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Protein-Losing Enteropathy Caused by Gastrointestinal Tract–Involved Langerhans Cell Histiocytosis

abstract

Protein-losing enteropathy (PLE) is frequently complicated in patients with gastrointestinal tract–involved Langerhans cell histiocytosis (LCH); however, LCH per se is not generally included in the list of diseases that cause PLE. We report here a case of infantile PLE that presented with continuous diarrhea at the onset of LCH. She was initially diagnosed as having allergic gastroenteropathy and, thus, received intravenous prednisolone, which was thought to have induced immunodeficiency and consequently resulted in life-threatening cytomegalovirus-associated hemophagocytic syndrome and disseminated intravascular coagulation. Because chemotherapy for hemophagocytic syndrome was transiently effective for underlying LCH as well, the diagnosis of LCH was delayed until its recurrence. Gastrointestinal tract–involved LCH, a rare but highly fatal disease, should be considered for infants with refractory gastrointestinal symptoms, especially for those with PLE; endoscopic biopsy is strongly recommended for immediate diagnosis. *Pediatrics* 2010;125:e426–e432

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KEY WORDS

Langerhans cell histiocytosis, protein-losing enteropathy, hemophagocytic syndrome, infants

ABBREVIATIONS

LCH—Langerhans cell histiocytosis

PLE—protein-losing enteropathy

HPS—hemophagocytic syndrome

CT—computed tomography

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Langerhans cell histiocytosis (LCH) is a rare disorder characterized by abnormal proliferation and dissemination of Langerhans cells derived from bone marrow.¹ The estimated annual incidence was recently reported to range from 4.1 to 8.9 cases per million in children aged <15 years.^{2–4} Although LCH can involve almost any organ, the extent of the disease and the frequency of involved organs are age dependent. Liver and spleen are the risk organs that are involved at a high rate in younger patients, mostly in infants who present with multisystem LCH.⁵ Most patients with single-system LCH have a good outcome with no or only local therapy; however, there is a subgroup of patients with multisystem LCH, especially with risk-organ involvement, who have a poor response to the initial 6 weeks of chemotherapy and have poor outcomes.⁶

LCH with gastrointestinal tract involvement is rare and has a poor outcome. We report here a case of protein-losing enteropathy (PLE) caused by gastrointestinal tract-involved LCH that was confused with allergic gastroenteropathy. The diagnosis of infants with refractory gastrointestinal symptoms, especially PLE, is often challenging, and we discuss the importance of LCH to be considered as a differential diagnosis.

CASE REPORTS

An 11-month-old girl presented with continuous diarrhea, vomiting, and edema of the extremities and was admitted to the local hospital. A diagnosis of PLE was made on the basis of hypoproteinemia (serum total protein: 3.2 g/dL) and visible tracer exudation in the intestine by technetium-99m-labeled albumin scintigraphy. The cause of PLE was suspected to be allergic gastroenteropathy, but administration of amino acid-based milk produced no effects, and intravenous infusion of prednisolone (2 mg/kg) was initiated. Four weeks after the initi-

ation of prednisolone, she presented with fever, pancytopenia, bloody diarrhea, and severe edema of the entire body. Bone marrow aspiration and blood analysis revealed hemophagocytic syndrome (HPS) and disseminated intravascular coagulation, and she was transferred to our hospital. On physical examination, she was pale and edematous with petechiae in the abdomen and extremities, and her spleen and liver were enlarged 8 cm below the costal margin. Laboratory findings showed pancytopenia, disseminated intravascular coagulation, and immunodeficiency (leukocyte count: $1 \times 10^9/L$; hemoglobin: 6.4 g/dL; platelet count: $33 \times 10^9/L$; activated partial thromboplastin time: 90.4 seconds; prothrombin time-international normalized ratio: 1.84; fibrinogen: 37 mg/dL; fibrin/fibrinogen degradation product: 5.3 $\mu g/mL$; antithrombin III: 46%; immunoglobulin G: 304 mg/dL; lymphocyte blastoid transformation by phytohemagglutinin: 2280 [normal range: 26 000–53 000]). Soluble interleukin 2 receptor level was 12 500

U/mL and natural killer activity was normal. A bone marrow aspiration demonstrated multiple hemophagocytosis of erythrocytes, leukocytes, and platelets by activating macrophages (Fig 1). Although there was no family history of hemophagocytic lymphohistiocytosis, Munc13-4, perforin, and syntaxin expression were analyzed for the possibility of genetic hemophagocytic lymphohistiocytosis, which all appeared normal. She was treated with dexamethasone, etoposide, and cyclosporine A and became afebrile the day after the initiation of chemotherapy. On day 7 of chemotherapy, a cytomegalovirus pp65 antigenemia assay detected cytomegalovirus antigenemia. Gancyclovir was initiated immediately, and chemotherapy was discontinued on day 16. A retrospective analysis revealed a negative serum cytomegalovirus–polymerase chain reaction result at the time of onset of PLE but a positive result just before the onset of HPS. Thus, HPS was determined to be associated with the cytomegalovirus infection, which re-

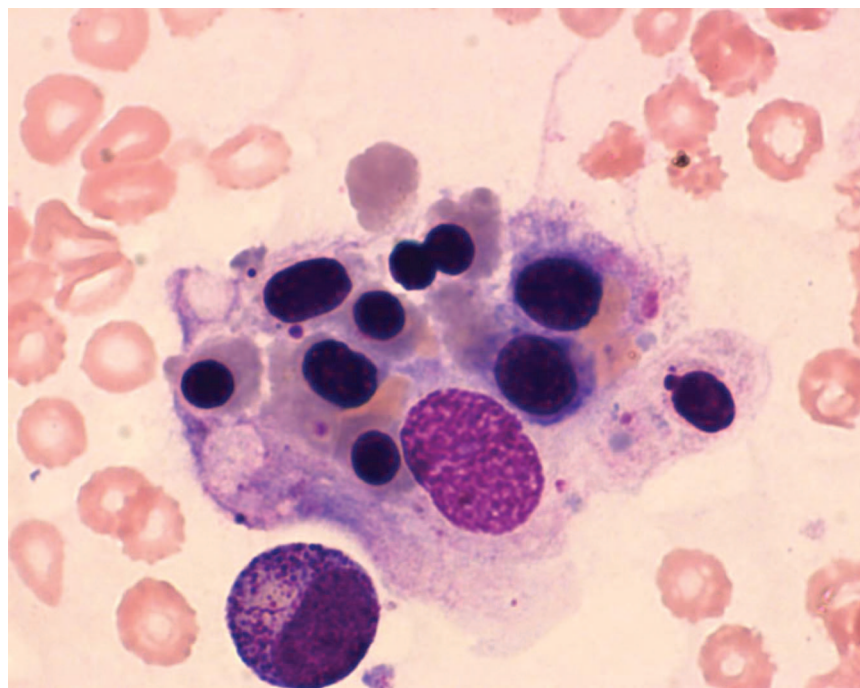


FIGURE 1

Bone marrow aspiration showing hemophagocytosis of erythrocytes, erythroblasts, and platelets by activating macrophages.

sulted from PLE- and prednisolone-induced immunodeficiency. Her bone marrow normalized and blood disappeared from her stool on days 23 and 29, respectively, and she was dis-

charged on day 60. An endoscopic examination and biopsies of the upper and lower tract on day 41 revealed slight inflammation with erosion in the gastric mucosa and haustral loss in the ascend-

ing colon, whereas the pathologic findings were unremarkable. She had normal bowel movements after consuming milk and infant food; however, there remained to be no weight gain.

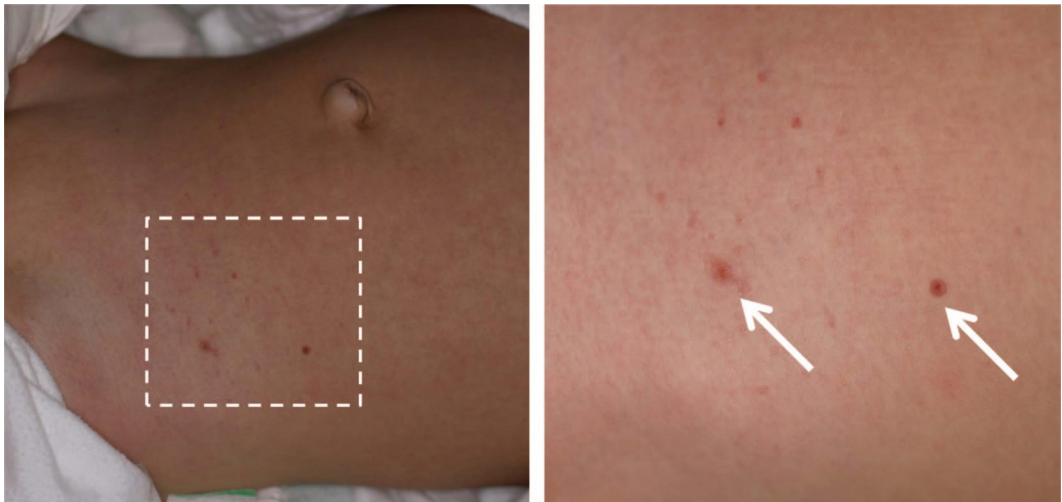


FIGURE 2
Several pink papules on the patient's lower abdomen.

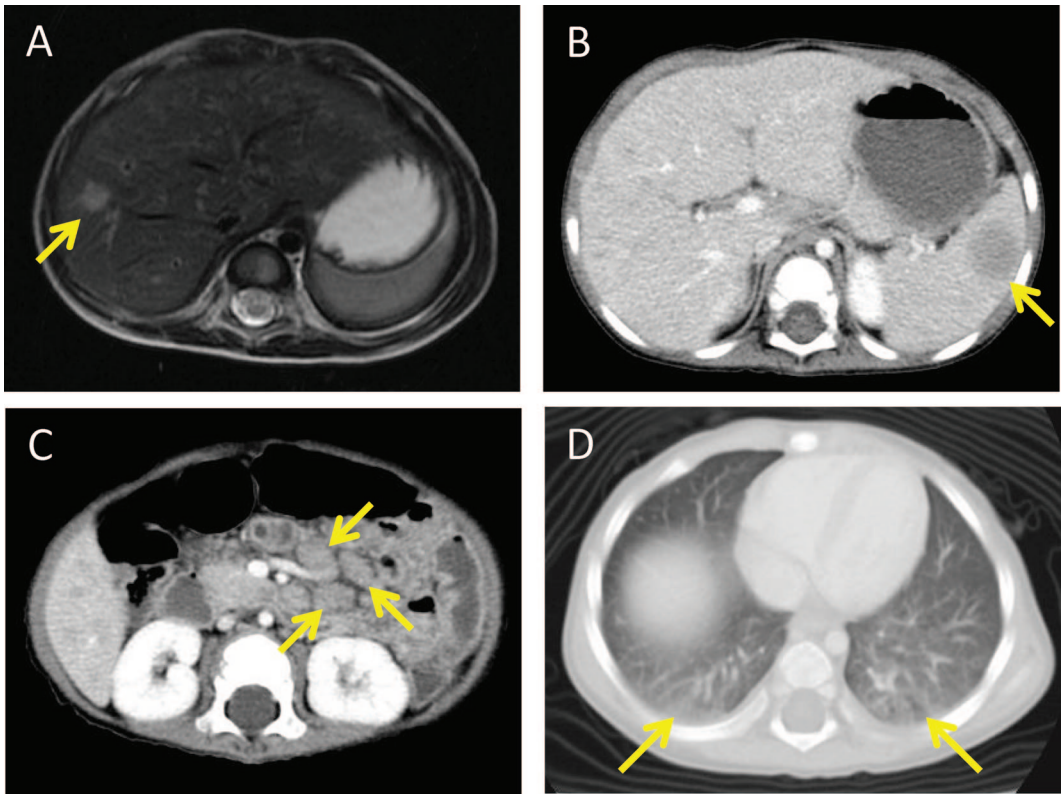
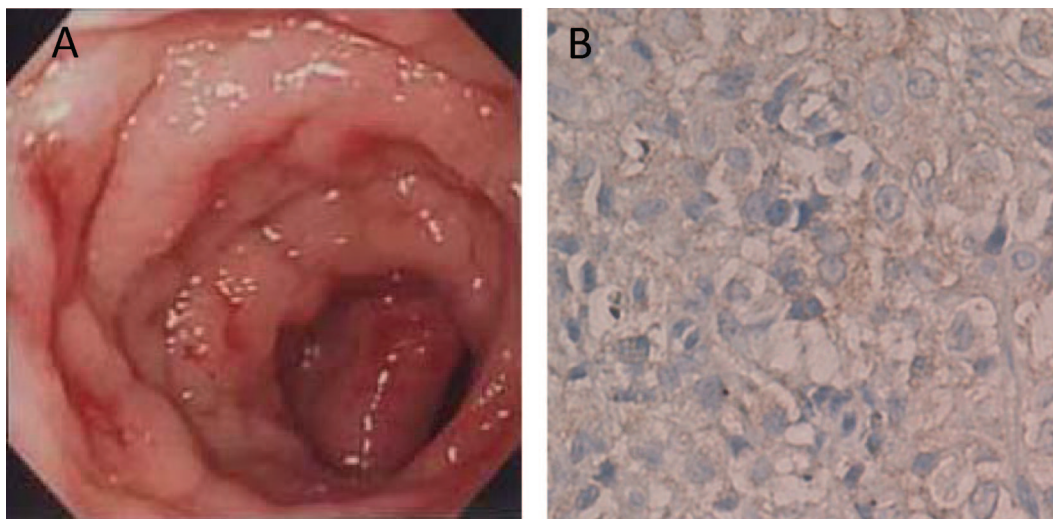


FIGURE 3
A, Abdominal MRI revealed a low-intensity lesion in the liver (arrow). B and C, Abdominal CT showed a low-density lesion in the spleen (B; arrow) and enlargement of multiple lymph nodes (C; arrows). D, Chest CT revealed ground-glass pattern in bilateral lungs.

**FIGURE 4**

A, Colon endoscopy revealed ulcerations with edematous changes in the mucous membrane of the transverse colon. B, Immunohistochemistry staining of colon mucous membrane showed infiltration of CD1a-positive histiocytes.

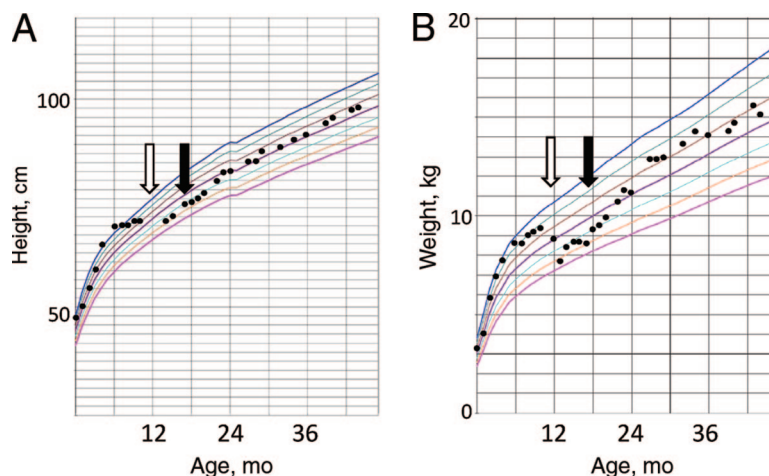
Three months later, she was admitted to our hospital again with recurrent bloody stool. Physical examinations showed several pink papules on the lower abdomen (Fig 2) and hepatosplenomegaly. MRI and computed tomography (CT) of the abdomen revealed a high-intensity lesion in the liver, a low-density lesion in the spleen, and enlargement of the multiple lymph nodes (Fig 3 A–C). Chest CT showed a ground-glass pattern in the inferior lobe of the bilateral lungs (Fig 3D). Brain MRI and whole bone scans were unremarkable. She underwent colon endoscopy, which revealed ulcerations with edematous changes to the mucous membrane (Fig 4A). A biopsy of the colon and skin papules demonstrated monomorphous infiltrate of histiocytes that were strongly positive for CD1a (Fig 4B, colon), but CD1a-positive cells were not observed in the bone marrow. She was diagnosed with multisystem LCH involving the skin, gastrointestinal tract, lungs, liver, and spleen. Although pink papules were probably present at the onset of PLE, wide-spread petechiae as a manifestation of HPS-associated pancytopenia obscured the skin involvement of LCH.

Chemotherapy was initiated according to the Japan LCH Study Group-02 protocol and consisted of intravenous vincristine, cytosine arabinoside, and oral prednisolone. Within 2 weeks of induction therapy, all manifestations of bloody stool, diarrhea, edema, and skin papules resolved. Her weight and height increased (Fig 5). After 6 weeks of induction therapy, she had achieved partial response with a marked reduction of all LCH-involved lesions. She

was discharged and continued maintenance therapy at the outpatient clinic for 10.5 months. She has been disease-free for 24 months.

DISCUSSION

Gastrointestinal tract involvement in patients with LCH is rare, with an incidence of <1%,⁷ and only 32 cases have been reported thus far.^{8,9} Gastrointestinal tract involvement is likely to be found in younger patients (<1 year old),¹⁰ and

**FIGURE 5**

Growth chart demonstrating no increase in stature (A) and weight loss (B) from the onset of PLE (white arrows) to the diagnosis of LCH. After the initiation of chemotherapy for LCH (black arrows), her weight and height increased, reaching to her previous channel.

TABLE 1 Patients With Gastrointestinal Tract–Involved LCH

	Patient	Gender	Age	Presentation	Initial Diagnosis	Laboratory Findings	Diagnosis of Gastrointestinal Tract Involvement	Other Organ Involvement	Outcome
1	Tamura et al ¹³ (1980)	Male	1 d	Eczematous skin eruption covering entire body	Letterer-Siwe disease	Thrombocytopenia, hypoproteinemia, anemia	¹³¹ I-PVP test for PLE, electron microscopy and autopsy of jejunum	Skin, bone marrow, ^a liver, ^b spleen, ^b lungs, ^b LNs, ^b adrenal glands, ^b thymus ^b (autopsy)	Died at day 46
2	Hyams et al ⁷ (1985)	Male	3 mo	Bloody diarrhea, otitis media, petechiae	Remained undiagnosed	Anemia, hypoalbuminemia	Ileum, colon autopsy	Liver, ^a LNs, ^b bone marrow, ^a spleen, ^b thymus ^b	Died at 5 mo
3	Egeler et al ¹⁰ (1990)	Male	5 mo	Bloody diarrhea, vomit, edema, skin rash	Crohn disease	Anemia, hypoproteinemia	Sigmoid biopsy, Cr ⁵¹ Cl ₂ test for PLE	Liver, spleen, ^a skin ^b	Alive in second CR
4	Egeler et al ¹⁰ (1990)	Male	4 mo	Failure to thrive, skin rash, vomiting, mucous diarrhea	Histiocytosis	Anemia, hypoproteinemia	Duodenal biopsy	Skin ^a	Died at 18 mo
5	Egeler et al ¹⁰ (1990)	Female	10 mo	Vomiting, failure to thrive, skin rash	Crohn disease	Hypoproteinemia	Duodenal, jejunum biopsy, Cr ⁵¹ -labeled albumin for PLE	Liver, spleen, mesenteric LNs ^a	Died at 16 mo
6	Patel et al ¹² (1991)	Female	4 mo	Bloody diarrhea at birth, skin rash, edema, weight loss, hepatomegaly	Histiocytosis X	Hypoalbuminemia, anemia	Small-bowel enema, laparotomy of jejunum (jejunum biopsy)	Bone marrow, ^a bone, ^a LNs, ^a orbital mass	Alive in CR
7	Boccon-Gibod et al ¹⁴ (1992)	Male	At birth	Skin rash, failure to thrive	LCH	Hypoalbuminemia, hyperbilirubinemia, anemia, thrombocytopenia	Duodenal biopsy, α 1-antitrypsin test for PLE	Liver, ^a skin ^a	Died at 17 wk
8	Boccon-Gibod et al ¹⁴ (1992)	Female	16 mo	Bloody stools, fever, hepatosplenomegaly, polyadenopathy, skin rash	LCH (von Willebrand disease at 4 mo)	Hypoalbuminemia, anemia, thrombocytopenia	Stomach, duodenal, sigmoid biopsy	Skin, ^a LNs, ^a bone marrow ^a	Alive in CR
9	Geissmann et al ¹⁵ (1996)	Female	16 mo	Bloody diarrhea, failure to thrive, skin rash, growth retardation	Gastroenteritis	Hypoproteinemia, hematologic dysfunction	Stomach, duodenal, colon biopsy, α 1-antitrypsin test for PLE	Skin ^a	Died at 32 mo
10	Geissmann et al ¹⁵ (1996)	Male	At birth	Vomiting, failure to thrive, skin rash	Gastroenteritis	Hematologic/hepatic dysfunction, hypoproteinemia	Duodenal biopsy, α 1-antitrypsin test for PLE	Skin, ^a liver ^a	Died at 4 mo
11	Geissmann et al ¹⁵ (1996)	Female	At birth	Bloody diarrhea, failure to thrive, skin rash	Gastroenteritis	Hematologic dysfunction, hypoproteinemia	Colon, rectal biopsy, α 1-antitrypsin test for PLE	Skin ^a	Died at 3.5 mo
12	Geissmann et al ¹⁵ (1996)	Male	0.5 mo	Diarrhea, failure to thrive, growth retardation, skin rash, pulmonary dysfunction	Gastroenteritis	Hematologic/hepatic dysfunction, hypoproteinemia	Duodenal biopsy, α 1-antitrypsin test for PLE	Skin, bone	Died at 22 mo
13	Santos-Machado et al ¹⁶ (1999)	Female	21 mo	Diarrhea, fever, anasarca, scalp ulcer, petechiae, hepatosplenomegaly, frontal tumor	LCH	Pancytopenia, hypoalbuminemia, hyperbilirubinemia, volume loss, low PT activity	Cr ⁵¹ -labeled albumin test for PLE	Skin, ^a bone marrow ^a	Died at 26 mo (2 mo after diagnosis)
14	Santos-Machado et al ¹⁶ (1999)	Male	18 mo	Jaundice, fever, pallor, diarrhea, weight loss, hepatomegaly, ascites, skin and mucosal lesion, diabetes insipidus	LCH	Hyperbilirubinemia, low PT activity, hypoalbuminemia	Cr ⁵¹ -labeled albumin test for PLE	Palate ^a	Died at 29 mo (5 mo after diagnosis)
15	Damry et al ¹⁶ (2000)	Female	9 mo	Diarrhea, failure to thrive, skin rash	LCH	Anemia, thrombocytopenia, hypoalbuminemia	Radiograph with barium (abnormal jejunum)	Bone, liver, spleen, bone marrow, skin ^a	Alive in CR
16	Levy et al ¹⁷ (2001)	Female	9 mo	Nonpitting edema, fever	LCH	hyponatremia, hypokalemia, hypoproteinemia	Stomach and duodenal biopsy	Skin	Alive in CR
17	Choi et al ¹⁸ (2003)	Male	7 mo	Failure to thrive, bloody diarrhea, fever, vomiting, skin rash	Allergic enterocolitis	Anemia, thrombocytopenia, hypoalbuminemia	Stomach, duodenum, and colon biopsy	Skin, ^a liver, spleen	Alive in CR
18	Our case	Female	11 mo	Diarrhea, vomiting, bloody stool, edema	Allergic gastroenteropathy	Hypoproteinemia	Colon biopsy, Tc ^{99m} -labeled albumin scintigraphy for PLE	Skin, ^a lungs, liver, spleen, mesenteric LNs	Alive in CR

PVP indicates polyvinylpyrrolidase; CR, complete remission; LNs, lymph nodes; Tc^{99m}, technetium-99m.

^a Biopsy site.

^b Autopsy site.

86% of patients have skin involvement.⁸ Endoscopic biopsies of the gastrointestinal tract are useful for diagnosis and provide a high rate of detecting histologic evidence of LCH.⁸ Fifty-nine percent of patients with gastrointestinal tract involvement reportedly die within 18 months of diagnosis, which suggests a poor prognosis.⁸

PLE is characterized by hypoproteinemia resulting from excessive loss of serum proteins into the gastrointestinal tract. PLE can be caused by a wide spectrum of disorders that can be classified mainly into 2 groups: (1) lymphatic obstructions (eg, lymphangiectasia) and (2) mucosal diseases (eg, with erosions: infections and inflammatory bowel disease; without erosions: Celiac disease and Ménétrier disease); determining the cause is often challenging. Allergic gastroenteropathy is one of the erosion-accompanying mucosal-related causes of PLE, with onset often in infancy, and cow milk protein is the most common cause.¹¹ Diagnosis is usually made without biopsies, and the symptoms resolve after appropriate dietary exclusion.¹¹ On the other hand, LCH is generally not included in the list of diseases that cause PLE, which may be be-

cause of the low incidence of gastrointestinal tract involvement. However, patients with gastrointestinal tract-involved LCH present with PLE at a high frequency (77%) and have a poor prognosis.^{8,9} Table 1 provides a list of patients with gastrointestinal tract-involved LCH who presented with hypoproteinemia, most of which had been diagnosed as having PLE.^{7,10,12–18} Most of these patients had difficulties with having their diagnosis made at initial presentation, and among 18 patients with LCH with PLE previously reported, only 7 patients were alive and in complete remission, and the remaining 11 patients died within 2 years after the diagnosis was made (Table 1).

Our patient was initially diagnosed as having allergic gastroenteropathy; however, amino acid–based formula was ineffective, and she was administered prednisolone, which adversely affected the immunodeficiency and was subsequently complicated with life-threatening cytomegalovirus-associated HPS. Moreover, chemotherapy for HPS was transiently effective for underlying LCH, which obscured the diagno-

sis of LCH. Although food allergies account for numerous gastrointestinal disorders during childhood, patients with poor response to dietary elimination of suspected food proteins should be considered for further examination, such as endoscopic biopsy, to exclude gastrointestinal tract involvement of LCH before initiating antiinflammatory medications.

CONCLUSIONS

We suggest that gastrointestinal tract involvement of LCH be included in the list of differential diagnoses for the causes of PLE, because LCH is often an unfamiliar disease to general pediatricians. Patients with gastrointestinal tract involvement of LCH have poor outcome, and efficient and accurate diagnosis is required. Because there is a high incidence in young children, frequently presenting with skin involvement, observation of infants with recurrent dermatitis in addition to gastrointestinal symptoms, especially PLE, suggests LCH, and endoscopic biopsy is strongly recommended. We thank Dr Hiroshi Kawasaki for kindly providing skin images.

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