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Case presentation

“Blueberry muffin” rash and large right thigh mass: a unique presentation of Langerhans cell histiocytosis

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Abstract

Langerhans cell histiocytosis (LCH) is a clonal proliferation of bone marrow derived antigen-presenting cells that can involve a spectrum of cutaneous findings, with or without internal organ involvement. Neonatal LCH almost always presents with skin findings usually petechial papules and/or erosions in a seborrheic distribution, with or without extracutaneous involvement. Previously described as varying entities, LCH is now considered a single disease process demonstrating a spectrum of clinical findings. We report a unique case of neonatal LCH presenting with a “blueberry muffin” rash in conjunction with a large soft tissue tumor.

Case Synopsis



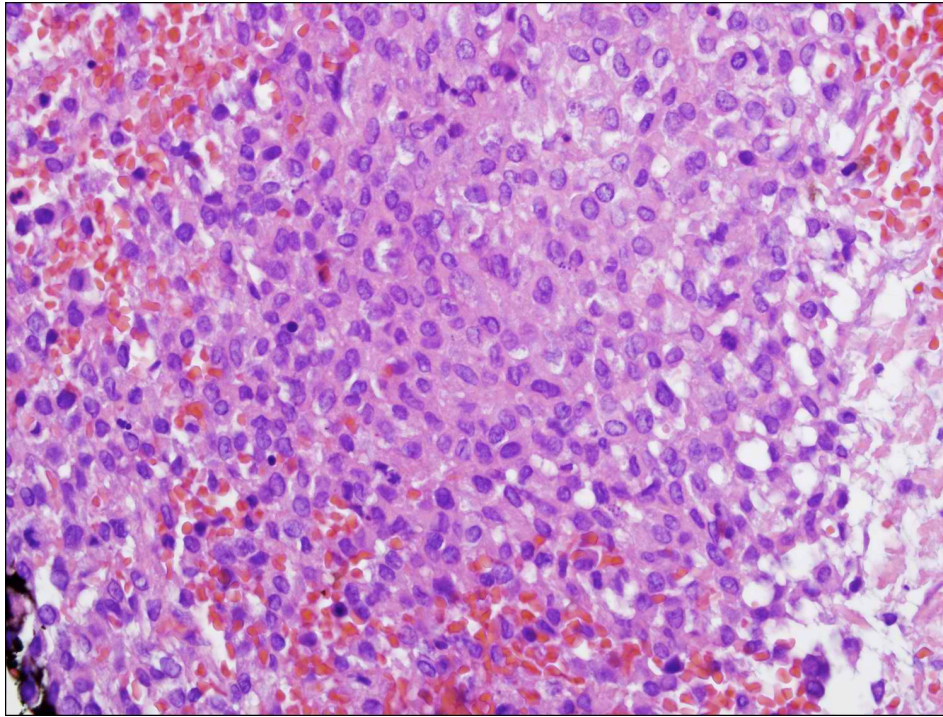
Figure 1. Large right thigh mass

Figure 2. Multiple erythematous and violaceous papules

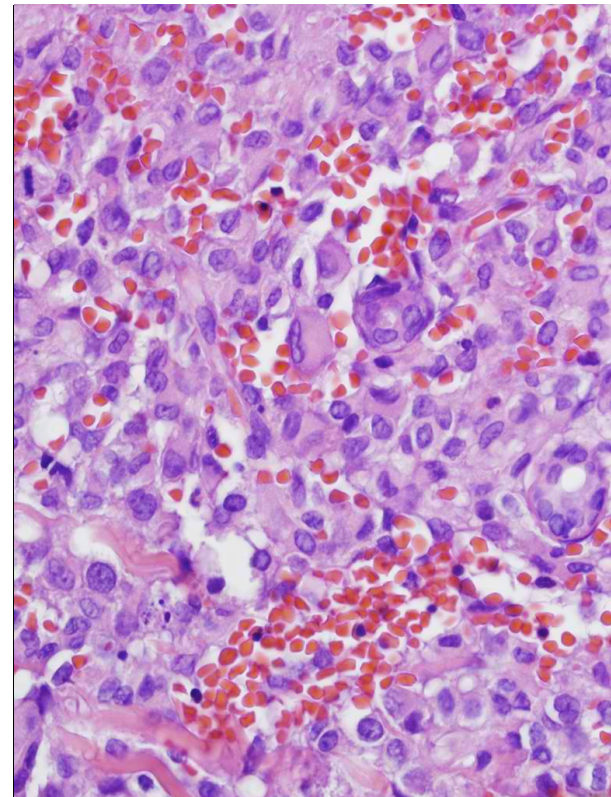
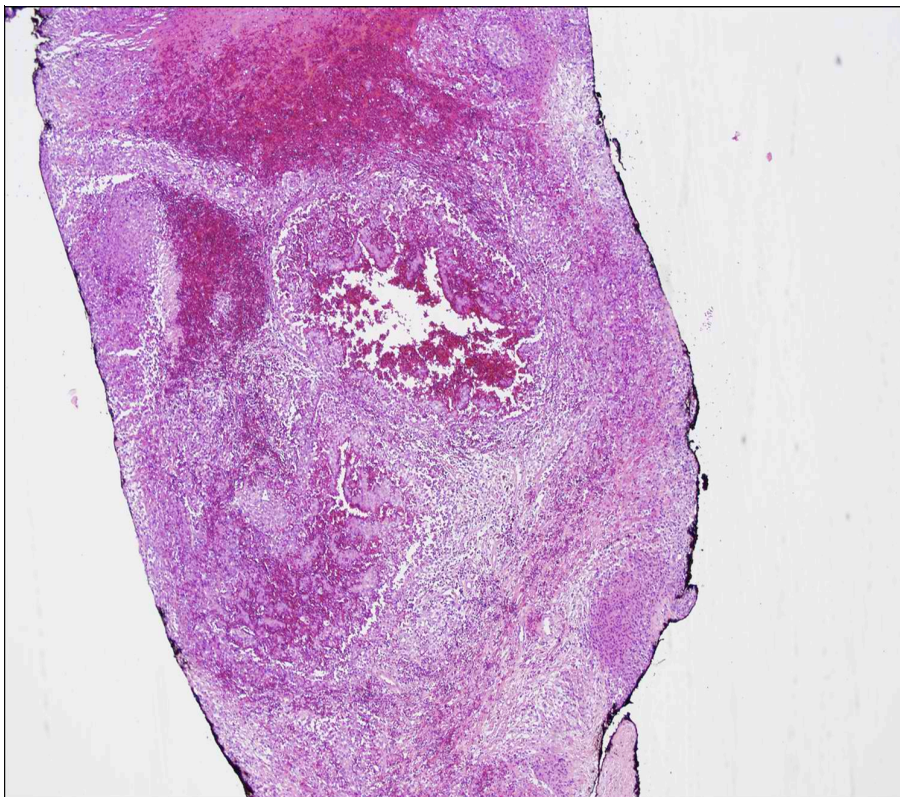
A full-term male infant was born with a “blueberry muffin” rash and a large, firm thigh mass. He was born via caesarian section following an uncomplicated prenatal course, including normal ultrasounds. Examination demonstrated a 12 x 8 cm firm, fixed mass of the right anterior thigh (Figure 1). He also had diffuse, non-blanching, purple macules and papules on the face, neck, and abdomen.

(Figure 2). The remainder of exam was normal, without dysmorphic features, cardiac/pulmonary abnormalities, oral lesions, hepatosplenomegaly, or lymphadenopathy.

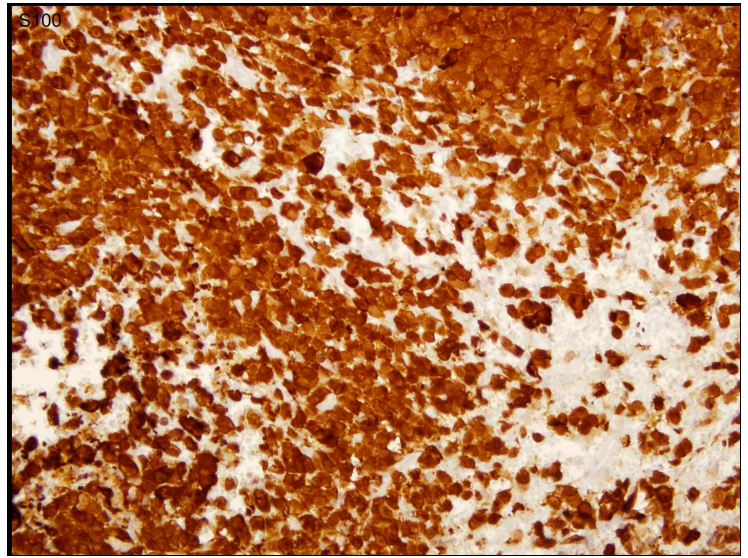
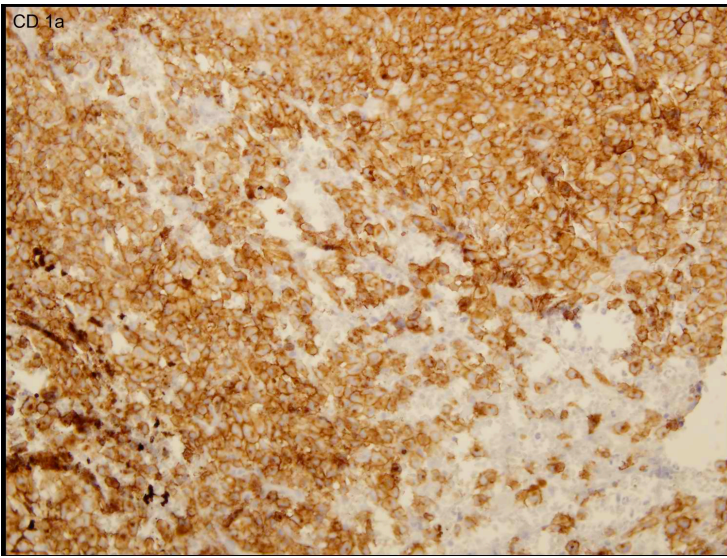
Laboratory evaluation demonstrated an abnormal white count of 24.2; hemoglobin/hematocrit, basic chemistry, and liver function tests were all normal. X-rays at 24-hours showed calcifications within the thigh mass.



**Figure 3. Biopsy of the abdomen demonstrates epithelioid cells with hemorrhage**

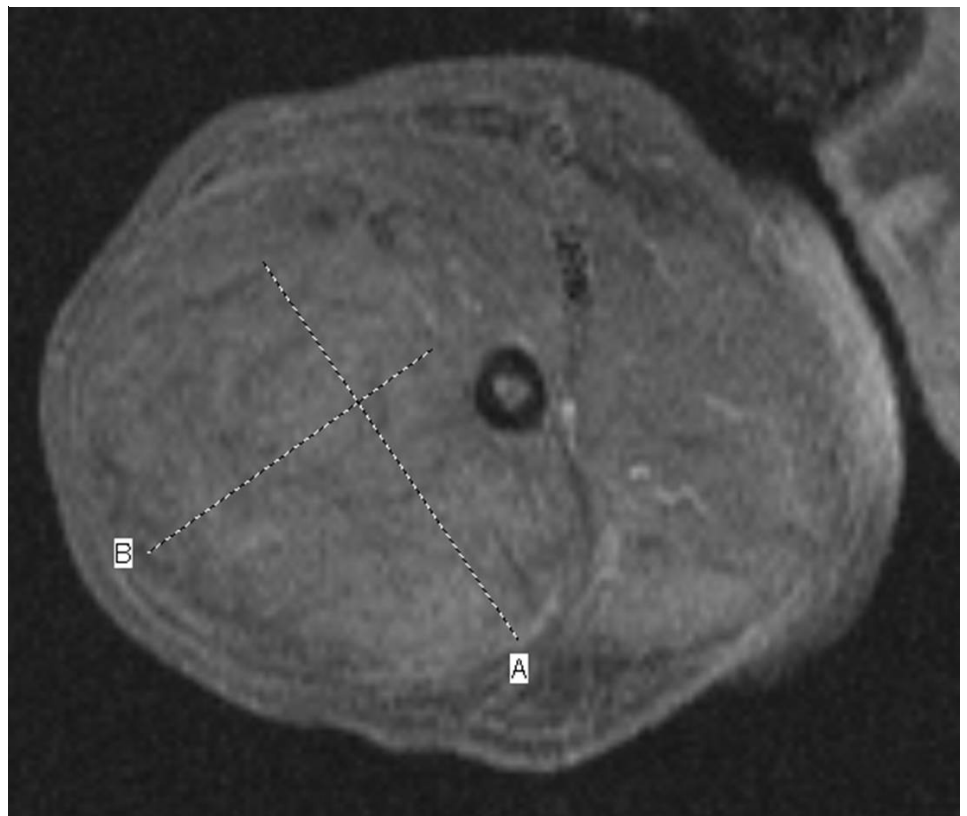
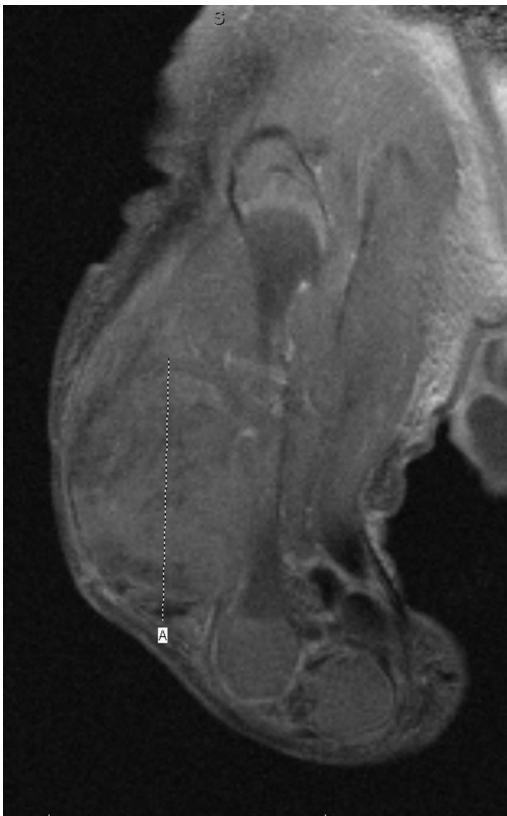


**Figure 4a, 4b. Punch biopsy of the right thigh mass. Low power (10x) with collections of epithelioid cells and hemorrhage. High power (40x) shows reniform shaped nuclei.**



**Figure 5a, 5b.** Immunohistochemical stains for the right thigh mass are diffusely positive for CD1a (a) and S100 (b).

Skin biopsies were obtained from the abdomen (Figure 3) and right thigh (Figure 4a and 4b). Both demonstrated identical findings: sheets of homogenous epithelioid cells strongly positive for CD1a (Figure 5a) and S100 (Figure 5b) stains. Incisional biopsy showed the same. MRI of the right leg revealed a 3.7 x 2.9 x 4.8 cm mass with T1 signal intensity isotense to muscle (Figure 6a and 6b). The bone, marrow, and lymph nodes were normal.

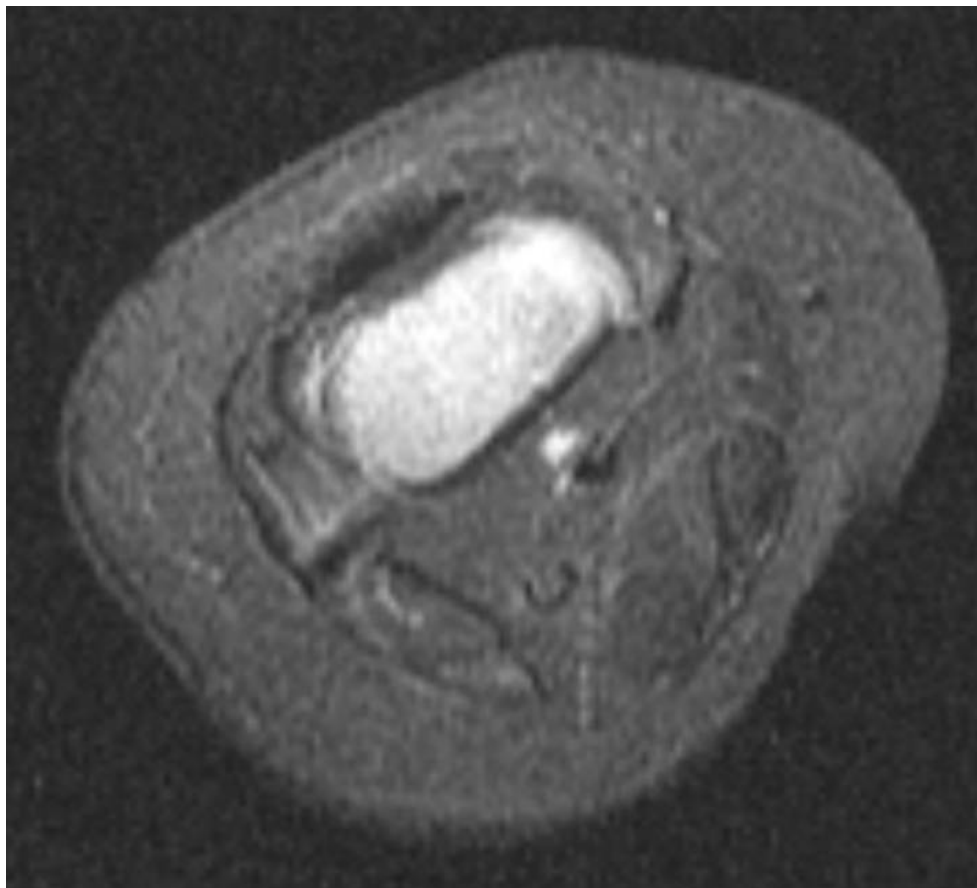


**Figure 6a, 6b.** MRI of the right thigh mass on day 3 of life

Further evaluation included: skeletal survey, chest x-ray, and chest/abdomen/pelvis CT - all normal. Our patient was therefore classified as low-risk multisystem LCH with involvement of the skin, soft tissue, and possibly muscle. Prednisone and vinblastine were initiated based on LCH-III international treatment protocol as published by the Histiocyte Society [1]. At 6 weeks of age and 4 rounds of chemotherapy, the thigh mass and skin lesions completely resolved clinically (Figure 7a and 7b) and by imaging (Figure 8). Chemotherapy will be continued for the next year.



**Figure 7a, 7b. Abdomen and legs status post 4 rounds of chemotherapy with prednisone and vinblastine**



**Figure 8. Follow-up MRI confirms resolution of the right thigh mass after 4 rounds of chemotherapy**

## **Discussion**

“Blueberry muffin rash” describes a diffuse purpuric eruption typically related to extramedullary hematopoiesis. The differential diagnosis includes: “TORCH” infections (toxoplasmosis, rubella, cytomegalovirus, herpes simplex), leukemia, lymphoma, neuroblastoma, LCH, neonatal lupus, hemolytic disease (ABO or Rh incompatibility), hereditary spherocytosis, twin-twin transfusion syndrome, multiple hemangiomas, multifocal lymphangioendotheliomatosis, blue rubber bleb nevus syndrome, and glomangiomas [2, 3]. The differential diagnosis for a fixed congenital mass includes rhabdomyosarcoma, myofibromatosis, infantile fibrosarcoma, and other tumors.

LCH (formerly Histiocytosis X) is characterized by a clonal proliferation of bone marrow derived Langerhans cells. Etiology is controversial, however, an oncogenic mechanism is favored over immune dysregulation [4]. Previously, the disease was separated into 3 classifications: eosinophilic granuloma, Hand-Schuller-Christian, and Letterer-Siwe [5]. Hashimoto-Pritzker syndrome, distinct from the above diagnoses, described neonates with spontaneously resolving cutaneous involvement [6].

Prognosis is based on: age of onset, number of organs involved, organ dysfunction, and severity of disease [7]. Treatment is guided by the extent of disease at diagnosis. Therefore, a new classification system has been employed. In 1990, the LCH Study Group (of the Histiocyte Society) adopted a stratification system [8]. 'Single-system' LCH is divided into single site (unifocal bone, skin, or lymph node) versus multiple sites (multifocal bone or lymph nodes). 'Multisystem' LCH (MS-LCH) is defined as 2+ organ systems at the time of diagnosis, with or without organ dysfunction. MS-LCH is subdivided into 'low-risk' and 'high-risk.' Low risk patients have no involvement of 'high-risk' organs (liver, lungs, spleen, hematopoietic). High-risk patients have one or more of these organs involved.

Evaluation of a patient with suspected LCH includes: complete blood count, basic metabolic panel, liver function tests, skeletal survey, and chest x-ray. Further imaging/studies are directed by detected abnormalities. The gold standard for diagnosis requires the presence of Birbeck granules on electron microscopy, but diagnosis can be made with the use of CD1a, S100 and/or CD45 immunostaining on histopathologic specimens [9,10].

Treatment is based on system(s) involved. For single-system organ involvement, options include: local and/or systemic treatment versus watchful waiting, on a case-to-case basis. Many children with isolated skin LCH spontaneously improve without treatment, but should be followed because they can progress to disseminated, sometimes even fatal, forms. Non-resolving skin nodules can be treated with topical steroids (first line therapy) and resistant cases with surgical excision, nitrogen mustard, and/or psoralen with ultraviolet photochemotherapy (PUVA). MS-LCH is almost always treated with chemotherapy. The goal of treatment is to reduce mortality and prevent reactivation and late sequelae. However, randomized chemotherapy trials initiated by the Histiocyte Society have identified regimens that are effective in terms of initial disease response but show reactivation rates of > 50%, which has prompted further analysis [8].

Our literature review revealed four reports of LCH presenting as a soft tissue tumor; none had skin involvement. In a 1970s review of 36 pediatric cases, one neonatal case with a soft tissue neck tumor was reported. Treatment involved local excision without evidence of disease at 4 years follow-up [11]. A second case described a solitary soft tissue tumor of the leg in a 48 year-old male without bone or skin involvement. He was treated with etoposide and prednisone and remained disease-free at 3 years follow-up [12]. A third report described a solid neck mass in a 2-week-old female. Seventy percent of the tumor was excised, secondary to involvement of major vessels, followed by systemic therapy (vinblastine/prednisolone) for 8 months. At 18-month follow-up, the patient was well with a small residual neck mass [13]. A final case describes an isolated congenital thigh mass in a 4-week-old male without bone or skin abnormalities. No treatment was rendered and at 12 months follow-up, imaging showed reduction of the mass without local sequelae [14]. Each of these cases was classified as single organ involvement LCH.

Whereas LCH presenting as extramedullary hematopoiesis and as congenital soft tissue tumor have been described separately, to our knowledge, this is the first report of congenital LCH presenting with both findings.

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