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BRAF V600E-Positive Multisite Langerhans Cell Histiocytosis in a Preterm Neonate

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Abstract

Hemorrhagic pustules with a “blueberry muffin” appearance accompanied by respiratory failure in a neonate present a challenging differential diagnosis that includes infections and neoplasms. We present a case of multiorgan, multisite Langerhans cell histiocytosis (LCH), positive for the oncogenic BRAF V600E mutation, in a preterm neonate. Infants with LCH pose a diagnostic challenge due to their heterogeneous presentations. This case is unusual in that the newborn presented with severe multiorgan involvement. Due to the rare incidence, wide spectrum of clinical manifestations, and high mortality rate, clinicians must maintain a high index of suspicion for LCH.

Keywords

► Langerhans cell histiocytosis
► BRAF V600E
► preterm neonate
► multiorgan
► multisite
► hemorrhagic pustules

“Blueberry muffin baby” is a term describing the cutaneous manifestations of various congenital infections and neoplastic diseases. Especially in infants in whom these cutaneous findings are accompanied by severe illness, providers must rapidly navigate the broad range of possibilities. Here, we outline the most likely diagnoses with this presentation and discuss a case of Langerhans cell histiocytosis (LCH) in a preterm neonate with severe multiorgan involvement.

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Case Report

A 4-day-old preterm male neonate was transferred to the neonatal intensive care unit (NICU) for evaluation of respiratory failure and cutaneous hemorrhagic pustular lesions. The neonate was born at 33\(\frac{1}{7}\) weeks’ gestation at 2,204 g to a 36-year-old gravida 5, para 2 mother. Maternal prenatal infectious history was negative. Prenatal ultrasounds detected a single lesion below the fetus’ left eye that could not be further characterized.

The neonate was born via spontaneous vaginal delivery. In the delivery room, the newborn required intubation and cardiopulmonary resuscitation due to apnea and bradycardia. He was subsequently transferred to the NICU. On exam, his weight and length were at the 75th percentile, with head circumference at the 25th percentile. Exam revealed multiple cutaneous lesions of varying size all over his body, including his oral mucosa, hands, and feet (Fig. 1A). The spleen tip and liver edge were both palpable 1 to 2 cm below the costal margin.

Initial laboratory evidence was significant for pH 6.6 with \(\text{PCO}_2\) 86 and \(\text{HCO}_3\) 24, hemoglobin 17 g/dL, WBC 19,000 cells/μL, platelet count 147,000 cells/μL, Gamma-Glutamyl Transpeptidase (GGT) 1,014 U/L, total bilirubin 11 mg/dL, direct bilirubin 2.5 mg/dL, prothrombin time 15.2 seconds and partial thromboplastin time 56 seconds. On peripheral blood smear, mature neutrophils were predominant, and no blasts were seen. These data were interpreted as showing severe uncompensated respiratory acidosis, mild erythroblastosis without evidence of marrow infiltration, and hepatic dysfunction leading to coagulopathy.

The newborn was transitioned from conventional mechanical ventilation to high-frequency ventilation and developed a pneumothorax. Upon transfer to a tertiary NICU, refractory hypoxia and a combined metabolic and respiratory acidosis persisted despite high-frequency ventilation and the addition of nitric oxide. A chest radiograph illustrated hyperinflation and cystic-appearing blebs. The neonate had negative tests for cytomegalovirus (CMV), herpes simplex virus (HSV), varicella zoster virus, human immunodeficiency virus, paramyxovirus, toxoplasma, syphilis, parvovirus B19, and rubella. Placental pathology was consistent with chronic and focal villitis. The initial microscopic appearance of this disease process on abdominal skin biopsy was highly atypical and suggestive of hematologic malignancy; Leukemia cutis was first considered, but immunohistochemistry suggested LCH. Despite maximal respiratory and cardiovascular support, the newborn’s condition deteriorated, and care was redirected toward comfort measures.

The family consented to a full autopsy. External examination demonstrated diffuse black papules and pustules preferentially involving the hands and feet. Internal examination revealed disease involvement of multiple sites in the chest and abdomen. Most striking were the lungs, which appeared consolidated and contained multiple cavitations and hemorrhagic nodules with interspersed normal-appearing parenchyma (Fig. 1B). The thymus was enlarged and friable. Tumor nodules were found on the gastrointestinal tract, liver, pancreas, and adrenal glands. Histologic analysis of the skin lesions, lungs, thymus, and abdominal tumor nodules demonstrated a histiocytic infiltrate with occasional eosinophils and other inflammatory cells. The histiocytes had poorly defined cell borders and grooved nuclei, and they exhibited immunohistochemical expression of S100, CD1a, and Langerin, establishing the diagnosis of multisite, multisystem LCH. DNA extracted from the lesional tissue was positive for the BRAF V600E mutation on pyrosequencing.

Discussion

The differential diagnosis of hemorrhagic vesicopustules and respiratory failure in a preterm neonate can be dichotomized into infectious and noninfectious etiologies. Congenital infections should always be considered, including those listed in Table 1. CMV and HSV can present with cutaneous manifestations and systemic illness as presented here, such as profound respiratory and multiorgan involvement.\(^1\) However, diagnoses like toxoplasmosis or syphilis are unlikely given the lack of lymphadenopathy.\(^2\)

In severely ill infants, congenital malignancies should be the noninfectious diagnoses highest on the differential. Congenital leukemias, most often acute myelogenous leukemia and occasionally acute lymphocytic leukemia, are the neonatal cancers most associated with cutaneous manifestations but are unlikely to directly cause lung disease.\(^3\) Neuroblastoma and rhabdomyosarcoma can present in
neonates with skin metastases and produce lung tumors, although these would be unlikely to be cystic.

LCH is a rare, proliferative disease of Langerhans cells, usually affecting children, with an incidence of five per million. What was formerly considered a group of distinct histiocytic disorders, including Hand-Schüller-Christian disease, Letterer-Siwe disease, eosinophilic granuloma, and histiocytosis X, is now unified into a single disease. This classification emerged with the discovery that the abnormal cells in all of these disorders have ultrastructural features and surface antigens characteristic of Langerhans cells. Today, LCH is classified based on number of sites and organs involved. Single-site disease is the most predominant and has a favorable prognosis. Multisystem disease without risk organ involvement has a good prognosis, whereas multisystem disease involving any risk organ (lung, liver, or bone marrow) is often fatal.

Infants with LCH pose a diagnostic challenge due to their heterogeneous presentations. There have been small case series attempting to correlate clinical findings with prognosis, but results are inconsistent and data are scant. One retrospective series found that the most common presenting skin lesions were erythematous, often crusted, and vesiculo-pustular in nature and, more importantly, that the type of skin lesions were erythematous, often crusted, and vesiculo-pustular in nature and, more importantly, that the type of skin lesions were erythematous, often crusted, and vesiculo-pustular in nature and, more importantly, that the type of skin lesions were erythematous, often crusted, and vesiculo-pustular in nature and, more importantly, that the type of skin lesions were erythematous, often crusted, and vesiculo-pustular in nature and, more importantly, that the type of skin lesions were erythematous, often crusted, and vesiculo-pustular in nature and, more importantly, that the type of skin lesions were erythematous, often crusted, and vesiculo-pustular in nature and, more importantly, that the type of skin lesions were erythematous, often crusted, and vesiculo-pustular in nature and, more importantly, 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