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LETTER TO THE EDITOR

Less IgA deposits with more severe disease: the immunoclinical paradox in Henoch-Schönlein Purpura with *MEFV* mutations

Ufuk İlgen[1] · Gökhan Nergizoğlu[2]

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Dear Editor,

We have read the article by Cakici et al. [1] with interest and would like to discuss the association of histopathological findings with *ME*diterranean *Fe**V*er gene (*MEFV*) mutations further. The authors reported that 38.9% vs 94% of the Henoch-Schönlein Purpura (HSP) patients with and without *MEFV* mutations, respectively, had immunoglobulin A (IgA) deposits on skin or renal biopsy. Previous reports of HSP cases without overt IgA deposits in patients with Familial Mediterranean Fever (FMF) supported their findings. Still, *MEFV* mutations, particularly the pathogenic exon 10 variants, were reported to be associated with a severe HSP phenotype [1]. Importantly, not the presence or intensity of immunostaining of IgA, but proliferative changes, glomerulosclerosis, tubular atrophy, and interstitial fibrosis, which are direct consequences of the inflammatory process, are prognostic in both HSP nephritis and a closely related, histopathologically indistinguishable entity, IgA nephropathy [2, 3]. No studies reported any association between *MEFV* mutations and the aforementioned prognostic histopathological features in HSP nephritis before, despite many reported clinical and laboratory associations. Regarding IgA nephropathy, the most common type of glomerulonephritis in adults, the only study on histopathology reported lack of an association between *MEFV* mutations and proliferative changes [4]. We provide detailed histopathological findings of IgA nephropathy patients of our adult glomerulonephritis cohort with respect to *MEFV* mutations in Table 1. Although the study group is small and the results are prone to type II error, higher segmental glomerulosclerosis and more severe interstitial fibrosis in *MEFV* mutation carriers are far from being explainable by chance (Table 1). *MEFV* mutation carrier rate was 27.3%, similar to that of the entire cohort, and higher than the expected rate for the normal population (see our previously published work [5] for detailed methodology and results). In contrast to HSP nephritis, we found that immunostaining intensities of the mesangium (Table 1) and the glomerular basement membrane (data not shown) for IgA, IgG, and complement component 3 (C3) were similar between cases with and without *MEFV* mutations. But as its name implies and unlike HPS, IgA nephropathy is a *histopathological* diagnosis which requires the presence of IgA deposits to be made.

It is interesting for immune complex-mediated vasculitides such as HSP and polyarteritis nodosa to be associated with FMF [6] and *MEFV* mutations to modify disease severity in HSP [1]. It may theoretically be speculated that inappropriately increased interleukin-1β secretion that results in a proinflammatory state, clinically in FMF and subclinically in heterozygous *MEFV* mutation carriers [7], should enhance the clearance of immune complexes by mononuclear phagocytes. Although there is no study on this speculation, it may be supported by the observation that interleukin-1β and interleukin-6 stimulate the expression of the complement receptor of the immunoglobulin family (CRIg), which is a major receptor for C3b whose function is to solubilize the immune complexes, on macrophages in vitro [8]. So, the presence of *MEFV* mutations may be related to enhanced clearance of IgA immune-complexes and/or deposits in HSP. Although the exact pathogenesis of HSP is not known, the genetic situation (i.e., the presence of *MEFV* mutations) that leads to less IgA deposits but more severe disease is an immunoclinical paradox. Although the rate of HSP in FMF is higher ten times compared with that in the normal population in FMF-prevalent regions of the world [6], *MEFV* was not identified as a susceptibility gene in the

✉ Ufuk İlgen
ufukilgen@gmail.com

[1] Department of Rheumatology, Trakya University Medical School, 22100 Edirne, Turkey

[2] Department of Nephrology, Ankara University, Ankara, Turkey

Table 1 Histopathological and direct immunofluorescence findings and *MEFV* mutations in patients with IgA nephropathy

	MEFV mutation*		
	Absent ($n = 24$)	Present ($n = 9$)	p value
Global glomerulosclerosis (%)**	8 (Q1–Q3: 0–80)	11 (Q1–Q3: 7–46)	0.627
Segmental glomerulosclerosis (%)**	0 (Q1–Q3: 0–0)	13 (Q1–Q3: 0–33)	0.038†
Glomerular fibrinoid necrosis			1.000
Absent, *n* (%)	23 (95.8)	9 (100)	
Present, *n* (%)	1 (4.2)	–	
Endocapillary proliferation			1.000
Absent, *n* (%)	23 (95.8)	9 (100)	
Present, *n* (%)	1 (4.2)	–	
Mesangial proliferation			0.442
Absent, *n* (%)	9 (37.5)	5 (55.6)	
Present, *n* (%)	15 (62.5)	4 (44.4)	
Extracapillary proliferation (crescent)			0.309
Absent, *n* (%)	21 (87.5)	6 (66.7)	
Present, *n* (%)	3 (12.5)	3 (33.3)	
Tubulointerstitial inflammation			0.088
Absent, *n* (%)	8 (33.3)	–	
Mild-to-moderate, *n* (%)	13 (54.2)	6 (66.7)	
Severe, *n* (%)	3 (12.5)	3 (33.3)	
Interstitial fibrosis			0.017‡
Absent, *n* (%)	8 (33.3)	1 (11.1)	
Mild-to-moderate, *n* (%)	14 (58.4)	3 (33.3)	
Severe, *n* (%)	2 (8.3)	5 (55.6)	
Tubular atrophy			0.081
Absent, *n* (%)	10 (41.7)	2 (22.2)	
Mild-to-moderate, *n* (%)	12 (50)	3 (33.3)	
Severe, *n* (%)	2 (8.3)	4 (44.5)	
Mesangial IgA staining			1.000
Negative, *n* (%)	2 (8.3)	–	
Mild-to-moderate, *n* (%)	2 (8.3)	1 (11.1)	
Intense, *n* (%)	20 (83.4)	8 (88.9)	
Mesangial IgG staining			0.873
Negative, *n* (%)	10 (41.7)	5 (55.6)	
Mild-to-moderate, *n* (%)	10 (41.7)	3 (33.3)	
Intense, *n* (%)	4 (16.4)	1 (11.1)	
Mesangial C3 staining			0.404
Negative, *n* (%)	5 (20.8)	4 (44.4)	
Mild-to-moderate, *n* (%)	3 (12.5)	1 (11.1)	
Intense, *n* (%)	16 (66.7)	4 (44.4)	

*MEFV ME*diterranean *Fe*V*er* gene, *Ig* immunoglobulin, *C3* complement component 3, *n* number

**MEFV* mutations (carrier rates) are E148Q (4/33), M694V (2/33), M680I (1/33), V726A (1/33), and E251K (1/33)

**Expressed as medians with quartiles 1–3 (Q1–Q3)

† Mann-Whitney *U* test

‡ Fisher's exact test

single genome-wide association study for HSP [9]. But this study was performed in patients of Spanish and European descent, focused on Human Leukocyte Antigen (HLA) region, and was not a whole exome sequencing study. The impact of the genetic background in HSP may differ according to race.

Compliance with ethical standards

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Informed consent Written informed consent was obtained from patients participated in this study.

Ethical approval Institutional Review Board of Ankara University Medical School approved this study.

Disclosures None.

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