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Brief Communication

Macrophage activation syndrome in neonates born to mothers with adult-onset Still's disease: Perinatal effect of maternal IL-18

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ABSTRACT

Overproduction of interleukin (IL)-18 is closely related to the pathogenesis of adult-onset Still's disease (AOSD) and the development of macrophage activation syndrome (MAS), a life-threating complication of AOSD. We reported three cases of MAS occurring in infants born to mothers with AOSD. The infants developed MAS at age 13 and 8 days and at birth. Serum IL-18 levels were extremely elevated in all infants (147,000 pg/mL; 378,000 pg/mL; 95,000 pg/mL) as well as in their mothers (58,500 pg/mL; 367,000 pg/mL; 84,000 pg/mL). Physicians should be aware that infants born to mothers with AOSD are at a risk of developing MAS. Serum IL-18 levels in mothers with AOSD and their infants should be monitored.

1. Introduction

Adult-onset Still's disease (AOSD) is a systemic inflammatory disorder of unknown etiology characterized by spiking fever, skin rash, myalgia, sore throat, hepatomegaly, splenomegaly, lymphadenopathy and arthritis [1]. Bywaters first described AOSD in 1971, noting that this condition shared clinical similarities with systemic juvenile idiopathic arthritis (s-JIA), although the age of onset is > 16 years [1].

Macrophage activation syndrome (MAS) is a severe, potentially life-threatening complication of both s-JIA and AOSD [2,3]. MAS occurs in 7%–10% of patients with s-JIA and 12–17% of patients with AOSD [2,3]. 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 [3]. MAS 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 [3]. A characteristic feature is seen on bone-marrow examination that often reveals numerous morphologically benign macrophages exhibiting hemophagocytic activity [3].

Recent investigations into the pathophysiology of s-JIA/AOSD have focused on mediators of the innate immune system [4,5]. In particular, serum interleukin (IL)-18 levels correlate with disease activity and secondary complications in both diseases [6–10]. We previously reported that patients with AOSD and s-JIA share a common cytokine profile pattern involving a significant increase in IL-18 [10]. Furthermore, a recent study showed serum IL-18 levels can distinguish MAS from hemophagocytic lymphohistiocytosis (HLH) as well as other autoinflammatory syndromes [11]. NK cell dysfunction is well-known consequence of familial HLH, a syndrome caused by genetic defects that impair granule-mediated cytotoxicity [12–16]. Decreased NK cell function was also reported in s-JIA and MAS [12–16]. High IL-18 levels are associated with the transient NK cell dysfunction observed in s-JIA and MAS [12].

We previously reported that IL-18 can pass from the mother to the fetus, resulting in significantly increased serum IL-18 levels in the newborn [17]. Furthermore, serum IL-18 levels are persistently elevated in the infant for nearly one month after birth. At birth, the infant had a significantly lower number of CD16+ $CD56^{dim}$ NK cells and impaired cell function. This impaired NK cell function closely correlated with serum IL-18 levels and recovered when these levels normalized. From these observations, we hypothesize that an infant born to a woman with AOSD may have increased serum IL-18 levels, and therefore, may be at risk of developing MAS/HLH. Here, we report

Abbreviations: MAS, macrophage activation syndrome; IL, interleukin; sTNFR, soluble tumour necrosis factor receptor; IFN, interferon; TNF, tumour necrosis factor; NK, natural killer

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three neonates born to mothers with AOSD who developed MAS and had extremely high serum levels of IL-18.

2. Case presentation

2.1. Patient 1

A male infant was delivered by Cesarean section at 34 weeks of gestation because his mother was experiencing HELLP syndrome. His mother had an 18-year-history of AOSD and was treated with prednisolone (PSL) (15 mg/day). At birth, the infant displayed mild tachypnea; however, his condition improved rapidly. At 7 days after birth, he presented with apnea and poor feeding. The next day, he presented with fever and a skin rash. Laboratory examinations at 8 days after birth showed elevated levels of C-reactive protein (CRP) (11.9 mg/L), aspartate aminotransferase (AST) (66 IU/L), lactate dehydrogenase (LDH) (708 IU/L), and D-dimer (13.9 μg/mL); and hypofibrinogenemia (173 mg/dL). Intravenous immunoglobulin and antibiotics were started, but the fever continued and he presented with hepatosplenomegaly. Laboratory examination at 13 days after birth revealed thrombocytopenia and elevated levels of AST, LDH, and hyperferritinemia (Table 1). Bone-marrow aspiration was not performed. The work-up for infectious pathogens were negative. The diagnosis of MAS was made, and the infant received dexamethasone palmitate. The patient's status and laboratory parameters gradually improved, and his clinical course was uneventful thereafter. He was discharged without sequelae. The serum IL-18 level at the time of MAS diagnosis (13 days after birth) was extremely elevated, as was that of the mother at 27 days after birth (Table 1). The high serum IL-18 levels of the infant persisted for approximately 2 months (Fig. 1A).

2.2. Patient 2

A female infant was delivered by Cesarean section at 34 weeks of gestation because the mother was suspected of having AOSD. The mother's laboratory data at birth showed elevations in white blood cell count (16.0×10^9/L) and anemia (9.7 g/dL) and thrombocytopenia (81×10^9/L); elevated levels of CRP (12.25 mg/L), AST (285 IU/L) and hyperferritinemia (12,236 ng/mL). At birth, the infant was well. However, at 8 days after birth, he presented with fever and hepatomegaly. Laboratory examinations showed elevations in white blood cell count, thrombocytopenia and hypofibrinogenemia; elevated levels of CRP, AST, LDH, D-dimer and hyperferritinemia (Table 1). Bone-marrow aspiration revealed hemophagocytosis. The work-up for infectious pathogens were negative. The diagnosis of MAS was made. The infant received two courses of replacement transfusion followed by prednisolone. The patient's status and laboratory parameters gradually improved, and his clinical course was uneventful thereafter. He was discharged without sequelae. His serum IL-18 level at the time of MAS diagnosis (8 days after birth) was extremely elevated, as was that of the mother (Table 1).

Table 1
Clinical characteristics of three infants with MAS born to the mothers with AOSD.

		Patient1	Patient2	Patient3
Days after birth		13	8	4
Sex		Male	Female	Female
Clinical symptoms				
Fever		+	+	+
Hepatomegaly		+	+	+
Splenomegaly		+	−	+
Petechiae		−	−	+
Hemophagocytosis in BM		ND	+	+
Laboratory findings				
	Normal range			
Ferritin (ng/ml)	25–200	7263	20,031	3904
White blood cells ($\times 10^9$/mm^3)	50–200	34.7	13.2	15
Platelets ($\times 10^9$/mm^3)	27–88	4.6	4.8	7.7
AST (IU/l)	21–64	63	96	110
ALT (IU/l)	12–50	32	17	45
LDH (IU/l)	201–405	604	959	871
Fibrinogen (mg/dl)	200–320	ND	193	172
Triglyceride (mg/dl)	30–149	106	ND	118
Serum IL-18 level at the time of MAS diagnosis (pg/ml)	< 500	147,000	378,000	95,000
Serum IL-18 level in the mother (pg/ml)	< 500	58,800 (27 days after birth)	367,000 (8 days after birth)	84,000 (1 day after birth)

2.3. Patient 3

A pregnant woman presented with fever, skin rash, arthralgia of bilateral knee joints, and liver injury at 34 weeks of gestation. A female infant was delivered by Cesarean section at 37 weeks of gestation because the mother was suspected of having AOSD and polyhydramnios was observed. At birth, the infant presented with fever, petechiae, and hepatosplenomegaly. Laboratory data at birth showed elevations in white blood cell count (16.87×10^9/L), thrombocytopenia (40×10^9/L); and elevated levels of C-reactive protein (1.79 mg/L), AST (132 IU/L), and hyperferritinemia (5337 ng/mL). Platelet transfusion was performed. Antibiotic treatment was started; however, the fever continued. Laboratory examinations at 4 days after birth showed elevations in white blood cell count, anemia and thrombocytopenia; elevated levels of CRP, AST, LDH, fibrin degradation products and hyperferritinemia and hypofibrinogenemia (Table 1). Bone-marrow aspiration revealed hemophagocytosis. The work-up for infectious pathogens were negative. The diagnosis of MAS was made. The baby received dexamethasone palmitate. The patient's status and laboratory parameters gradually improved, and his clinical course was uneventful thereafter. He was discharged without sequelae. Serum IL-18 level at the diagnosis of MAS (4 days after birth) was extremely elevated as was that of the mother at 1 day after birth (Table 1). High serum IL-18 levels persisted in the infant for approximately 2 months (Fig. 1B).

3. Discussion

Recent studies investigating the pathophysiology of AOSD and s-JIA focus on mediators of the innate immune system [4,5]. Specifically, interleukin IL-1β, IL-6, and IL-18 were found to correlate with disease activity and secondary complications [4,5]. We previously reported increased serum IL-18 levels in patients with AOSD and s-JIA [9,10]. Furthermore, two subsets of patients with AOSD and s-JIA exhibit certain distinct clinical features that correlate with IL-6 and IL-18 levels [10,18]. Patients in the IL-18–dominant subset were more likely to develop MAS [10,18]. These findings indicate that overproduction of IL-18 in AOSD and s-JIA might be closely associated with the development of MAS. Recently, direct evidence of a close association between IL-18 and the development of MAS in humans was provided by the observation of a patient with gain-of-function mutations in *NLRC4*, an inflammasome sensor, which caused a disease characterized by recurrent MAS episodes [19]. The most striking immunological abnormality in this patient was surprisingly high IL-18 levels, providing evidence that the NLRC4 is particularly important in regulating IL-18 production and further supporting the role of IL-18 as a predisposing factor for MAS [19]. These findings indicate that IL-18 overproduction may be closely related to the development of MAS.

NK cell dysfunction is a characteristic feature of primary HLH, and decreased NK cell function was also reported in s-JIA and MAS [12–16]. Excess IL-18 exposure may impair normal NK cell functions. de Jager et al. reported that IL-18-induced IFN-γ production by NK cells was

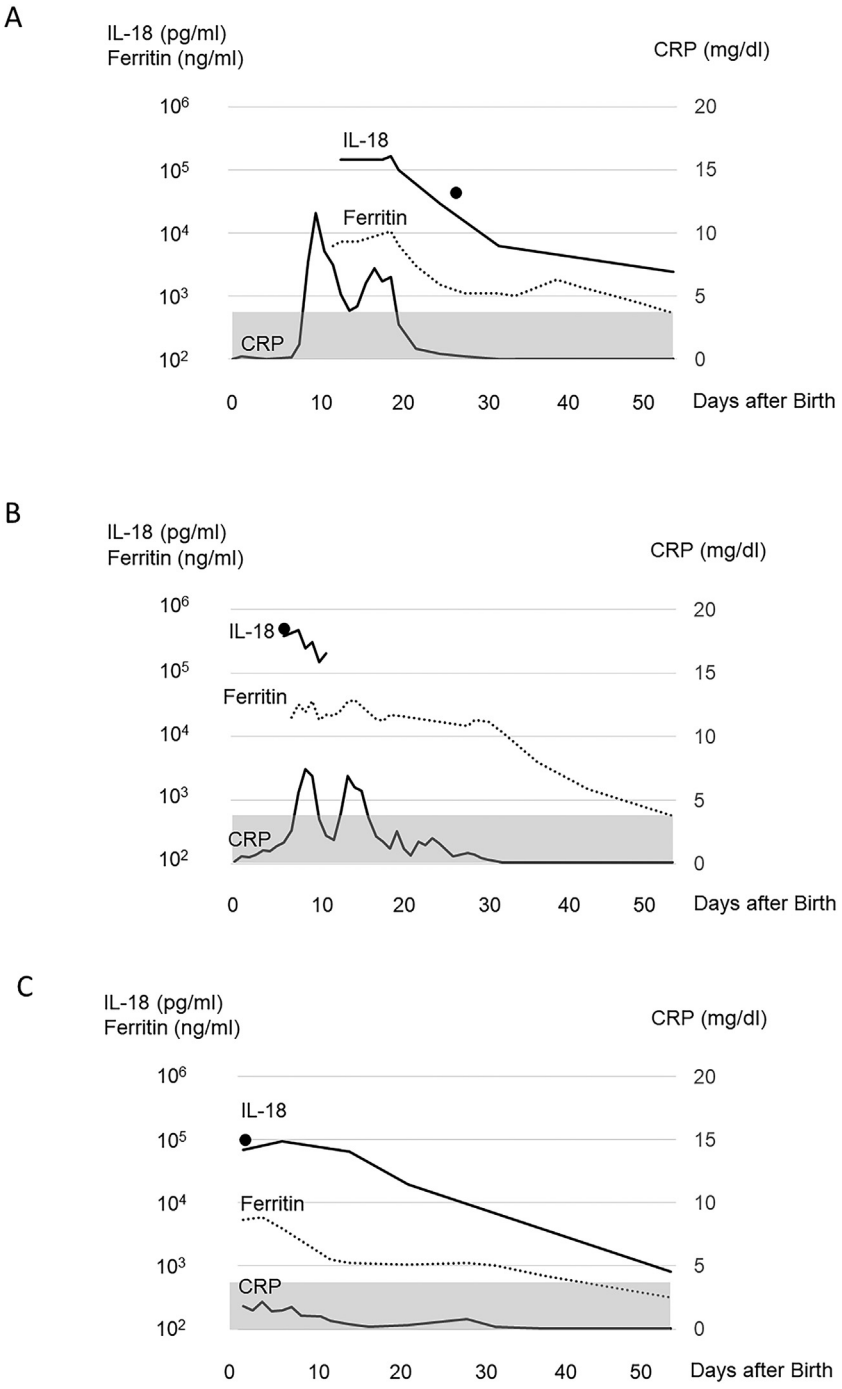

Fig. 1. Changes in serum IL-18 levels of the mothers and those in serum IL-18 levels in their newborns.
A. Patient 1, B. Patient 2, C. Patient 3.
Black circle: Serum IL-18 levels in the mother of each patient, Gray box: normal range of serum IL-18 levels.

defective in patients with s-JIA due to a defect in β phosphorylation of the IL-18 receptor [16]. Furthermore, we recently demonstrated that NK cell activation by IL-18 was impaired in patients with active s-JIA. Additionally, NK cell activation was recovered by exogenous IL-18 stimulation in patients with s-JIA in whom serum IL-18 levels were decreased after starting treatment [12]. These results indicate that NK cell dysfunction in patients with s-JIA is a transient defect caused by exposure to high IL-18 levels secondary to its overproduction. These findings indicate that high IL-18 concentrations resulting from overproduction might induce NK cell exhaustion and secondary transient NK cell dysfunction and is closely related to the development of MAS.

We previously reported the case of an infant born to a mother with AOSD presenting with transient impairment of NK cell function associated with increased serum IL-18 levels due to *in utero* transmission from the mother to the fetus [17]. Furthermore, Hashimoto et al. reported the case of MAS occurring in an infant born to a mother with AOSD [20]. In this study, we also report three neonates born to mothers with AOSD who then developed MAS with extremely high serum levels of IL-18. Serum IL-18 levels were persistently elevated in each infant for one to two months. These findings indicate that infants born to women with AOSD have increased serum IL-18 levels and therefore may be at risk of developing MAS. MAS can develop even if the mother's disease is

well controlled at the time of delivery. Therefore, careful monitoring of serum IL-18 levels is recommended in pregnant women with AOSD and their newborns.

In conclusion, we present three patients of MAS occurring in infants born to mothers with AOSD. Physicians should be aware that an infant born to a mother with AOSD is at a risk of developing MAS. Careful monitoring of serum IL-18 levels is recommended in pregnant women with AOSD and their newborns.

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Declaration of Competing Interest

None.

References

[1] E.G. Bywaters, Still's disease in the adult, Ann. Rheum. Dis. 30 (1971) 121–133, https://doi.org/10.1136/ard.30.2.121.
[2] Y. Jamilloux, M. Gerfaud-Valentin, F. Martinon, A. Belot, T. Henry, P. Sève, Pathogenesis of adult-onset Still's disease: new insights from the juvenile counterpart, Immunol. Res. 61 (2015) 53–62, https://doi.org/10.1007/s12026-014-8561-9.
[3] A. Ravelli, A.A. Grom, E.M. Behrens, R.Q. Cron, Macrophage activation syndrome as part of systemic juvenile idiopathic arthritis: diagnosis, genetics, pathophysiology and treatment, Genes Immun. 13 (2012) 289–298, https://doi.org/10.1038/gene.2012.3.
[4] E.D. Mellins, C. Macaubas, A.A. Grom, Pathogenesis of systemic juvenile idiopathic arthritis: some answers, more questions, Nat. Rev. Rheumatol. 7 (2011) 416–426, https://doi.org/10.1038/nrrheum.2011.68.
[5] M. Gerfaud-Valentin, Y. Jamilloux, J. Iwaz, P. Sève, Adult-onset Still's disease, Autoimmun. Rev. 13 (2014) 708–722, https://doi.org/10.1016/j.autrev.2014.01.058.
[6] Y. Kawaguchi, H. Terajima, M. Harigai, M. Hara, N. Kamatani, Interleukin-18 as a novel diagnostic marker and indicator of disease severity in adult-onset Still's disease, Arthritis Rheum. 44 (2001) 1716–1717, https://doi.org/10.1002/1529-0131(200107)44:7<1716::AID-ART298>3.0.CO;2-I.
[7] M. Kawashima, M. Yamamura, M. Taniai, H. Yamauchi, T. Tanimoto, M. Kurimoto, S. Miyawaki, T. Amano, T. Takeuchi, H. Makino, Levels of interleukin-18 and its binding inhibitors in the blood circulation of patients with adult-onset Still's disease, Arthritis Rheum. 44 (2001) 550–560, https://doi.org/10.1002/1529-0131(200103)44:3<550::AID-ANR103>3.0.CO;2-5.
[8] N. Maeno, S. Takei, Y. Nomura, H. Imanaka, M. Hokonohara, K. Miyata, Highly elevated serum levels of interleukin-18 in systemic juvenile idiopathic arthritis but not in other juvenile idiopathic arthritis subtypes or in Kawasaki disease: comment on the article by Kawashima, et al, Arthritis Rheum. 46 (2002) 2539–2541, https://doi.org/10.1002/art.10389.
[9] M. Shimizu, T. Yokoyama, K. Yamada, H. Kaneda, H. Wada, T. Wada, T. Toma, K. Ohta, Y. Kasahara, A. Yachie, Distinct cytokine profiles of systemic-onset juvenile idiopathic arthritis-associated macrophage activation syndrome with particular emphasis on the role of interleukin-18 in its pathogenesis, Rheumatol. Oxf. 49 (2010) 1645–1653, https://doi.org/10.1093/rheumatology/keq133.
[10] N. Inoue, M. Shimizu, S. Tsunoda, M. Kawano, M. Matsumura, A. Yachie, Cytokine profile in adult-onset Still's disease: comparison with systemic juvenile idiopathic arthritis, Clin. Immunol. 169 (2016) 8–13, https://doi.org/10.1016/j.clim.2016.05.010.
[11] E.S. Weiss, C. Girard-Guyonvarc'h, D. Holzinger, A.A. de Jesus, Z. Tariq, J. Picarsic, E.J. Schiffrin, D. Foell, A.A. Grom, S. Ammann, S. Ehl, T. Hoshino, R. Goldbach-Mansky, C. Gabay, S.W. Canna, Interleukin-18 diagnostically distinguishes and pathogenically promotes human and murine macrophage activation syndrome, Blood 131 (2018) 1442–1455, https://doi.org/10.1182/blood-2017-12-820852.
[12] M. Takakura, M. Shimizu, T. Yakoyama, M. Mizuta, A. Yachie, Transient natural killer cell dysfunction associated with interleukin-18 overproduction in systemic juvenile idiopathic arthritis, Pediatr. Int. 60 (2018) 984–985, https://doi.org/10.1111/ped.13679.
[13] J. Villanueva, S. Lee, E.H. Giannini, T.B. Graham, M.H. Passo, A. Filipovich, A.A. Grom, Natural killer cell dysfunction is a distinguishing feature of systemic onset juvenile rheumatoid arthritis and macrophage activation syndrome, Arthritis Res. Ther. 7 (2005) R30–R37, https://doi.org/10.1186/ar1453.
[14] A.A. Grom, J. Villanueva, S. Lee, E.A. Goldmuntz, M.H. Passo, A. Filipovich, Natural killer cell dysfunction in patients with systemic-onset juvenile rheumatoid arthritis and macrophage activation syndrome, J. Pediatr. 142 (2003) 292–296, https://doi.org/10.1067/mpd.2003.110.
[15] A.A. Grom, Natural killer cell dysfunction: a common pathway in systemic-onset juvenile rheumatoid arthritis, macrophage activation syndrome, and hemophagocytic lymphohistiocytosis? Arthritis Rheum. 50 (2004) 689–698, https://doi.org/10.1002/art.20198.
[16] W. de Jager, S.J. Vastert, J.M. Beekman, N.M. Wulffraat, W. Kuis, P.J. Coffer, B.J. Prakken, Defective phosphorylation of interleukin-18 receptor beta causes impaired natural killer cell function in systemic-onset juvenile idiopathic arthritis, Arthritis Rheum. 60 (2009) 2782–2793, https://doi.org/10.1002/art.24750.
[17] M. Shimizu, Y. Sakakibara, M. Kawano, A. Yachie, Transient impairment of NK cell function in an infant born to a mother with adult-onset Still's disease: perinatal effect of maternal IL-18, Clin. Immunol. 143 (2012) 273–274, https://doi.org/10.1016/j.clim.2012.03.004.
[18] M. Shimizu, Y. Nakagishi, N. Inoue, M. Mizuta, G. Ko, Y. Saikawa, T. Kubota, Y. Yamasaki, S. Takei, A. Yachie, Interleukin-18 for predicting the development of macrophage activation syndrome in systemic juvenile idiopathic arthritis, Clin. Immunol. 160 (2015) 277–281, https://doi.org/10.1016/j.clim.2015.06.005.
[19] S.W. Canna, A.A. de Jesus, S. Gouni, S.R. Brooks, B. Marrero, Y. Liu, M.A. DiMattia, K.J. Zaal, G.A. Sanchez, H. Kim, D. Chapelle, N. Plass, Y. Huang, A.V. Villarino, A. Biancotto, T.A. Fleisher, J.A. Duncan, J.J. O'Shea, S. Benseler, A. Grom, Z. Deng, R.M. Laxer, R. Goldbach-Mansky, An activating NLRC4 inflammasome mutation causes autoinflammation with recurrent macrophage activation syndrome, Nat. Genet. 46 (2014) 1140–1146, https://doi.org/10.1038/ng.3089.
[20] M. Hashimoto, S. Ogata, A. Yamaguchi, K. Kawada, M. Kenmochi, T. Ebato, K. Nomoto, Y. Bando, S. Shimodera, H. Shibata, S. Ono, M. Nakayama, T. Yasumi, M. Ishii, Hemophagocytic lymphohistiocytosis with high serum levels of IL-18 and predominant lymphocyte activation in a neonate born to a mother with adult-onset Still's disease, Clin. Immunol. 180 (2017) 95–96, https://doi.org/10.1016/j.clim.2017.04.007.