

Disseminated Langerhans' cell histiocytosis and massive protein-losing enteropathy

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Abstract

Symptomatic involvement of the gastrointestinal (GI) tract as a prominent symptom in Langerhans' cell histiocytosis (LCH) is uncommon, occurring in less than 1 to 5% of all cases, even when the disease is in its disseminated form. Up to now, there have been reports of 18 cases of LCH with GI manifestations, including our 2 cases, with diarrhea (77.7%), protein-losing enteropathy (33.3%) and bloody stool being the most frequent findings. The authors present two patients with severe diarrhea and refractory hypoalbuminemia, and with the protein-losing enteropathy documented by Cr⁵¹-labeled albumin studies. A review of the literature indicated that the presence of GI symptoms is often associated with systemic disease as well as with poor prognosis, mainly under 2 years of age. Radioisotopes are useful for documenting protein loss in several diseases with high specificity and sensitivity, and their utilization in the cases reviewed here permitted diagnoses in 6 children, as well as improved therapeutic management.

Key words

- Langerhans' cell histiocytosis
- Histiocytosis X
- Gastrointestinal involvement
- Protein-losing enteropathy
- Hypoalbuminemia
- Cr⁵¹-labeled albumin test

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Introduction

In 1953, Lichtenstein (1) introduced the term histiocytosis X to integrate Hand-Schüller-Christian syndrome, Letterer-Siwe disease, and eosinophilic granuloma of the bone, a group of diseases with similar histopathological characteristics. In 1973, histiocytosis X was described as local proliferation as well as dissemination of Langerhans' histiocytes (2). Since Langerhans' histiocytes are considered to be the main lesion cells in this disorder, in 1983, Risdall et al. (3) suggested naming the disease Langerhans' cell

histiocytosis (LCH).

Confidence levels for the diagnosis of LCH have been established by the Histiocyte Society (4). A "presumptive diagnosis" is based on the examination of conventionally processed tissue that presents a lesion which is consistent with those described in the literature, such as Langerhans' cells (large cells that have abundant, pale cytoplasm, with folded or grooved nuclei). A higher confidence level for diagnosis, simply called a "diagnosis", is arrived at when findings from a presumptive diagnosis are complemented by the presence of at least two of the follow-

ing characteristics: immunohistochemical confirmation with staining for S-100 protein, ATPase, alpha-D-mannosidase, or peanut lectin binding. A "definite diagnosis" requires the presence of Birbeck granules in the lesion cells upon electron microscopic examination or demonstration of T6 (CD1A) antigenic determinants on the surface of the lesion cells.

Although the literature on LCH is extensive, this disorder in combination with gastrointestinal (GI) involvement is rarely described (5-7). Even in these few cases, GI complications seldom appear as prominent clinical manifestations. The main clinical findings regarding intestinal disease include diarrhea (sometimes bloody) and protein-losing enteropathy (8).

In this study, we report two patients with disseminated LCH admitted to the Instituto da Criança (ICr). Both cases involved massive protein-losing enteropathy demonstrated by tests performed with Cr⁵¹-labeled albumin. Based on our experience and on a review of the existing literature on GI involvement in LCH, we discuss the role of enteral protein loss in the maintenance of hypoalbuminemia as an aggravating factor in patients with disseminated LCH.

Case reports

Case 1

A 2-year-old white girl with a three-month history of diarrhea, daily fever, anasarca, oliguria, an ulcerated lesion of the scalp, disseminated petechiae, hepatomegaly and splenomegaly, as well as a tumor on the left frontal region was examined in our service.

Initial laboratory findings revealed: hemoglobin level = 3.7 g/dl; hematocrit value = 12%; white blood cell count = 1,900/mm³; platelet count <5,000/mm³; blood urea nitrogen level = 137 mg/dl (considered as dehydration); creatinine clearance level = 0.5 mg/dl; serum albumin level = 1.1 g/dl; total

bilirubin level = 4.6 mg/dl (or 3.5 mg/dl of direct bilirubin); prothrombin activity = 24.4%; skin and bone marrow biopsy results consistent with LCH.

The patient continued with anasarca, persistent hypoalbuminemia, and massive diarrhea, in spite of several blood and albumin transfusions, as well as administration of parenteral nutritional support. Enteral protein loss was investigated by Cr⁵¹-labeled albumin tests. The dose administered was equivalent to 0.5 microcurie/kg. Results revealed an enteral loss equivalent to 81.5 ml of plasma per day (normal value = 14.6 ± 9 ml/day).

The patient did not respond to support with daily albumin. Her hypoalbuminemia persisted in spite of treatment with vinblastine, methotrexate, prednisone, and etoposide. She died two months after diagnosis due to respiratory and cardiac failure, digestive hemorrhage, and hemorrhagic ascites.

Case 2

A 2-year-old white boy with a six-month history of jaundice, fever, pallor, diarrhea, loss of weight, hepatomegaly, ascites, skin and mucosal lesions, and diabetes insipidus was examined in our service.

Laboratory findings revealed: hemoglobin level = 11.9 g/dl; white blood cell count = 22,200/mm³; platelet count = 310,000/mm³; blood urea nitrogen level = 43 mg/dl (considered as dehydration); creatinine clearance level = 0.6 mg/dl; total bilirubin level = 10.3 mg/dl (or 9.7 mg/dl of direct bilirubin); prothrombin activity = 38%; serum albumin level = 2.1 g/dl; biopsy results of a palate lesion consistent with LCH.

The patient continued with anasarca, persistent hypoalbuminemia, and massive diarrhea in spite of several blood and albumin transfusions, as well as administration of parenteral nutritional support. Enteral protein loss, determined by Cr⁵¹-labeled albumin tests, as done in case 1, revealed an

enteral loss equivalent to 75 ml of plasma per day.

Despite daily albumin administration, diarrhea and hypoalbuminemia persisted. Treatment with prednisone, cyclophosphamide, chlorambucil, and hydroxyurea was unsuccessful. The patient developed severe thrombocytopenia and died five months after diagnosis.

The families of both children refused permission for further studies at autopsies.

Discussion

LCH with GI tract involvement is rare and is usually recognized only at post mortem examination of patients with multi-organ lesions (9-13). Although most studies that have included large series of patients with disseminated LCH do not report GI symptoms (6,7,14), two children admitted to our service had diarrhea, representing 4.6% of all patients with LCH seen at our institution between 1976 and 1991.

In spite of the difficulty in assessing the frequency of GI involvement, Hyams et al. (15) reported GI symptoms in less than 1% of all patients, based on a review of other series that included 145 patients (12,16-18). Skopnic et al. (19) showed an estimated incidence of 5% of GI tract involvement in disseminated LCH. Idliki and Hamoudi (20) discussed a case with primary LCH of the bowel at the time of diagnosis.

Virtually all children described in the literature had multi-systemic disease, but GI disorders were rarely a prominent feature. Typically, LCH occurs either at sites in the skin or lymph nodes, where Langerhans' cells or their precursors thrive, or in organs such as the lung or liver, as a result of certain pathological conditions (21,22). Although it would seem that GI tract invasion would be related to multi-systemic, widespread disease, Keeling and Harries (11) have demonstrated that histological involvement of the GI tract in LCH may be more frequent than

the classical textbook descriptions of this disease suggest.

A summary of 18 reported cases, including ours, is presented in Table 1. Patients' ages ranged from the neonatal period (congenital form) to 3 years, with a median age of 4 months. Two thirds of the affected children were females. Table 2 outlines the most frequent clinical manifestations of LCH with GI complications, including diarrhea (sometimes bloody), vomiting, and protein-losing enteropathy. Malabsorption and intestinal ulceration with melena and perforation were rarely described (11,23-25). As Table 2 illustrates, LCH patients with intestinal disease present a high frequency (33.3%) of protein-losing enteropathy.

Even though GI tract dysfunction has not been identified as critical for prognosis (26), most of the patients affected by it have fared poorly, probably due to multi-systemic dissemination of the disease. According to Jaffe et al. (8), the definitive diagnosis of LCH based on the Histiocyte Society criteria (4) is usually made beforehand at another site. Although histologic findings confirm the presence of S-100 protein, clinical findings are often sufficient to document GI involvement.

After confirming our diagnoses by positive stains of S-100 protein from skin biopsies, we documented the protein loss with Cr⁵¹-labeled albumin tests, a method that is widely used to identify enteric protein loss (27).

Cr⁵¹-labeled albumin is neither significantly absorbed nor secreted into the GI tract. Following intravenous administration of Cr⁵¹-labeled albumin, normal adult subjects excrete 0.1 to 0.7% of the administered radioactive element in their stools during a subsequent four-day period (28). Pediatric patients with enteric protein loss excrete a greater amount of the administered dose during similar periods (28,29). No false-negative or false-positive results were found in over 200 studies that used Cr⁵¹-labeled albu-

Table 1 - Clinical manifestations of GI tract involvement in LCH in 18 children, including our 2 cases.

*Congenital; EM = electron microscopy; PLE = protein-losing enteropathy; ? = not reported.

Case/author (Reference)	Age at diagnosis	Sex	Clinical findings	Diagnostic method	Follow-up after diagnosis
1 Keeling and Harries (11)	2 months	F	Diarrhea, malabsorption, PLE	Presumptive	Death, 5.8 months
2 Tamura et al. (30)	1 day	M	PLE	EM	Death, 1.5 months
3 Deprettere et al. (31)	8 months	F	Diarrhea (bloody)	EM	Death, 5.0 months
4 Hyams et al. (15)	4 months	F	Diarrhea (bloody)	EM, CD1A	Death, 5.5 months
5 Idliki and Hamoudi (20)	9 months	F	Diarrhea, malabsorption	S-100	Death, 2.5 years
6 Sutphen and Fechner (23)	3 years	F	Diarrhea, intestinal perforation	Presumptive	Alive, 5.0 years
7 Raney Jr and D'Angio (13)	?	?	?	?	Alive, 7.2 years
8 Egeler et al. (25)	6 months	M	Diarrhea (bloody), vomiting	EM, CD1A	Alive, 2.0 years
9 Egeler et al. (25)	10 months	F	PLE, vomiting	EM	Death, 1.2 years
10 Egeler et al. (25)	4 months	M	Diarrhea, vomiting	EM	Death, 1.5 years
11 Lee et al. (22)	3 weeks*	F	Diarrhea (bloody)	EM, CD1A	Death, 10.0 months
12 Lee et al. (22)	1 month*	F	Diarrhea (bloody)	EM, CD1A	Death, 5.5 months
13 Boccon-Gibod et al. (24)	2 weeks*	M	PLE	EM, CD1A	Death, 1.0 month
14 Boccon-Gibod et al. (24)	28 months	F	Diarrhea, melena	EM, CD1A	Alive, 1.5 years
15 Pittschieler et al. (17)	12 months	F	Diarrhea, vomiting	EM, CD1A, S-100	Death, 1.0 month
16 Skopnik et al. (19)	10 months	F	Diarrhea (bloody)	?	?
17 Santos-Machado et al. (present study)	24 months	F	PLE, diarrhea	S-100	Death, 2.0 months
18 Santos-Machado et al. (present study)	24 months	M	PLE, diarrhea	S-100	Death, 5.0 months

Table 2 - Clinical and laboratory findings (%) in 18 LCH patients with GI tract symptoms, including our 2 cases.

Symptoms	Number of cases	%
Diarrhea	14	77.7
Protein-losing enteropathy	6	33.3
Bloody stool	6	33.3
Vomiting	4	22.2
Malabsorption	2	11.1
Melena	1	5.5
Perforation	1	5.5
No information available	1	5.5

min (27). Our patients presented massive protein losses of 81.5 ml/day, while the normal value is 14.6 ± 9 ml/day.

In six cases reviewed in the literature in which protein-losing enteropathy was present, all patients (100%) died. Deaths occurred 1 month to 1.5 years after diagnosis. Patients who did not experience protein loss lived longer, possibly due to the absence of refractory hypoalbuminemia. Tamura et al. (30) believe that loss of serum protein through the bowel is another contributing factor to the poor prognosis of patients with multi-

systemic LCH lesions.

We suggest the use of Cr⁵¹-labeled albumin to investigate protein-losing enteropathy in patients with disseminated LCH, with or without important GI symptoms. The iden-

tification of protein-losing enteropathy, at least in the most severe cases, allows for better clinical management of patients with disseminated LCH.

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