Digestive Tract Symptoms in Congenital Langerhans Cell Histiocytosis: A Fatal Condition in an Illness Usually Considered Benign

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Introduction: Congenital Langerhans cell histiocytosis is usually limited to cutaneous lesions and has a good prognosis. In rare cases of gut involvement, mortality is high and early and aggressive treatment essential.

Materials and Methods: We report a case of histiocytosis in a newborn with bowel involvement, and performed a literature review of 13 similar cases worldwide documented between 1973 and 2008.

Results: Skin eruptions are usually the initial symptoms at birth. Bloody stools or protein-losing enteropathy are the first signs of bowel involvement that appear mostly in the first 4 weeks of life. Risk organs (hematopoietic system, liver, spleen) are often affected in the newborns with intestinal Langerhans cell histiocytosis. Prognosis is usually poor, with 78.5% mortality.

Conclusions: Even if histiocytosis in a neonate appears limited to autoinvoluting skin lesions, it is important to exclude all other organ involvement, including the bowel and stomach, as early treatment is vital.

Key Words: newborn, congenital Langerhans cell histiocytosis, gastrointestinal tract, skin disease, spontaneous remission

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Langerhans cell histiocytosis (LCH) can involve many organs. The neonatal form of LCH usually presents as a cutaneous eruption. The morphologic characteristics of the skin lesions, even their spontaneous regression, do not indicate the extent and prognosis of the disease.[1] We report a neonate with multiple congenital autoinvoluting papular purpuric skin lesions and involvement of the bowel. The gastrointestinal tract (GIT) is not considered a risk organ in LCH by The Histiocyte Society. To assess the impact of neonatal LCH gastrointestinal (GI) involvement, a literature review of gut LCH in this age period was made.

CASE REPORT

A term female baby was born after an uneventful pregnancy. Maternal serologies including hepatitis C and B, HIV, and gonorrhea were negative, and immunity to rubella virus was demonstrated. Group B streptococcus was negative. Birthweight was 3800 g. Multiple skin purpuric macules and papules, on the trunk, face, scalp, and plantar skin, resembling a "Blueberry Muffin Baby," were noted at birth. They ranged in size from 2 to 6 mm (Fig. 1A). The infant had a healthy appearance and was nondismorphic. Complete blood cell count revealed a thrombocytopenia of 20,000/μL platelets requiring transfusion of platelets. Liver and renal function tests, blood coagulation, urine analysis, serologies, blood and urine cultures, and lymphocyte population including CD1a were normal. Cardiac, abdominal, and cerebral ultrasounds were normal. At 2 days of life C-reactive protein was elevated with ascending values in the following days up to 14 mg/dL. A wide-spectrum antibiotherapy was started. Skin biopsy of 2 representative papules showed a dermal diffuse infiltration of large histiocytic cells with renoform nuclei staining for S100. A CD1-positive immunohistochemical stain and detection of Birbeck granules by electron microscope confirmed the diagnosis of LCH (Figs. 1B–D).

The skeletal survey, chest, and cranial x-rays showed no evidence of systemic involvement. At 15 days of age, when cutaneous lesions had almost disappeared, the patient presented bloody diarrhea. A colonoscopy was scheduled, and the intestinal biopsy demonstrated LCH in the colon. At the same time acute phase parameters (C-reactive protein) were very high; a chest computed tomography showed bilateral diffuse consolidations and multiple nodular or cystic lesions and another bone.

The x-ray evidenced lytic lesions of ribs, scalp, and the right femur. After the diagnosis of LCH with multisystem involvement, therapy with intravenous prednisone (daily) and Vinblastin (weekly) was begun, as recommended by The Histiocyte Society. The patient presented global improvement after 6 weeks of treatment, with diminished pulmonary and bone lesions and absence of intestinal infiltration. After initial course of treatment, continuous therapy followed with oral Prednisone and Vinblastin every 3 weeks and daily Mercaptopurine. New gastric and intestinal biopsies at 4 months were performed with a normal result. At 5 months of life, a gastrostomy was performed to avoid continuous tube feeding as the patient refused oral intake. The patient presented a few episodes of fever during the treatment and 1 episode of a cutaneous unspecific transitory rash. At 12 months of age chemotherapy treatment was stopped. Reevaluation at 13 months of life with a skeletal survey, lung computed tomography, intestinal biopsies, lymphatic populations, and abdomen ultrasound showed that all were normal. She is currently 28 months of age and has had no relapse.

DISCUSSION

Proliferation and dysfunction of Langerhans cells leads to the clinical spectrum of LCH.

Although multiple organ systems can be affected, cutaneous manifestation is often the first sign of the disease in neonates. It has been described as erythematous vesiculopustulous skin rash, as red-brown nodules, as a Blueberry Muffin Baby phenotype or as eczematous scaling lesions. Only about 20% present petequias or mucosal lesions.

LCH presenting with a congenital skin rash has been termed congenital self-healing reticulohistiocytosis to

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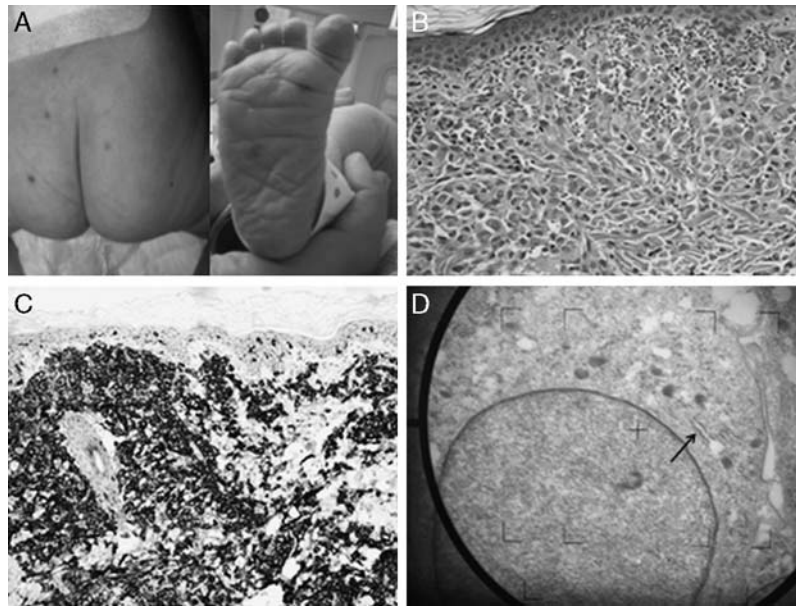

FIGURE 1. A, Multiple dark-blue to purple papules in the gluteal and plantar areas. B, Hematoxylin-eosin–stained cutaneous biopsy (original magnification: ×200). C, CD1a immunostaining in skin biopsy (original magnification: ×100). D, Rod-shaped or "tennis-racket" cytoplasmatic organelles (Birbeck bodies) in skin biopsy (original magnification: ×5000).

TABLE 1. Documented Cases in Literature of Neonates Affected by LCH With GIT Involvement

Case Number	Source	Age at Onset, Sex	Presenting Symptoms	Digestive Symptoms and GI Involvement	Other Organs Involved	Treatment	Outcomes
1	Current case	Birth, F	Skin lesions, diffuse violaceous macules, and papules	Bloody diarrhea at 2 wk of age, rectal and colon biopsies LCH +	Skin biopsy LCH + hematologic, pulmonary and bone involvement	Steroids, Vinblastine, Mercaptopurine	No active disease at 2 y
2	Aviner et al[4]	Birth, F	Skin lesions, vesiculopapulomacular lesions, discrete mucosa lesions	Bloody stools at 5 d of age, rectal biopsy LCH +	Skin biopsy LCH + cystic pulmonary lesions	Steroids, Vinblastine	Died at 26 d
3	Hait et al[3]	2 d of life, F	Skin lesions, white pustules on an erythematous base	Bloody stools in the first month of life, rectosigmoid, stomach biopsies LCH +	Skin biopsy LCH + , hematologic, liver and spleen involvement	Steroids, Vinblastine, low-dose Methotrexate, Mercaptopurine	Remission at 6 mo, relapsed at 13 mo and died
4	Stein et al[1]	< 1 mo, M	Skin lesions, eczematous (seborrhoea-like) dermatitis bloody stools	Bloody diarrhea < 1 mo of life	Skin LCH + , GI, bone, and liver	Prednisone, Vinblastine, Etoposide	No active disease at 4 y
5	Couderc et al[5]	Birth, F	Skin lesions, disseminated purpuric, nodulic, and maculopapulous elements at birth. Associated vomiting and diarrhea	Vomiting and diarrhea, EEP at 8 d, rectal biopsy LCH +	Skin LCH + , Bone marrow, liver, spleen	Steroids, Vinblastine, Etoposide, Vincristine, Cyarabine, Ciclosporine	Died at 32 mo
6	Geissmann et al[6]	Birth, F	Skin lesions	Diarrhea and bloody stools, EEP < 1 mo, colon and rectum biopsies LCH +	Skin LCH + , palate, hematologic dysfunction, hepatomegaly, and cholestasis	Steroids, Vinblastine, anti-CD1 antibodies	Died at 3.5 mo
7	Geissmann et al[6]	Birth, M	Skin lesions	Vomiting, EEP < 1 mo, duodenum biopsies LCH +	Skin LCH + , liver, hematologic dysfunction	Steroids, Vinblastine, Etoposide interferon-α	Died at 4 mo

TABLE 1. (*continued*)

Case Number	Source	Age at Onset, Sex	Presenting Symptoms	Digestive Symptoms and GI Involvement	Other Organs Involved	Treatment	Outcomes
8	Carlier-Mercier et al[7]	Birth, M	Skin lesions, purpuric, and xantomatous macules and papules	EEP at 11 d, duodenum biopsy LCH +	Skin LCH + , hepatic biopsy LCH +	Steroids, Vinblastine, Etoposide, Interferon	Died at 3.5 mo
9	Boccon-Gibod et al[8]	Birth, M	Skin lesions, generalized rash	EEP at day 14, duodenum and rectal biopsy LCH +	Skin LCH + , hematologic dysfunction, liver LCH +	Vinblastine, Etoposide	Died at 17 wks
10	Patel et al[9]	Birth, F	Bloody foul smelling, mucous diarrhea	Bloody foul smelling, mucous diarrhea, bile staining vomiting	Red scaly skin rash at 6 wk, jejunum and bone biopsies LCH + , lungs	Unspecified chemotherapy plus radiation	No active disease at 2 y
11	Lee et al[10]	Birth, F	Skin lesions, erythematous rash	From age 1 wk bloody diarrhea, rectal biopsy LCH +	Skin LCH + , osteolytic bone lesions, lung, liver, spleen	No treatment commented	Died at 16 wk
12	Lee et al[10]	Birth, F	Skin lesions, papulovesicular	From age 2 wk, bloody diarrhea, rectal biopsy LCH +	Skin LCH +	Steroids, Vinblastine, Mercaptopurine, Etoposide	Died at 10 mo
13	Tamura et al[11]	Birth, M	Skin lesions, eczematous, crusting, and bleeding eruptions	EEP first days of life	Skin LCH + , autopsy find liver, spleen, lung, intestine, bone marrow, adrenals, skull and thymus infiltration	Steroids, Vinblastine	Died at 46 mo
14	Keeling and Harries[12]	Birth, F	Skin lesions	Diarrhea at 6 wk, malabsorption, ileum, jejunum, and duodenum LCH +	Skin LCH + , autopsy revealed lung, hepatic involvement	Steroids, Vinblastine	Died at 11 wk

EEP indicates exudative enteropathy; GI, gastrointestinal; GIT, gastrointestinal tract; LCH, Langerhans cell histiocytosis.

emphasize the good prognosis. This term can cause confusion as multiple organs may be severely affected at the moment of diagnosing LCH or during follow up.[1–3] It seems that the morphologic characteristics of the skin lesions, even their spontaneous regression, do not indicate the extent and prognosis of the disease.

In the case series reported by Stein et al,[1] neonates with multisystem disease had a mortality rate of 16% but only 1 child had GI involvement.

To find cases of LCH in neonates with GIT involvement, Google and Pubmed literature searches were performed using the key words "Langerhans cell histiocytosis," "neonatal," and "gastrointestinal involvement." We found 13 similar cases. Presenting symptoms, GI symptoms, other organs affected, and outcomes are summarized in Table 1.

We reviewed 14 documented cases in the last 40 years including the present patient. From these, 8 cases were female and 6 male. The presenting symptom was in almost all neonates, a skin eruption at birth (13 of 14 cases), described as purpuric papules and macules, papulovesicular lesions, or as an eczematous rash. Only in 1 case skin eruptions appeared after GI symptoms at 6 weeks of age. GI symptoms occurred in 8 cases in the first 2 weeks of life, in 5 in the first month, and in 1 case at 6 weeks. Most of the neonates (8) presented bloody stools, 5 were diagnosed with exudative enteropathy and 1 with malabsorption. It seems that in cases of bowel involvement, other organs are often affected: the liver (9 cases), spleen (3), hematopoetic system (6), bones (4), and the lung (9).

Although the described case presently has a full remission at 2 years of age, prognosis in other similar cases has been poor, with 78.5% mortality. A total of 50% of these children (7) died in the first 4 months.

CONCLUSIONS

Literature shows that GIT involvement in LCH in the neonatal period is rare. Although the GIT is not considered a risk organ in LCH by The Histiocyte Society, prognosis was not good in most of neonatal cases reviewed. Skin lesions almost always preceded GIT disease, therefore, cutaneous LCH in the neonatal period requires aggressive evaluation and early treatment.

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