Congenital papulovesicular eruption mimicking TORCH syndrome in newborn

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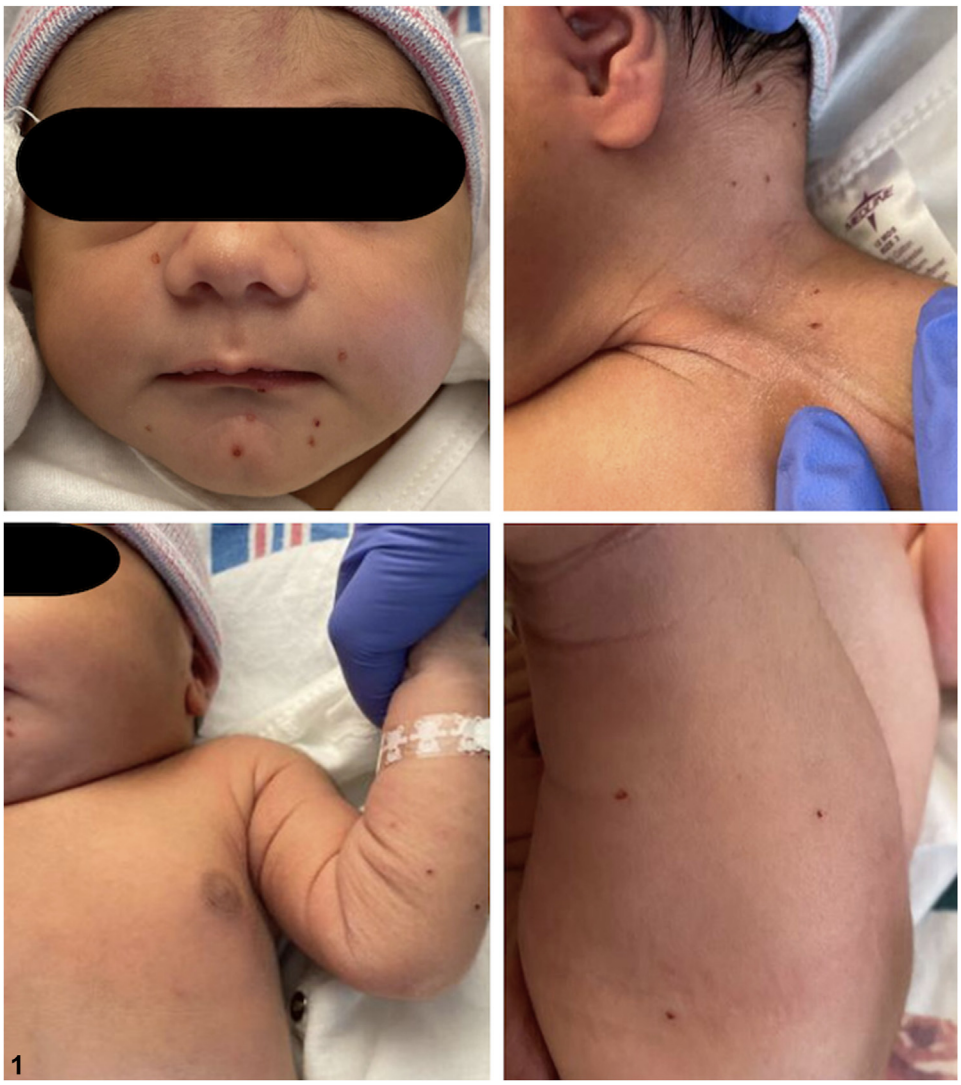

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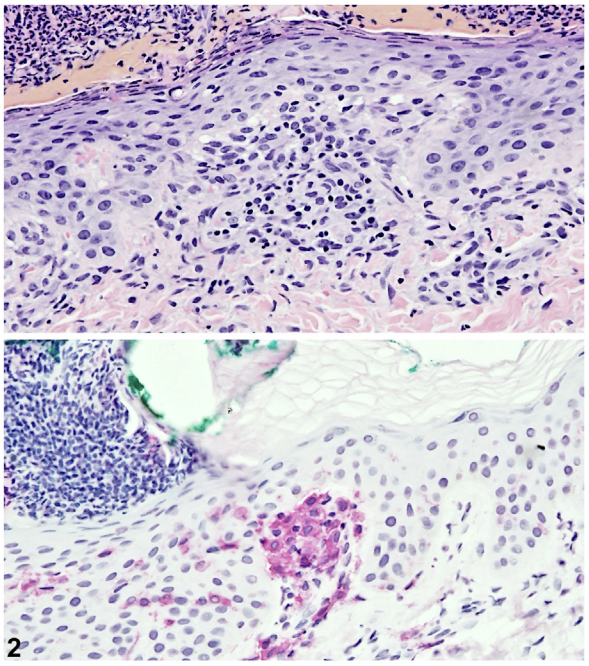

HISTORY

A 2-day-old full-term female presented with an eruption on the face, neck, trunk, and extremities. A total body skin exam revealed multiple crusted erythematous papulovesicles scattered on perioral skin, neck, arms, and legs (Fig 1). Viral swab of crusted papulovesicles for herpes simplex virus-1/2 and varicella zoster virus polymerase chain reaction and blood toxoplasmosis, other (syphilis, hepatitis B), rubella, cytomegalovirus, herpes simplex -panel were negative. A 3-mm punch biopsy of an eroded papule on the left posterior thigh revealed an ulcerated epidermis, beneath which was a collection of epithelioid histiocytic cells with reniform nuclei (Fig 2 top). The lesional cells were immunoreactive for antibodies directed against cluster of differentiation 1a (Fig 2 bottom).

Question 1: What is the most likely diagnosis?

A. Erythema toxicum neonatorum

B. Seborrheic dermatitis

C. Langerhans cell histiocytosis (LCH)

D. Congenital herpes simplex infection

E. Rosai-Dorfman disease

Answers:

A. Erythema toxicum neonatorum — Incorrect. Erythema toxicum neonatorum typically present with erythematous macules and vesicles that begin on the face and spread cephalocaudally to the trunk and extremities with spontaneous regression within the first few days to weeks of life. Biopsy is not necessary but can show dermal and periadnexal eosinophilic predominant infiltrate.

B. Seborrheic dermatitis — Incorrect. Seborrheic dermatitis presents with rough scaly patches on the scalp and intertriginous folds between 2 weeks and 12 months of age.

C. LCH — Correct. LCH is a clonal proliferative disorder comprised of Langerhans cells that is diagnosed in early childhood, typically within the first 3 years of life.[1] LCH is a great masquerader of benign cutaneous disorders of childhood, particularly in the neonatal period. Not uncommonly, LCH can be mistaken for seborrheic dermatitis, extramedullary hematopoiesis, congenital TORCH infections, and newborn pustular dermatosis including erythema toxicum neonatorum.[1-3] Clinicopathologic correlation is instrumental in arriving at the correct diagnosis. Histologically, Langerhans cells exhibit prominent nuclear grooves and stain positive for cluster of differentiation 1a, S100, and langerin (cluster of differentiation 207).[1,2]

D. Congenital herpes simplex infection — Incorrect. Congenital herpes simplex infection can present with grouped vesicles and is acquired through vertical transmission during delivery or shortly thereafter. Diagnostic confirmation requires testing with HSV-1/2 polymerase chain reaction.

E. Rosai-Dorfman disease — Incorrect. Rosai-Dorfman disease is a non-LCH characterized by massive lymphadenopathy and extranodal disease presenting as painless cutaneous nodules, papules, or plaques. Histologically, Rosai-Dorfman disease is characterized by emperipolesis.

Question 2: At 1 week follow-up, all crusted papulovesicles on the patient's face, neck, trunk, and extremities spontaneously resolved. Laboratory evaluation including complete blood chemistry, basic metabolic panel, liver function tests, urinalysis, and head and abdominal ultrasound were within normal limits. What is the most likely subtype of this disease?

A. Multisystem LCH (Letterer-Siwe disease)

B. Congenital self-healing reticulohistiocytosis (CSHR) (Hashimoto-Pritzker disease)

C. Langerhans cell granulomatosis (Hand-Schüller-Christian disease)

D. Eosinophilic granuloma (EG)

E. Erdheim-Chester disease

Answers:

A. Multisystem LCH (Letterer-Siwe disease) — Incorrect. Multisystem LCH (Letterer-Siwe disease) is the most severe form of LCH, involving multiple organ systems including the skin, bone marrow, spleen, liver, and lung.[1]

B. CSHR (Hashimoto-Pritzker disease) — Correct. CSHR, formerly known as Hashimoto-Pritzker disease, is a rare and benign variant of LCH that is characterized by single or multiple red, brown, or violaceous papules, vesicles, or petechial-like lesions present at birth or shortly thereafter with spontaneous regression within the first few weeks to months of life.[3] While CSHR is generally a benign entity, relapses and internal organ involvement can occur, warranting careful initial work-up including skin biopsy and additional laboratory and imaging tests.[3] Close long-term follow-up with Pediatric Dermatology and Hematology-Oncology is critical to monitor for LCH disease recurrence and progression.

C. Langerhans cell granulomatosis (Hand-Schüller-Christian disease) — Incorrect. Langerhans cell granulomatosis (Hand-Schüller-Christian disease) is characterized by the clinical triad of exophthalmos, lytic bone lesions, and diabetes insipidus.[1]

D. EG — Incorrect. EG typically involves the axial skeleton with the skull being the most common site in children and mandible in adults. The presentation of EG is usually solitary bone lesion (monostotic EG), or less commonly multiple bone lesions (polyostotic EG).

E. Erdheim-Chester disease — Incorrect. Erdheim-Chester disease is a type of non-LCH that manifest as multifocal sclerotic lesions involving long bones in adults. Neonates and children are rarely affected.

Question 3. Which of the following gene mutations is most commonly associated with this disease?

A. *PIK3CA*

B. *BRAF*

C. *CDKN2A*

D. *MSH2*

E. *PTEN*

Answers:

A. *PIK3CA* — Incorrect. *PIK3CA* mutations have been recently reported in Erdheim-Chester disease. It is not the most commonly mutated gene in LCH.

B. *BRAF* — Correct. *BRAF,* in particular *BRAF V600E* mutations have been reported in approximately 36.8% to 54.6% of individuals with LCH.[4,5] While the exact clinical significance of *BRAF V600E* mutational status has yet to be elucidated, *BRAF V600E* mutated LCH has been shown to be an independent predictive marker for high-risk LCH with multisystem involvement, younger age of onset (<2 years), treatment resistance, and disease relapse.[5] Genetic testing for *BRAF* and other somatic mutations in RAF-MEK-ERK pathway necessitates careful discussion between the health care provider and the patient and patient's family. Nonetheless, *BRAF* mutation can serve as a useful biomarker to select patients with high-risk LCH features who may benefit from targeted therapy.

C. *CDKN2A* — Incorrect. *CDKN2A* mutation is commonly associated with familial melanoma and pancreatic adenocarcinoma. It is not the most commonly mutated gene in LCH.

D. *MSH2* — Incorrect. *MSH2* along with *MSH6* and *MLH1* mutations are associated with Muir-Torre syndrome and hereditary nonpolyposis colorectal cancer. It is not the most commonly mutated gene in LCH.

E. *PTEN* — Incorrect. *PTEN* mutations are associated with PTEN hamartoma syndromes such as Cowden syndrome. It is not the most commonly mutated gene in LCH.

Abbreviations used:

CSHR: congenital self-healing reticulohistiocytosis
EG: eosinophilic granuloma
LCH: langerhans cell histiocytosis

Key words

congenital self-healing reticulohistiocytosis; Hashimoto-Pritzker Disease; Langerhans cell histiocytosis; toxoplasmosis, other (syphilis, hepatitis B), rubella, cytomegalovirus, herpes simplex syndrome

Conflicts of interest

None disclosed.

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