Sweet's syndrome in a neonate with non-B54 types of human leukocyte antigen

Kentaro Omoya, Yasuhiro Naiki, Zenichiro Kato, Seiichiro Yoshioka, Yasushi Uchida, Toshiaki Taga, Yoshinori Aoki, Hideki Deguchi, Naomi Kondo

Gifu, Japan

Background: **Sweet's syndrome (acute febrile neutrophilic dermatosis) is characterized by fever, polymorphonuclear leukocytosis of blood, painful plaques on the limbs, face and neck, and histologically a dense dermal infiltration with mature neutrophils. Sweet's syndrome is often a complication of hematologic malignant disease or drug-induced sensitivity reactions and has a significant susceptibility correlated with certain human leukocyte antigen (HLA).**

Methods: **A 5-week-old Japanese girl with Sweet's syndrome confirmed by skin biopsy was successfully treated and HLA analysis was performed.**

Results: **The patient was one of the youngest patients reported with Sweet's syndrome, suggesting the importance of the genetic background. Although the HLA types of the patient did not have B54, which was reported as a significant susceptibility correlation, structural analysis of the patient's HLAs suggested a similar possible motif for the bound peptides.**

Conclusion: **Studies on the HLA bound peptides and HLA structural analysis for patients with Sweet's syndrome would be valuable for understanding the molecular mechanism of the pathogenesis.**

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Key words: **acute febrile neutrophilic dermatosis; human leukocyte antigen; infant; rectovaginal fistula; Sweet's syndrome**

Author Affiliations: Department of Pediatrics, Nagahama City Hospital, Nagahama, Shiga, Japan (Omoya K, Naiki Y, Yoshioka S, Uchida Y, Taga T); Department of Pediatrics, Graduate School of Medicine, Gifu University, Gifu, Japan (Omoya K, Kato Z, Kondo N); Center for Emerging Infectious Diseases (CEID), Gifu University, Japan (Kato Z, Kondo N); Center for Advanced Drug Research (CADR), Gifu University, Japan (Kato Z, Kondo N); Department of Dermatology, Nagahama City Hospital, Nagahama, Shiga, Japan (Aoki Y, Deguchi H)

Corresponding Author: Zenichiro Kato, MD, PhD, Department of Pediatrics, Graduate School of Medicine, Gifu University, Yanagido 1-1, Gifu 501-1194, Japan (Tel: +81 (58) 230 6386; Fax: +81 (58) 230 6387; Email: zen-k@gifu-u.ac.jp)

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Case report

Introduction

Sweet's syndrome (SS) (acute febrile neutrophilic dermatosis) is characterized by four features: fever, polymorphonuclear leukocytosis of blood, painful plaques on the limbs, face and neck and histologically a dense dermal infiltration with mature neutrophils.[1,2] SS is often a complication of hematologic malignant disease or drug-induced sensitivity reactions and has a significant susceptibility correlated with certain human leukocyte antigens (HLA).[3,4] We describe here a case of a 5-week-old Japanese girl who suffered from SS with rectovaginal fistula, one of the youngest SS patients reported, suggesting the importance of HLA analysis in infant cases.

Case report

A 5-week-old Japanese girl, born to unrelated parents after a full-term, uneventful pregnancy, had rash with a high grade of fever for 3 days. On admission, her body temperature was 38.4ºC. The rash on her cheeks, trunk and extremities was unusual eruption that was multiple, a few millimeters to several centimeters in diameter, firm, round to irregularly shaped papules and plaques with central umbilication and hypopigmentation. Some of her skin lesions had dark bulbous centers (Fig. 1A-C).

White blood cell count was 29 500/mm^3, hemoglobin level 12.4 g/dL, hematocrit 35.5%, and platelet count 349 000/mm^3. C-reactive protein was 2.2 mg/dL, while other laboratory test results including serum immunoglobulin concentrations were normal. The patient was given intravenous ampicillin for 3 days and then flomoxef sodium for 3 days, but her fever and skin lesions did not improve. Bacterial cultures from her

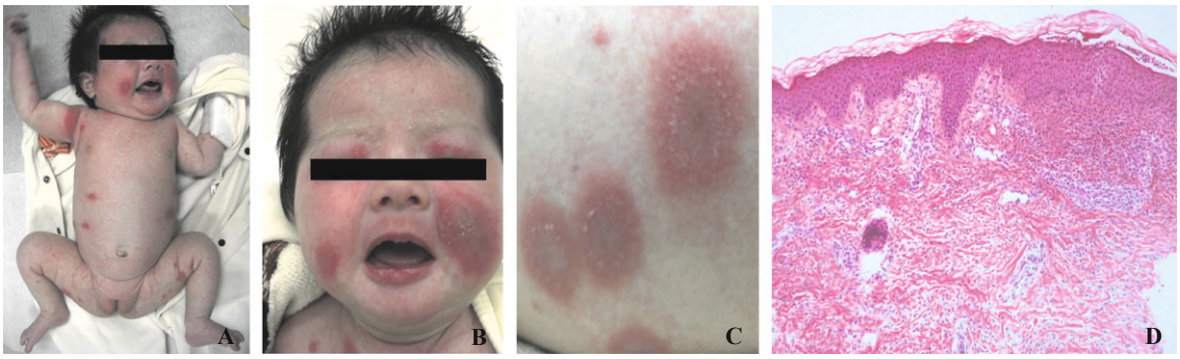

Fig. 1. Skin eruption of the infant. Multiple round erythematous papules and plaques with central crusted erosions and hypopigmentation. **A:** general view; **B & C:** magnification of the face or trunk; **D:** Skin biopsy revealing a dense band-like inflammatory infiltrate composed predominantly of neutrophils with occasional macrophages, lymphocytes, and eosinophils associated with dermal edema and predominantly involving the upper dermis (hematoxylin-eosin stain, original magnification × 100).

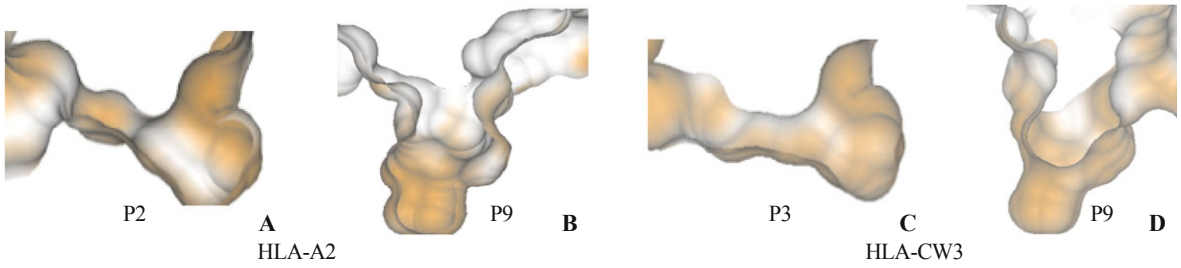

Fig. 2. Peptide binding anchor pockets in the HLAs. **A & B:** P2 or P9 pocket of HLA-A2; **C & D:** P3 or P9 pocket of HLA-CW3. P2 of HLA-A2 or P3 of HLA-CW3 is shallow but hydrophobic, while P9 of HLA-A2 or -CW3 is deep and highly hydrophobic. The molecular surface is calculated and drawn using MOE (CCG, Inc, Canada). The hydrophobicity of the molecular surface is colored in brown.

pharyngeal swab, blood, stool, urine and cerebrospinal fluid were negative.

A skin biopsy on the third hospital day revealed sheet-like infiltration of neutrophils and lymphocytes in dermis without vasculitis (Fig. 1D). The diagnosis of SS was based on the clinical and histological findings.[1,2] After dexamethason 2 mg/kg was administered on the fifth hospital day, the body temperature fell under 38ºC and the skin lesion resolved completely. The amount of dexamethason was tapered gradually and was terminated on the 14th hospital day without any reactivation of SS. Hematologic malignancy was ruled out by histological examination of bone marrow aspiration and peripheral blood specimen. On the 6th hospital day her stool was excreted through the vagina and rectovaginal fistula was revealed by urological examination. The HLA type of this patient was confirmed as A2, A31, B48, B61, and Cw3.

Discussion

Generally, SS has been classified by the associations as classic/idiopathic, parainflammatory, paraneoplastic, and pregnancy associated.[1,2] Infection has been noticed as a trigger of an autoreactive response possibly through a molecular mimicry mechanism of its antigens to self-antigens.[3,4] In this patient, infection due to her rectovaginal fistula could be a trigger of SS suggesting a parainflammatory associated type, as has been reported in SS (Table).[5-16] Neonatal cases should be recognized as the possible examples with a much greater contribution of their genetic background compared to the adult patients (Table).[5-16]

A significant correlation with HLA has been confirmed especially in adult Japanese patients, but HLA studies of infantile SS have not been reported yet.[3,4] The frequency of HLA-B54 is significantly higher in patients with SS, and recently it has also been confirmed in neurological SS with an additional evidence of correlation with HLA-Cw1.[4] According to previous reports, B54 and Cw1 had similar but subtle different motifs of peptides bound to HLA: proline (Pro) in position 2 (P2) and hydrophobic residues such as leucine (Leu), isoleucine, or alanine in position 9 (P9) on B54 and Pro in P3 and hydrophobic residues in P9 on Cw1.[5] This feature suggests that the same or similar peptides from a putative autoantigen in SS could be presented on these HLAs against autoreactive T cells as a primary target of the immunological responses.[3,4,17]

Table. Reported infantile Sweet's syndrome (<1 year old)

Age at onset	Sex	Country background	Predominant symptoms	Date before admission /diagnosis	Treatment before admission	Treatment after admission	Prognosis	Other information	Ref. No	Year
2 w	M	United States white	R	ND / ND	none	dapsone, colchicin, IVIG, steroid	recurrence (+)	IVIG in 3 weeks Sibling of the case below	5	2003
2 w	M	United States white	R, F	ND / ND	none	AB, steroid, colchicine, potassium iodide, azathioprine	recurrence (+) death	Cause of death pulmonary hypertension (4 y old)	5	2003
5 w	F	Japan Japanese	R, F	0 d / 4HD	none	AB, steroid	recurrence (-)	SS with rectovaginal fistula	Present case	
7 w	M	United States white	R, F, I, A	4 d / 5HD	antibiotics	AB, acyclovir, steroid	recurrence (-)	SS with URI and otitis media, aseptic meningitis	6	1992
10 w	M	France ND	R, F	ND / ND	antibiotics	AB, steroid, antimycotics	recurrence (-)	Chronic granulomatous disease 3 w: dermatitis, 5 w: otitis media	7	1994
3 m	F	Japan Japanese	R, F, rhinorrhea	1 m / ND	antibiotics, steroid	AB, steroid	recurrence (+)	ND	8	1980
3 m	M	United States African American	F, I, A	0 d / 6HD	none	AB, topical AM	recurrence (-) death	HIV infection Cause of death pneumonia (6 m)	9	1999
4 m	M	Ireland ND	R	1 m / ND	topical steroid	AB, steroid	recurrence (+)	Recurrent respiratory symptoms like pneumonia	10	1991
4 m	M	Belgium Caucasian	R, F, I	2 w / 3HD	antibiotics	AB, steroid	recurrence (-)	Acute arthritis (8 m)	11	1999
4 m	F	United States white	R, F, I, A	about 20 d /3HD	topical antibiotics	AB, steroid	recurrence (-)	SS with acute respiratory distress requiring intubation until initiation of steroid therapy	12	1994
8 m	M	Lebanon ND	R, F	25 d / 3HD	antibiotics, iodine	AB, steroid	recurrence (-)	ND	13	1985
9 m	F	South Africa African	R, F	ND / ND	antibiotics	AB, blood transfusion	recurrence (+)	SS with tonsillitis	14	1978
9 m	M	United States ND	R	5 w / ND	antibiotics	AB, steroid	recurrence (-)	SS with subglottic narrowing requiring tracheotomy	15	1983
10 m	M	United States ND	R	2 w / ND	antibiotics	AB, steroid	recurrence (+)	SS with otitis media	15	1983
11 m	M	United States ND	R, F	3 w / ND	ND	steroid	ND	ND	16	1996

w: week; m: month; d: day; y: year; M: male; F: female; ND: not described; R: rash; F: fever; I: irritability; A: appetite loss; AB: antibiotics; AM: antimycotics; IVIG: intravenous IgG; URI: upper respiratory tract infection; HD: hospital day; HIV: human immunodeficiency virus; SS: Sweet's syndrome.

Case report

Our patient had HLA-A2, A31, B48, B61, and Cw3, not B54 or Cw1, which is closely associated with SS adult patients.[3,4] However, when we look at the reported motifs of the eluted peptides from these HLAs, they have some similarity with those of B54 or Cw1: Leu or Pro in P2 and hydrophobic residues in P9 on HLA-A2 and Pro in P3 and hydrophobic residues in P9 on HLA-Cw3. And structural analysis of HLA-A2 (PDB: 3BHB) and HLA-Cw3 (PDB: 1EFX) revealed that these residues could be accommodated into the respective pockets that have hydrophobic nature (Fig. 2).[18] These findings suggest a possible contribution of HLA as in adult patients, but further studies especially on peptide sequences bound to HLA of SS patients should be valuable for understanding the molecular mechanism of the pathogenesis. Moreover, SS is usually well treated with steroid or immunosuppressant, but some cases require more intensive therapies.[1,2] Studies on the HLA bound peptides and HLA structural analysis for patients with SS would be valuable for understanding the molecular mechanism of the pathogenesis.[19,20]

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Contributors: Omoya K, Naiki Y, Yoshioka S, Echidn Y, and Taga T performed the patient care. Aoki Y and Deguchi H performed the skin biopsy and the analysis. Omoya K and Kato Z wrote the first draft of this paper. Kato Z and Kondo N performed the clinical investigations including HLA analysis. All the authors contributed to the intellectual content and approved the final version. Kondo N is the guarantor.

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