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Extensive serum biomarker analysis in patients with macrophage activation syndrome associated with systemic lupus erythematosus

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ABSTRACT

The present study employed an antibody array that simultaneously detects 174 cytokines to identify cytokines involved in the development of macrophage activation syndrome (MAS) associated with systemic lupus erythematosus (SLE) with a view to elucidating potential predictive markers. Eight SLE patients, including four with MAS, were analyzed. Levels of 31 cytokines were significantly elevated in the MAS phase compared with those in the active phase of SLE. Among these cytokines, the MAS/active phase ratios of CXCL9 and soluble tumor necrosis factor receptor II (sTNFR-II) were highest. Elevated serum CXCL9 and sTNFR-II levels during the MAS phase were confirmed by ELISA and were strongly correlated with other inflammatory markers, reflecting the disease activity of MAS associated with SLE. These results highlight the clinical significance of serum CXCL-9 and sTNFR-II levels, and indicate they may be useful biomarkers for the diagnosis of MAS associated with SLE.

1. Introduction

Systemic lupus erythematosus (SLE) is an autoimmune inflammatory disorder that affects multiple organ systems and causes significant morbidity and mortality. Childhood-onset SLE accounts for approximately 10%–20% of all SLE patients [1]. Pediatric SLE is more severe than adult-onset SLE, and has a more aggressive clinical presentation and course, such as severe renal involvement [2].

Macrophage activation syndrome (MAS) is a severe, potentially life-threatening complication of childhood systemic inflammatory disorders and is clinically characterized by fever, hepatosplenomegaly, lymphadenopathy, profound depression red blood cells, white blood cells, and platelets, impaired liver function, intravascular coagulation, and central nervous system dysfunction [3]. Bone marrow examination reveals numerous macrophages exhibiting hemophagocytosis. MAS is considered a secondary hemophagocytic lymphohistiocytosis (HLH) as it closely resembles a group of HLH syndromes [4,5].

MAS is most often complicated in children with systemic juvenile idiopathic arthritis (s-JIA). However, MAS has also been observed in patients with SLE [6,7]. The reported prevalence of MAS in SLE ranges from 0.9% to 4.6%; however, it has been suggested that MAS associated with SLE may be more common than previously recognized [8]. Diagnosis of MAS in patients with SLE is challenging as it may mimic the clinical features of the underlying disease or be confused with an infectious complication. It is essential to differentiate MAS from these conditions to select the appropriate therapeutic approach. However, there are currently no definitive serum biomarkers to establish the diagnosis of SLE-associated MAS.

The predominant hallmark of MAS is an uncontrolled and dysfunctional immune response, which leads to marked hypercytokinemia [9]. Massive hypercytokinemia is strongly associated with the pathogenesis of MAS associated with SLE; however, the pathogenesis and the kinetics of cytokine release of MAS associated with SLE remain poorly understood.

The present study employed the RayBiotech C-Series 2000 antibody array system (an antibody array that simultaneously detects 174 cytokines) to identify cytokines involved in the development of MAS associated with SLE, with a view to identifying potential predictive markers for this condition. Levels of serum CXCL9 and soluble tumor necrosis factor receptor type II (sTNFR-II) were measured to confirm their

Abbreviations: MAS, macrophage activation syndrome; SLE, systemic lupus erythematosus; IL, interleukin; sTNFR, soluble tumor necrosis factor receptor; IFN, interferon; TNF, tumor necrosis factor

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Table 1
Clinical characteristics of the study patients.

	Active (n = 5)	MAS (n = 4)
Age at disease onset (median/ range, year)	10 (5–15)	15 (11–15)
Sex (male/female, n)	0 / 5	0/4
Clinical symptoms (n)		
Malar rash	3	2
Discoid rash	0	0
Photosensitivity	1	0
Oral or nasal ulcer	2	4
Arthritis	1	3
Nephritis	5	4
CNS disease	0	0
Serositis	0	1
Hematologic involvement	3	4
Immunoserology	5	4
ANA positivity	5	4
Hepatosplenomegaly	0	0
bleeding	0	0
Laboratory findings (median/range)		
Platelets (/mm^3)	185,000 (27100–377,000)	35,400 (12800–103,000)
Ferritin (ng/ml)	356 (65.3–396)	13,091.5 (3051–28,212)
AST (IU/l)	26 (17–41)	229 (123–338)
Treatments (n)		
Predonisolone	0	1
Dexamethasone	0	1
Cyclosporine	0	1

CNS: central nervous system, ANA: antinuclear antibody, AST, aspartate aminotransferase.

clinical significance as potential indicators of disease activity in MAS associated with SLE, and their correlation with disease activity and severity was determined.

2. Material and methods

2.1. Patients and samples

Four SLE patients with MAS, four SLE patients without MAS, and four healthy controls (HCs) were enrolled. Among the four SLE patients with MAS, serum samples were obtained in both the acute and MAS phases from one patient and only in the MAS phase from three patients. Therefore, we analyzed a total of five serum samples during the acute phase and four samples during the MAS phase. The clinical characteristics of SLE patients during the acute and MAS phases are shown in Table 1. SLE was diagnosed according to the American College of Rheumatology criteria [10] and MAS was diagnosed according to the guidelines proposed by Parodi et al. [6]. Serum was separated from cells, aliquoted, and stored at −80 °C until analyzed. The study was approved by the Institutional Review Board of Kanazawa University, and all participants provided informed consent.

2.2. Quantification of serum cytokines

The RayBio human cytokine antibody array (C-Series 2000 antibody array, RayBiotech, Norcross, GA, USA) was used for the detection of 174 cytokines in frozen stock sera obtained from SLE patients, s-JIA patients, and HCs according to the manufacturer's protocol. Relative levels were determined by the ratio of the intensity of each sample to that of an internal positive control. The intensity of the samples and controls was measured using Java ImageJ image processing software. Serum levels of CXCL9 and sTNFR-II were by analyzed by enzyme linked immunosorbent assay (ELISA) according to the manufacturer's instructions (CXCL9, sTNFR-II: R&D Systems, Minneapolis, MN, USA).

2.3. Comparison of cytokine expressions in MAS associated with SLE and MAS associated with systemic juvenile idiopathic arthritis

We recently reported that CXCL9 showed the most significant increase following the development of systemic juvenile idiopathic arthritis (s-JIA) associated MAS based on the analysis using the same human cytokine antibody array in this study [11]. In this study, we selected the data from the s-JIA patients not receiving tocilizumab in our previous study [11], and compared the expressions of top five significant increased cytokines following the development of MAS in patients with SLE and s-JIA. Serum samples obtained from 10 patients during both the acute phase of s-JIA and the MAS phase were analyzed. Diagnosis of s-JIA was based on the criteria established by the International League of Associations for Rheumatology [12], and diagnosis of MAS was based on the 2016 EULAR/ACR/PRINTO classification criteria [13]. The clinical characteristics of s-JIA patients during the acute and MAS phases are shown in Supplementary Table 1.

2.4. Statistical analysis

Statistical analysis was performed using GraphPad Prism 7 software (GraphPad, San Diego, CA, USA). Cluster analysis was performed using JMP 13 (SAS Institute Inc. Tokyo, Japan). Data were summarized as median and range. Comparisons between several groups were performed using one-way analysis of variance with Tukey's multiple comparisons test. Within-group comparisons were performed using the Mann–Whitney U test. Correlations were expressed using the Spearman rank correlation coefficient. $P < .05$ denoted statistical significance.

3. Results

3.1. Cytokine expression in SLE patients

As shown in Fig. 1 and Table 2, levels of 31 cytokines (CXCL9, sTNFRII, GCP2, GDNF, EGF, IFN-γ, MCP-1, Siglec5, BMP6, IL-1ra, Flt-3 ligand, IL-1R2, CCL23, VEGF-R3, IL-1β, IL-3, CNTF, TGF-β3, IL-16, CXCL16, SDF-1β, SCF-R, MCP-4, MCP-2, IGF-1, IGFBP2, ErbB3, ICAM2, CD14, L-selectin, and NAP-2) were significantly increased during the MAS phase compared with levels observed during the active phase. Of note, in these patients, the levels of three cytokines (Acrp30, IL-11, and I-TAC) were significantly increased during the active phase compared with the MAS phase.

The MAS/active ratios of CXCL9 and sTNFR-II were the highest among the 31 cytokines that were significantly elevated during the MAS phase compared with the active phase of SLE (Table 2 and Fig. 2). Increased MAS/active ratios of CXCL9 and sTNFR-II in MAS were observed not only in patients with SLE, but also in those with s-JIA (Fig. 2).

3.2. Clinical significance of serum sTNFR-II and CXCL9 levels in MAS-associated SLE

To verify these results, serum levels of CXCL9 and sTNFR-II were measured by ELISA. As shown in Fig. 3A, serum CXCL9 levels in SLE patients were significantly elevated during the MAS phase (median, 27,870 pg/mL; range, 5764–67,612 pg/mL) compared with levels observed during the active phase (median, 180 pg/mL, range, 99–1540 pg/mL) ($P < .05$) and in HCs (median, 59 pg/mL; range, 31–83 pg/mL) ($P < .001$). Receiver operating characteristic (ROC) curve analysis revealed a cutoff value and area under the ROC curve value for CXCL9 of 3652 pg/mL and 1.0, respectively. As shown in Fig. 3B, serum sTNFR-II levels in SLE patients were significantly elevated during the MAS phase (median, 33,900 pg/mL; range, 21,000–58,300 pg/mL) compared with levels observed during the active phase (median, 8400 pg/mL; range, 7600–17,500 pg/mL) ($P < .05$) and in HCs (median, 3215 pg/mL; range, 2580–4200 pg/mL)

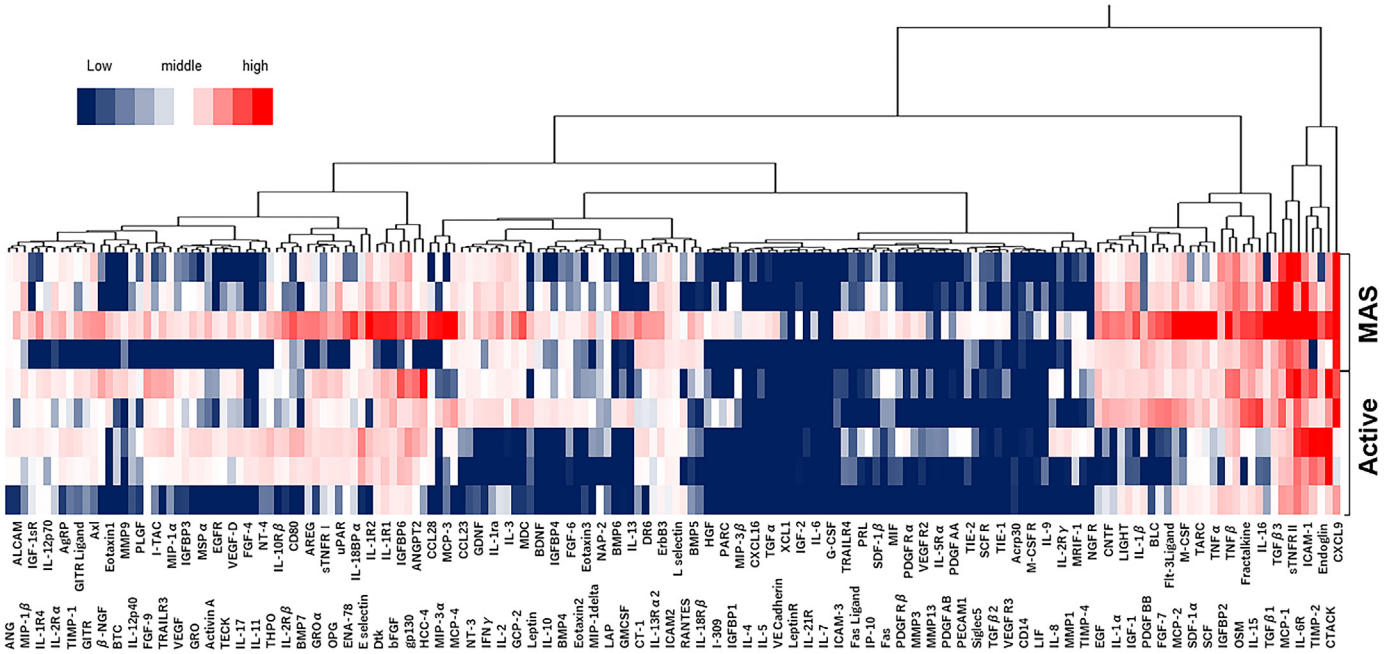

Fig. 1. Cytokine expression in patients with systemic lupus erythematosus and macrophage activation syndrome.
Heat map of the expression of 174 cytokines in patients with systemic lupus erythematosus and macrophage activation syndrome. Data represent the relative expression to healthy controls.
Active, active phase of systemic lupus erythematosus; MAS, macrophage activation syndrome.

Table 2
Comparison of cytokine expression levels in SLE patients between active phase and MAS phase.

	Active phase		MAS phase		*P*-Value	MAS/Active
	Median	Range	Median	Range		Ratio
CXCL9	8.876	1.3–28.47	50.32	18.29–105.5	0.0021	5.6692
sTNFR-II	6.522	4.4–19.6	26.78	10.97–44.54	0.0003	4.1061
GCP2	1.11	0.2535–6.965	4.123	3.203–13.16	0.0117	3.7144
GDNF	1.256	0.3115–4.156	4.103	2.4–7.528	0.0155	3.2667
EGF	1.795	0.122–9.197	5.729	3.619–10.23	0.0205	3.1916
IFN-γ	1.112	0–4.606	3.45	1.401–6.076	0.0343	3.1025
MCP-1	6.731	4.643–14.51	20.48	9.149–31.78	0.0009	3.0426
Siglec5	0.6471	0.2223–1.475	1.968	1.435–2.196	< 0.0001	3.0413
BMP6	0.6266	0.03825–3.834	1.72	0.6348–11.74	0.0343	2.7450
IL-1ra	1.609	0.5808–4.906	4.072	3.152–7.537	0.0155	2.5308
Flt-3 ligand	1.629	0.756–12.18	4.039	3.082–17.02	0.0343	2.4794
IL-1R2	3.347	0.65–7.233	7.995	2.466–26.61	0.0205	2.3887
CCL23	1.548	0.69–5.563	3.676	2.252–6.603	0.0062	2.3747
VEGF-R3	0.6702	0.1347–1.766	1.576	0.5007–3.149	0.0266	2.3515
IL-1β	2.952	0.6699–5.915	6.851	3.393–18.36	0.0155	2.3208
IL-3	1.849	0.6222–4.263	4.244	2.152–6.545	0.0044	2.2953
CNTF	2.153	0.8902–9.534	4.939	2.545–12.39	0.0434	2.2940
TGF-β3	4.372	2.198–13.51	9.894	3.433–64.44	0.0205	2.2630
IL-16	5.238	0.9614–20.8	11.31	7.725–20.18	0.0117	2.1592
CXCL16	0.4865	0.3334–0.7922	1.029	0.2483–4.029	0.0434	2.1151
SDF-1β	1.169	0.18–1.678	2.23	0.2884–5.609	0.0434	1.9076
SCF-R	0.7367	0.3222–1.282	1.346	0.7222–2.57	0.0205	1.8271
MCP-4	2.163	0.4684–10.47	3.886	3.109–29.79	0.0117	1.7966
MCP-2	3.93	1.452–10.27	6.893	5.08–27.68	0.0205	1.7539
IGF-1	4.276	0.9326–7.305	7.115	3.847–11.43	0.0434	1.6639
IGFBP2	4.441	0.9602–6.32	7.303	4.935–10.5	0.0031	1.6444
ErbB3	3.191	2.034–5.129	5.217	1.993–11.04	0.0155	1.6349
ICAM2	2.704	1.917–3.531	4.356	3.453–4.755	< 0.0001	1.6109
CD14	0.7732	0.5379–1.181	1.114	0.9088–1.363	0.0044	1.4408
L-selectin	2.61	1.937–2.965	3.241	2.325–3.664	0.0343	1.2418
NAP-2	1.652	0.913–2.12	1.985	1.631–2.106	0.0434	1.2016
Acrp30	0.9878	0.7462–1.145	0.8539	0.8522–0.8725	0.0343	0.8644
IL-11	0.6861	0.309–4.814	0.3125	0.0139–2.49	0.0343	0.4555
I-TAC	2.968	1.174–8.048	1.304	0.05274–3.454	0.0266	0.4394

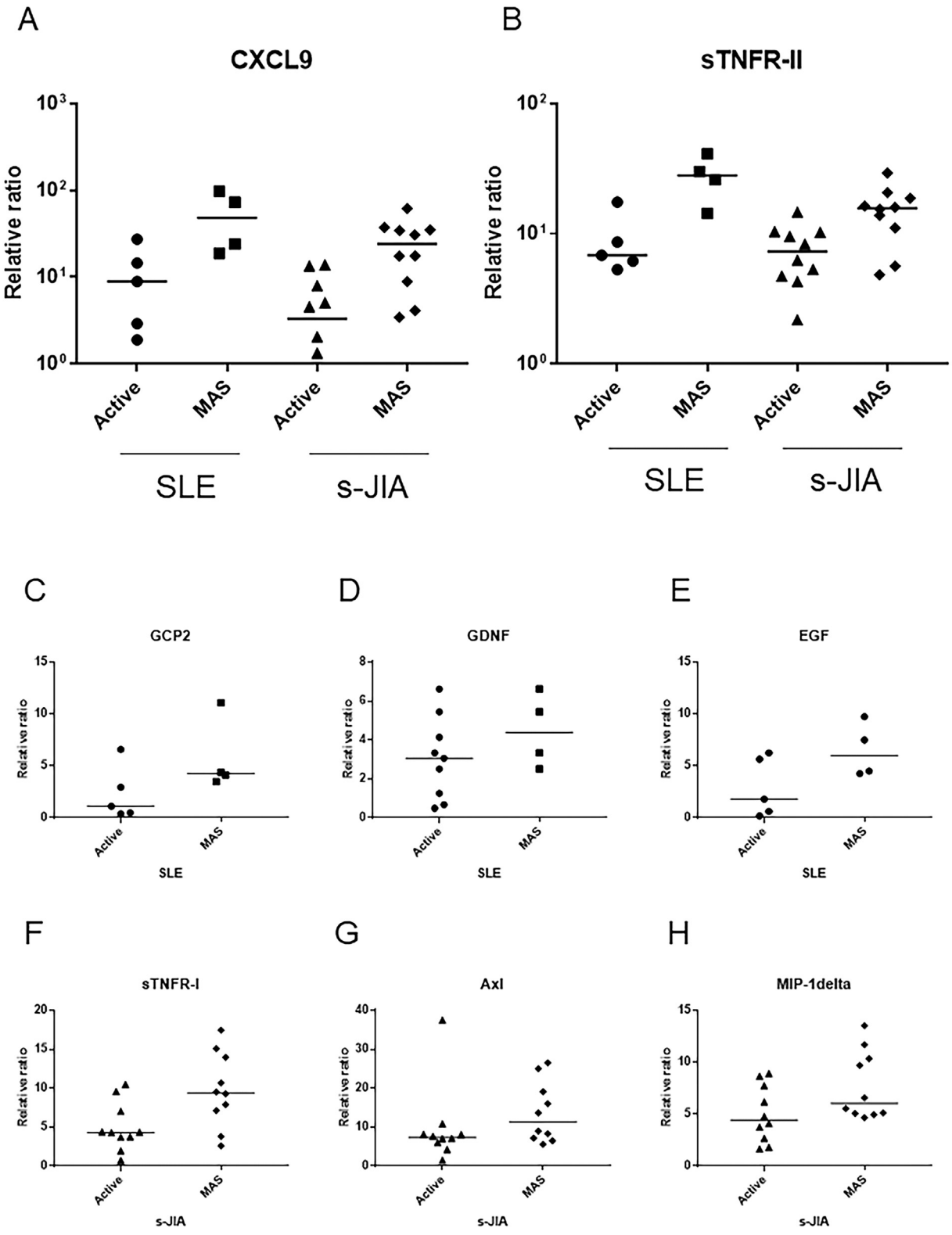

Fig. 2. Comparison of the MAS/active ratios of cytokines between patients with systemic lupus erythematosus and systemic juvenile idiopathic arthritis.
MAS/active ratios of the top five cytokines that were significantly elevated during the MAS phase compared with the active phase were compared between systemic lupus erythematosus and systemic juvenile idiopathic arthritis.
Bars represent median values with range.
A. CXCL9, B. sTNFR-II, C. GCP2, D. GDNF, E. EGF, F. sTNFR-I, G. Axl, H. MIP-1 delta.

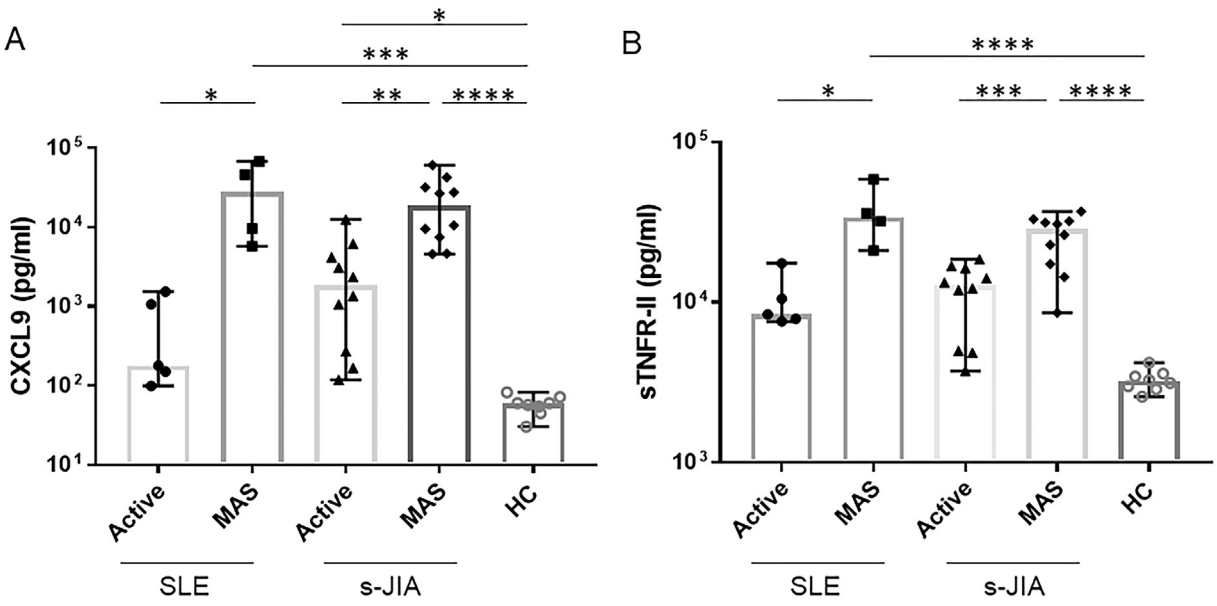

Fig. 3. Serum levels of CXCL9 and sTNFR-II in patients with systemic lupus erythematosus and macrophage activation syndrome.
(A) Levels of CXCL9 in patients with systemic lupus erythematosus and macrophage activation syndrome. (B) Levels of sTNFR-II in patients with systemic lupus erythematosus and macrophage activation syndrome.
Bars represent median values with range. $^{*}P < .05$, $^{***}P < .001$.
Active, active phase of systemic lupus erythematosus; HCs, healthy controls; MAS, macrophage activation syndrome.

($P < .001$). ROC curve analysis revealed a cutoff value and area under the ROC curve value for sTNFR-II of 19,250 pg/mL and 1.0, respectively. In addition to MAS associated with SLE, serum CXCL9 levels in s-JIA patients were significantly elevated during the MAS phase (median, 18,712 pg/mL; range, 4576–60,961 pg/mL) compared with levels observed during the active phase (median, 1854 pg/mL; range, 119–12,539 pg/mL) ($P < .01$) (Fig. 3A). In s-JIA patients, serum sTNFR-II levels were significantly elevated during the MAS phase (median, 28,550 pg/mL; range, 8600–36,800 pg/mL) compared with levels observed during the active phase (median, 12,750 pg/mL; range: 3730–18,500 pg/mL) ($P < .05$) (Fig. 3B).

Serum CXCL9 and sTNFR-II levels were serially monitored in one case with MAS associated with SLE to investigate the relevance of these levels in the pathogenesis of MAS (Fig. 4). Levels of these cytokines were found to be markedly and rapidly increased as MAS developed.

3.3. Correlation between serum CXCL9 and sTNFR-II levels and disease activity in patients with SLE

Levels of ferritin, aspartate aminotransferase (AST), and platelets are commonly used as clinical indicators of disease activity in MAS. Assessment of the correlation between serum CXCL9 and sTNFR-II levels and these indicators in the active and MAS phases revealed that levels of CXCL9 and sTNFR-II were positively correlated with ferritin and AST levels (Fig. 5).

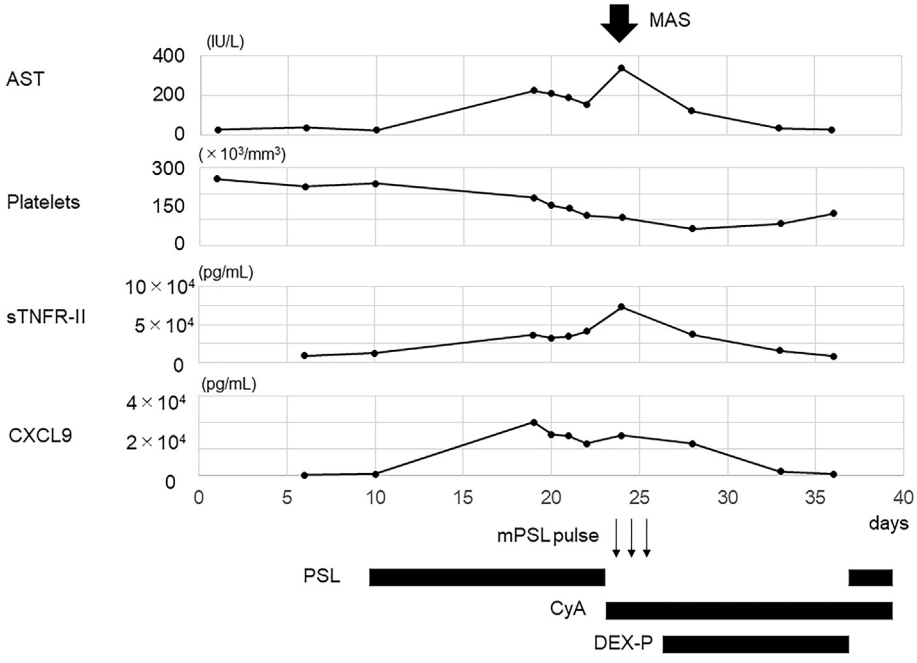

Fig. 4. Longitudinal follow-up of serum CXCL9 and sTNFR-II levels in a patient with MAS.
Lower panels show changes in serum CXCL9 and sTNFR-II levels and upper panels show AST levels and platelets counts.
AST, aspartate aminotransferase; CyA, cyclosporineA; DEX-P, dexamethasone palmitate; MAS, macrophage activation syndrome; mPSL, methylprednisolone; PSL, prednisolone.

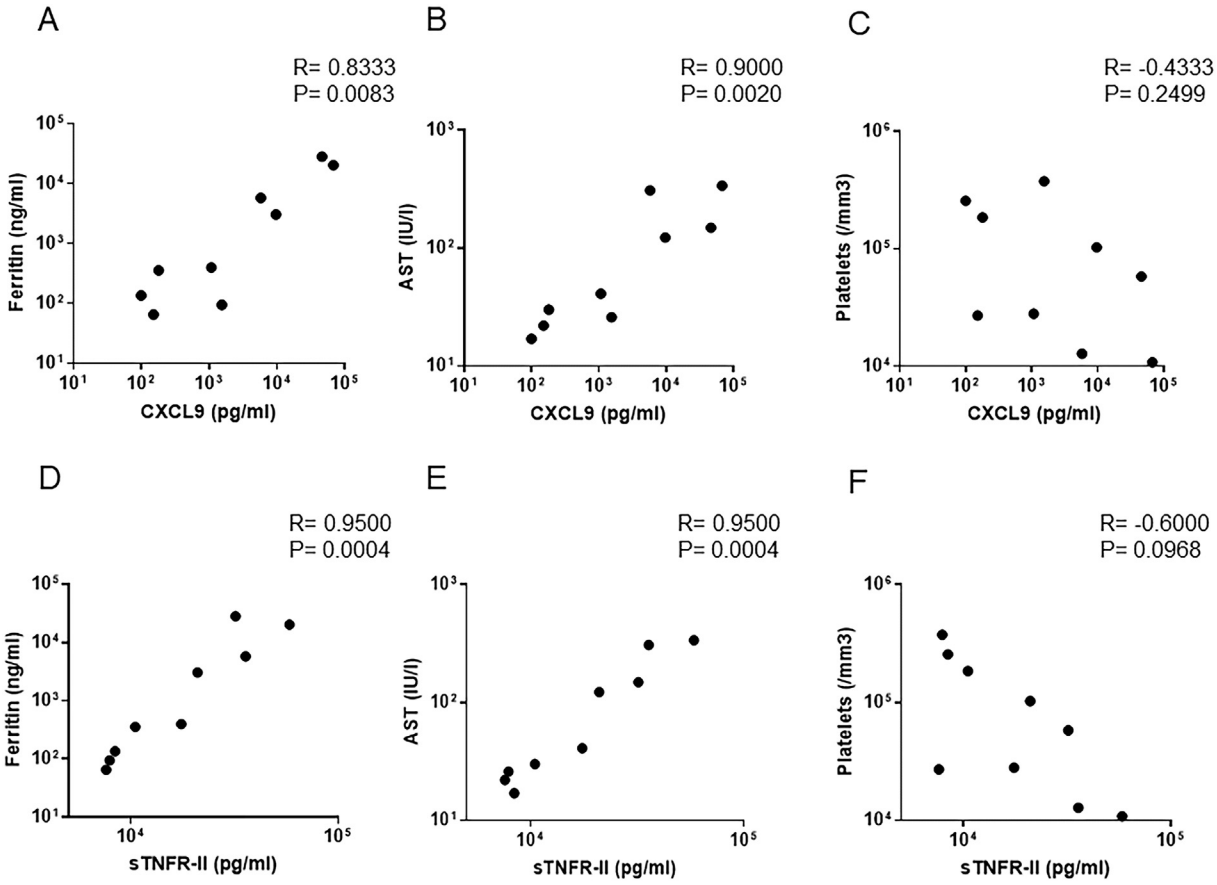

Fig. 5. Correlations between serum CXCL9 and sTNFR-II levels and disease activity of macrophage activation syndrome.
CXCL9 and ferritin, (B) CXCL9 and AST, (C) CXCL9 and platelet counts,
(D) sTNFR-II and ferritin, (E) sTNFR-II and AST, and (F) sTNFR-II and platelet counts.
AST, aspartate aminotransferase.

4. Discussion

The present study investigated serum cytokine profiles in SLE patients between the active and MAS phases. Thirty one cytokines were significantly elevated during the active phase compared with the MAS phase. Among these 31 cytokines, the MAS/active ratios of CXCL9 and sTNFR-II were higher compared with other cytokines. These findings were confirmed by ELISA.

CXCL9 expression is specifically and exclusively induced by IFN-γ [14]. A previous study showed that hemophagocytosis was induced in macrophages treated with IFN-γ [15]. Furthermore, hemophagocytosis did not develop in two HLH patients with IFN-γ receptor deficiency [16]. Binding of IFN-γ to the IFN-γ receptor induces phosphorylation of STAT1 by JAK1/2 in the cytoplasm. STAT1 activation via IFN-γ induces micropinocytosis, leading to the engulfment and degradation of red blood cells via hemophagocytosis [17]. These findings indicate that IFN-γ is closely associated with the development of HLH. In the present study, serum CXCL9 levels were significantly elevated in SLE patients during the MAS phase, reflecting the disease activity of MAS associated with SLE. Furthermore, serum CXCL9 levels were strongly correlated with other inflammatory markers, indicating that serum CXCL9 levels may be a useful biomarker for the diagnosis of MAS associated with SLE.

TNF-α is another key cytokine that plays a central role in the pathogenesis of primary and secondary HLH [18]. A previous study reported that hemophagocytic macrophages could produce TNF-α in liver biopsies from patients with MAS [18]. sTNFR-II is one of the most important modulators of the biological function of TNF-α. It mediates the host response and determines the course and outcome of the disease by interacting with TNF-α. In the present study, serum sTNFR-II levels were significantly elevated in SLE patients during the MAS phase, reflecting the disease activity of MAS associated with SLE. Furthermore, serum sTNFR-II levels were strongly correlated with other inflammatory markers. These results indicate that serum sTNFR-II levels may also be a useful biomarker for the diagnosis of MAS associated with SLE.

The pathogenesis of MAS associated with SLE remains unclear; however, massive hypercytokinaemia is strongly associated with its pathogenesis. Recent studies showed the presence of high levels of IFN-γ and of IFN-γ-induced chemokines in patients with secondary HLH [11,19]. Furthermore, serum CXCL9 levels were strongly correlated with biochemical parameters related to the severity of secondary HLH [19]. We previously reported that serum sTNFR-II levels were significantly increased in the MAS phase compared with levels reported in the active phase of s-JIA and Kawasaki disease (KD) [20,21]. In the present study, we found that increased serum levels of CXCL9 and sTNFR-II were common in MAS associated with both SLE and s-JIA. These findings indicate that IFN-γ and TNF-α play central roles in the pathogenesis of not only primary HLH, but also secondary HLH, including MAS-associated SLE. Therefore, serum CXCL9 and sTNFR-II levels may be useful biomarkers for the diagnosis of MAS/HLH.

The cytokine release pattern in MAS varies among patients with different etiologies [22]. We previously reported that serum IL-18 levels were increased in active s-JIA (median 35,750 pg/mL, IQR 16,475-94,750), and were increased further in patients with s-JIA-related MAS (145,000, 65,000-263,000) [22,23]. Furthermore, recent studies reported that high levels of free IL-18 increases the risk of developing MAS [24,25]. These findings indicate that IL-18 is causatively involved

in the development of MAS. IL-18 is a well-known IFN-γ-inducing cytokine, and increased levels of free IL-18 and induction of IFN-γ may be closely associated with the development of MAS in the pathogenesis of s-JIA. On the other hand, serum IL-18 levels are not increased in patients with MAS associated with SLE (1640 pg/ml) or those with KD (280, 234–440) or Epstein-Barr virus HLH (3825, 2570–7000) [22,26]. These findings indicate that the pathogenesis of MAS may differ among patients with different etiologies. Further studies are required to elucidate the mechanisms involved in the development of MAS in SLE patients.

The present study has some limitations, such as a small number of patients with s-JIA. However, despite this, we found that elevated levels of CXCL9 and sTNFR-II, and their correlation with disease activity of MAS indicated a pivotal role of IFN-γ and TNF-α in MAS associated with SLE. Monitoring serum CXCL9/sTNFR-II levels may be useful for the evaluation of disease activity in patients with MAS associated with SLE. Future larger studies including a comparison of the sensitivity and specificity between CXCL9 and sTNFR-II are warranted to confirm their clinical significance in the diagnosis of MAS-associated SLE.

5. Conclusions

In conclusion, we extensively investigated serum cytokine profiles in SLE patients between the active and MAS phases. Thirty one cytokines were significantly elevated in the active phase compared with the MAS phase. Among these, serum CXCL-9 and sTNFR-II levels in SLE patients were significantly elevated during the MAS phase, reflecting the disease activity of MAS associated with SLE. Furthermore, serum CXCL-9 and sTNFR-II levels were strongly correlated with other inflammatory markers. These results indicate that serum CXCL-9 and sTNFR-II levels may represent useful biomarkers for the diagnosis of MAS associated with SLE.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clim.2019.108255.

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Declaration of Competing Interest

None.

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