

A Case of Diffuse Cutaneous Mastocytosis in a Newborn

Mi-Na Park, M.D., Geun-A Kim, M.D., MyoungJae Chey, M.D., and Gyu Hong Shim, M.D.

*Department of Pediatrics, Sanggye Paik Hospital,
Inje University College of Medicine, Seoul, Korea*

Diffuse cutaneous mastocytosis (DCM) is a rare variant of mast cell disease with widespread erythema and is clinically apparent in early infancy. We report the case of a 1-day-old female neonate who presented with diffuse flush, pruritus, and extensive blistering. DCM was diagnosed by immunohistochemical staining with anti-CD117, which revealed mast cell infiltration. DCM is a severe and heterogeneous cutaneous disease, and is associated with mast cell mediator-related symptoms and risk of anaphylactic shock. We describe this case and provide the first literature review of neonatal onset DCM in Korea.

Key Words : Cutaneous mastocytosis, Diffuse cutaneous mastocytosis, Newborn

Mast cell disease is a condition characterized by mast cell hyperplasia in the skin, bone marrow, liver, spleen, lymph nodes, gastrointestinal tract, or a combination of these organs. The World Health Organization (WHO) recently adopted updated diagnostic criteria and consensus classification based on refinements of previous systems.¹ There are two main variants of mast cell disease. The systemic variant forms include indolent systemic mastocytosis, systemic mastocytosis with associated hematologic non-mast cell clonal disease, aggressive systemic mastocytosis, and mast cell leukemia.² Cutaneous mastocytosis (CM) is the second variant, which encompasses solitary mastocytoma, urticaria pigmentosa, and diffuse cutaneous mastocytosis (DCM).³ DCM is a rare, severe cutaneous form of mast cell disease that generally presents in the neonatal period and has an unclear prognosis.⁴ Here, we report a neonatal case that challenges our current knowledge of the disease.

Case report

A 1-day-old female neonate, who was the second child of healthy parents, was born at 41 weeks' gestation with a birth weight of 3,500 g via spontaneous vaginal delivery to a 31-year-old mother. The pregnancy was uncomplicated, and no abnormalities were detected on prenatal ultrasound examination. Apgar scores were 8 and 9 at 1 and 5 minutes. The patient had multiple erythematous lesions and bullous lesions on the trunk, head, and neck at birth. She was subsequently transferred to our neonatal intensive care unit (NICU). Physical examination revealed that the whole skin surface was covered with a leathery erythrodermic rash; tense, partly hemorrhagic vesicles; and blisters of varying size. Erosions and hemorrhagic crusts were found on the face, scalp, and large areas of the trunk (Fig. 1). After admission, blistering and hemorrhagic vesicles developed on the scalp, face, trunk, and extremities.

Darier's sign, in which gentle rubbing of the trunk lesion produced urtication, was present. Abdominal ultrasound showed hepatosplenomegaly and mesenteric lymphadenopathy, but findings of brain ultrasound and transthoracic echocardiogram were normal. Histological

Received : May 27, 2014, Revised : June 19, 2014

Accepted : June 30, 2014

Correspondence : Gyu Hong Shim, M.D., Department of Pediatrics, Sanggye-Paik Hospital, Inje University College of Medicine, 1342, Dongil-ro, Nowon-gu, Seoul, Korea

Tel : +82-2-950-1632, Fax : +82-2-950-1246

E-mail: peddoc@paik.ac.kr

Copyright© By The Korean Society of Perinatology

examination of a skin biopsy revealed dense monomorphous infiltration in the dermis composed of round-to-oval shaped cells (Fig. 2). Immunohistochemical typing with anti-tyrosine-protein kinase Kit (CD117) confirmed that the infiltration consisted almost entirely of mast cell (Fig. 3). The patient had a score of 72.5 on the scoring mastocytosis (SCORMA) Index,⁵ which is used for scoring the clinical extent of mastocytosis. Routine hematologic and serum chemistry profiles were performed, and complete blood counts and other che-

mistry profiles were normal. The serum tryptase level was 4.7 ng/mL (normal value <20 ng/mL). Cultures from skin swabs detected oxacillin-resistant, coagulase-negative *Staphylococcus*. Skeletal surveys showed 11 paired ribs, and the patients karyotype was 46,XX,inv(9)(p12q13). Bone marrow aspirations were not conducted during the evaluation. After NICU discharge, the patient was visited to the emergency center, and then re-admitted twice at 1 month and 2 months of age because of unfounded crying and irritability. She



Fig. 1. Clinical presentation: Patient at birth with diffuse erythematous rash on back (A). Partly hemorrhagic vesicle and bulla on axilla (B). Hemorrhagic crusts and erosion found on the face (C). Diffuse cutaneous mastocytosis with erythema and leathery thickened skin on abdomen (D).

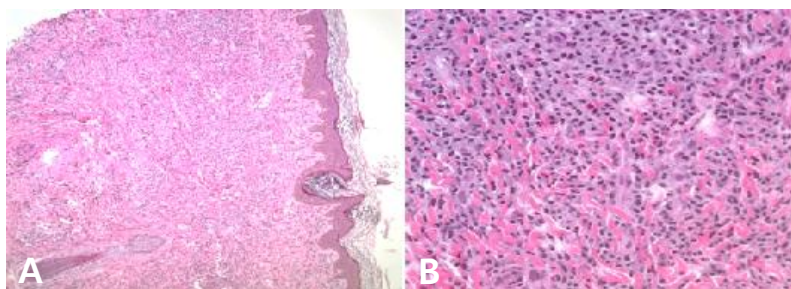


Fig. 2. Histopathology and immunohistochemistry of tissue specimens from skin lesions. Histological appearance of a patient with diffuse cutaneous mastocytosis (A, magnification $\times 100$). Diffuse infiltration of mast cells in the dermis (B, magnification $\times 400$).

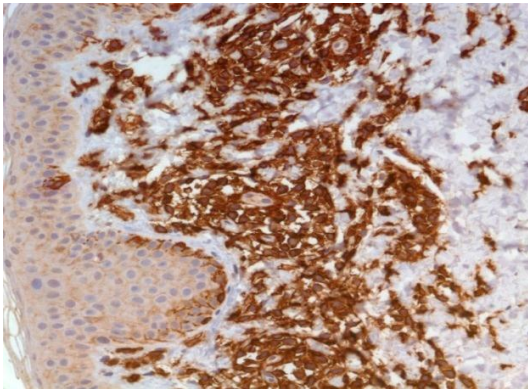


Fig. 3. Mast cell infiltration was demonstrated by CD117 staining (brown).

had recurrent suspected anaphylactic reactions with facial redness and whole body multiple erythematous lesions. The patient was treated with intramuscular epinephrine at 0.01 ml/kg (1:1,000) every 5 minutes, intravenous H_2 receptor blockers, dexamethasone, and 1st antihistamine until the symptoms resolved. Afterwards, the patient had 3 episodes of cough, rhinorrhea, and upper respiratory infection. Four months later, a multiple allergen simultaneous test on food allergen was performed and the results were normal. The patient subsequently gained weight well and developed normally. At 12 months of age, the lesions remained hyperpigmented, but no further anaphylactic episodes had occurred.

Discussion

Many conditions manifest as blisters or erosions in the newborn period, and may be due to infectious, non-infectious, traumatic, or inherited causes, thereby confounding the differential diagnosis. Bullous impetigo, staphylococcal scalded skin syndrome, pseudomonas, herpes simplex, *Varicella*, candidiasis, and *Aspergillus* are infectious causes. Noninfectious causes include epidermolysis bullosa, epidermolytic ichthyosis, incontinentia pigmenti, cutaneous mastocytosis, aplasia cutis,

and Langerhans cell histiocytosis.⁵ Mast cell disease represents a clonal proliferation of mast cell hematopoietic progenitors caused by gain-of-functional mutations in *KIT*, the gene encoding c-kit. *KIT* mutation heterogeneity likely contributes to difficulties in making genotype-phenotype correlations in this disease. DCM is a rare subtype of cutaneous mastocytosis that is characterized by partly hemorrhagic bullae, erosions, and crusts.⁶

We report the case of a 1-day-old female in Korea who presented with diffuse flush, pruritus, extensive blistering, and accompanied anaphylactic shock. The patient was fretful and irritable because of the pruritus and was relieved after symptomatic treatment. Histological examination of a skin biopsy revealed a dense monomorphous infiltration into the dermis that was composed of round to oval shaped cells. Immunohistochemical typing with anti-CD117 confirmed that the infiltration consisted almost entirely of mast cell. The detection of CD117 plays an important role in the diagnosis of cutaneous mastocytosis.⁷ DCM patients have the highest frequency of systemic disease, including involvement of the gastrointestinal, skeletal, or respiratory systems.^{5,8} Evaluation of serum tryptase levels appears to be a useful tool in monitoring DCM patients because it is closely correlated with the disease course and is considered a surrogate marker of disease severity.⁸⁻¹⁰ Our patient had diffuse skin lesions and her tryptase level was 4.7 ng/mL. There was no evidence of gastrointestinal, skeletal, or respiratory involvement. We used the SCORMA Index to evaluate the severity of DCM, as this method provides standardized information on the extent and activity of cutaneous mastocytosis and imposes no burden on the patient, which is particularly important in children.² Five subjective symptoms (triggering factors, flushing, diarrhea, itch, and local bone pain) are scored in the SCORMA Index, with values

lying between 5.2 and 100.8.⁵ Our patient had a score of 72.5 upon initial assessment and a score of 25.7 at 3 months after birth. Repeated SCORMA Index measurements can provide a rapid impression of changes in the clinical state of mastocytosis.

In addition, hyperpigmentation of lesions may occur due to the melanocyte-stimulating effects of mast cell growth factor,⁹ and it is interesting to note that our case had increased skin pigmentation. Mast cell-dependent mediators include histamine, heparin, leukotrienes, interleukins, interferon gamma, tumor necrosis factor alpha, acid hydrolase, granulocyte-macrophage colony-stimulating factor, and prostaglandin D2. They are either released from cytoplasmic granule stores or immediately synthesized in response to various physical, chemical, or immunological stimuli, including vaccination, insect bites, emotional and physical stress, infections, drugs, or histamine-rich foods.¹¹ Therefore, we recommend avoiding potential immunologic and non-immunologic triggers of mast cell degranulation in patients with mast cell disease.¹²

Treatment of mastocytosis is divided into two strategies: (i) symptomatic treatments, including antihistamines, H2 antagonists, disodium cromoglycate, corticosteroids, and psoralen ultraviolet A (PUVA), which inhibit the effects of mast cell mediators; and (ii) treatments to reduce mast cell load. Use of imatinib is also a potential mast cell load-reducing therapy, and it functions by inhibiting cytokine-mediated or mutation-induced pathogenic activation of the transmembrane tyrosine kinase receptor protein KIT (CD117), leading to subsequent deregulated cellular maturation, proliferation, and migration.¹³⁻¹⁵ Our patient was treated with topical corticosteroids, mupirocin, and daily dressing of the wounds in the NICU. After being discharged, the patient was readmitted to the emergency center at 1 month and 2 months of age because of recurrently anaphylactic

reactions. The patient was treated with evidence-based therapies targeting mast cell mediator-induced symptoms, including trigger avoidance, antihistamines, and epinephrine supplementation as needed. Specialists in dermatology and pediatrics will follow the patient for treatment of the pigmented lesions as an outpatient.

In conclusion, DCM should be suspected in newborns with bullous skin lesions, and a biopsy, appropriate treatments, and follow up are required.

References

- 1) Valent P, Akin C, Escribano L, Födinger M, Hartmann K, Brockow K, et al. Standards and standardization in mastocytosis: consensus statements on diagnostics, treatment recommendations and response criteria. *Eur J Clin Invest* 2007;37: 435-53.
- 2) Valent P, Horny HP, Escribano L, Longley BJ, Li CY, Schwartz LB, et al. Diagnostic criteria and classification of mastocytosis: a consensus proposal. *Leuk Res* 2001;25:603-25.
- 3) Muñoz LS, Twose IA, Garcí'a-Montero AC, Teodosio C, Acevedo MJ, Pedreira CE, et al. Evaluation of the WHO criteria for the classification of patients with mastocytosis. *Mod Pathol* 2011;24:1157-69.
- 4) Koga H, Kokubo T, Akaishi M, Iida K, Korematsu S. Neonatal onset diffuse cutaneous mastocytosis: a case report and review of the literature. *Pediatr Dermatol* 2011;28:542-6.
- 5) Heide R, Middelkamp Hup MA, Mulder PG, Oranje AP. Clinical scoring of cutaneous mastocytosis. *Acta Derm Venereol* 2001;81:273-6.
- 6) Yanagihori H, Oyama N, Nakamura K, Kaneko F. C-kit mutations in patients with childhood-onset mastocytosis and genotype-phenotype correlation. *J Mol Diagn* 2005;7: 252-7.
- 7) Chang SE, Kang SK, Jee MS, Choi JH, Sung KJ, Moon KC, et al. Clinicopathological study of 30 cases of cutaneous mastocytosis. *Korean J Dermatol* 2002;40:501-5.
- 8) Kanwar AJ, Dhar S. Diffuse cutaneous mastocytosis: a rare entity. *Pediatr Dermatol* 1993;10:301-2.
- 9) Murphy M, Walsh D, Drumm B, Watson R. Bullous mastocytosis: a fatal outcome. *Pediatr Dermatol* 1999;16:452-5.
- 10) Arock M, Valent P. Pathogenesis, classification and treatment of mastocytosis: state of the art in 2010 and future perspectives. *Expert Rev Hematol* 2010;3:497-516.
- 11) Schwartz LB, Irani AM. Serum tryptase and the laboratory diagnosis of systemic mastocytosis. *Hematol Oncol Clin*

- North Am 2000;14:641-57.
- 12) DiBacco RS, DeLeo VA. Mastocytosis and mast cell. J Am Acad Dermatol 1982;7:709-22.
- 13) Miyachi Y, Kurosawa M. Mast cells in clinical dermatology. Australas J Dermatol 1998;39:14-8.
- 14) Kleewein K, Lang R, Diem A, Vogel T, Gubo GP, Bauer JW, et al. Diffuse cutaneous mastocytosis masquerading as epidermolysis bullosa. Pediatr Dermatol 2011;28:720-5.
- 15) Metcalfe DD. Mast cells and mastocytosis. Blood 2008;112: 946-56.

= 국 문 초 록 =

신생아의 미만성 피부 비만세포증 1례

인제대학교 상계백병원 소아청소년과
박미나·김근아·최명재·심규홍

미만성 피부 비만 세포증은 일반적으로 초기 유아기 단계에서 임상적으로 명백한 광범위 홍반을 가지는 비만 세포 질환의 희귀한 변종이다. 광범위한 홍조와 가려움 및 미만성 수포를 동반한 생후 1일 된 신생아가 본원으로 전원되었다. 확진을 위하여 시행된 피부 생검 결과에서는 CD117을 통한 비만 세포의 조밀한 피부 침투소견이 관찰되었다. 미만성 피부 비만세포증은 다양한 중증의 피부 질환으로 나타나며, 중재자 관련 증상을 보이고 아나필락시스의 위험성도 가지고 있는 질환이다. 저자들은 신생아에서 발생한 미만성 피부 비만세포증 1례를 경험하였기에 이를 보고하고 문헌고찰을 하고자 하는 바이다.

중심 단어 : 피부 비만세포증, 미만성 피부 비만세포증, 신생아