in 12 of the 14 clinically diagnosed patients with MVV. Direct immunofluorescence showed positivity for at least one immunoreactant in 62 per cent of the patients and the most common deposit was C3 followed by IgG, IgA and IgM.**

***Interpretation & conclusions*: Majority of our patients with cutaneous vasculitis were idiopathic. Histologically, SVV was seen in most of our patients. No association was seen between history of drug intake and tissue eosinophilia and also between histologically severe vasculitis and clinical severity. The presence of immunoreactant IgA was not specific for HSP.**

Key words Henoch Schonlein purpura - hypersensitivity vasculitis - medium vessel vasculitis - small vessel vasculitis

Cutaneous vasculitis is an inflammatory process affecting the vessel wall that leads to its damage and subsequent haemorrhagic features[1]. It may be a primary disorder or a presenting sign of primary systemic vasculitis such as polyarteritis nodosa (PAN), Wegener's granulomatosis (WG), Churg Strauss syndrome (CSS) or secondary to drugs, infections or systemic diseases such as connective tissue disease (CTD) and malignancy[2]. Based on the size of the vessel wall affected, cutaneous vasculitis is classified as small vessel vasculitis (SVV), medium vessel vasculitis (MVV) and large vessel vasculitis[3]. Skin is affected in both SVV and MVV. Patients with predominantly SVV have palpable purpura, urticaria, vesicobullous lesions

and targetoid lesions whereas MVV is characterized by subcutaneous nodules, livedo reticularis, ulcer, infarct, digital pitted scars and gangrene[1,2].

Although there is a multitude of causes of cutaneous vasculitis, yet most of the cases are idiopathic. The frequency of each of the cause is variable depending upon the epidemiological difference and prevalence of infections. From a pooled data, cutaneous vasculitis is due to infections in 22 per cent; drugs in 20 per cent; CTD in 12 per cent; Henoch Schonlein purpura (HSP) in 10 per cent and <5 per cent each due to malignancy, primary systemic vasculitis or systemic inflammatory disease such as sarcoidosis and cryoglobulinemia[2]. Histopathology can be significantly variable and several overlapping features are seen between SVV and MVV. The histopathological features may not show any association with the clinical lesions.

There are only few studies from India on cutaneous vasculitis[4,5]. Hence we undertook this study to evaluate the aetiological factors and clinicopathological association with clinical lesions in patients with cutaneous vasculitis in a tertiary care hospital in north India.

Material & Methods

All consecutive patients were selected. No sample size was fixed *a priori*. Patients with biopsy proven cutaneous vasculitis were recruited from the out patient departments of Dermatology & Venereology and Medicine, All India Institute of Medical Sciences (AIIMS), New Delhi, between November 2006 to October 2008. Patients with bleeding diatheses, those unwilling to give informed written consent and pregnant females were excluded. The study was approved by the Institutional Ethics Committee.

The study protocol included detailed history and clinical examination. The following investigations were done: complete haemogram, renal and liver function tests, urine analysis, antinuclear antibody (ANA), antineutrophilic cytoplasmic antibody (ANCA), Rheumatoid factor (RF), C-reactive protein (CRP), cryoglobulins, anti-cardiolipin antibody (IgG and IgM), lupus anticoagulant, HBsAg, anti HCV antibody, anti streptolysin O (ASO) titre, throat swab for culture and sensitivity, Chest X-ray and Mantoux test. Other tests carried out depending upon the clinical indications included stool for occult blood, 24 hour urinary protein, sputum for acid fast bacilli (AFB), HBV RNA, Anti HBc IgM, dsDNA, anti Ro/anti La antibody, IgA, IgG, IgM, C3, HIV serology, X-ray of wrist and feet, nerve conduction studies, arterial and venous doppler, ultrasonography (USG) abdomen, echocardiography, renal biopsy, contrast enhanced computed tomography of chest, digital subtraction angiography (DSA) and contrast enhanced magnetic resonance angiography. Two skin biopsies (punch biopsy, 4 mm) were taken in all cases, one each for routine histopathology and direct immunoflourescence (DIF). All the laboratory tests were performed as per the standard guidelines within the AIIMS laboratories.

All historical, clinical, histopathological and laboratory features were evaluated. Patients were classified according to the standard criteria laid by the American College of Rheumatology (ACR)[6] with some modifications. Modifications in ACR criteria: (*i*) Age factor was relaxed in both Hypersensitivity vasculitis and Henoch Schonlein purpura (*ii*) Urticarial vasculitis, microscopic polyangitis, and vasculitis associated with connective tissue diseases were included as separate categories owing to their distinctive clinico-pathological features (*iii*) patients who do not fulfil any of the entities were classified as unclassified vasculitis.

Statistical analysis: The proportion of cutaneous vasculitis with each aetiology was determined along with 95 per cent confidence interval. The quantitative variables such as age were expressed as mean. Results of qualitative variables were expressed as percentage. Association of aetiology and diagnosis with immunoflourescence features, drug history with histopathological features were examined by using Pearson's Chi-square test. $P<0.05$ was considered significant.

Results

Of the 80 patients with clinically suspected vasculitis screened, 61 had histological features of vasculitis and were included in the study. Nineteen patients were excluded (misdiagnosis-2; Non-confirmatory histopathology - 3; Declined - 5; lost to follow-up -9). There were 35 males (57.4%) and 26 females (42.6%) with an age range of 7 to 64 yr. The mean age was 29.4±27 and 35.5±14.98 yr for males and females, respectively. The maximum number of patients (n=20, 36%) was seen in the age group of 16-30 yr followed by 31-45 (n=20, 32.7%). The duration of the illness ranged from as short as one day to 10 yr. Palpable purpura was the most common type of cutaneous lesion seen in 43 (70.5%) patients. The other cutaneous lesions were crusted plaques, ulcers, wheals and haemorrhagic vesicles. Clinical presence

of deep seated nodules/ulcers/gangrene (suggestive of MVV) was seen in 14 patients. Thirty two (52.4%) patients had involvement of upper limbs, trunk or face in combination with involvement of lower limbs.

Constitutional features were present in 24 patients (39.3%) [arthralgia in 19 (31.1%); myalgia in 11 (18%); and fever in six (9.8%)]. Systemic symptoms were seen in 23 patients (37.7%) and included arthritis in 17 (27.9%), abdominal pain and melena in 5 (8.2%) each and haematuria in three (4.9%) cases. Other associated symptoms were oral ulcers in four patients (6.5%), patchy sensory loss over feet and palpitations in three (5%) each, exertional dyspnoea and paresthesia in two (3.3%) each, dry eyes and dry mouth, uveitis, epistaxis in one (1.6%) each. After complete investigations, systemic involvement was found in 32 (52.45%) patients with renal involvement in 19 patients (31.1%), arthritis in 17 (27.9%), gastrointestinal involvement in five (8.2%), neuropathy and pulmonary involvement in one (1.6%) each.

History of chronic drug intake was present in seven patients for hypertension, diabetes mellitus, rheumatic heart disease, rheumatoid arthritis and hypothyroidism. Drug intake up to one month prior to onset of cutaneous lesions was considered relevant. Such association was present in 12 patients (19.7%). Non steroidal anti-inflammatory drugs (NSAIDs) were the commonest drugs in five (41.6%) followed by unknown drugs in four, antihistaminics in three, antibiotics in two and others in three patients. The other aetiological factors identified were infections in seven, CTD in four and cryoglobulinemia in one patient.

The two most common forms of vasculitis were hypersensitivity vasculitis (HSV) (23 patients, 37.7%) (Fig. 1a) and HSP (16 patients, 26.2%). Though urticarial vasculitis (Fig. 1b), microscopic polyangiitis (MPA) and CTD were not part of the ACR classification, the patients were classified into these groups because of distinctive clinical findings and investigations. Ten patients (16.3%) did not qualify for any group despite having features of vasculitis, and were labelled as unclassified vasculitis.

The most common laboratory abnormality was elevated ESR found in 38 (62.2%) patients, 11 were positive for ANA and all were HIV negative (Table I). Eighteen patients (29.5%) had urinary abnormalities of which 12 had hematuria with proteinuria, 4 had hematuria alone and 2 had proteinuria alone. The liver and renal function tests were normal in all patients except for one who had unconjugated hyperbilirubinaemia.

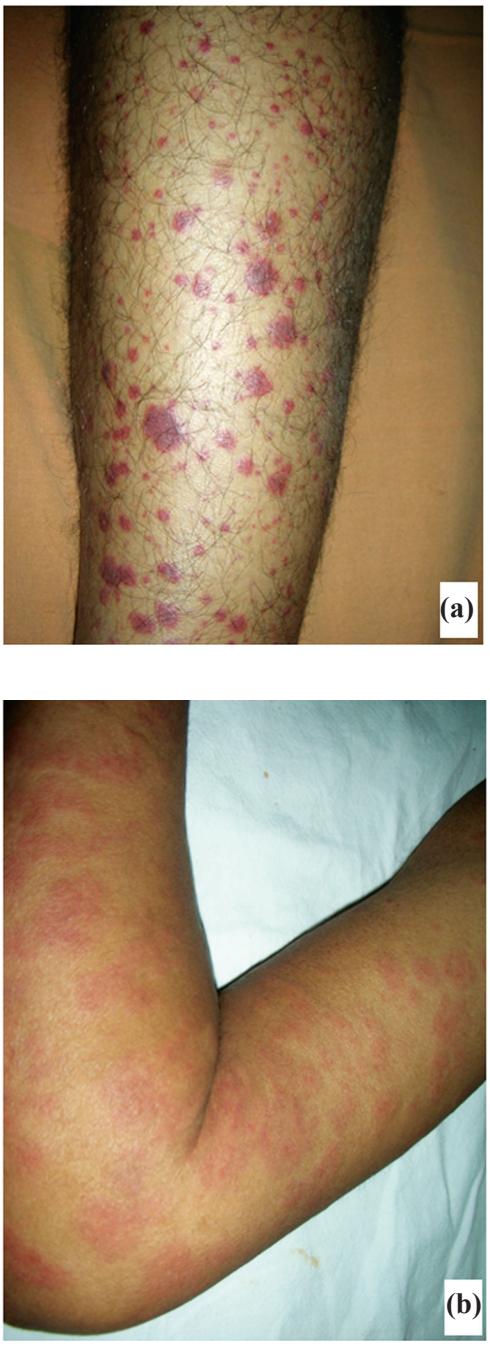

Fig. 1 (a). Hypersensitivity vasculitis showing palpable purpura on the lower leg; **(b).** Urticarial vasculitis showing urticarial plagues on the upper extremity.

Histopathological features: Of the 61 patients, 53 biopsy specimens of 52 patients were re-analyzed. SVV was seen in 51 and MVV in 2 specimens only (Table II). In the SVV group, leukocytoclasia was

Table I. Laboratory parameters of the patients (n=61)

Laboratory parameters	No. of patients (%)
Haemogram	
Raised ESR	38 (62.5)
Anaemia	14 (22.9)
Leukocytosis with neutrophilia	8 (13.1)
Eosinophilia	1 (1.6)
Thrombocytosis	1 (1.6)
ANA	11 (18)
Homogenous	6
Speckled	4
Nucleolar	1
RF	5 (8.1)
P-ANCA (n=54)	1(1.8)
Cryoglobulin (n=52)	1(1.9)
Raised anticardiolipin antibodies (n=52)	
IgG	3 (5.8)
IgM	2 (3.8)
Elevated CRP (n=51)	7 (13.7)
HbsAg (n=53)	1 (1.8)
Anti HCV (n=53)	1 (1.8)
ASLO titre (n=45)	3 (6.6)
Mantoux test (n=49)	24 (48.9) (>10mm) 6 (12.2) (<10mm)
HIV serology (n=12)	Negative in all
Serum IgG (n=31)	Increased in 6, Decreased in 3, Normal in 22
Serum IgA (n=31)	Increased in 8, Decreased in 1, Normal in 22
Serum IgM (n=31)	Increased in 3, Decreased in 10, Normal in 18
Serum C3 (n=12)	Increased in 7, Decreased in 1, Normal in 4

ESR, erythrocyte sedimentation rate; ANA, antinuclear antibody; ANCA, antineutrophilic cytoplasmic antibody; CRP, C-reactive protein; RF, rheumatoid factor; ASLO, anti streptolysin-O; C3, complement 3

present in 45 biopsies (84.9%), endothelial cell swelling in 44 (83%), fibrinoid necrosis in 47 (88.6%), RBC extravasation in 48 (90.5%) and dermal oedema in 45 (84.9%) (Fig. 2). Most of them showed mild to moderate vasculitis. DIF was performed in 40 patients who had early active purpura. C3 was the commonest (perivascular) immune-reactant seen in 19 (47.5%) patients followed by IgG in 12 (30%), IgA in 11(27.5%), and IgM in 10 (25%). The positivity for

Table II. Classification based on size of blood vessel and composition of inflammatory infiltrate

	No. of specimens	95% confidence interval
Small vessel vasculitis		
Only neutrophilic	10 (19.6)	9.8-33.1
Neutrophilic and eosinophilic	37 (72.5)	58.3-84.1
Predominantly neutrophilic	18 (48.6)	31.9-65.6
Predominantly eosinophilic	4 (10.8)	3.0-25.4
Lymphocytic	4 (7.8)	2.2-18.9
Medium vessel vasculitis	2	
Lymphocytic	1	
Neutrophilic	1	

Values in parentheses are percentages

IgA was statistically insignificant for different groups of vasculitis including HSP.

Clinicopathological association: In patients with HSV (n=23), leukocytoclastic vasculitis (SVV) was seen in 20 biopsy specimens. Three patients showed lymphocytic vasculitis. DIF was positive for at least one immunoreactant in seven of 13 (53.84%) and negative in six (46.1%) patients. C3 was positive in six (46.1%), IgM in three (23%) and IgG and IgA in two (15.4%) each. SVV was seen in 16 patients with HSP. DIF showed positivity for at least one immunoreactant in 10 patients (83.3%). The most

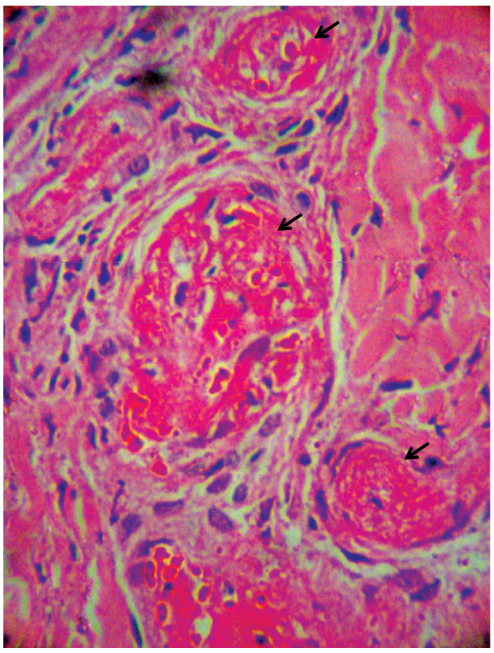

Fig. 2. Showing lecucytoclastic vasculatis with fibrinoid necrosis (shown in arrows) (H & E, X200).

Table III. Comparison between clinical diagnosis, histological and immunoflourescence features (n=61)

Clinical diagnosis (No.)	Histological diagnosis	DIF
Hypersensitivity vasculitis (23)	Leukocytoclastic vasculitis:20	N=13
	Neutrophilic-7	Neg(5), C3(2), IgG+C3(2)
	Neutrophilic+ eosinophilic-13	IgM(1)
	Lymphocytic vasculitis-3	Neg(1), IgA+C3+IgM(2)
Henoch Schonlein purpura: Classical (7)	Leukocytoclastic vasculitis: 7	N=5
	Neutrophilic + eosinophilic: 7	IgA, IgG, C3(1), C3(1), Neg(2), IgG, IgA, IgM, C3(1)
Henoch Schonlein purpura Adult (9)	Leukocytoclastic vasculitis:9	N=7
	Neutrophilic+ eosinophilic: 8 (N>E)	Neg(1), IgA(1), IgA, IgG, C3(1),
	Neutrophilic-1	IgM, IgG, C3(1), IgG, C3(1),C3(1), IgA, IgM, C3(1)
Microscopic polyangiitis (1)	Leukocytoclastic vasculitis	--
	Neutrophilic + eosinophilic	
Connective tissue disease (4)	Leukocytoclastic vasculitis: 4	N=3
Rheumatoid arthritis (2)	Neutrophilic + eosinophilic: 4 (N>E)	IgG,C3(1), IgA, IgG(1), IgA, IgM, IgG, C3(1)
SLE (1)		
Sjogren's syndrome (1)		
Urticarial vasculitis (4)	Leukocytoclastic vasculitis: 4	N=2
	Neutrophilic+eosinophilic: 4	Neg (1), IgA, IgM, C3 (1)
Wegener's granulomatosis (1)	Leukocytoclastic vasculitis of small vessels	--
	Neutrophilic+eosinophilic with granuloma	
Polyarteritis nodosa (1)	Leukocytoclastic vasculitis of small vessels	--
	Lymphocytes > neutrophils	
Takayasu's arteritis (1)	Vasculitis of small and medium vessels with lymphocytes and histiocytes	IgM, IgA, IgG
Unclassified vasculitis (10)		N=6
Small vessel (9)	Leukocytoclastic vasculitis: 8	Neg(4), C3 (1)
	Neutrophilic (4)	
	Neutrophilic+eosinophilic (3)	
	Lymphocytic (1)	
Medium vessel (1)	Neutrophilic (1)	Neg (1)

common immunoreactant was C3 seen in eight (66.6%) patients, followed by IgA and IgG in five (41.6%) each and IgM in three (25%) patients. In patients with CTD, predominantly neutrophilic infiltrate was seen admixed with eosinophils. DIF was done in three patients and all were positive and showed positivity for IgG in all three patients, C3 and IgA in two patients each and IgM in one patient. Predominantly eosinophilic vasculitis was seen in two patients with urticarial vasculitis and the DIF showed positivity for IgA, IgG and C3 in one and was negative in the other. The comparison between clinical diagnosis, histological and DIF features (in 52 patients the slides were re-analyzed and in the remaining nine only the reports were analyzed) is shown in Table III.

Histologically severe vasculitis (characterized by extensive fibrinoid necrosis of the vessel wall with RBC extravasation and dermal oedema) was seen in 6 cases (HSP-2, HSV-1, and unclassified 3). The clinical presentation and the systemic involvement did not show any association with the severity of vasculitis (mild, moderate or severe). Forty seven (77%) of clinically diagnosed SVV cases, showed histologic features of SVV. But only two of the fourteen patients (14.3%) with clinically diagnosed MVV showed histological features of MVV. The remaining 12 had features of SVV.

Of the 12 patients with prior drug history, tissue eosinophilia was present in eight while in the remaining four tissue eosinophilia was absent. In another 32 patients with tissue eosinophilia, prior drug history was absent and two patients had urticarial vasculitis. Peripheral eosinophilia was present in only one patient.

Discussion

In this cross-sectional study we report findings in 61 consecutive patients with cutaneous vasculitis.

HSV (23) and HSP (16) represented the maximum number of patients, which is similar to earlier studies[7]. Palpable purpura was the most common cutaneous lesion seen in our patients as reported by others also[7-10]. Systemic involvement was seen in more than half of our patients as already been reported[8,9]. We observed renal involvement as the most common feature which is in contrast to musculoskeletal system involvement in other series[8,9,11]. Eight per cent of our patients had gastrointestinal involvement as reported by others[7,9]. In a recent series from India, 22 per cent of the patients had GI involvement[5]. Consistent with the earlier studies, elevated ESR was the most common laboratory abnormality seen in nearly two-thirds of our patients[4,9-11].

A causal agent or an underlying condition has been reported in 20-85 per cent of the cases with vasculitis[7,8,11-14]. The aetiological association was seen in 40 per cent of our cases. Infections and CTD are the two most common associated conditions in Europe[8,11,12]. In our study, drugs were found to be the commonest factor associated with vasculitis, as reported from Kuwait[9]. In Mexico, drugs were implicated in less than 2 per cent of the cases[13]. The most commonly implicated drugs in our study were NSAIDs whereas antibiotics were the most common cause in other studies[7,9,11,12]. 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 withdrawl of drug and rechallenge. No difference was observed in the clinical outcome between these patients and those without drug history. Also, rechallange was not done in any of our patients. Therefore, the definitive causal association could not be established. The overall frequency of infection was 11 per cent 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%)[7-9,12,13].

Histologically, we observed SVV (96%) in most of our patients and MVV in only 4 per cent. This was in contrast to Sais *et al*[10] who reported SVV and MVV in 60 and 40 per cent respectively. 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 involved medium sized vessel leading to sampling bias. Multiple skin biopsies could have been taken at different times. The infiltrate was localized 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 50 per cent as compared to 76 per cent by Sais *et al*[10]. Leukocytoclasia and fibrinoid necrosis were present in 85 and 89 per cent respectively while others have reported these changes in more than 95 per cent of the cases[10,15]. RBC extravasation was seen in 90.5 per cent of our cases as compared to 100 per cent in other studies[10,15]. Most of the patients with HSV and HSP showed SVV with both neutrophilic and eosinophilic infiltrate. Three 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 eosinophils which is similar to the observations reported earlier[16]. Tissue eosinophilia was found to be a reliable indicator of drug induced vasculitis[17] but we did not find any significant difference for tissue eosinophilia in those patients with and without drug history.

DIF analysis revealed presence of at least one of the immunoreactants in 62 per cent of patients. Other studies have reported DIF positivity in 55-92 per cent of cases[12,15,18]. Consistent with the previous reports[19], 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*[20] found C3 and IgG as the most common, while IgA as predominant immunoreactant in a study from Kuwait[9]. Sanchez *et al*[18] found IgM, C3 and fibrin as the most common immunoreactants. In concordance with other reports[12], no specific patterns of DIF results were found in vasculitis with the different aetiologies and types.

In conclusion, the two most common forms of cutaneous vasculitis were HSV and HSP. Possible aetiological association was seen in 39.6 per cent of cases. Drugs were probably the most common cause (historically) seen. Majority of the cases were idiopathic. Histologically, SVV was the most common pattern. No association was seen between history of drug intake and tissue eosinophilia, and also between histologically severe vasculitis and clinical severity. The presence of immunoreactant IgA was not specific for HSP.

Based on our data, work-up for patients with cutaneous vasculitis including clinical history and examination, skin biopsy, haemogram, ANA, routine biochemical profile, and urine examination is recommended.

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