Spontaneously Resolved Suspected Hemophagocytic Lymphohistiocytosis or Macrophage Activating Syndrome Associated with Neonatal Lupus Erythematosus: A Case Report

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Objectives: To present a rare case of neonatal lupus erythematosus (NLE) associated with suspected hemophagocytic lymphohistiocytosis (HLH) or macrophage activation syndrome (MAS).
Case presentation: A female infant weighing 2,995 g was born to a mother without medical history of any disease. At birth, the patient had erythematous papules on her face and trunk. She was admitted at 1 day of age with elevated C-reactive protein levels. The patient was diagnosed with NLE based on the presence of anti-Ro/SSA and anti-La/SSB antibodies. Thereafter, it became clear that the antibody levels in her mother were also elevated. At 20 days of age, the infant showed elevated transaminases, ferritin, triglyceride, and soluble interleukin-2 receptor levels. Although HLH or MAS was suspected, she did not fulfill the diagnostic criteria. Thereafter, these abnormal values spontaneously improved, and the skin rash improved with the use of topical steroids. The patient was discharged at 39 days of age. At 1 year of age, the patient's growth and development were normal.
Conclusion: NLE should be considered in infants with an unexplained skin rash at birth. When a diagnosis is made, close observation of the infant's clinical features is needed to determine whether they will develop HLH or MAS.

Key words: neonatal lupus erythematosus, hemophagocytic lymphohistiocytosis, macrophage activation syndrome, diagnostic criteria, autoimmune diseases

INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening hyperinflammatory syndrome characterized by an uncontrolled immune response caused by the activation of cytotoxic lymphocytes and macrophages [1, 2]. HLH is classified into two groups: primary HLH, which is caused by a hereditary disorder, and secondary HLH, which is caused by various factors, such as infection, malignancy, surgical operations, autoimmune diseases, post-allogeneic hematopoietic stem cell transplantation, and drug hypersensitivity [1–3]. Macrophage activation syndrome (MAS), one of the types of secondary HLH, is the term used to describe severe complications of systemic inflammatory diseases such as autoimmune or autoinflammatory diseases [4]. Among the types of secondary HLH, neonatal lupus erythematosus (NLE) complicated with HLH or MAS is rare, and little information is available regarding its clinical characteristics and prognosis [5–7].

Herein, we present a case of suspected HLH or MAS associated with NLE in a newborn infant which spontaneously resolved without fulfilling the diagnostic criteria for HLH or MAS associated with NLE and review the literature.

CASE PRESENTATION

A female infant, weighing 2,995 g, at 40 weeks and 2 days of gestation, was born from a 27-year-old woman (gravida 1, para 1) who had no medical history of disease, including during pregnancy. Although the infant had erythematous papules on her face and trunk at birth, she was in the same room as her mother because she had no other symptoms. The infant's C-reactive protein (CRP) level was checked because the erythematous papules had spread by the age of 1 day. She was admitted to our neonatal intensive care unit because of an elevated CRP value of 3.47 mg/dL. Her body temperature was normal, and other vital signs were stable. The platelet count of the infant was low ($10.2 \times 10^4/\mu L$). In contrast, her aspartate aminotransferase (AST) levels were slightly elevated; however, other laboratory values were normal (Table 1). Antibiotics and acyclovir were started after performing culture tests, including blood cultures for presumptive sepsis and viral antibody tests for herpes simplex virus antibodies. After treatment initiation, her CRP levels gradually improved (Table 1). These treatments were discontinued after negative results for bacterial and viral infections were obtained. At 6

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Table 1 Trend of blood examinations related to hemophagocytic lymphohistiocytosis in our patient

Values (unit)	Day 1	Day 2	Day 6	Day 13	Day 20	Day 26	1 month	3 months	6 months	1 year
Hemoglobin (g/dL)	14.1	13.4	13.4	12.9	8.2	10.8	9.2	9.6	13	11.7
Leukocytes ($\times 10^3/\mu L$)	18.8	n/a	8	8	8.2	9.1	5.8	4.7	9.4	7.5
Neutrophil ($\times 10^3/\mu L$)	n/a	n/a	n/a	3.4	2.5	3.1	2.4	0.9	1.8	3.2
Platelet count ($\times 10^4/\mu L$)	10.2	n/a	13	15.3	24.8	16.0	17.9	35.2	26.3	35.4
Triglyceride (mg/dL)	n/a	n/a	n/a	n/a	1107	581	275	n/a	546	116
Fibrinogen (mg/dL)	n/a	n/a	n/a	n/a	280	n/a	n/a	n/a	n/a	n/a
AST (U/L)	96	n/a	44	77	205	107	57	54	54	43
ALT (U/L)	22	n/a	15	36	106	78	41	49	30	21
Ferritin (ng/mL)	n/a	n/a	n/a	809	1626	696	455	197	12	< 4
sIL-2R (U/mL)	n/a	n/a	n/a	n/a	3380	n/a	3030	n/a	n/a	n/a
CRP (mg/dL)	3.47	2.83	0.54	0.17	< 0.09	< 0.09	< 0.09	< 0.09	< 0.09	< 0.09
Procalcitonin (ng/mL)	n/a	3.3	n/a	n/a	n/a	0.236	0.315	n/a	n/a	n/a
Anti-Ro/SSA (U/mL)	n/a	n/a	410	n/a	n/a	n/a	n/a	n/a	8.3	< 1.0
Anti-La/SSB (U/mL)	n/a	n/a	> 1000	n/a	n/a	n/a	n/a	n/a	17.4	< 1.0
ANA (times)	n/a	n/a	160	n/a	n/a	n/a	n/a	n/a	< 40	< 40

AST, aspartate aminotransferase; ALT, alanine aminotransferase; sIL-2R, soluble interleukin-2 receptor; CPR, C-reactive protein; Anti-Ro/SSA, anti-Ro/SSA antibody; Anti-La/SSB, anti-La/SSB antibody; ANA, antinuclear antibody; n/a, not anal

days of age, autoimmune antibodies were tested because the erythematous papules in the infant did not improve. Anti-Ro/SSA, anti-La/SSB, and anti-nuclear antibodies (ANA) were elevated up to 410 U/mL, more than 1,000 U/mL, and 160 dilution, respectively. Thereafter, it became obvious that maternal anti-Ro/SSA, anti-La/SSB, and ANA levels were elevated. On the basis of these results, the infant was diagnosed with NLE. Electrocardiography and echocardiographic findings of the infant were normal. At 14 days of age, topical steroids were started because the erythematous papules did not improve despite sun avoidance. At 20 days of age, her CRP level was negative and thrombocytopenia improved (Table 1). However, the results of several blood examination values worsened as follows: hemoglobin, 8.2 g/dL; AST, 205 U/L; alanine aminotransferase (ALT), 106 U/L; and ferritin, 1,626 ng/mL (Table 1). Leukocyte and platelet counts were normal. Additional blood tests were performed to rule out the development of HLH. The triglyceride and soluble interleukin-2 receptor (sIL-2R) levels were 1,107 mg/dL and 3,380 U/mL, respectively. The infant had no fever, lymphadenopathy, or hepatosplenomegaly. A skin biopsy was not performed due to lack of parental consent. The infant did not fulfill the diagnostic criteria for HLH at that time. Although close observation was continued, regardless of whether she developed HLH or not, the abnormal values in the blood examinations gradually improved. Moreover, the erythematous papules gradually improved with topical steroid application. The patient was discharged at 39 days of age. The patients' clinical condition was monitored at the outpatient clinic. Abnormal hemoglobin, AST, ALT, and ferritin values improved with growth (Table 1). At 4 months of age, topical steroid application was completed because of the disappearance of her skin rash. The patient had normal growth and development at 1 year of age. Autoimmune antibodies transferred from the mother tested negative (Table 1). The mother underwent close observation with no treatment and had no clinical symptoms suggestive of autoimmune diseases, except for anti-SS-A, anti-SS-B, and ANA positivity.

DISCUSSION

Herein, we presented a rare case of HLH associated with NLE, which spontaneously resolved without fulfilling the diagnostic criteria for HLH associated with NLE. Generally, the HLH-2004 criteria are used to diagnose HLH [8], and cases must fulfill five or more of the eight criteria if hereditary factors are not detected or are unknown [1, 3]. Our patient fulfilled three criteria (hypertriglyceridemia, hyperferritinemia, and a high sIL-2R value) at 20 days of age. In patients with HLH, it is thought that hypertriglyceridemia is caused by the inhibition of lipoprotein lipase activity due to

Table 2 Summary of the clinical features between the present case and five infants with hemophagocytic lymphohistiocytosis or macrophage activation syndrome associated with neonatal lupus erythematosus

Patient	GA, BW, Sex	Onset	Antibodies	Skin rash	Clinical features related to the diagnostic criteria for HLH	Therapy	Prognosis	Reference
1	40 weeks, 3,292 g, M	Day 0	Anti-Ro/SSA Anti La/SSB	−	Fever, Splenomegaly, Cytopenia, Hypertriglyceridemia, Hyperferritinemia, High sIL-2R value	Hydrocortisone	SNDI	Suzuki 2013
2	39 weeks, 3,064 g, M	Day 0	Anti-Ro/SSA Anti-La/SSB	+	Fever, Splenomegaly, Cytopenia, Hyperferritinemia, High sIL-2R value	Prednisolone	Good	Shimozawa 2015
3	37 weeks, 2,550 g, F	Day 10	Anti-Ro/SSA ANA	−	Fever, Splenomegaly Cytopenia, Hypertriglyceridemia, Hyperferritinemia	mPSL pulse, Cyclosporine, Prednisolone	Good	Park 2015
4*	GA: n/d, BW: n/d, M	Day 0	Anti-Ro/SSA Anti-La/SSB ANA	+	Splenomegaly, Cytopenia, Hemophagocytes in bone marrow	Steroids	Good	Kelgeri 2019
5*	37 weeks, 2,330 g, F	Day 29	Anti-Ro/SSA Anti-La/SSB ANA Anti-ENA	+	Fever, Hypertriglyceridemia, Hyperferritinemia, High sIL-2R value	Prednisolone	Good	Heijstek 2021
Our case	40 weeks, 2,995 g, F	Day 20	Anti-Ro/SSA Anti-La/SSB ANA	+	Hypertriglyceridemia, Hyperferritinemia, High sIL-2R value	No therapy	Good	−

GA, gestational age; BW, birth weight; M, male; F, female; n/d, not described; Anti-Ro/SSA, anti-Ro/SSA antibody; Anti-La/SSB, anti-La/SSB antibody; ANA, anti-nuclear antibody; Anti-ENA, anti-extractable nuclear antigen; HLH, hemophagocytic lymphohistiocytosis; sIL-2R, soluble interleukin-2 receptor; mPSL pulse, methylprednisolone pulse therapy; SNDI, severe neurodevelopmental impairment. *Patients 4 and 5 were reported as infants with macrophage activation syndrome but not HLH because they did not fulfill the diagnostic criteria for HLH.

elevated levels of tumor necrosis factor-α, which is a cytokine [9]. Ferritin and sIL-2R are useful markers of cytokine production, and extremely high levels of these markers reflect hypercytokinemia [1]. Therefore, our patient likely presented with the pathophysiology of hypercytokinemia that is well recognized in patients with HLH. Our patient also showed decreased hemoglobin levels and elevated AST and ALT levels. Cyotopenia affecting two or more lineages is one of the diagnostic criteria for HLH. Although our patient did not meet the criteria for cytopenia, because only hemoglobin values decreased, the possibility of developing HLH was not ruled out. Elevated AST levels are always observed in patients with HLH and are typically higher than ALT levels [1]. This finding is compatible with that of our case. Unfortunately, we could not directly analyze cytokine profiles. Further information might have been obtained if these values had been measured.

Macrophage activation syndrome (MAS), which is classified as secondary HLH, occurs in rheumatological diseases such as systemic juvenile idiopathic arthritis (sJIA), adult-onset Still's disease, or systemic lupus erythematosus (SLE) [4, 10]. Recently, it has been reported that infants with HLH associated with NLE or infants born to mothers with other autoimmune diseases without fulfilling the diagnostic criteria for HLH are also considered to have MAS [11, 12]. Therefore, the definition of MAS remains unclear.

The 2016 classification criteria for MAS complicated by sJIA were proposed in addition to the HLH-2004 criteria [4]. A febrile patient, with known or suspected sJIA, is classified as having MAS if their ferritin level is more than 684 ng/mL and any two or more out of the following four symptoms are met: platelet count less than or equal to 181×10^9/L, AST more than 48 U/L, triglycerides more than 156 U/L, or fibrinogen less than or equal to 360 mg/dL. According to this classification, a case of MAS associated with NLE was recently reported [11]. In this report, hemophagocytosis was detected via a skin biopsy. Therefore, the authors stated that skin biopsies for diagnosing MAS associated with NLE may have additional value. Since our patient met the criteria for MAS except for fever, hemophagocytosis might have been recognized if a skin biopsy had been performed.

Table 2 shows the clinical features between the present case and five infants reported to have HLH or MAS associated with NLE. Among them, Patient's 4 and 5 were reported as infants with MAS but not with HLH because they did not fulfill more than five of the eight criteria for HLH. All five patients had both anti-Ro/SSA and anti-La/SSB suggesting that both antibodies may be key to the development of HLH or MAS.

Various clinical features were related to the diagnostic criteria for HLH in patients with HLH or MAS associated with NLE (Table 2). From this perspective, it may be difficult to diagnose HLH or MAS associated with NLE early. However, fever and hyperferritinemia were recognized in four of the five patients. Therefore, these two criteria may contribute to the early diagnosis of HLH or MAS associated with NLE.

The prognosis of all patients was good, except for that of Patient 1. This patient had severe neurodevelopmental impairment due to severe circulatory collapse at 22 h of age due to marked hypercytokinemia from HLH. Because our patient was also suspected to have hypercytokinemia, we carefully monitored her clinical course. Fortunately, the abnormal blood examination values in our case spontaneously improved without HLH or MAS developing. Intravenous steroid monotherapy was performed in four of five patients and

was effective [5–7, 11, 12]. Although our patient did not receive intravenous steroids, topical steroids were administered at 14 days of age. This medication might have affected the infant's clinical course in some ways. Further studies are required to clarify whether topical steroids are effective in restricting the development of NLE-associated HLH or MAS.

CONCLUSION

When infants present with an unexplained skin rash at birth, the possibility of NLE should be considered in the differential diagnosis. Subsequently, when a diagnosis is made, close observation is required to determine whether the patient will develop HLH or MAS. Further studies are required to clarify whether topical steroids are effective in restricting the development of NLE-associated HLH or MAS.

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CONFLICT OF INTEREST DISCLOSURES

The authors have no conflicts of interest to disclose.

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INFORMED CONSENT

Written informed consent was obtained from the patient's family for publication of this case.

REFERENCES

1) Morimoto A, Nakazawa Y, Ishii E. Hemophagocytic lymphohistiocytosis: pathogenesis, diagnosis, and management. Pediatr Int 2016; 58: 817–25.
2) Griffin G, Shenoi S, Hughes GC. Hemophagocytic lymphohistiocytosis: an update on pathogenesis, diagnosis, and therapy. Best Pract Res Clin Rheumatol 2020; 34: 101515.
3) Suzuki N, Morimoto A, Ohga S, Kudo K, Ishida Y, Ishii E; HLH/LCH Committee of the Japanese Society of Pediatric Hematology. Characteristics of hemophagocytic lymphohistiocytosis in neonates: a nationwide survey in Japan. J Pediatr 2009; 155: 235–8.
4) Ravelli A, Minoia F, Davì S, Horne A, Bovis F, Pistorio A, *et al*. 2016 classification criteria for macrophage activation syndrome complicating systemic juvenile idiopathic arthritis: a European League Against Rheumatism/American College of Rheumatology/Paediatric Rheumatology International Trials Organisation Collaborative Initiative. Arthritis Rheumatol 2016; 68: 566–76.
5) Suzuki Y, Takahashi N, Yada Y, Koike Y, Matano M, Nishimura H, *et al*. Hemophagocytic lymphohistiocytosis in a newborn infant born to a mother with Sjögren syndrome antibodies. J Perinatol 2013; 33: 569–71.
6) Shimozawa H, Kono Y, Matano M, Suzuki Y, Koike Y, Yada Y, *et al*. Cytokine profile in two siblings with neonatal lupus erythematosus. Pediatr Int 2015; 57: 1211–4.
7) Park JH, Kim SH, Kim HJ, Lee SJ, Jeong DC, Kim SY. Macrophage activation syndrome in a newborn infant born to a mother with autoimmune disease. J Perinatol 2015; 35: 158–60.
8) Henter JI, Horne A, Aricó M, Egeler RM, Filipovich AH, Imashuku S, *et al*. HLH-2004: diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer 2007; 48: 124–31.
9) Ponnatt TS, Lilley CM, Mirza KM. Hemophagocytic lymphohistiocytosis. Arch Pathol Lab Med 2022; 146: 507–19.
10) Okamoto N, Yokota S, Takei S, Okura Y, Kubota T, Shimizu M, *et al*. Clinical practice guidance for juvenile idiopathic arthritis (JIA) 2018. Mod Rheumatol 2019; 29: 41–59.
11) Heijstek V, Habib M, van der Palen R, van Doorn R, Muller PH. Macrophage activation syndrome in a newborn: report of a case associated with neonatal lupus erythematosus and a summary of the literature. Pediatr Rheumatol Online J 2021; 19: 13.
12) Kelgeri C, Al Abadi E, Gupte G. Neonatal liver failure with hemophagocytosis and skin rash. J Pediatr Gastroenterol Nutr 2019; 68: e105.