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Case Report

Toxic Shock Syndrome Toxin-1-producing *Staphylococcus aureus* Bacteremia and Exanthematous and Purpuric Disease with Leukocytoclastic Vasculitis in an Infant

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Staphylococcus aureus exotoxin toxic shock syndrome toxin-1 (TSST-1) can cause a wide spectrum of immunopathological conditions, from toxic shock syndrome (TSS), a life-threatening illness, to neonatal TSS-like exanthematous disease (NTED), a self-limited mild disease. Leukocytoclastic vasculitis, which develops in the skin, is another immunopathological condition that is commonly observed in patients with IgA vasculitis during childhood. We report the case of an infant with an NTED-like exanthematous rash and IgA vasculitis-like purpuric skin lesions that were histopathologically diagnosed as leukocytoclastic vasculitis. A blood culture yielded methicillin-sensitive *Staphylococcus aureus* producing TSST-1, suggesting an etiological role in the aforementioned skin lesions. (99 words)

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Introduction

A *Staphylococcus aureus* exotoxin toxic shock syndrome toxin-1 (TSST-1) activates the immune system as a superantigen and causes immunopathological conditions such as toxic shock syndrome (TSS) and neonatal TSS-like exanthematous disease (NTED)[1]. Although the underlying mechanism of TSS and NTED is fundamentally the same, the former is much more serious than the latter. In addition, TSST-1-related pathological conditions that occupy an intermediate position between TSS and NTED (in terms of severity) have been reported in infants and young children[2-4], suggesting that the host immune status greatly contributes to the severity of the TSST-1-mediated pathogenesis[5].

Leukocytoclastic vasculitis, which is histopathologically characterized by evidence of vessel disruption by neutrophils with fibrinoid necrosis, is associated with a wide spectrum of systemic inflammatory conditions, malignancies, infections, and drug hypersensitivities, but most commonly with IgA vasculitis (formally Henoch-Schönlein purpura [HSP]) during childhood[6, 7].

Case Report

We herein describe the case of an infant with bacteremia due to *Staphylococcus aureus* producing TSST-1, who developed exanthematous disease along with histopathologically-diagnosed leukocytoclastic vasculitis, a clinical condition that seemed to be related to TSST-1.

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The patient was an 11-month-old boy. He was delivered uneventfully at full term and all of his developmental milestones had been appropriate for his age. He had an allergy to egg and atopic dermatitis, which occasionally required topical steroid treatment. He presented with skin rash on his face and limbs and general swelling of the right arm and left leg. The condition did not appear to be toxic. On admission, his temperature was 38.5° C, his blood pressure was 133/86 mmHg, his pulse rate was 160/min, and his respiratory rate was 40/min. He had maculopapular rash (diameter: <5 mm) on the cheeks, lower jaw, buttocks and extremities (not including the palms or plantar regions (Figure 1). He also had petechiae and purpura, some of which were palpable, on the buttocks and extremities. Overall swelling and tenderness were found on his right upper limb and left lower limb. A blood analysis revealed the following findings: WBC count, 12,100/ μ L (neutrophils, 75%; lymphocytes, 22%; eosinophils, 4%; and monocytes, 2%); hemoglobin, 12.3 g/dL; platelet count, 433,000/ μ L; CRP, 2.17 mg/dl; PT-INR, 1.00 (normal range: 0.53-1.26); APTT, 28 s (32.0-55.2); fibrinogen, 305 mg/dl (162-352); D-dimer, 17.1 μ g/ml (<1); FDP, 11.5 μ g/ml (<10); aspartate aminotransferase, 23 IU/L; and alanine aminotransferase, 12 IU/L. A blood culture yielded methicillin-sensitive *Staphylococcus aureus* (MSSA). A multiplex polymerase chain reaction for a panel of exotoxin genes revealed that the MSSA strain from the patient was positive for TSST-1, but negative for enterotoxin C, Panton-Valenline leucocidin and exofoliative toxin B. A biopsy specimen from a purpuric skin lesion in the patient's left thigh showed findings compatible with leukocytoclastic vasculitis (*i.e.*, strong inflammatory cell infiltration mainly composed of neutrophils around the blood vessels from the dermis to the subcutaneous tissue, subcutaneous bleeding and fibrinoid necrosis of the blood vessels).

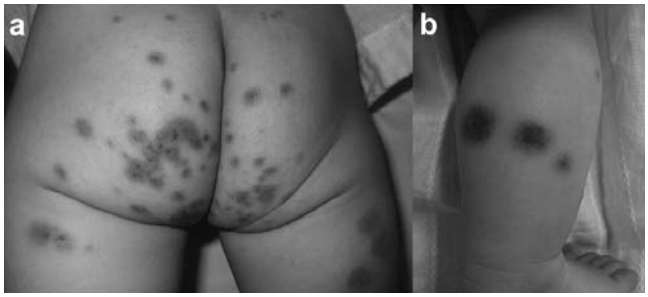

Figure 1
The patient's skin lesions
An exanthematous skin lesion on the buttock (a) and palpable purpura on the lower thigh (b) are shown.

Treatment with intravenous cefotaxime was initiated immediately after admission; this was replaced with cefazolin based on the blood culture results. On the third day of hospitalization, he became afebrile and his skin lesions and leg swelling showed rapid improvement. We stopped cefazolin therapy on the ninth day of hospitalization. He was discharged to return home on the eleventh day of hospitalization, after making a full recovery.

Discussion

While TSS is a life-threatening superantigen disease with multiorgan involvement, NTED is basically a mild self-limited illness. Since the neonatal immune system is immature, prone to immune tolerance, and biased toward Th2 immunity, the expansion of the TSST-1 reactive Vβ2+ T cell population in neonates with NTED is modest; this is followed by an anergic response. Even beyond the neonatal period, the TSST-1-induced immune responses appear to be weaker in infants and young children who have been reported to develop NTED-like illness or a relatively benign course of TSS [2-4], suggesting a wide clinical spectrum of TSST-1-induced disease due to differences in the host immune response that are highly influenced by age.

The skin lesions in the present case were characterized not only by exanthematous rash resembling that of NTED but also by palpable purpura resembling IgA vasculitis that was histologically confirmed as leukocytoclastic vasculitis. While the former is expected in mild forms of TSST-1 induced disease, the coexistence of the latter is interesting in that the previous studies have reported the isolation of Staphylococci from patients with HSP or leukocytoclastic vasculitis; however, none of these studies showed evidence of proved TSST-1 production [6-9]. Individuals with atopic dermatitis are believed to be at an increased risk of *Staphylococcus* bacteremia (10). The MSSA detected in a blood culture might have invaded via a part of the abrasion showing atopic dermatitis, although this is pure supposition, as we did not perform any investigations of other sites, including of the patient's skin, for bacterial colonization, and the patient's atopic dermatitis was well controlled.

Our study is associated with two major limitations. First, although we isolated TSST-1-producing *S. aureus*, we could not perform flow cytometry to demonstrate the expansion of Vβ2+ T cells in response to the superantigen. Second, a direct immunofluorescence analysis, which is necessary for the histopathological diagnosis of IgA vasculitis, was not carried out due to the very small size of the specimen that were able

to obtain. Nevertheless, the present case report is unique in several aspects: TSST-1-producing *S. aureus* was isolated from a blood culture; the patient developed both NTED-like exanthematous rash and IgA vasculitis-like purpuric skin lesions; and the IgA vasculitis-like purpuric skin lesions were histologically confirmed to be leukocytoclastic vasculitis. The accumulation of additional cases and further investigations is needed in order to clarify the etiological roles of bacterial superantigens in the immunopathogenesis of this type of skin lesion during childhood.

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Conflict of interest:

None.

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