

A Term Infant of Neonatal Toxic Shock Syndrome-Like Exanthematous Disease Complicated with Hemophagocytic Syndrome

Akimune Kaga,^{1,2} Hiroshi Watanabe,¹ Hiroki Miyabayashi,¹ Takaya Metoki,¹ Setsuko Kitaoka¹ and Satoru Kumaki¹

¹Department of Pediatrics, National Hospital Organization Sendai Medical Center, Sendai, Miyagi, Japan

²Division of Neonatology, Tohoku Kosai Hospital, Sendai, Miyagi, Japan

Neonatal toxic shock syndrome-like exanthematous disease (NTED) is a newly recognized neonatal infectious disease, caused by the superantigen toxic shock syndrome toxin-1 (TSST-1). TSST-1 is mainly produced by methicillin-resistant *Staphylococcus aureus*, and the immune responses to TSST-1 are known to cause toxic shock syndrome, a life-threatening infectious disease. The clinical symptoms of NTED are skin rash, fever, and thrombocytopenia, but severe thrombocytopenia is rare in term infants with NTED. Although the cause of NTED is the same as that of toxic shock syndrome, the clinical symptoms of NTED are milder than toxic shock syndrome. The mild phenotype of NTED has been explained by selectively elevated serum levels of anti-inflammatory cytokine interleukin (IL)-10, which suppress immune responses to TSST-1. In the present study, we report a term female infant of NTED complicated with hemophagocytic syndrome (HPS). HPS is characterized by systemic inflammation and hemophagocytosis, caused by uncontrolled activation of T cells and macrophages. The serum IL-10 level of the patient at 4 days of age was relatively low (67 pg/mL) for NTED but still higher than normal controls (< 2.0 pg/mL). The patient also showed severe thrombocytopenia. We speculate that the serum IL-10 level of the patient was enough to suppress immune responses to TSST-1, thereby resulting in NTED, but not enough to suppress the onset of HPS. This is the first reported case of NTED complicated with HPS. If a physician encounters an NTED patient with severe cytopenia, microscopic examination of peripheral blood smear should be carried out to exclude HPS.

Keywords: hemophagocytic syndrome; interleukin-10; methicillin-resistant staphylococcus aureus; thrombocytopenia; toxic shock syndrome-like exanthematous disease

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Introduction

Neonatal toxic shock syndrome-like exanthematous disease (NTED) is a newly recognized neonatal infectious disease caused by the superantigen toxic shock syndrome toxin-1 (TSST-1), which is mainly produced by methicillin-resistant *Staphylococcus aureus* (MRSA) (Takahashi et al. 1998; 2009b; 2013). Immune responses to TSST-1 are known to be a cause of toxic shock syndrome (TSS), which is a life-threatening infectious disease. Although TSS and NTED appear to have the same cause, most term infants with NTED exhibit mild clinical symptoms, and severe thrombocytopenia is rare (Takahashi et al. 2009b). The mild phenotype of NTED is in part due to the increased serum levels of anti-inflammatory cytokine interleukin (IL)-10 (Takahashi et al. 2009a).

In the present study, we report a term infant of NTED

complicated with hemophagocytic syndrome (HPS). HPS is a condition characterized by systemic inflammation and hemophagocytosis caused by uncontrolled T cells and macrophages. The patient's serum IL-10 level was higher than normal controls but relatively low for NTED. To the best of our knowledge, this is the first reported case of NTED complicated with HPS.

Case Presentation

The patient was a Japanese female born at 38 weeks and 0 day of gestation with a birth weight of 3,252 g. Her mother was 34 years old with a history of Gravida 2, Para 2. At 35 weeks of pregnancy, the mother was diagnosis with MRSA vaginosis. The patient was born after an uncomplicated delivery with Apgar scores of 9 at 1 min and 10 at 5 min. She was transferred to our hospital at 2 days of age because of fever. On the following day, diffuse macular

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Correspondence: Akimune Kaga, Division of Neonatology, Tohoku Kosai Hospital, 2-3-11 Kokubun-cho, Aoba-ku, Sendai, Miyagi 980-0803, Japan.

e-mail: kagakimune@yahoo.co.jp

erythema appeared on her trunk (Fig. 1). A complete blood count showed leukocytes $14,000/\text{mm}^3$ with 68.0% neutrophils, 5.0% lymphocytes, 11.0% monocytes and 0.0% atypical lymphocytes, red blood cells $5.31 \times 10^6/\text{mm}^3$, hemoglobin 18.1 g/dL, hematocrit 51.0% and platelets $69,000/\text{mm}^3$. The patient was diagnosed with NTED.

At 4 days of age, the patient was febrile (38.2°C), but splenomegaly was not observed. The blood cell count showed leukocytes $11,500/\text{mm}^3$ with 35.0% neutrophils, 31.0% lymphocytes, 4.0% monocytes and 16.0% atypical lymphocytes, red blood cells $4.47 \times 10^6/\text{mm}^3$, hemoglobin 15.1 g/dL, hematocrit 42.1%, platelets $27,000/\text{mm}^3$, lactate dehydrogenase 667 international unit (IU)/L (control range:



Fig. 1. Macular erythema on the patient's trunk. On 2 days of age, diffuse macular erythema was present on the patient's trunk.

120-245 IU/L), creatine kinase 151 IU/L, aspartate aminotransferase 33 IU/L, alanine aminotransferase 23 IU/L, ferritin 624.5 ng/mL (control range: 5-282 ng/mL), soluble interleukin-2 receptor (sIL-2R) 5,048 U/mL (control range: 190-650 U/mL), C-reactive protein 0.8 mg/dL, IL-10 67 pg/mL (control: less than 2.0 pg/mL) and IL-6 5.9 pg/mL (control: less than 4.0 pg/mL) (Takahashi et al. 2009a). The peripheral blood smears revealed macrophages with phagocytized neutrophils (Fig. 2a) and foamy macrophages containing cell fragments (Fig. 2b). Under a diagnosis of HPS, the patient was treated with intravenous gamma globulin, platelet transfusion and vancomycin. With the therapy, the platelet count increased to $100,100/\text{mm}^3$. MRSA was the only bacteria isolated from her skin. Viral culture of her throat was negative. Serum immunoglobulin (Ig) M antibodies against herpes simplex, cytomegalovirus, and rubella virus were all negative. Polymerase chain reaction (PCR) analyses for herpes simplex virus 1/2, Epstein-Barr virus, varicella-zoster virus, cytomegalovirus, human herpes virus 6A/B and human herpes virus 7 were all negative.

At 16 days of age, the patient was discharged, with platelets $560,100/\text{mm}^3$ and no further evidence of thrombocytopenia.

Written informed consent was obtained from the patient's legal guardian for publication of this case report and any accompanying images.

Discussion

Since 1992, many neonates in neonatal intensive care units in Japan have been developing fever, systemic exanthema, and thrombocytopenia. In 1998, Takahashi et al. (1998) named this neonatal disease NTED. The clinical diagnostic criteria of NTED are skin rash (generalized macular erythema), positive for one or more of three

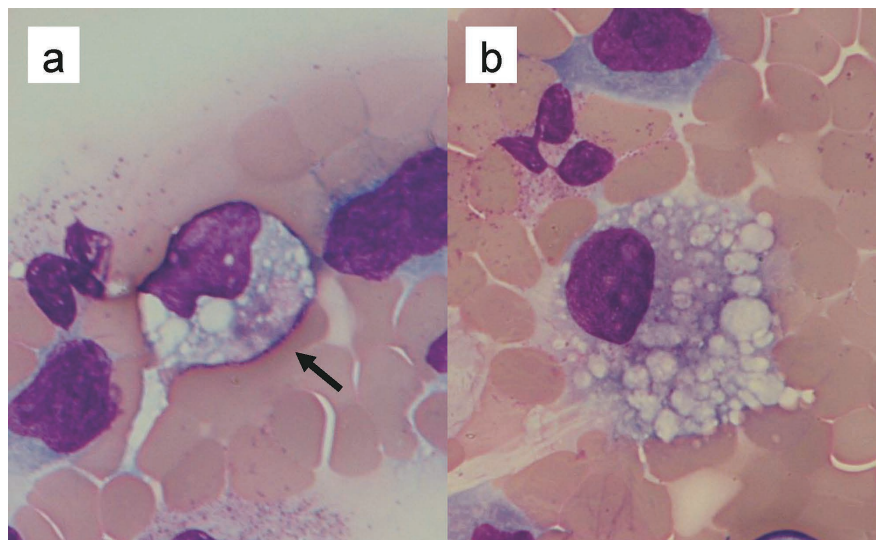


Fig. 2. The peripheral blood smears. Microscopic examination of the peripheral blood smears revealed (a) a macrophage with a phagocytized neutrophil (black arrow, May-Grunwald Giemsa, $\times 1,000$) and (b) a foamy macrophage containing cell fragments (May-Grunwald Giemsa, $\times 400$).

clinical signs (fever; thrombocytopenia; positive but lower value of C-reactive protein), and exclusion of other known diseases (Takahashi et al. 1998, 2013). In addition, a previous study demonstrated that the number of T cells positive for T-cell-receptor $V\beta 2$, reactive to TSST-1, was increased in NTED patients (Takahashi et al. 1998). In our case, the clinical features of the patient fulfilled the diagnostic criteria of NTED although the $V\beta 2$ positive T cells were not evaluated. As mentioned in the Case Presentation, results of the viral culture, serum IgM antibodies, and PCR of herpes viruses were all negative. Taken together, the patient was diagnosed with NTED.

Takahashi et al. (2009a) reported that the serum levels of anti-inflammatory cytokine IL-10 were selectively elevated in NTED infants (mean concentration of IL-10 was more than 1,200 pg/mL; control: less than 2.0 pg/mL), although they did not compare the severity of clinical symptoms with IL-10 values at the individual level. They speculated that immune responses of term infants to the superantigen TSST-1 were actively suppressed by IL-10. In our patient, serum level of IL-10 at 4 days of age was relatively low (67 pg/mL) for an NTED patient but still higher than normal controls and some NTED patients who were described in a previous report (Takahashi et al. 2009a), in which the values of IL-10 in 4 out of 13 NTED patients were less than 40 pg/mL. Thus, it is possible that immune responses to TSST-1 were suppressed by the relatively high level of serum IL-10, resulting in NTED instead of TSS. In addition, antibodies against TSST-1 play a crucial role in the pathogenesis of NTED. Previous studies have demonstrated that the occurrence of NTED is related to the maternally transferred anti-TSST-1 IgG antibody titer in patients because the antibodies were found to neutralize the superantigenic activity of TSST-1, and the higher amounts of anti-TSST-1 IgG antibodies are effective in protecting against the development of NTED (Takahashi et al. 2000, 2013). Therefore, the mild clinical phenotype of our term NTED patient could be due to the maternally transferred antibodies against TSST-1 as well, because the patient's mother was suffering from MRSA vaginosis at 35 weeks of pregnancy.

HPS is a condition characterized by uncontrolled activation of T cells and macrophages. The patient was diagnosed with HPS because she had fever, thrombocytopenia, hemophagocytosis on the peripheral blood smear, and higher titers of serum ferritin and sIL-2R. We treated the patient with intravenous gamma globulin according to previous reports (Aygun et al. 2003; Yoshiyama et al. 2008) prior to fulfilling the HLH-2004 criteria (Imashuku et al. 2000; Henter et al. 2007; Suzuki et al. 2009) because delayed diagnosis may result in fatal condition in neonates. Platelet transfusion and vancomycin were used for prevention of neonatal intracranial haemorrhage and for a possible MRSA sepsis, respectively. A previous study indicated that increased levels of IFN- γ and IL-10 were specific to HPS (Xu et al. 2012). However,

serum IL-10 level of our patient at 4 days of age was relatively low (67 pg/mL) for an NTED patient. It is interesting to note that about half of the patients with HPS were reported to have relatively lower values of IL-10 (less than 100 pg/ml) (My et al. 2010). Because IL-10 is an anti-inflammatory cytokine, it is possible that the relatively low level of IL-10 was not enough to suppress development of HPS in our patient as demonstrated by the marked elevation of sIL-2R and the mild elevation of ferritin and LDH. These results are in part consistent with a previous study, which showed that high concentrations of IL-10 were protective against the development of hemophagocytosis in a mouse model (Behrens et al. 2011). Although we did not evaluate cytokines other than IL-10 and IL-6, analyses of serum cytokine profiles would provide insight into the state of immunological pathophysiology in patients with neonatal infectious diseases including HPS.

To the best of our knowledge, this is the first reported case of NTED complicated with HPS. It is possible that HPS has been underestimated in previously reported cases because hemophagocytosis on peripheral blood smear is rare and might be missed in many cases.

In conclusion, we report a term infant of NTED complicated with HPS. If a physician encounters an NTED patient with severe cytopenia, microscopic examination of peripheral blood smear should be carried out to exclude HPS.

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Conflict of Interest

The authors declare no conflict of interest.

References

- Aygun, C., Tekinalp, G. & Gurgey, A. (2003) Infection-associated hemophagocytic syndrome due to *Pseudomonas aeruginosa* in preterm infants. *J. Pediatr. Hematol. Oncol.*, **25**, 665-667.
- Behrens, E.M., Canna, S.W., Slade, K., Rao, S., Kreiger, P.A., Paessler, M., Kambayashi, T. & Koretzky, G.A. (2011) Repeated TLR9 stimulation results in macrophage activation syndrome-like disease in mice. *J. Clin. Invest.*, **121**, 2264-2277.
- Henter, J.I., Horne, A., Aricó, M., Egeler, R.M., Filipovich, A.H., Imashuku, S., Ladisch, S., McClain, K., Webb, D., Winiarski, J. & Janka, G. (2007) HLH-2004: diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. *Pediatr. Blood Cancer*, **48**, 124-131.
- Imashuku, S., Tanaka, T., Togari, H., Teramura, T., An, B., Okubo, H., Itoh, H. & Hibi, S. (2000) Detection of hemophagocytes in blood smears in fatal disseminated neonatal herpes simplex virus infection. *Int. J. Pediatr. Hematol. Oncol.*, **6**, 425-428.
- My, L.T., Lien, B., Hsieh, W.C., Imamura, T., Anh, T.N., Anh, P.N., Hung, N.T., Tseng, F.C., Chi, C.Y., Dao, N.T., Le, D.T., Thinh, Q., Tung, T.T., Imashuku, S., Thuong, T.C., & Su, I.J. (2010) Comprehensive analyses and characterization of haemophagocytic lymphohistiocytosis in Vietnamese children.

- Br. J. Haematol.*, **148**, 301-310.
- Suzuki, N., Morimoto, A., Ohga, S., Kudo, K., Ishida, Y. & Ishii, E.; HLH/LCH Committee of the Japanese Society of Pediatric Hematology (2009) Characteristics of hemophagocytic lymphohistiocytosis in neonates: a nationwide survey in Japan. *J. Pediatr.*, **155**, 235-238.
- Takahashi, N., Hasegawa, H., Komiyama, M., Ohki, T., Yada, Y., Koike, Y., Kawamata, R., Honma, Y. & Momoi, M. (2009a) Selective excretion of anti-inflammatory cytokine Interleukin-10 in a superantigen-inducing neonatal infectious disease. *Cytokine*, **45**, 39-43.
- Takahashi, N., Imanishi, K. & Uchiyama, T. (2013) Overall pictures of an emerging neonatal infectious disease induced by superantigenic exotoxin mainly produced by methicillin-resistant *Staphylococcus aureus*. *Microbiol. Immunol.*, **57**, 737-745.
- Takahashi, N., Kato, H., Imanishi, K., Miwa, K., Yamanami, S., Nishida, H. & Uchiyama, T. (2000) Immunopathophysiological aspects of an emerging neonatal infectious disease induced by a bacterial superantigen. *J. Clin. Invest.*, **106**, 1409-1415.
- Takahashi, N., Nishida, H., Kato, H., Imanishi, K., Sakata, Y. & Uchiyama, T. (1998) Exanthematous disease induced by toxic shock syndrome toxin 1 in the early neonatal period. *Lancet*, **351**, 1614-1619.
- Takahashi, N., Uehara, R., Nishida, H., Sakuma, I., Yamasaki, C., Takahashi, K., Honma, Y., Momoi, M.Y. & Uchiyama, T. (2009b) Clinical features of neonatal toxic shock syndrome like exanthematous disease emerging in Japan. *J. Infect.*, **59**, 194-200.
- Xu, X.J., Tang, Y.M., Song, H., Yang, S.L., Xu, W.Q., Zhao, N., Shi, S.W., Shen, H.P., Mao, J.Q., Zhang, L.Y. & Pan, B.H. (2012) Diagnostic accuracy of a specific cytokine pattern in hemophagocytic lymphohistiocytosis in children. *J. Pediatr.*, **160**, 984-990.
- Yoshiyama, M., Kounami, S., Nakayama, K., Aoyagi, N. & Yoshikawa, N. (2008) Clinical assessment of Mycoplasma pneumoniae-associated hemophagocytic lymphohistiocytosis. *Pediatr. Int.*, **50**, 432-435.
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