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A neonate with Langerhans cell histiocytosis presenting as blueberry muffin rash: Case report and review of the literature

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Abstract

In our case report, we discuss a 1-day-old boy presenting with blueberry muffin syndrome diagnosed with Langerhans cell histiocytosis. The diagnosis complicated by an initial difficult-to-interpret biopsy showing only a hint of perifollicular CD1a-positive cells; however, given our team's strong clinical suspicion of Langerhans cell histiocytosis, a second biopsy of a more mature lesion was done and showed typical histopathology. This case introduces the possibility of perifollicular Langerhans cells early in this condition, demonstrates the importance of appropriate biopsy site selection, and highlights the importance of maintaining a high degree of suspicion when there is poor clinicopathologic correlation. Our case report contains a comprehensive table which reviews the systemic and cutaneous clinical features, as well as the laboratory, pathology, and imaging findings for the differential diagnoses of blueberry muffin baby.

Keywords

Blueberry muffin baby, Langerhans cell histiocytosis, Blueberry muffin syndrome, CD1a, histopathology, histiocytosis, Hashimoto–Pritzker

Introduction

Langerhans cell histiocytosis (LCH) is a disorder characterized by proliferation and infiltration of clonal Langerhans cells into tissue(s) that is thought to occur through both inflammatory and neoplastic mechanisms.[1,2] The BRAF V600E mutation has been implicated and may promote expansion of myeloid dendritic cell precursors.[1,3,4] Historically, the disorder was divided into four subtypes (Letterer–Siwe disease, Hand–Schüller–Christian disease, eosinophilic granuloma, and Hashimoto–Pritzker disease), but is now considered a clinical spectrum that ranges from single system to extensive multisystemic disease (MSD).[5–8] Herein, we report a case of LCH that was nearly missed due to atypical histopathology on initial skin biopsy, which suggests a potential novel origin of clonal cells early in the disease.

Case report

A 1-day-old term male presented to hospital with multiple necrotic skin lesions. His mother was healthy; however, the antenatal course was complicated by presumed viral gastroenteritis in the first trimester, three viral upper respiratory infections in the second trimester, and a two-day history of diarrhea and nausea 2 weeks prior to delivery. The pregnancy was otherwise unremarkable with protective serologies, negative group B streptococcus screening, and normal ultrasounds. Family history was unremarkable and there was no history of travel. The family had dogs, chickens, turkey, and sheep. Labor was precipitous, with the patient born via spontaneous vaginal delivery to paramedics at term. Apgars were

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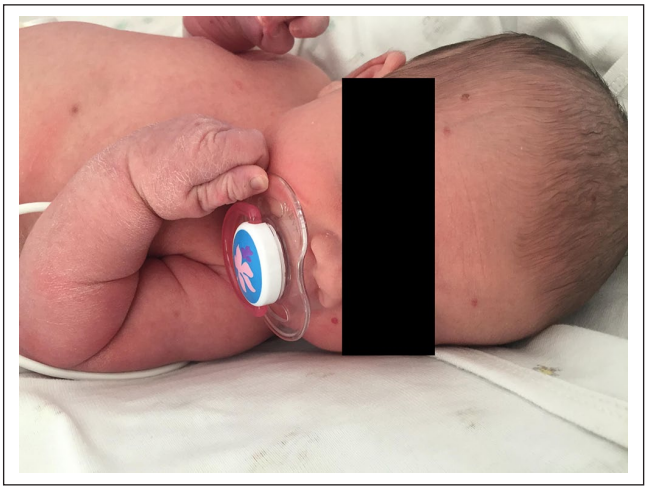

Image 1. In this photo, several brown macules and purple-blue-black necrotic and hemorrhagic-crusted papulonodules are visible on the right forehead, and abdomen.

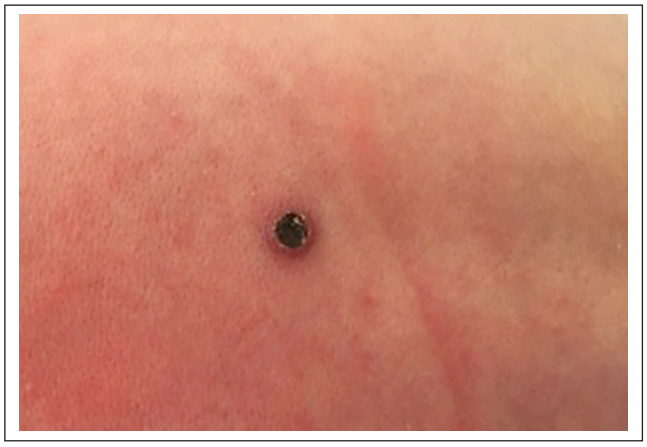

Image 2. Larger lesion 0.5 cm purple-blue-black necrotic and hemorrhagic-crusted papulonodule on the patient's upper back.

10 and 10, and the placenta was delivered intact. A midwife arrived shortly after delivery and recommended urgent evaluation for his skin lesions.

Examination revealed approximately 20 cutaneous lesions ranging from brown macules to purple-blue-black necrotic and hemorrhagic-crusted papulonodules (Image 1). The two largest lesions were each 0.5 cm in diameter, located on the midline back and shoulder (Image 2). In addition to full skin examination, a thorough full physical examination verified by multiple pediatricians and pediatric specialists was normal.

A punch biopsy was performed on a subtly violaceous crusted macule on the right forearm (Image 3). Pathology demonstrated an isolated focus of dense perifollicular histiocytic and dendritic cellular infiltrate sparing the epidermis (Image 4(a)). Eosinophils were not identified. Immunohistochemistry for CD1a (Image 4(b)), CD163, S100, and Cyclin-D1 were

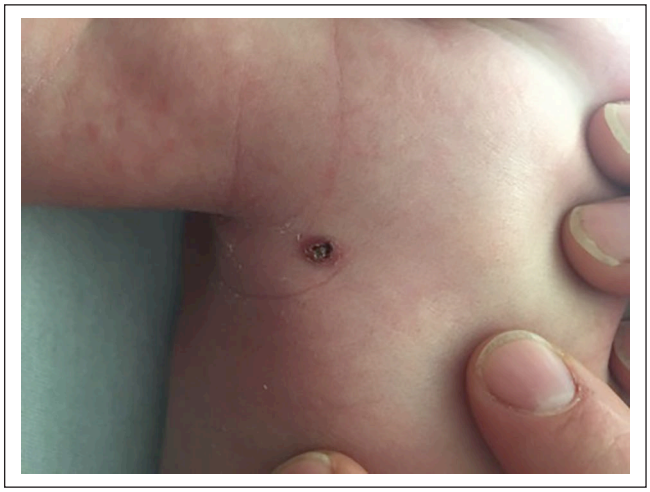

Image 3. Smaller 0.3 cm violaceous crusted macule on the patient's arm.

strongly positive in the lesional cells and confirmed them to be Langerhans cells. A repeat biopsy (Image 5(a)) of a fully developed crusted necrotic blue-black papule was pursued given the poor clinicopathologic correlation. This second sample revealed extensive epidermal ulceration and dense infiltrates of eosinophils and CD1a-positive Langerhans cells with vesicular nuclei with prominent grooves and ample eosinophilic cytoplasm in the dermis and subcutaneous tissue (Image 5(b)). BRAF mutation testing was negative.

Laboratory and imaging investigations following the recommendations of the Histiocyte Society confirmed the diagnosis (for details, see LCH in Table 1). Infectious serologies, including a TORCH screen, were negative. Complete blood count, liver transaminases, electrolytes, bilirubin, urea, and creatinine were all within normal limits. Skeletal survey, chest radiograph and abdominal and head ultrasounds of our patient revealed no evidence of systemic involvement. Our patient was reassessed by both pediatric dermatology and pediatric oncology at 2 weeks of age, and then regularly every 3 months until the age of 2. All LCH lesions had resolved by 18 months of age. He continues to be followed every 6 months and has no evidence of internal organ involvement on repeat bloodwork or imaging.

Discussion

Blueberry muffin syndrome refers to red-to-violaceous indurated macules, papules, or nodules present within 2 days of life.[9] The differential diagnosis is extensive and includes infections, cancers, and hematologic disease. Distinguishing clinical and laboratory features of potential causes are summarized from up-to-date publications in Table 1.[10–20] In all cases, these unique lesions occur due to the presence of extramedullary erythropoiesis in the dermis.

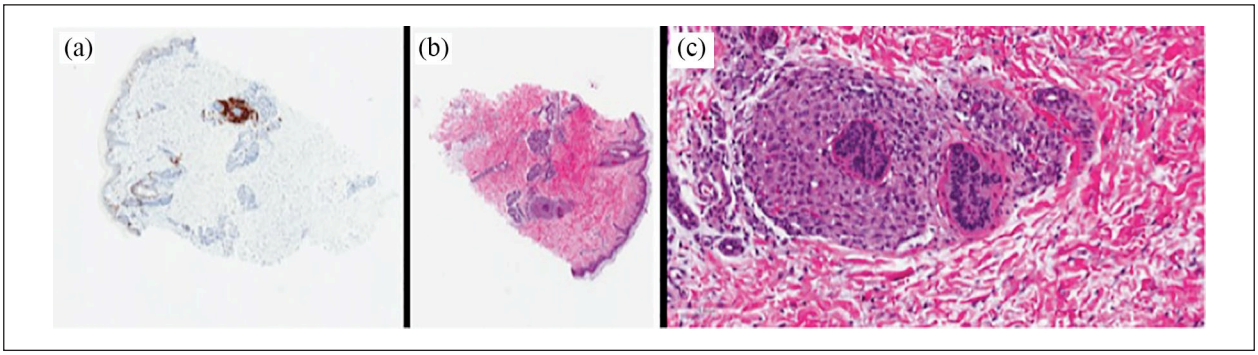

Image 4. Immunophenotypic features of the initial punch biopsy. (a) Langerhans cells highlighted by CD1a (IHC CD1a 40×). (b) and (c) Langerhans cells showing perifollicular cellular infiltrate. Note spared intact epidermis and no notable eosinophils were present (H&E 40× and H&E 200×).

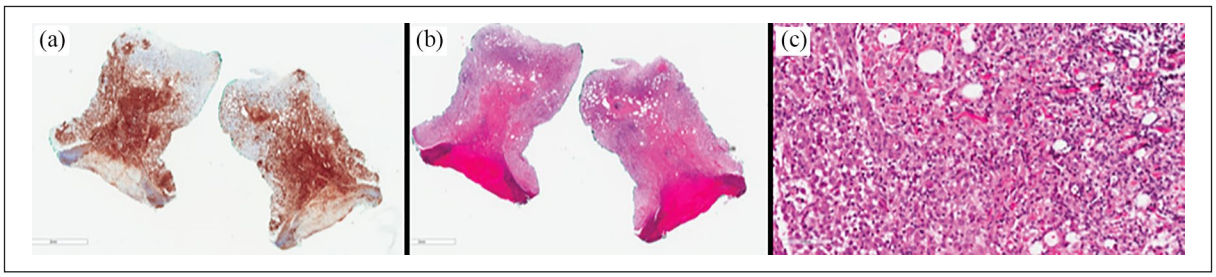

Image 5. Immunophenotypic features of the follow-up punch biopsy. (a) Langerhans cells highlighted by CD1a (IHC CD1a 40×). (b) Langerhans cells showing diffuse cellular infiltrate extending to fascia. Note epidermal ulceration. (c) High power view showing Langerhans cells admixed with abundant eosinophils (H&E 200×).

In our case, the diagnosis of LCH was confirmed by histopathology and exclusion of other causes. The first biopsy revealed a sparse, unusual pattern with an isolated focus of deep perifollicular infiltrate consisting exclusively of CD1a-positive Langerhans cells without the characteristic eosinophils or epidermotropic infiltrate. The histopathology of LCH can be variable, but typically consists of a heavy infiltrate of Langerhans cells with reniform nuclei invading the basal layer of the epidermis with accompanying lymphocytes and eosinophils.[2,21] Given our strong suspicion for LCH, a second biopsy of a more mature lesion was pursued and clinched the diagnosis. This case demonstrates the importance of clinicopathologic correlation and repeat biopsy when the two do not fit, as well as the importance of obtaining a mature lesion for biopsy to ensure typical histopathology.

LCH is believed to have an inflammatory and/or neoplastic etiology, although the mechanism of tissue infiltration remains unknown.[1] Interestingly, the first biopsy in our case revealed Langerhans cells clustered around the base of a hair follicle which suggests that perifollicular infiltration of the clonal cells may occur early in the disease. One previous case report noted a similar perifollicular infiltration of Langerhans cells on histopathology.[22] Normal resident Langerhans cells of the epidermis may not be the origin of LCH, instead LCH may originate from deep periadnexal precursors, highlighting that the classic epidermotropism associated with LCH is a progressive infiltration that becomes established only in well-developed lesions. How the infiltrate expands from perifollicular to densely dermal with epidermotropism remains to be elucidated and warrants further investigation. This possible early perifollicular histology of LCH is important for pathologists to be aware of in order to avoid missed diagnoses when faced with a biopsy of new LCH lesions. LCH can be single site (monostotic bone involvement, isolated skin involvement, and solitary lymph node involvement) or multiple site disease (polyostotic bone involvement, multifocal bone disease affecting two or more different bones, and multiple lymph involvement).[23] Our patient has single site histiocytosis, historically called "congenital self-healing reticulohistiocytosis," characterized by skin lesions that rapidly involute and eventually self-resolve, typically over a number of weeks to months.[2] Distinguishing self-limited cutaneous disease from MSD is imperative to direct management and appropriately counsel patients' families. Unfortunately, the initial presentations of both diseases can be clinically and histopathologically indistinguishable, and there is little available evidence to definitively conclude that limited cutaneous involvement at presentation will not evolve into MSD. Negative imaging at diagnosis does not rule out the possibility of systemic involvement at a later time. Features

Table 1. Differential diagnosis of blueberry muffin baby,[1–11] including Histiocyte Society guidelines for evaluation for children (<18 years) with suspected LCH.

Diagnosis	Clinical features		Laboratory findings
	Systemic features	Unique or additional cutaneous features	
Infectious			
Congenital syphilis	60%–90% of neonatal cases are asymptomatic. "Early congenital syphilis" symptoms are present at birth and may include jaundice, nasal discharge, hepatosplenomegaly, and generalized lymphadenopathy.	As lesions fade they may become dusky red or copper colored. If present at birth, may be diffuse and bullous. Late onset neonates may present with condylomata lata. A generalized papulosquamous eruption, similar to that seen in secondary syphilis in adults, follows at 2–6 weeks of age.	CBC: anemia (early), neutropenia (early), thrombocytopenia (early), lymphocytosis (late neonate). Reactive maternal VDRL. Reactive CSF VDRL, (+) Treponema IgM. Classic findings on long-bone radiographs in early congenital syphilis. Diagnosis confirmed by presence of *Treponema pallidum* on dark field examination of mucocutaneous lesions.
Neonatal varicella-zoster	Fever. In disseminated disease, patients can develop pneumonitis, encephalitis, purpura fulminans, widespread bleeding, and hypotension.	Begin as macules which progress to papules prior to developing into characteristic clustered vesicular lesions. Often starts on the head before disseminating. Can appear similar to HSV.	Diagnosis can be made clinically. (+) VZV IgG titer. (+) Tzanck smear: multinucleated giant cells. Diagnosis confirmed by molecular studies from scrapings of lesions: DFA or PCR (+) VZV. PCR is preferred if available.
Congenital rubella	Microcephaly, low birth weight, large anterior fontanel, hepatosplenomegaly, cloudy cornea or cataracts, cardiac defects, and hearing loss. Retroauricular, posterior cervical, and posterior occipital lymphadenopathy.	Blueberry muffin rash lasts for 3 days. Forchheimer spots (rose-colored macules on the soft palate) may also be present in 20% of patients.	CBC: anemia, leukocytosis or leukopenia, thrombocytopenia is rare. Blood smear: hemolysis (hemolytic anemia). Rubella-specific IgM and IgG antibodies, PCR (+) rubella RNA. Viral culture from nasopharyngeal secretion or blood. Long-bone radiography may reveal radiolucent bone lesions.
Congenital cytomegalovirus	Jaundice, hepatosplenomegaly, microcephaly, hepatitis, chorioretinitis, hearing abnormalities, and lethargy.	Blueberry muffin rash may appear more petechial.	CBC: thrombocytopenia, less commonly may present with hemolytic anemia, neutropenia, lymphopenia, lymphocytosis. Elevated liver transaminases. Elevated direct and indirect serum bilirubin. Salivary viral culture and urine PCR.
Neonatal herpes simplex	Intrauterine infection can present with chorioretinitis, skin lesions, and microcephaly. Skin, eyes, and mouth disease (SEM) is the most common presentation (45%); however, a significant number present as CNS (30%) or disseminated (25%). In CNS disease, presenting features may include lethargy, seizures, decreased feeding, or other symptoms of encephalitis.	In SEM, 1–2 mm clustered red papules and vesicles are seen on the scalp and face, including eyes and corners of the mouth, in babies born via vertex vaginal delivery or on the feet or buttocks in babies born breech.	CBC: thrombocytopenia, elevated liver transaminases, viral hepatitis, or acute liver failure. Surface specimen viral culture (+) HSV. PCR studies not recommended in neonates for surface specimens. CSF for PCR (+) HSV. Serum PCR (+) HSV DNA. Blood culture to rule out bacterial co-infection. Brain, pulmonary, and abdominal imaging should be pursued based on suspected extent of disease.

(Continued)

Table 1. (Continued)

Diagnosis	Clinical features		Laboratory findings
	Systemic features	Unique or additional cutaneous features	
Congenital toxoplasmosis	Chorioretinitis, fever, hydrocephalus, jaundice, hepatosplenomegaly, may be asymptomatic.	Main cutaneous finding is blueberry muffin rash.	CBC: thrombocytopenia, anemia. (+) Toxoplasmosis IgG, IgM, and IgA Ab titers. (+) PCR for *Toxoplasma gondii* in CSF, urine, or WBC PCR. CT head may show intracranial calcifications.
Neonatal parvovirus B19	In utero exposures may result in spontaneous abortion or hydrops fetalis. If fetus survives, most common presenting features include CNS, ophthalmologic, and facial anomalies.	Main cutaneous finding is blueberry muffin rash.	If maternal infection or exposure confirmed on serum with (+) B19 IgM, fetal infection confirmed with (+) B19 DNA from amniotic fluid.
Congenital Epstein–Barr virus	Rare. In utero maternal infection can resolve without consequence, but has also been associated with non-immune fetal hydrops and fetal death. Scant case reports of encephalopathy, meningitis, and severe CNS abnormalities associated with in utero exposure.	Main cutaneous finding is blueberry muffin rash.	CBC: rarely thrombocytopenia and anemia.
Neoplastic			
Langerhans cell histiocytosis (LCH)	Systemic features are highly dependent on organ system involvement, but may include bone pain and/or fractures, CNS involvement, endocrine disorders secondary to pituitary or hypothalamus involvement, respiratory symptoms, lymphadenopathy, otitis externa, mucosal erosions, exophthalmos, diarrhea, and hepatomegaly.	Cutaneous findings are a common presenting feature. In addition to the blueberry muffin rash, LCH can also present with vesiculopustules, eczema like dermatitis with seborrhea, oral lesions, erythematous papules, and generalized petechia.	Dependent on organ affected. As per the Histiocyte Society guidelines for evaluation for children (<18 years), the following should be performed on all suspected cases of LCH: CBC: may reflect thrombocytopenia and anemia. Total chemistry (total protein, albumin, bilirubin, ALT, AST, γGT, creatinine, and electrolytes) may reflect elevated liver enzymes and bilirubin. Coagulation studies (INR/PT, APTT/PTT, and fibrinogen/factor I). ESR, TSH, and growth hormone level should be done on all patients and may reflect hypothyroidism and growth hormone deficiency. Histopathology of biopsied cutaneous lesions: dense dermal infiltrate of histiocytic cells with kidney-shaped nuclei and eosinophilic cytoplasm. Abdominal ultrasound (noting size and structure of liver, spleen and any abdominal lymph nodes), chest radiograph, and skeletal radiograph.
Congenital leukemia cutis	Lethargy, hepatosplenomegaly, fever, CNS involvement, respiratory distress (if lung infiltrates).	Specific cutaneous lesions, which are rarely painful, have predilection for the face and neck. May also have petechia, purpura, ecchymosis, or pyodermas.	CBC: leukocytosis and anemia. Histopathology of cutaneous lesions shows an atrophic, intact epidermis with dense diffuse pleomorphic mononuclear cell infiltrate with atypical mitotic figures.

(Continued)

Table 1. (Continued)

Diagnosis	Clinical features		Laboratory findings
	Systemic features	Unique or additional cutaneous features	
Neuroblastoma	Malaise, cachexia, bone pain, diarrhea, cachexia, ataxia, and oculogyric crises.	Specific cutaneous nodules may maintain a blanched circumference for 30–60 min after palpation, which has a refractory period. Periorbital eccyhmosis and heterochromia iridis can also be seen.	Increased urinary catecholamines and metabolites. Increased serum ferritin and increased neuron-specific enolase. Bone marrow biopsy will demonstrate characteristic histopathology with small uniform cells with hyperchromatic nuclei, rosettes, and ++ mitoses.
Congenital rhabdomyosarcoma	Often presents as an enlarging subcutaneous nodule most commonly in the head and neck region, extremities, genitourinary tract, trunk, orbit, intrathoracic region, or retroperitoneum.	Blueberry muffin represents metastases to the skin and is rare, although often presents in infancy on the face when it does occur. Initial lesion may mimic the appearance of a deep hemangioma.	Histopathology of the lesion shows a low degree of differentiation with four possible subtypes, thus immunohistochemistry required for diagnosis.
Hematologic			
Hemolytic disease of the newborn	Patients exposed in utero: severe hydrops fetalis with anasarca, heart failure, pulmonary edema, hepatosplenomegaly, pallor, jaundice within first 24 h life. Patients exposed at birth: may be asymptomatic other than jaundice within first 24 h and lethargy.	Main cutaneous finding is blueberry muffin rash.	CBC: increased reticulocytes in context of no blood loss, and mild anemia due to rapidly falling hemoglobin. Hyperbilirubinemia in first 24 h of life. ABO incompatibility with mother. Positive Coombs test. RBC smear: spherocytes.
Hereditary spherocytosis	Hydrops fetalis, jaundice, and splenomegaly.	Main cutaneous finding is blueberry muffin rash.	CBC: mean corpuscular hemoglobin concentration $>\geqslant$ 36.0 g/dL and anemia. Blood smear: mild to severe hemolytic anemia with spherocytes. Hyperbilirubinemia. Osmotic fragility test confirms presence of spherocytes.
Twin–twin transfusion syndrome	Donor twin utero: hypovolemia, intrauterine growth restriction, polyhydramnios, and chronic hypoxia.	Main cutaneous finding is blueberry muffin rash.	CBC: anemia or polycythemia. Often diagnosed on routine anatomy ultrasounds in utero.

Source: Adapted from American Academy of Pediatrics,[12] see Table 2.

ALT: alanine transaminase; TSH: thyroid-stimulating hormone measurement; CT: computed tomography; CBC: complete blood count, including hemoglobin, white blood cell, differential count, and platelet count; CNS: central nervous system; CSF: cerebrospinal fluid; VDRL: venereal disease research laboratory test; VZV: varicella-zoster virus; IgG: immunoglobulin G; PCR: polymerase chain reaction; HSV: herpes simplex virus; WBC: white blood cell count; IgA: immunoglobulin A; IgM: immunoglobulin M; DFA: direct fluorescent antibody; APTT/PTT: activated partial thromboplastin time/partial thromboplastin time; AST: aspartate transaminase; γGT: gamma-glutamyltransferase; INR/PT: international normalized ratio/prothrombin time; ESR: erythrocyte sedimentation rate.

associated with a self-healing, limited cutaneous form of this disease include early disease onset of isolated skin involvement, quick resolution of skin lesions, and lack of BRAF mutation.[24]

Authors' note

The views expressed in the submitted article are that of the authors and not an official position of the institution.

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Informed consent

Informed consent was obtained from the patient's parent for the use of non-identifying photos of his lesions for academic purposes.

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