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Clinical features of neonatal toxic shock syndrome-like exanthematous disease emerging in Japan

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Summary *Objectives:* An epidemic of neonatal toxic shock syndrome (TSS)-like exanthematous disease (NTED) has emerged in Japan. NTED is caused by TSS toxin-1 produced predominantly by methicillin-resistant *Staphylococcus aureus* (MRSA). Using a large-scale investigation, the present study aimed to elucidate the overall clinical picture of NTED in Japan.
Methods: We performed nationwide surveys regarding NTED in Japanese neonatal intensive care units (NICUs) in 2000, 2002 and 2005, and summarized the clinical findings of 540 patients. We also performed a case-control study to identify the relationship between patients' clinical findings and NTED.
Results: The frequency of NTED in Japanese NICUs in 2000 was 52.2% and declined to 28.3% in 2005. The number of NTED patients in 2000 was 240 and decreased to 139 in 2005. In 2005, the isolation of methicillin-sensitive *S. aureus* (MSSA) increased to 20.0% in term patients. Although no term infants suffered shock or death, preterm patients sometimes developed severe symptoms.
Conclusions: The number of NTED patients decreased over the 5-year period from 2000 to 2005, even though more than 100 patients contracted NTED in Japanese NICUs in 2005. MSSA as well as MRSA can cause NTED, and NTED is more severe in preterm infants than in term infants.

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Introduction

A new neonatal disease first appeared in the early 1990s in Japan[1,2] that was characterized by exanthema, fever and thrombocytopenia. Although it resembled many viral infections, selective expansion of V$\beta2^+$ T cells in the peripheral blood was noted during the acute phase.[3] Selective expansion of T cells having a specific Vβ repertoire indicates that patients have been exposed to a superantigen. We confirmed that the expansion of the V$\beta2^+$ T cells was polyclonal induced by a superantigen by investigating DNA sequences.[3] Further microbiological investigations clarified that the disease was caused by strains of toxic shock syndrome (TSS) toxin-1-producing *Staphylococcus aureus*, predominantly methicillin-resistant *S. aureus* (MRSA).[4,5]

TSS is a life-threatening infectious disease in children and adults caused by exotoxins including TSST-1 produced by *S. aureus* or *Streptococcus pyogenes*.[6–9] Although the new neonatal disease and TSS appear to have the same cause, clinical symptoms of the new disease do not match the clinical criteria for TSS. We concluded that this new neonatal disease was a special form of TSS, and designated it neonatal TSS-like exanthematous disease (NTED).[3,10]

Since our early reports, the proportion of NICUs with NTED patients has increased. According to the epidemiological data from 1995 to 1998, the number of patients with NTED in Japan rapidly increased from 25.7% in 1995 to 85.6% in 1999.[11] Since the majority of NTED cases were secondary to hospital-acquired MRSA infection, NTED has become a serious social issue in Japanese neonatal medicine. Recently, a case suspected to be NTED was reported in France, suggesting that the disease has spread to Europe.[12]

Clinical features of NTED appear different from those of TSS, as observed in a limited number of infants with NTED.[3,4] Clinical symptoms spontaneously regress in a few days from the onset in most term infants with NTED, although symptoms are severe in some preterm patients.[3,4] This disease resembles many viral infections in newborn infants. Therefore, it became important to investigate the clinical features of NTED on a larger scale. We retrospectively summarized NTED patient data from major Japanese NICUs using nationwide surveys in 2000, 2002 and 2005. We also performed a case-control study in order to identify the relationship between the clinical findings and the disease in patients admitted to a university hospital.

Materials and methods

Nationwide surveys of patients with NTED in major NICUs

We conducted nationwide surveys regarding patients with NTED in Japanese neonatal intensive care units (NICUs) in collaboration with the Japan Association of Neonatologists. The association comprises approximately 60% of the major NICUs in Japan. We sent questionnaires to NICUs where members of the association were working in 2001, 2003 and 2006. We asked for the annual number of patients with NTED and the clinical data of patients admitted to the various NICUs in 2000, 2002 and 2005. We also investigated the NTED patients' microbiological data in 2000 and 2005 in order to determine whether MRSA or methicillin-sensitive *S. aureus* (MSSA) was isolated from any patient site.

All patients were diagnosed according to clinical criteria,[3] including the combination of exanthema and at least one of the following: (1) thrombocytopenia (platelet count $<150 \times 10^3/\mu l$); (2) low-positive levels of C-reactive protein (CRP) (10–50 mg/l); or (3) fever ($>38.0\,^{\circ}C$). The exanthema is diffuse with generalized macular erythema; a typical exanthema in a patient with NTED is shown in Fig. 1. The clinical criteria also require exclusion of known disease processes. We summarized data from 540 cumulative patients.

Comparison of clinical features of patients with NTED and control patients (case-control study)

In order to identify the true relationship between the clinical findings and NTED, we retrospectively conducted a case-control study. Fifty-four patients with NTED were observed at Jichi Medical University Hospital (JMUH) in 2000, 2002 and 2005. Data from these patients had already been included in our nationwide surveys. For the case-control study controls, we extracted patients without NTED admitted to the NICU of JMUH in 2000, 2002 or 2005 randomly chosen from the admission database of JMUH. Patients with congenital anomalies and those who died within 5 days of life were excluded from the study. We reviewed clinical charts of 54 patients with NTED and 217 patients without NTED.

Statistical analysis

Fisher's exact test was used to compare the prevalence of complications, and a non-paired Student's *t*-test was used to compare laboratory data. Fisher's exact test was also used to compare the prevalence of clinical findings

Figure 1 Typical exanthema of patients with NTED. The exanthema, a diffuse macular erythema, spreads from the face, trunk, and extremities to include the palms and soles. The rash generally lasts 2–4 days. Unlike in patients with TSS, desquamation of the fingers is not observed in most patients with NTED.