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Cytokine profile in adult-onset Still's disease: Comparison with systemic juvenile idiopathic arthritis

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ABSTRACT

To compare pro-inflammatory cytokine profiles and kinetics in patients with adult-onset Still's disease (AOSD) to those in patients with systemic juvenile idiopathic arthritis (s-JIA), we analyzed serum cytokine concentrations in 33 patients with AOSD and 77 patients with s-JIA and compared them with clinical features. Patients with AOSD and s-JIA shared a common cytokine profile pattern of a significant increase in IL-18. Patients with AOSD were classified into two subgroups based on serum IL-6 and IL-18 levels. The number of patients with arthritis was significantly higher in the IL-6-dominant subgroup. The cytokine patterns associated with s-JIA and AOSD share common features, such as a significant and predominant increase in IL-18. Distinct IL-6- and IL-18-based cytokine profiles might be responsible for distinct clinical manifestations. The presence of two distinct subgroups in patients with both diseases further supports the view that s-JIA and AOSD share a disease category.

Systemic juvenile idiopathic arthritis (s-JIA), which was first described in 1897 by the British pediatrician George F. Still, is a systemic inflammatory disorder of unknown etiology characterized by arthritis and systemic signs, such as spiking fever, skin rash, generalized lymphadenopathy, hepatosplenomegaly, and serositis [1]. In 1971, Bywaters first described adult-onset Still's disease (AOSD) and noted that this condition shared clinical similarities with s-JIA, despite the age of onset being >16 years [2]. A comparison of the epidemiologies, genetic backgrounds, clinical presentations, and courses of these diseases convincingly suggests that s-JIA and AOSD are identical [3–5]. However, some differences between these disorders have been reported, including an increased frequency of fever, skin rash, myalgia, sore throat, weight loss, liver dysfunction, and neutrophilia in AOSD relative to s-JIA [3,6]. The precise AOSD pathogenesis remains to be elucidated, and it remains unknown whether s-JIA and AOSD share the same pathogenesis.

Macrophage activation syndrome (MAS) is a severe, potentially life-threatening complication of both s-JIA and AOSD [7–9]. MAS occurs in 7%–10% of patients with s-JIA and 12%–17% of patients with AOSD [9]. The hallmark of MAS is an uncontrolled and dysfunctional immune response involving the continual activation and expansion of T lymphocytes and macrophages, leading to marked hypercytokinemia [10]. This condition is clinically characterized by fever, hepatosplenomegaly, lymphadenopathy, a profound decrease in all three blood cell lineages, liver function dysregulation, intravascular coagulation, and central nervous system dysfunction [11]. The evaluation of bone marrow from a patient with MAS reveals the characteristic feature of numerous morphologically benign macrophages with hemophagocytic activity.

Recent studies have shown that inflammatory cytokines, including interleukin (IL)-1, IL-6, IL-18, interferon (IFN)-γ, and tissue necrosis factor (TNF)-α play pathogenic roles in the disease processes of both s-JIA and AOSD [12,13]. Furthermore, biological therapies intended to block these cytokines yield dramatic effects in patients with s-JIA and AOSD [14,15]. These findings suggest that inflammatory cytokines play major roles in the pathogenesis of both diseases.

We previously reported increased serum IL 18 levels in patients with active s-JIA [16]. Their levels are further elevated in patients with s-JIA-related MAS. This increase appears to be condition-characteristic because although other forms of secondary hemophagocytic lymphohistiocytosis are associated with high serum IL 18 levels, these levels are lower than those observed in patients with s-JIA [16–18].

Abbreviations: AOSD, Adult onset Still's disease; s-JIA, Systemic juvenile idiopathic arthritis,; MAS, Macrophage activation syndrome; IL, Interleukin; CRP, C reactive protein; PSL, Prednisolone; MTX, Methotrexate; sTNF-R, Soluble tissue necrosis factor-a receptor; GTP, Guanosine triphosphate; NK cell, Natural killer; Th1 cell, Type 1 helper T cell.

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Furthermore, we demonstrated the existence of two subgroups of s-JIA patients with distinct clinical features and different IL-6/IL-18 ratios [19]. Serum IL-18 levels are also elevated in patients with AOSD and can be used as a diagnostic biomarker and therapeutic response indicator [20,21].

We hypothesized that the cytokine release patterns in patients with s-JIA and AOSD would share common features and that s-JIA and AOSD belong to the same disease category. To test this hypothesis, we compared the pro-inflammatory cytokine profiles and cytokine kinetics in patients with both the active and inactive AOSD with those in patients with s-JIA. Furthermore, to assess the roles of IL-6 and IL-18 in AOSD pathogenesis, we analyzed their levels in patients with AOSD and compared them with the clinical features of AOSD.

1. Materials and methods

1.1. Patients and samples

Thirty-three patients with AOSD and 77 patients with s-JIA were included in this study. Six of 33 patients with AOSD presented with MAS at the time of study referral. Twenty of 77 patients with s-JIA presented with MAS. Eleven of these 20 patients presented with MAS at the time of study referral; the other nine patients developed complicating MAS while in the active disease phase and after starting steroid therapy.

Serum samples from six patients with AOSD and 20 patients with s-JIA were obtained at the time of MAS diagnosis. Serum samples from nine of 20 patients with s-JIA were also obtained during the active phase before developing MAS complication. Serum samples were obtained from 27 patients with AOSD without MAS and 57 patients with s-JIA without MAS during the active phase. Serum samples were also obtained from 13 patients with AOSD and 25 patients with s-JIA during the inactive phase.

AOSD was diagnosed according to the criteria proposed by Yamaguchi [22]. s-JIA was diagnosed according to the criteria of the International League of Associations for Rheumatology [23]. AOSD-associated MAS was diagnosed according to the criteria proposed by Imashuku et al. [24]. s-JIA-associated MAS was diagnosed according to the criteria proposed by Ravelli et al. [25]. The following criteria were used to define the active phase of s-JIA: active arthritis, fever, rash, hepatosplenomegaly, generalized lymphadenopathy, and serositis, as well as an increased erythrocyte sedimentation rate and C-reactive protein (CRP) level. The following criteria were used to define the inactive phase of s-JIA while using medication: a lack of clinical symptoms observed during the active phase, as well as a normal erythrocyte sedimentation rate and CRP level. Serum samples were separated from cells, divided into aliquots, frozen, and stored at −80 °C until further analysis. This study was approved by the Institutional Review Board at Kanazawa University, and all specimens were used after the receipt of informed consent.

The clinical characteristics of patients with active-phase AOSD and s-JIA are shown in Table 1. Twelve of 27 patients with active AOSD had not received treatment. The remaining 15 patients were treated with prednisolone (PSL). One patient was treated with methotrexate (MTX) in addition to PSL. Forty-seven of 66 patients with s-JIA had not received treatment. The remaining 19 patients were treated with PSL. In addition to PSL, four patients were treated with cyclosporine and two with MTX. No patient had been treated with anti-IL-1 or anti-IL-6 biological drugs at the time of blood collection. The clinical characteristics of patients with MAS are shown in Supplementary Table 1. Two of six patients with AOSD-associated MAS had not received treatment, and the remaining four were treated with PSL. Eight of 20 patients with s-JIA-associated MAS had not received treatment, and the remaining 12 were treated with PSL. None of these patients had been treated with anti-IL-1 or anti-IL-6 biological drugs at the time of blood collection.

Table 1
Clinical characteristics of patients with active-phase adult-onset Still's disease (AOSD) and systemic juvenile idiopathic arthritis (s-JIA).
F: female; M: male.

	AOSD	s-JIA	p value
Patients	27	66	
Age	48.7 ± 17.3	7.3 ± 5.5	<0.0001
Sex(M/F)	6/21	34/32	0.0114
Physical examination findings			
Rash	19 (70)	47 (71)	1.0000
Lymphadenopathy	12 (44)	23 (35)	0.4804
Hepatomegaly	11 (41)	10 (15)	0.0127
Splenomegaly	9 (33)	8 (12)	0.0351
Arthritis	7 (26)	35 (53)	0.0219
Laboratory findings			
hyperleukocytosis	20 (74)	52 (79)	0.5984
Elevation of transaminase	16 (59)	31 (47)	0.3621
Ferritin (ng/ml)	11,091 ± 25,425 (n = 22)	2553 ± 5181 (n = 63)	0.0200

1.2. Measurement of serum cytokine levels

The serum concentrations of IL-18, IL-6, neopterin, sTNF-RI, and sTNF-RII were evaluated using commercial enzyme-linked immunosorbent assays according to the manufacturer's instructions (IL-18: MBL, Nagoya, Japan; IL-6, sTNF-RI, and sTNF-RII: R&D Systems, Minneapolis, MN, USA; neopterin: IBL, Hamburg, Germany). Neopterin, a 2-amino-4-hydroxy-(1′2′3′-trihydroxypropyl)-pteridine, is produced from guanosine triphosphate (GTP) via GTP cyclohydrolase I by activated monocytes/macrophages [26]. The activity of this enzyme is greatly enhanced by IFN-γ [26]. IFN-γ, which is released by activated type 1 helper T (Th1) lymphocytes and natural killer (NK) cells, is the most potent inducer of neopterin production. Serum TNF-α levels were undetectable. Instead, we measured serum sTNF-RI and -RII levels.

1.3. Statistical analysis

Intra-group comparisons were performed using the Mann–Whitney test or Fisher's exact probability test, where appropriate. A p value of <0.05 was considered to indicate a significant difference.

2. Results

2.1. Serum cytokine profiles of patients with AOSD

We determined the serum levels of cytokines, including IL-6, IL-18, neopterin, sTNF-RI, and sTNF-RII, in patients with AOSD. As shown in Fig. 1, the serum levels of all evaluated cytokines were elevated in active-phase patients compared with those in healthy controls. Furthermore, serum IL-18 levels were markedly elevated even in patients with inactive-phase disease, whereas other cytokines that had been elevated during the active phase normalized once patients had achieved clinical remission. Serum neopterin, IL-18, sTNF-RI, and sTNF-RII levels were significantly higher during the MAS phase than during the active phase, although IL-6 levels did not differ between these phases. These findings were similar to those in patients with s-JIA (Supplementary Fig. 1).

2.2. Markedly elevated serum IL-18 levels in patients with AOSD and s-JIA

We compared the serum cytokine profiles between patients with AOSD and those with s-JIA (Table 2). Consequently, we used a radar chart to depict these cytokine profiles (Fig. 2). Massively elevated serum IL-18 levels were a common feature of both active-phase AOSD and s-JIA (Fig. 2A, D). Significant increases in serum neopterin, IL-18,

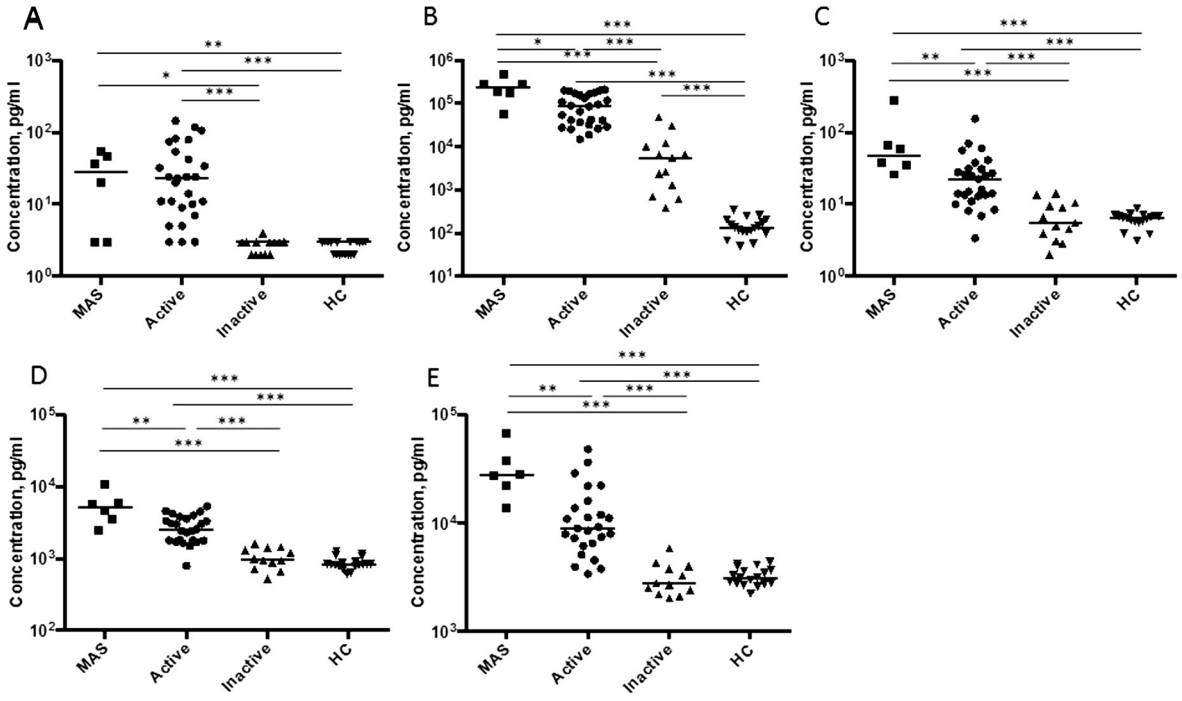

Fig. 1. Serum cytokine profiles of patients with adult-onset Still's disease (AOSD). Serum concentrations of (A) interleukin (IL)-6, (B) IL-18, (C) neopterin, (D) soluble tumor necrosis factor receptor type I (sTNF-RI), and (E) sTNF-RII are shown. Bars indicate median values. Statistically significant differences between each patient group are indicated as follows: $^{*}p < 0.05$, $^{**}p < 0.01$, and $^{***}p < 0.001$.

sTNF-RI, and sTNF-RII were observed during the MAS phases of both diseases (Fig. 2B, E). Furthermore, the serum IL-18 levels remained markedly elevated during the inactive phases of both diseases, whereas other cytokines that were elevated during the active phases normalized once patients achieved clinical remission (Fig. 2C, F).

As shown in Table 2, the serum IL-18 levels of patients with active AOSD (95,604 ± 68,089 pg/ml) were significantly higher than those in patients with s-JIA (72,512 ± 84,208 pg/ml; $p < 0.05$). The serum neopterin levels in patients with active AOSD (29.0 ± 30.3 nmol/l) were also significantly higher than those in patients with s-JIA (17.7 ± 17.5 nmol/l; $p < 0.05$).

2.3. Comparison of the clinical characteristics of AOSD and s-JIA

The clinical characteristics of patients with active-phase AOSD and s-JIA are shown in Table 1. A significant female predominance was observed among patients with AOSD ($p < 0.05$). Hepatomegaly and splenomegaly were observed significantly more frequently with AOSD ($p < 0.05$). In contrast, arthritis was observed significantly more frequently with s-JIA than with AOSD ($p < 0.05$). Serum ferritin levels were significantly higher in patients with AOSD than in those with s-JIA ($p < 0.05$).

Table 2
Serum cytokine levels in patients with adult-onset Still's disease (AOSD) and systemic juvenile idiopathic arthritis (s-JIA) in each disease phase.

		AOSD	s-JIA	p value
Neopterin (nmol/l)	Active	29.0 ± 30.3	17.7 ± 17.5	0.0127
	MAS	83.5 ± 96.5	45.7 ± 26.8	0.4093
	Inactive	6.8 ± 4.3	4.4 ± 2.4	0.0545
IL-6 (pg/ml)	Active	36.0 ± 39.2	75.3 ± 147.3	0.4725
	MAS	27.2 ± 22.0	51.4 ± 88.5	0.9160
	Inactive	3.1 ± 0.3	3.4 ± 1.3	0.7975
IL-18 (pg/ml)	Active	95,604 ± 68,089	72,512 ± 84,208	0.0311
	MAS	246,917 ± 136,301	223,665 ± 203,616	0.3604
	Inactive	9847 ± 14,613	9320 ± 8549	0.5975
sTNF-RI (pg/ml)	Active	2790 ± 1154	2956 ± 1600	0.9440
	MAS	5493 ± 2897	3866 ± 1712	0.2289
	Inactive	1051 ± 339.3	1033 ± 487.5	0.5165
sTNF-RII (pg/ml)	Active	12,920 ± 10,905	9967 ± 8406	0.1195
	MAS	32,683 ± 18,617	22,842 ± 11,399	0.2795
	Inactive	3168 ± 1138	2916 ± 1500	0.4862

2.4. Distinct clinical features of the two subgroups of patients with AOSD based on serum IL-6 and IL-18 levels

As shown in Fig. 3, patients with AOSD could be divided into two subgroups based on their serum IL-6 and IL-18 levels: IL-6-dominant (IL-18/IL-6 < 5000; n = 16) and IL-18-dominant (IL-18/IL-6 > 5000; n = 11). As shown in Table 3, the serum IL-6 levels were significantly higher in the IL-6-dominant subgroup (mean ± standard deviation: 53.3 ± 42.8 pg/ml) than in the IL-18-dominant subgroup (10.8 ± 9.4 pg/ml; $p < 0.001$). In contrast, serum IL-18 levels were higher in the IL-18-dominant subgroup (129,809 ± 71,023 pg/ml) than in the IL-6-dominant subgroup (72,088 ± 56,790 pg/ml), although this difference was not statistically significant. In addition, serum ferritin levels were significantly higher in the IL-18-dominant subgroup (21,348 ± 37,947 pg/ml) than in the IL-6-dominant subgroup (3989 ± 6140 pg/ml; $p < 0.05$).

Next, we compared the clinical features of each subgroup (Table 3). The number of patients with arthritis was significantly higher in the IL-6-dominant subgroup than in the IL-18-dominant subgroup ($p < 0.05$). No patient in the IL-18-dominant subgroup presented with arthritis.

3. Discussion

AOSD has been regarded as the adult manifestation of a disease spectrum that includes s-JIA. Similarities in the clinical and laboratory features of both diseases suggest that similar pathogenic mechanisms might underlie the development of these entities. Recently, the characterization of autoinflammatory diseases has led to a renewed classification of immune-mediated rheumatic diseases [27]. Recent reports

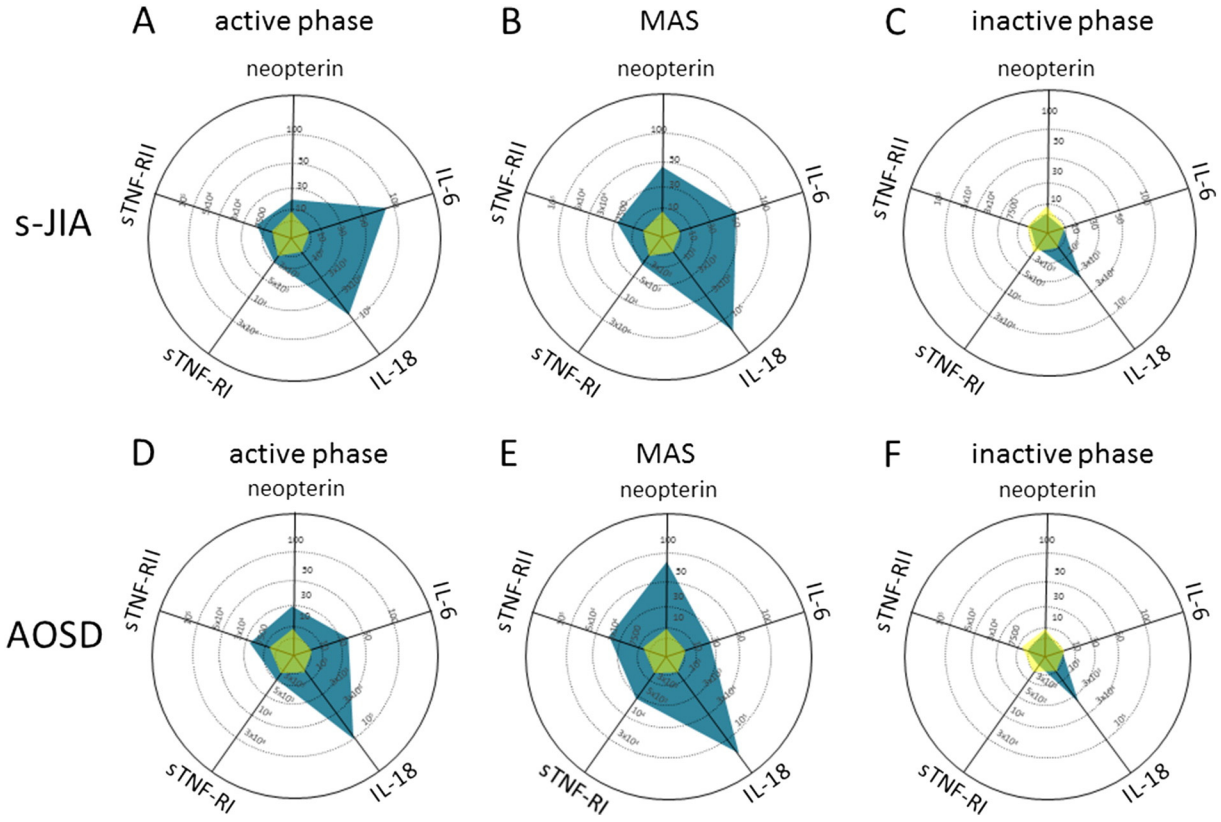

Fig. 2. Serum cytokine profiles and radar charts of patients with adult-onset Still's disease (AOSD) and systemic juvenile idiopathic arthritis (s-JIA) during each disease phase. Representative profiles of serum cytokines, including neopterin, interleukin (IL)-6, IL-18, soluble tumor necrosis factor receptor type I (sTNF-RI), and sTNF-RII are shown.

suggest that s-JIA is more likely to belong to the group of autoinflammatory diseases that follow the same continuum as AOSD [12,28,29]. However, whether s-JIA and AOSD are the same disease remains controversial.

In the present study, we observed similar cytokine release patterns in both clinical entities, characterized by a common significant increase in IL-18 expression. Notably, the serum IL-18 levels were markedly increased in both patients with s-JIA and those with AOSD. Interestingly, the serum IL-18 levels of patients with both diseases remained elevated relative to control levels, even in patients with inactive-phase disease. These findings suggest that abnormal IL-18 production is highly characteristic of both s-JIA and AOSD.

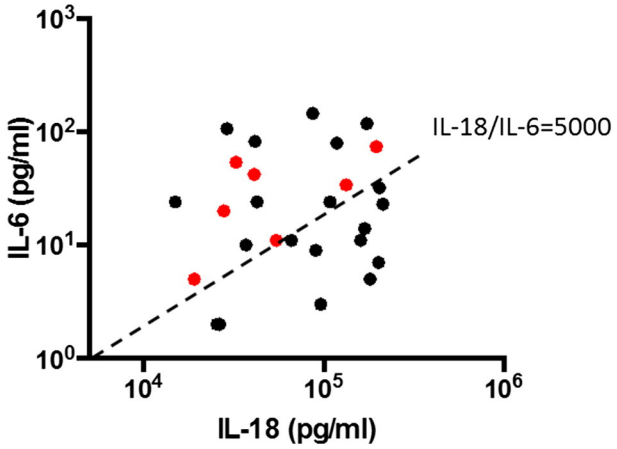

Fig. 3. Distinct subgroups of patients with adult-onset Still's disease (AOSD) based on serum interleukin (IL)-6 and IL-18 levels. Patients with arthritis are represented by red circles.

IL-18 plays an important role in the regulation of NK cell activity. Previous reports described reduced NK cell function in patients with s-JIA and AOSD [30–33]. The mechanism underlying impaired NK cell function in patients with s-JIA has been associated with a defect in IL-18 receptor β phosphorylation [34]. Another report found that an imbalance between IL-18 and its natural inhibitor, IL-18-binding protein, resulted in Th1 lymphocyte and macrophage activation; this process

Table 3
Clinical features of two subgroups of patients with adult-onset Still's disease based on serum interleukin (IL)-6 and IL-18 levels.
F: female; M: male.

	IL-6 dominant subgroup (IL-18/IL-6 < 5000)	IL-18 dominant subgroup (IL-18/IL-6 > 5000)	p value
Patient	16	11	
Age	46.8 ± 15.9	51.6 ± 19.4	0.5849
Sex(M/F)	4/12	2/9	1.0000
Clinical features			
Rash	11 (69)	8 (73)	1.0000
Arthralgia	14 (88)	7 (64)	0.1874
Lymphadenopathy	5 (31)	7 (64)	0.1302
Liver dysfunction	7 (44)	9 (82)	0.1090
Sore throat	5 (31)	4 (36)	1.0000
Myalgia	2 (13)	1 (9)	1.0000
Hepatomegaly	9 (56)	2 (18)	0.1090
Splenomegaly	6 (38)	6 (55)	0.6924
Arthritis	7 (44)	0 (0)	0.0216
Laboratory data			
hyperleukocytosis	13 (81)	7 (64)	0.3913
Ferritin (ng/ml) (n = 22)	3989 ± 6140	21,348 ± 37,947	0.0304
IL-6 (pg/ml)	53.3 ± 42.8	10.8 ± 9.4	0.0005
IL-18 (pg/ml)	72,088 ± 56,790	129,809 ± 71,023	0.0564

escaped the control conferred by NK cell-mediated cytotoxicity and thus might have allowed the development of secondary hemophagocytic syndrome [35]. We previously reported that an infant born to a mother with active AOSD and high serum IL-18 levels exhibited persistently decreased NK cell function [36]. However, this NK cell dysfunction recovered as the infant's serum IL-18 levels decreased [36]. Furthermore, we recently reported a significant increase in serum IL-18 levels during the active phase in patients with MAS compared with those without MAS [19]. These findings indicate that a nonfunctional IL-18/NK cell axis, induced by sustained high serum IL-18 levels, might be closely related to MAS development in both s-JIA and AOSD. Thus, IL-18 might play a key role in the complex network underlying inflammation in patients with s-JIA and AOSD.

In this study, serum IL-18 levels were significantly higher in patients with active AOSD than in those with s-JIA. This result was comparable with those of previous studies conducted on Japanese patients [21,37]. Serum neopterin levels were also significantly higher in patients with active AOSD than in those with s-JIA. Cytokine production develops in an age-dependent manner [38]. Therefore, pediatric immunological immaturity might account for the differences in serum IL-18 and neopterin levels observed between patients with s-JIA and AOSD.

Previous studies that compared the clinical features and laboratory findings of s-JIA and AOSD revealed that these two entities share many common characteristics and might actually represent the same clinical spectrum, thus differing only in age distribution [3–6]. In support of this view, the present study found no differences between these conditions except for hepatomegaly and splenomegaly, which were more frequently observed in AOSD, and arthritis, which was more frequently observed in s-JIA. Previous studies reported significant differences between s-JIA and AOSD with regard to the frequencies of fever, skin rash, and sore throat, all of which occurred more frequently with AOSD [3,6]. The enrollment of more pediatric patients in our study relative to previous studies on clinical disease expression might account for the observed discrepancies. Furthermore, the diagnostic criteria of s-JIA include the presence of arthritis. However, some patients who present with systemic features characteristic of s-JIA never develop arthritis. These findings might also explain the significantly increased frequency of arthritis in patients with s-JIA compared with those in patients with AOSD. In addition to clinical symptoms, most laboratory abnormalities were common to both patients with s-JIA and those with AOSD. However, serum ferritin levels were significantly higher in patients with AOSD than in those with s-JIA [5,6]. These findings were comparable with those of previous studies. Furthermore, 26% of patients with s-JIA in this study developed MAS. This was in line with recent reports [39,40] rather than with an older report [41].

In addition to IL-18, increased serum IL-6 levels were also observed in patients with s-JIA and AOSD. In reports on both conditions, serum IL-6 levels have been correlated with specific markers of disease activity, including joint involvement, skin rash, pyrexia, CRP and ferritin levels, elevated liver enzymes, and leukocytosis [42–47]. Macrophages and endothelial cells are the main sources of IL-6, a cytokine that is responsible not only for the production of acute-phase proteins by hepatocytes, but also for hyperferritinemia, characterized by the uptake of free iron and ferritin synthesis [48,49]. Furthermore, IL-6 is also closely related to the development of arthritis in both s-JIA and AOSD. Previous reports have demonstrated a correlation between serum IL-6 levels and arthritis severity in patients with s-JIA [46] and rheumatoid arthritis [50].

Biological agents that inhibit innate inflammatory cytokines (specifically, IL-1 and IL-6) have induced a paradigm shift in s-JIA treatment [14,15,51]. The inhibition of IL-1 or IL-6 is highly efficacious in many patients with s-JIA, yielding improvements in both systemic symptoms and arthritis [52,53]. Furthermore, recent studies demonstrated the identification of two subgroups of s-JIA with distinct clinical features [19,52,53]. In the present study, we demonstrated the similar existence of two subgroups of patients with AOSD and certain distinct clinical features that could be distinguished based on IL-6 and IL-18 levels. Interestingly, a recent study reported the existence of two subgroups of patients with AOSD that were based on serum IL-18 levels [54]. Patients with severe systemic inflammatory disorders (non-RA subtype) presented with high IL-18 levels, whereas those that developed severe arthritis (RA subtype) presented with low IL-18 levels [54]. The present study findings were consistent with those earlier findings and indicate that s-JIA and AOSD might be pathogenically identical.

Some patients with s-JIA and AOSD were treated with steroids and/or immunosuppressive drugs at the time of blood collection, thus representing a potential limitation of this study. Specifically, these drugs might have affected cytokine production.

Despite this limitation, as expected, our results suggest that the patterns of cytokine release in s-JIA and AOSD share common features, including a significant increase in IL-18 production. Abnormal IL-18 production appears to be characteristic of both s-JIA and AOSD. Furthermore, distinct cytokine profiles based on IL-6 and IL-18 production might be responsible for the distinct clinical expression patterns. The presence of two distinct subgroups among patients with both diseases further supports the view that s-JIA and AOSD belong to the same disease category.

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Conflict of interest

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