

Generalized Bullous Eruption after Routine Vaccination in a Child with Diffuse Cutaneous Mastocytosis

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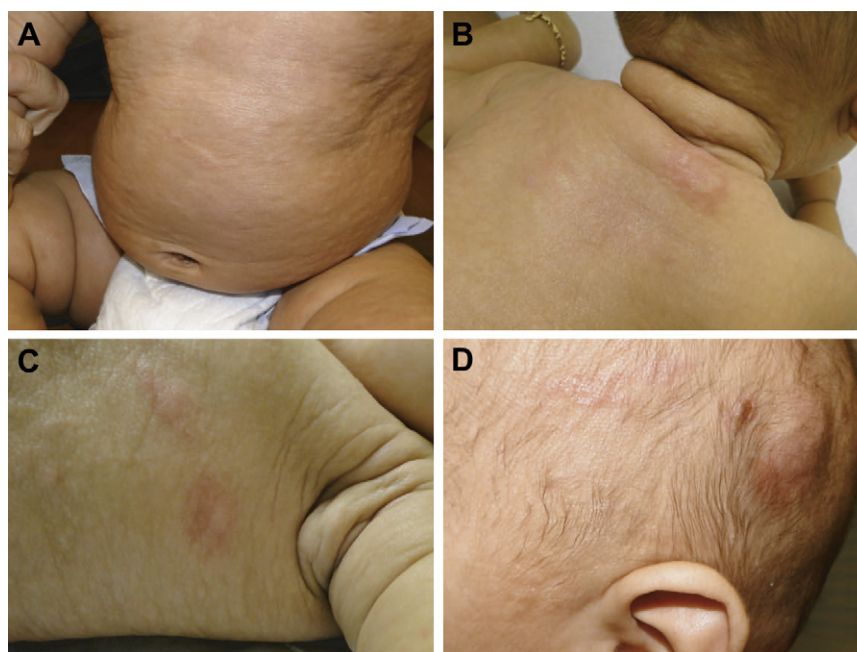


FIGURE 1. Diffuse thickening of the skin with leathery skin appearance (peau d'orange) and multiple nodules (A), exaggerated skin folds in the neck (B) and underarm (C). Spontaneous Darier sign (urtication of a lesion after friction) can be seen in the neck area (B) and left chest area (C). A mastocytoma (aggregation of a large number of mast cells) in the temporo-occipital area (D).

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A 5-month-old boy presented for evaluation of a raised apparently pruritic rash with episodic blisters. He was the product of an uncomplicated, full-term pregnancy with normal delivery. At 2 months of age, the skin of his abdomen and back became progressively rough and stiff with wheal formation surrounded by "raw" red areas of flare at the site of physical stroking. Skin biopsy was obtained from the right flank to confirm a suspected diagnosis of diffuse cutaneous mastocytosis (DCM).

Review of systems was noteworthy for history of colicky abdominal pain. There was no history of wheezing, loss of consciousness, diarrhea, vomiting, or abdominal distention. He was following his growth curve and reached all age-appropriate developmental milestones.

Physical examination showed an alert, well-appearing boy in no evident distress, appropriately interactive. No lymphadenopathy or organomegaly was observed. Skin was notable for confluent skin-colored papules and plaques with peau d'orange appearance covering his trunk with urtication on minimal touch (Figure 1). Hyperpigmented patches of several centimeters in diameter were present on the extremities.

Laboratory results showed a 24-hour collection urinary histamine level of 873 $\mu\text{g/g}$ creatinine (reference range, $<35 \mu\text{g/g}$).

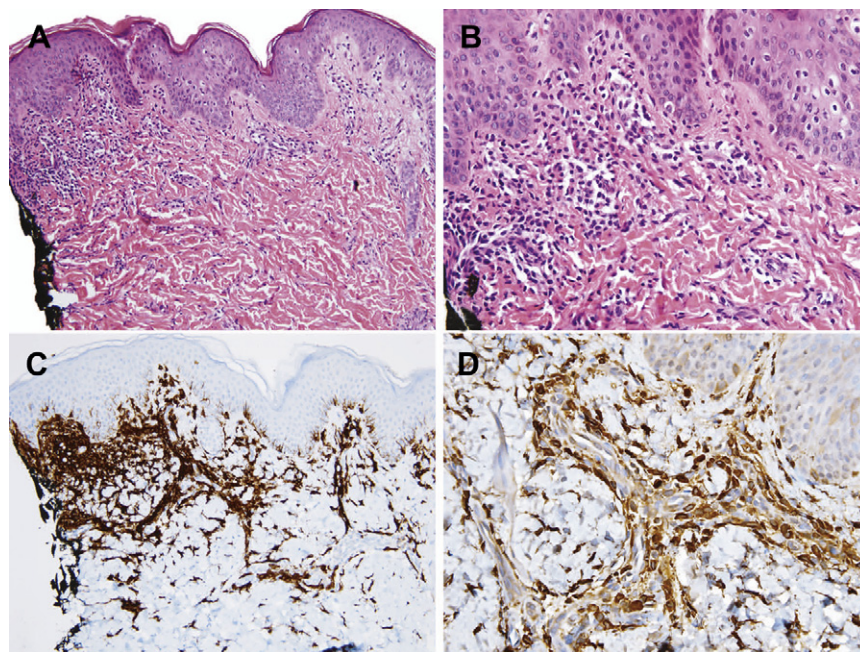


FIGURE 2. Skin biopsy demonstrating cutaneous mastocytosis. Hematoxylin and eosin stain showing a dense interstitial and perivascular infiltrate of mononuclear cells in the papillary and reticular dermis at low-power (A) and high-power (B) magnification. By immunohistochemistry, the mononuclear cells are positive for c-kit (CD117) (C) and tryptase (D), typical of mast cells.

creatinine), total serum tryptase of 64 ng/mL (reference range, <15 ng/mL), and mature tryptase of 3.1 ng/mL (reference range, <1 ng/mL). Blood cell counts were 12,000 white blood cells/ μ L, 4,690 red blood cells/ μ L, and 473,000 platelets/ μ L with mild eosinophilia of 550 cells/ μ L, and otherwise normal differential. Liver function tests were normal (alanine aminotransferase, 23 μ kat/L; aspartate aminotransferase, 34 μ kat/L).

Lesional skin biopsy showed a patchy band-like infiltrate of mononuclear cells in the superficial dermis. Immunostaining for tryptase and CD117 was positive, confirming that the infiltrate primarily consisted of mast cells (Figure 2).

The diagnosis of DCM was made on the basis of these clinical and histopathologic findings.

At 5 months of age, the patient received his scheduled 4-month vaccinations, including *Haemophilus influenzae*; protein-conjugated pneumococcal vaccine; poliomyelitis vaccine; diphtheria, pertussis, and tetanus toxoid; and rotavirus vaccine. Within 12 hours of vaccine administration, he became colicky. A day later, he began developing blisters filled with clear fluid that became confluent. The areas most affected included the back (which was covered with extensive bullae), skin fold areas of the upper arms, and the lower abdomen (Figure 3) distant from the area of injection. He had no fever and was in no acute distress. He was treated with a 5-day course of low-dose oral steroids and recovered with no residual skin changes. Since then, he has had 2 additional episodes of blistering associated with vaccination and viral illness. These episodes have become milder after initiation of a regimen with oral and topical sodium cromoglycate.

DISCUSSION

Pediatric-onset mastocytosis is a rare disease that manifests as urticaria pigmentosa, solitary cutaneous mastocytoma, or DCM. DCM is the least frequent of the 3 types with reported incidence

of 1% to 8% in case series of pediatric mastocytosis.¹⁻³ Initial presentation of DCM is usually at birth or in early infancy.³

DCM is characterized by diffuse infiltration of the dermis with mast cells that cause generalized thickening of the skin with a leathery appearance, yellowish discoloration, accentuation of hair follicles (termed *peau d'orange*), and increased folding in the creases, hands, and feet. Superimposed nodules and plaques that resemble mastocytomas are common as well.²

The most common symptom in DCM, like in other types of mastocytosis, is pruritus (80% of patients).³ Mast cell mediator-induced symptoms include flushing (100% of patients)² and diarrhea (40% of patients).³ Extracutaneous infiltration with mast cells can lead to lymphadenopathy (40% of patients), splenomegaly (40% of patients), and hepatomegaly (25%-60% of patients).³

The diagnosis of DCM is confirmed by skin biopsy to detect mast cells. Laboratory studies may show elevated serum tryptase and urinary histamine levels. Diagnostic evaluation for extracutaneous involvement should be guided by clinical examination.⁴

Blister formation is a hallmark of the disease and reported in 62% to 66% of patients with DCM.² The bullous eruption is characterized by tense, thin-walled blisters filled with clear fluid. The blisters may occur in a linear or grouped fashion and often develop on the trunk, scalp, and extremities.⁵ They present in a variety of sizes and initially contain clear fluid that may become hemorrhagic with time, secondary to the release of heparin from the activated mast cells. Hemorrhagic blisters are associated with higher mortality rates, secondary to hypotension, gastrointestinal bleeding, and superinfection.⁵

Biopsies of blisters suggest a disruption of the dermo-epidermal junction. Blister fluid contains mast cells and eosinophils by cytology.⁵ Bullae formation is likely a direct consequence of mast cell activation and degranulation with release of mast cell proteases. Briggaman et al⁶ showed that chymase and cathepsin G, two mast

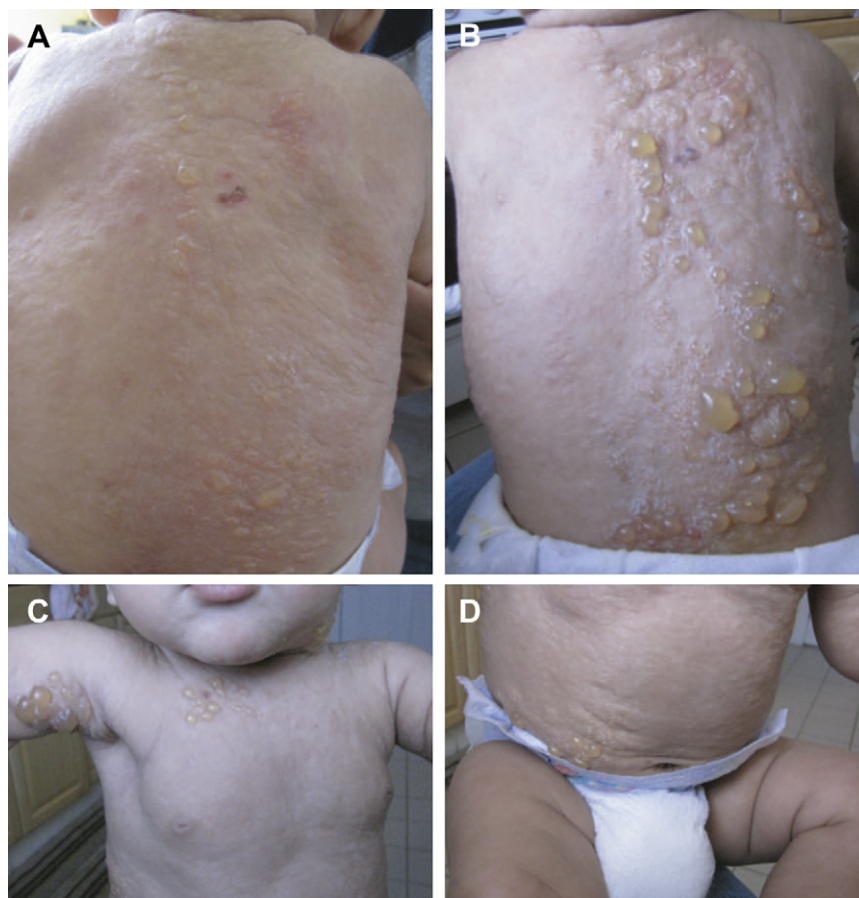


FIGURE 3. Blister formation after administration of scheduled vaccines. Initial blistering 24 hours after vaccination (A), multiple tense bullae covering an extensive area on the back, abdomen, neck and axillae with serous and some with hemorrhagic fluid (B-D).

cell proteases, cause loss of anchoring filaments and disruption of the basal membrane of the epidermis.

Known triggers for mast cell activation are trauma (including surgery and minor procedures), radiographic dyes, as well as pharmacologic agents (including narcotics and anesthetics).⁷ Immunologic stimuli can also cause mast cell degranulation through activation via Toll-like receptors.⁸ Infections are known to cause blistering in children with DCM.⁵ Brockow et al⁷ reported a case of anaphylaxis after vaccination in a child with DCM.

Protocols for premedication with steroids, antihistamines, and leukotriene receptor antagonists have been successful in prevention of complications. Mast cell stabilizers such as cromolyn improve disease control.⁹ In our experience, steroids are the preferred therapy for cases with blister formation, as has been previously reported in the literature.⁵

Our report shows the importance of considering all triggers for activation and degranulation in children with DCM. Besides anaphylaxis, severe generalized blister formation is also considered a life-threatening event, especially if evolving into the hemorrhagic form. Vaccinations are not contraindicated but should be cautiously addressed because of the potential for massive mediator release and hemorrhagic bullae formation. The use of precautions with procedures, vigilance for common triggers (infections and immunizations), and adequate premedication is essential to reduce the risk of

these severe complications. Children with DCM should preferably receive the vaccines on a “one-at-a-time basis” per routine vaccination schedules.

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