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Case Report

# Macrophage activation syndrome in neonatal lupus presenting with fever and rash

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Neonatal lupus can occur in infants born to mother with autoimmune disorders through transplacental auto-antibodies. Clinical manifestations in neonatal lupus include cutaneous lesions and hematologic or hepatobiliary findings resembling those seen in systemic lupus erythematosus. In autoimmune state, macrophage activation syndrome (MAS) represent a critical and potentially fatal complication that can result in mortality if not immediately identified and managed with the appropriate care. Here we present a 33-day-old girl diagnosed with neonatal lupus and serious MAS. She was delivered by a primipara mother who did not exhibit any autoimmune symptoms. The patient visited the hospital due to fever and pancytopenia. Laboratory data were compatible with MAS, including pancytopenia, high level of ferritin, soluble interleukin-2, and decreased natural killer cell activity. In addition, autoimmune study showed positive results for anti-nuclear antibody (ANA), anti-Sjogren syndrome antigen A (SSA), and SSB, The autoimmune study for mother also showed positive results for ANA, anti-SSA, and SSB. The patient recovered after she received high dose steroid and supportive care. Our case indicates that neonatal lupus should be taken into consideration when fever, erythematous skin rash, and pancytopenia are observed in infants, even if their mothers have no prior history of autoimmune conditions.

**Keywords:** Macrophage activation syndrome, Neonatal systemic lupus erythematosus

## INTRODUCTION

Clinical manifestations in neonatal lupus include skin rash, hematologic or hepatobiliary events, and occasionally serious congenital heart block [1,2]. These clinical features can occur due to transplacental auto-antibodies from mother with autoimmune disease including systemic lupus erythematosus [1-3]. Neonatal lupus is developed through passively acquired autoimmune disease. Clinical findings except heart block in neonatal lupus usually disappear at 6 months of age [1,2,4].

Macrophage activation syndrome (MAS) is a serious inflammatory condition caused by overproduction of cytokines from immune cells including macrophage due to infection or autoimmune disease. It is fatal unless there is an appropriate treatment after prompt diagnosis [5,6]. MAS is not common in neonatal lupus. Most cases are related to mothers with previous autoimmune manifestations [7-9].

Here, we report a serious case of MAS in neonatal lupus, which initially manifested with fever and skin rash. The baby was born to a mother without any autoimmune clinical symptoms, although she had auto-antibodies. This data was approved from Institute of Review Board in Seoul St. Mary's

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## CASE REPORT

A 33-day-old girl was admitted due to fever with pancytopenia. She presented erythema marginatum like skin rash on the whole body (Figure 1). Her birth weight was 2.78 kg and her gestational age was 37+2 weeks from a primipara mother without any autoimmune disorders at a local clinic. She was hospitalized at another hospital at post-natal 5 days due to skin rash and subsequently diagnosed with neonatal lupus, because her mother's autoimmune study showed positive results for antinuclear antibody (ANA), anti-Ro/SSA (Sjogren syndrome type A antigen), and anti-La/SSB (Sjogren syndrome type B antigen). On admission, the complete blood cell counts (CBC) revealed a hemoglobin level of 5.6 g/dL, a white blood cell count of 1,100/μL (with an absolute neutrophil count of 110/μL), and a platelet count of 71,000/μL. In terms of inflammatory biomarkers, the C-reactive protein level was elevated at 9.17 mg/dL (normal range <0.5 mg/dL), procalcitonin was measured at 1.88 ng/mL, and ferritin was significantly elevated at 1,507 ng/mL. The disseminated intravascular coagulation (DIC) profiles indicated severe abnormalities, including a prothrombin time INR exceeding 5, an aPTT over 120 seconds, antithrombin III levels at 64.2%, and elevated fibrinogen levels of 401 mg/dL. In terms of blood chemistry, the results showed elevated levels of aspartate aminotransferase at 128 U/L, alanine aminotransferase at 89 U/L, and lactic dehydrogenase at 285 U/L. Electrocardiography showed sinus tachycardia. She was administered packed red cell transfusion, fresh frozen plasma, and anti-thrombin III. We began empirical antibiotics due to neonatal fever with DIC profiles and high dose methylprednisolone (mPD, 30 mg/kg/day) therapy for MAS. Her body temperature was normalized at 3 days later after mPD treatment. We then switched to oral dexamethasone (1.5 mg/kg/day). We obtained results of decreased natural killer cell activity (about 8.8% of normal activity in effector versus target ratio 1:20) and high-level of soluble interleukin (IL)-2 (5,187 U/mL, normal level: 158~623 U/mL). Her autoimmune study showed ANA (1:320, Speckled), anti-Ro/SSA (+3), and anti-La/SSB (+3). Therefore, the diagnosis of MAS in neonatal lupus was established according to MAS criteria [5,10]. The baby with normal vital sign was showed good activity and feeding, and laboratory data including CBC and blood chemistry recovered on the 7th hospital day (HD) except a high level of

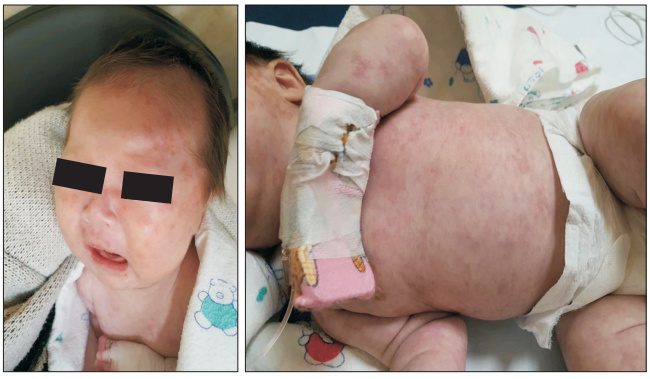
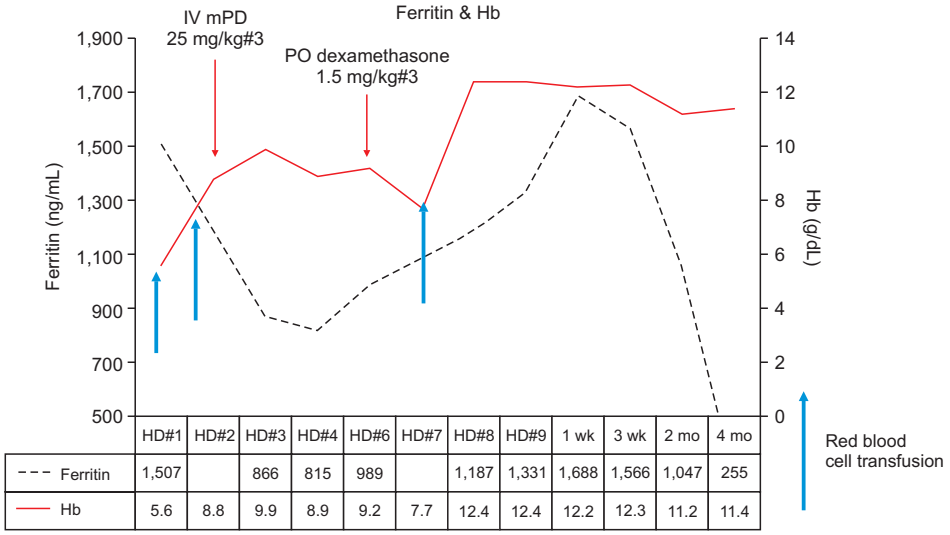


**Figure 1.** Erythema marginatum like skin rash on whole body of the patient on admission.




| | HD#1 | HD#2 | HD#3 | HD#4 | HD#6 | HD#7 | HD#8 | HD#9 | 1 wk | 3 wk | 2 mo | 4 mo |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Ferritin | 1,507 | | 866 | 815 | 989 | | 1,187 | 1,331 | 1,688 | 1,566 | 1,047 | 255 |
| Hb | 5.6 | 8.8 | 9.9 | 8.9 | 9.2 | 7.7 | 12.4 | 12.4 | 12.2 | 12.3 | 11.2 | 11.4 |

**Figure 2.** Changes in ferritin and hemoglobin (Hb) of the patient after hospitalization. At the beginning of treatment, the ferritin level was decreased, which had rose again after the red blood cell transfusion. It recovered to the normal range over time. IV mPD: intravenous methylprednisolone, PO: per oral, HD: hospital day.

ferritin (Figure 2). She was discharged with oral dexamethasone on the 10th HD, and steroid was stopped according to tapering schedule 1 month later. Her mother without any autoimmune manifestations showed ANA (1:1,280, Speckled), anti-Ro/SSA (+), and anti-Lo/SSB (+). Nine months later, baby's growth and development along with laboratory data were within normal ranges. Also, mother did not exhibit any autoimmune manifestations, despite the presence of auto-antibodies. The patient's laboratory data during clinical course are shown in Table 1.

## DISCUSSION

In this case, the patient showed fever with erythema marginatum like skin rash. She developed fever with pancytopenia and skin rash although she was diagnosed with neonatal lupus at another hospital several days ago [1,2]. At that time, her mother's auto-antibodies were identified although the mother did not have any autoimmune features. The delivery and mother's history were not specific. Pediatricians commonly consider neonatal sepsis for febrile infants because neonatal fever is a very serious clinical presentation [11]. However, this baby was diagnosed with neonatal lupus at another hospital on the basis of auto-antibodies. This baby was initially not compatible with hemophagocytic lymphohistiocytosis (HLH) diagnostic criteria [6]. At admission, we identified fever, erythema marginatum like skin rash, pancytopenia, high level of ferritin, and splenomegaly. These findings represented as early prediction for proposed MAS in systemic juvenile idiopathic arthritis and preliminary diagnostic guideline [10,12]. Finally, the baby was diagnosed with secondary HLH after we obtained results of high soluble IL-2 and decreased natural killer cell activity [6,10]. Skin lesions are not part of the diagnostic criteria for HLH or MAS. However, skin eruption can be a significant clinical manifestation in HLH or MAS. While we did not conduct a skin biopsy, it is worth noting that in cases of HLH/MAS, a skin biopsy can be clinically relevant, as it may reveal lymphohistiocytic infiltrates in the dermis without any epidermal abnormalities [7]. Therefore, opting for a skin biopsy rather than bone marrow examination can confirm the diagnosis of MAS in neonatal lupus. MAS is a form of secondary HLH that can be triggered by diseases such as infections or rheumatic diseases. In our case, she had been previously diagnosed with neonatal lupus at another hospital, which could be diagnosed as a manifestation of MAS, although clinical findings were compatible with HLH.

In our case, fever and high ferritin with pancytopenia were initial clinical findings, similar to other reported MAS in neonatal lupus [7-9]. Thrombocytopenia with high levels of ferritin and soluble IL-2 are common features in neonatal lupus with MAS. Neonatal lupus with MAS also shows increased levels of aspartate transferase or alanine transferase [7]. However, the level of soluble IL-2 is difficult to confirm as initial clinical manifestations [5,6]. Therefore, preliminary guideline for MAS in juvenile systemic lupus erythematosus is very useful in clinical fields for all rheumatic disorders [10].

In our case, a primiparous healthy mother without any autoimmune features was found to have auto-antibodies including ANA, compatible with the infant's blood. However, the baby was diagnosed with neonatal lupus by auto-antibodies, which were compatible with the mother's results. Mother with auto-antibodies did not manifest any clinical features of autoimmune disease until the follow-up period. The underlying mechanism behind the production of auto-antibodies during pregnancy remains uncertain. However, there is some immunological understanding for the development of autoimmune response

**Table 1.** The patient's laboratory data according to clinical course

| | HD1 | IV methylprednisolone (30 mg/kg/day) | | | Oral dexamethasone (1.5 mg/kg/day) | | |
|---|---|---|---|---|---|---|---|
| | | HD2 | HD3 | HD4 | HD6 | HD8 | HD10 |
| WBC (/μL) | 1,100 | 1,290 | 2,690 | 1,210 | 6,500 | 9,420 | 12,300 |
| ANC (/μL) | 10 | 30 | 30 | 20 | 130 | 190 | 5,700 |
| PLT (x10$^6$/μL) | 71 | 105 | 99 | 116 | 240 | 277 | 314 |
| CRP (mg/dL) | 9.17 | 16.18 | 13.41 | 10.4 | 4.93 | 0.49 | 0.62 |
| AST (U/L) | 128 | 43 | 48 | 33 | 24 | 17 | 18 |
| ALT (U/L) | 89 | 51 | 39 | 32 | 22 | 14 | 14 |

IV: intravenous, HD: hospital day, WBC: white blood cell counts, ANC: absolute neutrophil counts, PLT: platelet counts, CRP: C-reactive protein, AST: aspartate aminotransferase, ALT: alanine aminotransferase.

during pregnancy. Pregnancy can trigger immune responses because a semi-allograft exists in a pregnant woman with fetus carrying paternal gene [13]. Immune responses dominantly skew towards the Th2 type in order to maintain tolerance to the fetus with paternal antigen. Th2 type immune responses can induce an increase of IL-4 production, rescue auto-reactive B cell from apoptosis, enhance their survival, activate auto-reactive B cells, and promote autoimmune reaction [13]. Microchimerism with fetal cells might be possible mechanisms for autoimmune development during pregnancy. Microchimerism can be developed during pregnancy after mother is exposed to fetal cells or tissues, which can induce autoimmune reactions [14].

MAS can be treated with steroid therapy as a monotherapy. In the present case, the baby received high dose mPD with oral dexamethasone following the HLH 2004 protocol [6] and recovered, although she required transfusion. Her ferritin level was high three weeks later, which might be related to three times red blood cell transfusions [15]. It normalized at 4 months. Relapsed cases show use of hydrocortisone and delayed diagnosis [7-9]. Hydrocortisone has lesser anti-inflammatory potency than other steroids [9]. Also, delayed diagnosis could progress to severe inflammation, although intravenous immunoglobulin and mPD were administered for MAS [8]. Therefore, optimal treatment time and strong anti-inflammatory therapy might be needed for improvement, especially for neonatal lupus with MAS [7,10]. In our case, the patient was well after a one-time therapy. These findings suggested that the MAS was due to neonatal lupus, not due to a genetic problem [6].

## SUMMARY

We report a case of neonatal lupus with MAS presented with fever and pancytopenia. The baby was born from a primiparous mother without any autoimmune manifestations. Thus, neonatal MAS should be considered when an infant presents fever with pancytopenia, although the baby is born from a healthy mother without any autoimmune findings.

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## CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

## AUTHOR CONTRIBUTIONS

J.Y.Y.: description of this study, drafting the manuscript, T.W.K.: drafting the manuscript, Y.J.K.: patient care and comment, H.M.K.: interpretation of data, revising the manuscript, I.H.Y.: interpretation of data, revising the manuscript, J.W.R.: revising the manuscript, S.Y.L.: interpretation of data, revising the manuscript, D.C.J.: conception of and design of study, analysis and interpretation of data, drafting the manuscript critically for important intellectual content.

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