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Letter to the Editor

Serum and urinary macrophage migration inhibitory factor (MIF) in primary Sjögren's syndrome

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Primary Sjögren's syndrome (pSS) is a heterogeneous, chronic systemic autoimmune disease, characterized by a sicca syndrome caused by immune-mediated damage to exocrine glands. Patients are prone to systemic complications and are at a higher risk of developing lymphoma [1]. The pleiotropic pro-inflammatory cytokine macrophage migration inhibitory factor (MIF) has been reported to play a key role in autoimmune diseases including systemic lupus erythematosus and rheumatoid arthritis [2–4]. To date, only one study has investigated the role of MIF in pSS, which showed increased serum MIF levels in pSS compared to healthy individuals [5]. Herein, we describe the first study investigating the presence and clinical relevance of urinary MIF in pSS, paired with analysis of serum MIF.

Adult patients who met the 2002 American–European SS classification Consensus Criteria [6] and attended The Queen Elizabeth Hospital between April 2013 and August 2014 were included in this study. Disease activity was assessed using the European League Against Rheumatism SS disease activity index (ESSDAI) [7]. Low, moderate and high pSS disease activity were defined as ESSDAI < 5, 5 ≤ ESSDAI ≤ 13 and ESSDAI ≥ 14, respectively [7]. Two separate healthy control (HC) groups were recruited to compare urinary and serum MIF levels in pSS patients. Written, informed consent was obtained from all subjects. Human research ethics

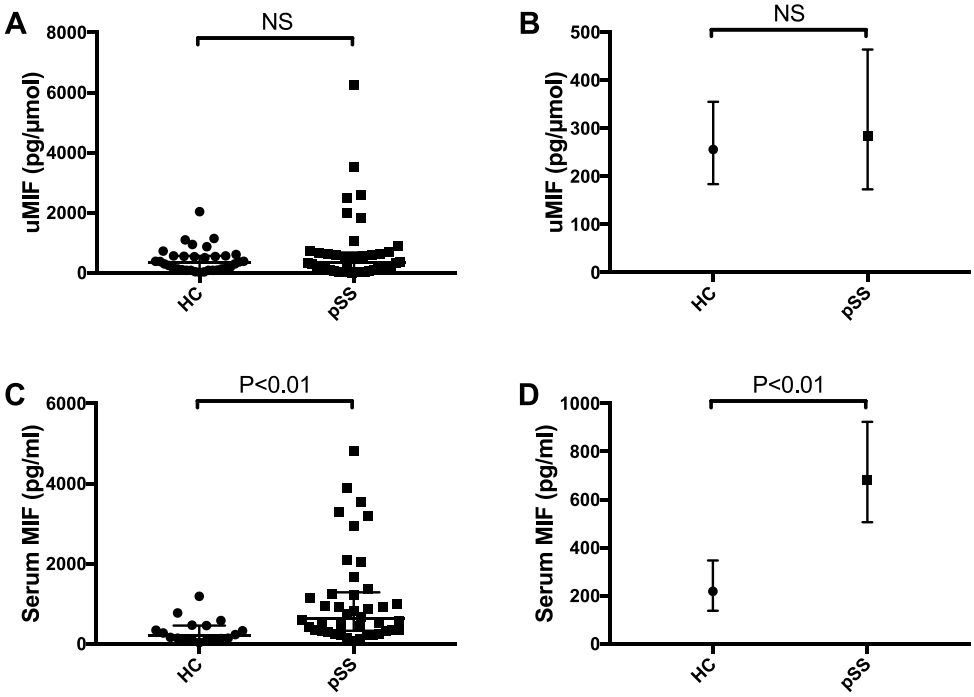

Fig. 1. Serum and urinary MIF in pSS. A. uMIF concentrations in HC (median [IQR]: 332 [103, 561] pg/µmol; $n = 34$) and pSS (median [IQR]: 348 [107, 672] pg/µmol; $n = 42$). B. Geometric mean (GM) of uMIF concentrations in HC (GM (95% CI): 256 (184, 355) pg/µmol; $n = 34$) and pSS (GM (95% CI): 284 (173, 464) pg/µmol; $n = 42$) derived using univariable linear regression analysis. Ratio of the GMs was 1.11 with 95% CI between 0.6 and 2.04. C. Serum MIF concentrations in HC (median [IQR]: 633 [333, 1254] pg/mL; $n = 18$) and pSS (median [IQR]: 197 [115, 457] pg/mL; $n = 42$). D. GM of serum MIF concentrations in HC (GM (95% CI): 219 (138, 347) pg/mL; $n = 18$) and pSS (GM (95% CI): 683 (506, 924) pg/mL; $n = 42$) derived using univariable linear regression analysis. Ratio of the GMs was 3.12 with 95% CI between 1.8 and 5.41. In panels A & C, horizontal bars indicate the median [IQR], and difference in medians was examined using Wilcoxon rank-sum test. ESSDAI: European League Against Rheumatism Sjögren's syndrome Disease Activity Index; HC: healthy control; MIF: macrophage migration inhibitory factor; NS: not significant; pSS: primary Sjögren's syndrome.

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Table 1
Serum and urinary MIF according to demographic and clinical parameters in pSS.

	n	pSS patients (*n* = 42)			
		Serum MIF		uMIF	
		Median [IQR]	*P*-value	Median [IQR]	*P*-value
Demographics					
Age			0.68		0.92
< 60	15	879 [236, 2088]		340 [41, 642]	
≥ 60	17	518 [333, 1223]		313 [106, 624]	
Gender			0.65		0.61
Female	28	582 [281, 1521]		333 [79, 633]	
Male	4	562 [401, 2739]		209 [44, 533]	
Clinical features					
ESSDAI[a]			0.98		0.68
Low (< 5)	11	518 [213, 2954]		199 [50, 624]	
Moderate to high (≥ 5)	21	600 [315, 1254]		340 [52, 642]	
ESSDAI[a]					
Low (< 5)	11	518 [213, 2954]	0.75	199 [50, 624]	0.88
Moderate (≥ 5 & ≤ 13)	9	600 [315, 1139]		325 [106, 607]	
High (≥ 14)	12	722 [322, 1735]		432 [41, 668]	
Active lymphadenopathy disease			0.41		0.56
Absent	26	633 [253, 2053]		333 [50, 672]	
Present	6	345 [315, 1139]		386 [52, 524]	
Active glandular disease			0.16		0.17
Absent	20	412 [232, 1718]		356 [175, 776]	
Present	12	1035 [512, 1458]		140 [44, 565]	
Active articular disease			0.71		0.24
Absent	20	592 [339, 1458]		256 [51, 610]	
Present	12	582 [232, 2168]		399 [137, 1519]	
Active cutaneous disease			0.29		0.64
Absent	26	739 [333, 1661]		343 [52, 624]	
Present	6	401 [228, 666]		333 [46, 1060]	
Active pulmonary disease			0.81		0.81
Absent	22	592 [310, 2053]		333 [52, 613]	
Present	10	582 [333, 1223]		418 [41, 881]	
Active haematological disease			0.7		0.11
Absent	25	565 [315, 1382]		234 [46, 536]	
Present	7	879 [310, 1661]		613 [313, 695]	
Active biological disease			0.45		0.43
Absent	19	459 [236, 2954]		340 [52, 695]	
Present	13	879 [468, 1254]		313 [46, 607]	
Laboratory markers					
Anti-La Ab			0.16		0.71
No	4	339 [293, 406]		303 [119, 498]	
Yes	26	772 [315, 1661]		319 [50, 642]	
Anti-Ro52 Ab			0.11		0.6
No	4	293 [245, 401]		279 [119, 475]	
Yes	27	666 [315, 1661]		340 [50, 642]	
Anti-Ro60 Ab			0.19		0.68
No	4	339 [293, 406]		303 [119, 498]	
Yes	27	666 [310, 1661]		325 [50, 642]	

Data are presented as median [IQR] as indicated.
Ab: antibody; ESSDAI: European League Against Rheumatism Sjögren's syndrome Disease Activity Index; IQR: inter-quartile range; MIF: macrophage migration inhibitory factor; pSS: primary Sjögren's syndrome.
[a] Calculated in the 32 pSS patients in whom ESSDAI was assessed.

approvals were obtained from The Queen Elizabeth Hospital, Monash Health and Monash University. Matching urine and serum samples were collected at routine clinic visits. Serum and urinary MIF levels were quantified using human MIF DuoSet® Enzyme-Linked Immunosorbent Assay (ELISA) kit (R&D Systems; MN, USA), according to the manufacturer's instructions. Urinary MIF concentrations were normalized against the creatinine concentration to correct for effects of urinary dilution. Urinary MIF/creatinine ratio was designated as uMIF [8]. Statistical analyses were performed using Stata version 14 (StataCorp, College Station, Texas, USA). Continuous variables were compared using Wilcoxon rank-sum or Kruskal–Wallis tests between two or ≥ 3 groups, respectively. Categorical variables were compared using Fisher's exact test. Correlation between continuous variables was examined using Spearman's correlation test. Linear regression analyses were performed using $\log_{10}$ transformed serum and urinary MIF data. A *P*-value of < 0.05 was considered statistically significant.

Forty-two pSS patients and 51 HC (serum HC cohort: *n* = 18; urine HC cohort: *n* = 34) were enrolled in this study [Appendix A, Table S1; See the supplementary material associated with this article online]. Serum and urinary MIF were detectable in all samples. No significant difference in uMIF levels was observed between pSS and HC (Fig. 1A–B). In contrast, serum MIF was significantly increased in pSS compared to HC (Fig. 1C-D). Multivariable, linear regression analysis investigating the association between serum MIF in pSS compared to HC further confirmed that serum MIF levels were > 2 times higher in pSS patients (adjusted ratio of geometric mean 2.42, 95% CI: 1.04, 5.62, *P* = 0.04). In this model, we adjusted for age because HC were not age-matched to the pSS cohort.

We examined both serum and urinary MIF levels according to several demographics, clinical parameters and laboratory markers in pSS patients and the results are shown in Table 1. In brief, no statistically significant difference in urinary or serum MIF levels was observed according to any patient characteristic.

Moreover, uMIF did not correlate with serum MIF levels ($r = -0.24$, $P = 0.12$).

This is the first study to report the presence of MIF in the urine of pSS patients. We were able to detect MIF in urine as well as in serum of all pSS patients and HC. Serum MIF was statistically significantly higher in pSS patients when compared to HC, in line with previous observations from Willeke et al. [5]. Neither urinary or serum MIF was associated with any clinical parameters. One previous study has shown that patients with proliferative nephropathies have higher levels of uMIF [8]. However, only two pSS patients had renal manifestations in our cohort; future research examining the potential of uMIF as a biomarker in pSS patients with renal involvement would be of value. Absence of correlation between urinary and serum MIF suggests that the presence of MIF in urine is not simply a consequence of its systemic excretion. Future studies in larger, well-characterised cohorts are needed to further understand the potential role of MIF as a biomarker in pSS.

Authors' contributions

Each individual named as an author has made substantial contributions to the conception and design of the study, acquisition of data, or analysis and interpretation of data. FV drafted the manuscript, and all authors revised it. All authors read and approved the final version of the manuscript to be submitted.

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Disclosure of interest

EM has been consultants to GSK and Eli Lilly. The other authors declare that have no competing interest.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.jbspin.2018.07.001.

References

[1] Nocturne G, Mariette X. Advances in understanding the pathogenesis of primary Sjogren's syndrome. Nat Rev Rheumatol 2013;9:544–56.
[2] Ayoub S, Hickey MJ, Morand EF. Mechanisms of disease: macrophage migration inhibitory factor in SLE, RA and atherosclerosis. Nat Clin Pract Rheumatol 2008;4:98–105.
[3] Sreih A, Ezzeddine R, Leng L, et al. Dual effect of the macrophage migration inhibitory factor gene on the development and severity of human systemic lupus erythematosus. Arthritis Rheum 2011;63:3942–51.
[4] Lang T, Foote A, Lee JP, et al. MIF: implications in the pathoetiology of systemic lupus erythematosus. Front Immunol 2015;6:577.
[5] Willeke P, Gaubitz M, Schotte H, et al. Increased serum levels of macrophage migration inhibitory factor in patients with primary Sjogren's syndrome. Arthritis Res Ther 2007;9:R43.
[6] Vitali C, Bombardieri S, Jonsson R, et al. Classification criteria for Sjogren's syndrome: a revised version of the European criteria proposed by the American–European Consensus Group. Ann Rheum Dis 2002;61:554–8.
[7] Seror R, Bootsma H, Saraux A, et al. Defining disease activity states and clinically meaningful improvement in primary Sjogren's syndrome with EULAR primary Sjogren's syndrome disease activity (ESSDAI) and patient-reported indexes (ESSPRI). Ann Rheum Dis 2016;75:382–9.
[8] Brown FG, Nikolic-Paterson DJ, Hill PA, et al. Urine macrophage migration inhibitory factor reflects the severity of renal injury in human glomerulonephritis. J Am Soc Nephrol 2002;13:S7–13.

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