Clinical and immunopathological features of idiopathic cutaneous IgM/IgG vasculitis versus idiopathic skin-limited IgA vasculitis

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To the Editor:

a dermatologic addendum[1] to the 2012 Revised International Chapel Hill Consensus Conference[2] recently turned the spotlights on cutaneous small vessel vasculitis as a distinct entity differing from systemic vasculitides with regard to clinicopathologic and laboratory features.[1]

A provisional entity named cutaneous IgM/IgG vasculitis (c-IgM/IgGV), involving post-capillary venules and histologically characterized by leukocytoclastic pattern, has been introduced.[1] Its direct immunofluorescence (DIF) hallmark is perivascular deposition of IgM- and/or IgG-dominant or codominant deposits. Its clinical differences with the most common skin-limited small vessel leukocytoclastic vasculitis, skin-limited IgA vasculitis (sl-IgAV), need to be elucidated.[1]

The objectives of the study were: (i) comparing initial clinical features between these two subtypes of skin-limited vasculitis; (ii) comparing outcomes regarding response to treatment and frequency of relapses; (iii) choosing treatment – systemic one versus topical one – according to extension and severity of skin lesions.

We retrospectively evaluated idiopathic cases of c-IgM/IgGV and sl-IgAV diagnosed at our Department from November 2006 to September 2018. Inclusion criteria were: (i) palpable purpura, livedo reticularis, haemorrhagic blisters, necrotic-ulcerative, urticaria-like or targetoid lesions; (ii) leukocytoclastic vasculitis;(iii) DIF revealing IgM- and/or IgG-dominant or codominant or, alternatively, IgA-dominant perivascular immune deposits;(iv) follow-up ≥ 18 months (to rule out systemic involvement). Exclusion criteria were:(i) other forms of cutaneous vasculitis[1]; (ii) association with probable etiology, i.e. post-infectious, septic or drug-induced cutaneous vasculitis, or with systemic diseases (systemic lupus erythematosus, rheumatoid arthritis, sarcoidosis, Sjogren syndrome, etc.) [1];(iii) positivity for circulating autoantibodies[1];(iv) systemic involvement at baseline and/or during the follow-up.

Three categories were identified according to clinical response to treatment:(i) “Complete remission” (CR), absence of lesions;(ii) “Partial remission” (PR), persistence of lesions with partial tendency to heal;(iii) “No response” (NR), persistence of lesions without tendency to heal and/or appearance of

new lesions. CR/PR/NR were established based on patients' status during the 3-month period before last follow-up visit. Relapse was defined as development of new persistent lesions after CR. The patients were assessed monthly until achieving CR. Then, the patients were evaluated at 3-month intervals up to reaching 1 year upon complete remission. Then, the patients were re-evaluated at 1-year intervals or in case of relapse.

Statistical analysis was performed with Fisher's exact test and t-test for independent means.

A summary of data of 41 patients with c-IgM/IgGV and 14 with sl-IgAV is shown in Table 1.

Median total follow-up period was 80 (range=19-155) and 97 (range=24-125) months for c-IgM/IgGV and sl-IgAV, respectively. Assessing initial clinical pattern, haemorrhagic blisters were observed more frequently in sl-IgAV [n= 6/14 (42.9%)] than in c-IgM/IgGV [n=2/41 (4.9%)], with a significant difference (p=0.002). Targetoid lesions were seen in 3/14 (21.4%) sl-IgAV patients and in no c-IgM/IgGV patients (p=0.01). (Fig.1, A)

DIF examination (Fig.1, B) showed perivascular IgM deposits in all 41 patients with c-IgM/IgGV, while perivascular IgG deposits were detected only in 2/41 (4.9%) patients.

Thirty-two (78%) patients with c-IgM/IgGV and 10 (71.4%) with sl-IgAV received systemic treatments. In patients receiving systemic treatment, CR was achieved in most cases of both c-IgM/IgGV (n=27/32; 84.4%) and sl-IgAV (n=7/10; 30%), while PR was achieved in 5/32 (15.6%) c-IgM/IgG and in 3/10 (30%) sl-IgAV patients. Mean latency time between onset of vasculitis and achievement of CR in patients under systemic treatment was significantly higher in c-IgM/IgGV than in sl-IgAV (12.9 *versus* 9.5 months, respectively; p-value=0.011). Single-episode cases were predominant in both groups, with a single clinical episode of cutaneous vasculitis being reported in 31/44 (75.6%) c-IgM/IgGV and 9/14 (64.3%) sl-IgAV patients and a chronic-relapsing course with one or more flares being observed in 10 (24.4%) c-IgM/IgGV and 5 (35.7%) sl-IgAV patients. Extracutaneous involvement was not found in any patient.

Main limitations of our study were the small sample size and the possible confounding bias regarding clinical description accuracy in a retrospective data retrieval from files created during the long period of time of the study. Furthermore, the conclusions that may be drawn from this study apply only to the idiopathic subsets of c-IgM/IgG and sl-IgAV.

Haemorrhagic blisters were significantly more frequent in sl-IgAV than in c-IgM/IgG as well as targetoid lesions, which were present only in the sl-IgAV group, suggesting that these two features may help differentiating the two forms in areas where immunological tests are unavailable or unaffordable. Another finding was the striking predominance of perivascular IgM as compared to IgG deposits in the c-IgM/IgGV group. Interestingly, although the clinical course of cutaneous small vessel vasculitis is classically regarded as chronic-relapsing,[3,4] single-episode cases were predominant in both groups. Intriguingly, the time for achieving CR was longer in the sl-IgAV setting, supporting choosing a more aggressive systemic treatment in these patients.

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LEGENDS AND FIGURES

TABLE 1. Demographic, clinical and laboratory data of cutaneous IgM/IgG vasculitis and cutaneous IgA vasculitis patients

		Cutaneous IgM/IgG vasculitis (n=41)	Skin-limited IgA vasculitis (n=14)	P value
Female patients*		25 (61)	11 (78.6)	0.33
Mean age at diagnosis (years)		50.1	55.1	0.23
Clinical aspect of the lesions*	Palpable purpura	41 (100)	14 (100)	1
	Necrotic-ulcerative lesions	10 (24.4)	3 (21.4)	1
	Haemorrhagic blisters	2 (4.9)	6 (42.9)	**0.002**
	Targetoid lesions	0	3 (21.4)	**0.01**
	Urticaria-like lesions	0	2 (14.3)	0.06
	Livedo reticularis	1 (2.4)	1 (7.1)	0.44
Sites involved*	Legs (and not thighs)	26 (63.4)	11 (78.6)	0.34
	Legs and thighs	15 (36.9)	3 (21.4)	0.33
	Upper limbs	3 (7.3)	0	0.56
	Trunk	1 (2.4)	0	1
Extracutaneous involvement*		0	0	1
DIF findings*	IgG alone	0	-	-
	IgM alone	39 (95.1)	-	-
	IgG and IgM	2 (4.9)	-	-
	IgA alone	-	12 (85.7)	-
	IgA and IgM	-	2 (14.3)	-
Treatments*	Systemic corticosteroids **	30 (73.2)	10 (71.4)	1
	Topical steroids alone	11 (26.8)	4 (28.6)	1
	Topical steroids in combination with systemic treatments	7 (17.1)	4 (28.6)	0.44
	Dapsone	7 (17.1)	5 (35.7)	0.26
	Cyclosporine	3 (7.3)	2 (14.3)	0.6
	Hydroxychloroquine	1 (2.4)	0	1
Disease course*	Single episode	31 (75.6)	9 (64.3)	0.5
	One or more relapse	10 (24.4)	5 (35.7)	0.5
Response at the last follow-up in patients who underwent systemic treatment***	CR	27 (84.4)	7 (70)	0.37
	PR	5 (15.6)	3 (30)	0.37
	NR	0	0	1
Mean latency time from disease onset to initial complete remission (months) in patients who underwent systemic treatment ******		9.5	12.9	**0.011**

Mean number of relapses***	2	2.1	0.83

CR, complete remission; DIF, direct immunofluorescence; NR, no response; PR, partial response

*Values are expressed as n (%)

** Systemic corticosteroids were prednisone, methylprednisolone and/or deflazacort

*** Data were calculated on patients treated with systemic therapy, i.e. 32 patients with cutaneous IgM/IgG vasculitis and 10 patients with skin-limited IgA vasculitis

**** Data were calculated on patients treated with systemic therapy who achieved CR, i.e. 27 patients with cutaneous IgM/IgG vasculitis and 7 patients with skin-limited IgA vasculitis

***** Data were calculated on patients with one or more relapse, i.e. 10 patients with cutaneous IgM/IgG vasculitis and 5 patients with skin-limited IgA vasculitis

FIGURE 1. **A,** Main clinical features of cutaneous small vessel vasculitis: (a) palpable purpura; (b) necrotic-ulcerative lesions; (c) hemorrhagic blisters; (d) targetoid lesions. **B,** Direct immunofluorescence showing IgM (a) and IgA (b) deposits around dermal small vessels