Utility of Direct Immunofluorescence in the Diagnosis of Small Vessel Vasculitis of the Skin: A Cross-Sectional Study

Sir,

Small vessel vasculitis (SVV) of the skin presents clinically as palpable purpura, mainly on the lower extremities. Cutaneous small vessel vasculitis (CSVV), which affects post-capillary venules, is the most common type of SVV. Histopathology is essential for confirmation of diagnosis of CSVV,[1] and direct immunofluorescence (DIF) provides information regarding the type of immune-reactants. Histopathology is preferably done within 18–36 hours, and DIF within 6 hours of onset of skin lesions.[2] Only few studies have shown positive histopathology and DIF findings in lesions older than the above-mentioned period. Hence, many clinicians still wait for fresh lesions to appear for histopathology and DIF investigations. Most of the times DIF study is deferred because of higher rate of negativity, when performed for lesions older than 24 hours and also because of cost, with resultant delay in proper diagnosis. The purpose of this study was to establish the diagnostic utility of DIF, to assess the need of performing DIF in all patients of SVV of skin, and to compare the percentage of positivity of histopathology and DIF, in relation to the timing of these tests among patients with SVV of the skin. This study was conducted in the dermatology department of a government tertiary care teaching hospital, over a 1-year period.

All clinically diagnosed patients of SVV of the skin with palpable purpura were studied. Patients with thrombocytopenia and disorders of coagulation were excluded. Patients were classified into four groups based on clinical diagnosis. Infection-induced CSVV was diagnosed if the patients had concurrent or preceding infections; drug-induced CSVV, if there was history of consuming drugs known to cause CSVV during the preceding 1 month; Henoch Schonlein purpura (HSP), if the criteria suggested by Michel *et al*. (1992)[3] were satisfied; and idiopathic CSVV, if the patients could not be placed under the above-mentioned groups and lacked evidence of connective tissue diseases or underlying malignancies. Urinalysis, hemogram, erythrocyte sedimentation rate (ESR), renal and liver function tests, serum ASO titre, serum cryoglobulins, stool examination, Mantoux test, chest X-ray, and histopathological and DIF studies of skin lesions were performed. SVV of the skin was diagnosed histologically if there was inflammatory infiltrate (predominantly neutrophils) in and around the dermal blood vessels, vessel wall damage, and fragmentation of nuclei of neutrophils.[1] In DIF, the presence of IgM, IgG, nongranular IgA, C3, or fibrinogen deposits indicated CSVV, whereas granular IgA deposits was diagnostic of HSP.[4] Continuous variables were expressed as means with standard deviation (SD) and categorical variables as frequencies/proportions.

Among the total 35 patients, 18 were females. Age ranged from 11–60 years (mean, 33.5). All patients had purpuric lesions on the legs; additionally, 6 had ulcers and 3 had vesicles and bullae. Fifteen patients had extracutaneous manifestations – arthralgia, abdominal pain, hematuria, and melena. Clinical classification is shown in Table 1. Skin biopsy was diagnostic of vasculitis in 29 (82.8%) patients [Figures 1 and 2]. DIF was diagnostic of vasculitis in 34 (97%) patients; 19 (54.3%) of whom were diagnosed as HSP [Figures 3 and 4]. Thirteen (37.1%) patients who were diagnosed clinically as infection-induced (n = 7), idiopathic (n = 4), and drug-induced (n = 2) CSVV were diagnosed as HSP in DIF study. C3 and fibrinogen were the common immune-reactants seen in DIF [Table 2].

Table 1: Clinical diagnosis in patients with small vessel vasculitis (SVV) of the skin

Clinical diagnosis of SVV	Number of patients (n=35)	Percentage
Infection induced CSVV	12	34.3
Idiopathic CSVV	10	28.6
Drug Induced CSVV	7	20.0
Henoch Schonlein purpura	6	17.1

Table 2: Immune-reactants in patients with positive DIF study

Immunoreactants	Number of patients (n=34)	Percentage
IgA	23	67.6
IgM	6	17.6
IgG	2	5.9
C3	34	100
Fibrinogen	33	97

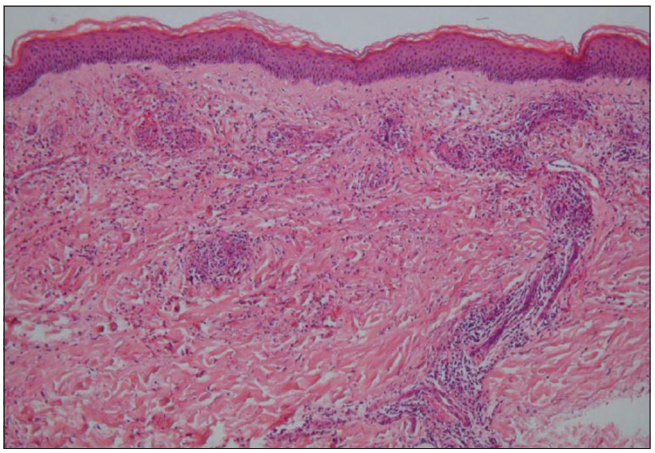

Figure 1: Histopathology of pupuric lesion showing inflammation in and around dermal blood vessels (Hematoxylin and Eosin, 10×)

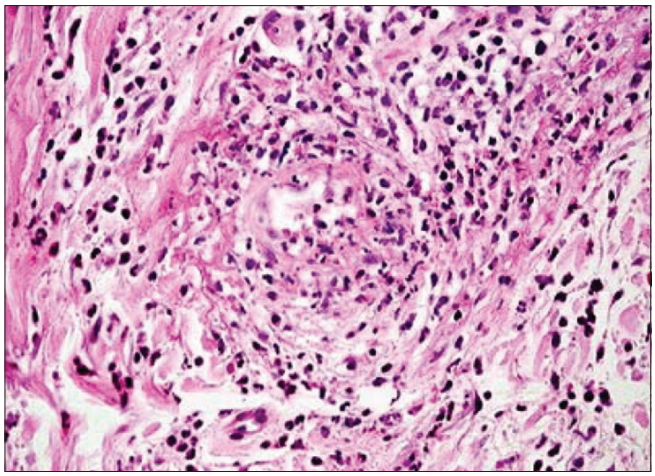

Figure 2: Neutrophilic infiltration with leucocytoclasia in and around dermal blood vessels (Hematoxylin and Eosin, 40×)

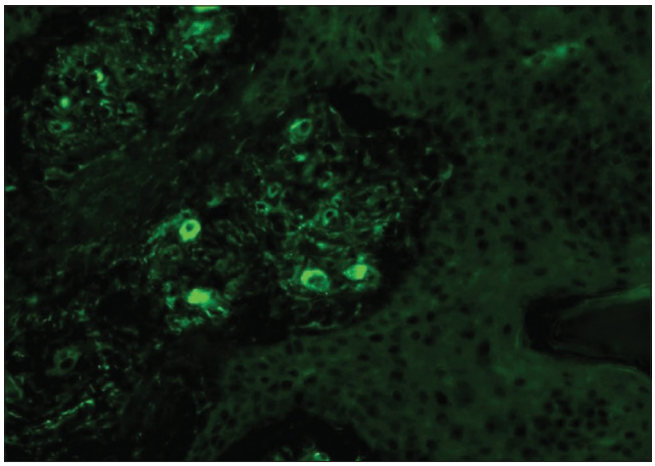

Figure 3: Direct immunofluorescence study showing granular IgA deposits in dermal blood vessel wall

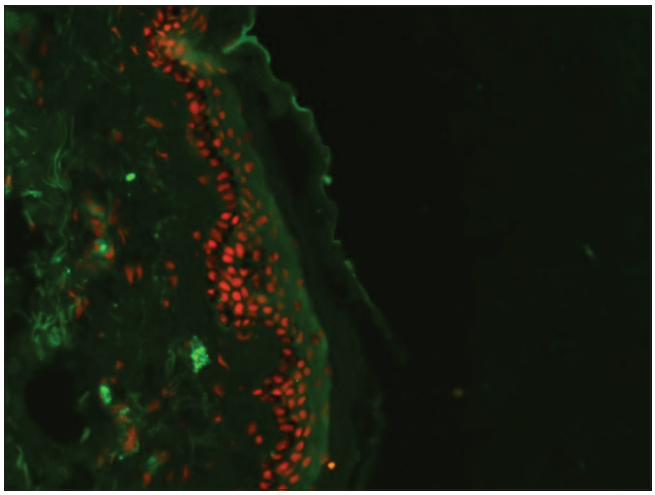

Figure 4: Direct immunofluorescence study showing C3 deposits in dermal blood vessel wall

In 14 patients who had lesions less than 2 days old, histopathology confirmed vasculitis in 12 (85%) while DIF was positive in 13 (92%) [Table 3]. Seventeen out of 19 patients (89%) who had lesions of 3–5 days duration could be diagnosed by histopathology while DIF was diagnostic in all of them. Overall, DIF was positive in 6 patients whose histopathology was not confirmatory, including 4 who had skin lesions older than 48 hours. DIF was positive in 2 patients who had lesions older than 5 days, in whom histopathology was nondiagnostic.

The sensitivity and positive predictive value of DIF were 96% and 82%, respectively, in those with skin lesions less than a week old. This was comparable to the findings of Bagai *et al*. (97.2%)[5] and Grunwald *et al*. (92%).[6] Nandeesh *et al*.[7] reported a positivity rate of 85% if specimen was taken within 7 days. Kulthanan *et al*.[8] reported a positivity rate of 74% in lesions aged 2–7 days.[8]

While only 6 patients (17.1%) were diagnosed as HSP clinically, DIF confirmed HSP in 19 (54.3%). It is important to identify patients with HSP because of higher risk of systemic involvement such as renal disease and need of rigorous follow up.

Though most workers emphasize that biopsy for histopathology and DIF should be done within 24 hours of onset of the lesions, we noted a high positivity rate for both histopathology (17/21; 80%) and DIF (21/21; 100%) even on lesions aged 3–7 days. DIF could provide a positive diagnosis in both the patients who had 5–7-day old lesions, in whom histopathology was not diagnostic.

The limitations of our study is absence of a long-term follow-up and possible missing of patients with predominant systemic involvement who were being treated in other departments.

We conclude that, even if the skin lesions of SVV are aged 3–7 days, histopathology and DIF can be diagnostic in a large number of patients. DIF may provide positive results in lesions aged 5–7 days where histopathology is not diagnostic. DIF is also helpful to diagnose HSP in several patients who may not satisfy its clinical criteria. This is important because these patients require long-term follow-up for systemic involvement.

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Conflicts of interest

There are no conflicts of interest.

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Table 3: Relationship between timing of biopsy, histopathology, and DIF in small vessel vasculitis (SVV) of the skin

Timing of biopsy	Number of patients	Histopathology		DIF	
		Diagnostic of SVV	Not diagnostic of SVV	Diagnostic of SVV	Not diagnostic of SVV
1-2 days	14	12	2	13	1
3-5 days	19	17	2	19	0
6-7 days	2	0	2	2	0

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