

Gastrointestinal Tract Involvement of Langerhans Cell Histiocytosis: Concerning Point of Diagnosis

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Abstract:

An 8-month-old girl presented with chronic mucous bloody diarrhea for 3 months. She was diagnosed as infective gastroenteritis and did not improve after antibiotic treatment. Three months subsequently, she was diagnosed with allergic gastroenteritis after developing generalized skin rash and was treated with amino acid-based formula but the symptoms of diarrhea deteriorated. The results of a biopsy of the gastrointestinal tract and skin lesions confirmed the diagnosis of Langerhans cell histiocytosis. Although Langerhans cell histiocytosis is uncommon with gastrointestinal tract involvement, Langerhans cell histiocytosis should be listed in the differential diagnosis for patients who present with chronic mucous bloody diarrhea that is unresponsive to multimodality treatment.

Keywords: chronic mucous bloody diarrhea, gastrointestinal tract involvement, langerhans cell histiocytosis

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Introduction

Langerhans cell histiocytosis (LCH) may involve many organs and can take many clinical manifestations. Gastrointestinal tract (GIT) involvement in LCH is very rare and may present a major clinical problem such as chronic diarrhea, protein losing enteropathy, failure to thrive, hematochezia or melena.¹ Usually, GIT involvement is most frequently associated with multisystem disease, occurrence in very young children, and half of the cases can be missed easily or result in a delayed diagnosis.² GIT manifestations can be confused with infectious, allergic, immunodeficiency or inflammatory bowel diseases.³ In this report, we revealed a patient who presented initially with chronic mucous bloody diarrhea and then subsequently developed generalized skin rash which can cause an easily missed or delayed diagnosis of LCH.

Case report

An 8-month-old female presented with chronic mucous bloody diarrhea. Her birth and postnatal history were unremarkable. At 1 month of age she developed recurrent mucous bloody diarrhea and intermittent emesis. She had no fever or rash or any other specific symptoms. She was diagnosed as infective gastroenteritis and treated with antibiotics off and on. All investigations for an infectious cause were negative. She was followed up at the out-patient department regularly but the symptom of diarrhea did not improve and concomitantly developed feeding intolerance over a 3-month period. Then, she subsequently developed a new-onset, widespread manifestation of scaly erythematous, seborrhea-like brown to red papules on the scalp and intertriginous zones particularly behind the ears. There was no pus discharge from the ear canal and other examinations were within normal ranges. After she had the skin rash

with mucous bloody diarrhea, a pediatrician at an outside hospital diagnosed her as allergic enterocolitis secondary to cow's milk protein allergy. Despite dietary changes to amino acid-based formula and treatment for infection for a 5-month period, her clinical symptoms did not improve. She was transferred to our hospital for further investigations.

At our hospital, she otherwise acted well; her body weight was 5.1 kilograms (kg) (less than 3rd percentile) and her height was 65 centimeters (cm) (as 10th percentile). The physical examination revealed that she was afebrile with mildly pale conjunctiva and no icteric sclera. Her abdomen was distended with hepatosplenomegaly. Her skin rash had spread from the forehead to her extremities, neck, and palmar creases. There were also areas of erosion and weeping lesions with development of serous crusts. A complete blood count revealed a hemoglobin level of 8.9 gram per deciliter (g/dL), platelet count of 136,000/millimeter (mm³), reticulocyte count of 8.7%, and a normal white cell count of 8,900/mm³. The renal and liver function tests revealed a normal profile (aspartate aminotransferase 14 units per liter (U/L), alanine aminotransferase 21 U/L, total bilirubin 0.6 milligrams per deciliter (mg/dL), direct bilirubin 0.2 mg/dL. The serum albumin level was 2.9 g/dL. The coagulogram was within normal limits. The immunoglobulin levels were normal values. Urine and blood cultures were negative for bacteria and fungi. The stool revealed numerous red blood cells and the occult blood test was positive but the culture and examination of the stool for ova, parasites, and bacteria were negative.

The skull and chest radiographs showed no abnormalities. A computerized tomography (CT) scan of the abdomen revealed a diffusely enlarged liver and spleen without focal lesion. The CT scan of the chest revealed

enlarged thymus with multiple punctate calcifications which is a specific finding in LCH, but no mediastinal lymph node enlargement. A whole body bone scan with Technetium-99m methylene diphosphonate showed no bony involvement. A bone marrow aspirate showed a normocellular marrow without evidence of LCH.

A gastrocolonoscopy was performed and biopsies from the stomach and the first and second parts of the duodenum revealed mucosal nodules and edematous changes in the gastric mucosal wall (Figure 1). The diagnosis of LCH was confirmed based on the gastrointestinal (GI) biopsy findings in which the tumor involved the gastric mucosal layer and infiltrated the lamina propria. Immunohistochemistry staining of the gastric mucosa showed infiltration of cluster of differentiation (CD) 1a positive histiocytes (Figure 2). In addition, a skin biopsy was consistent with LCH cells. Immunostains of a skin biopsy were positive for S-100, CD68, and CD1a. Birbeck granules were detected by electron microscopy.



Figure 1 Gastroscopy appearance of Langerhans cell histiocytosis showing mucosal nodules with edematous changes in the gastric mucosal wall

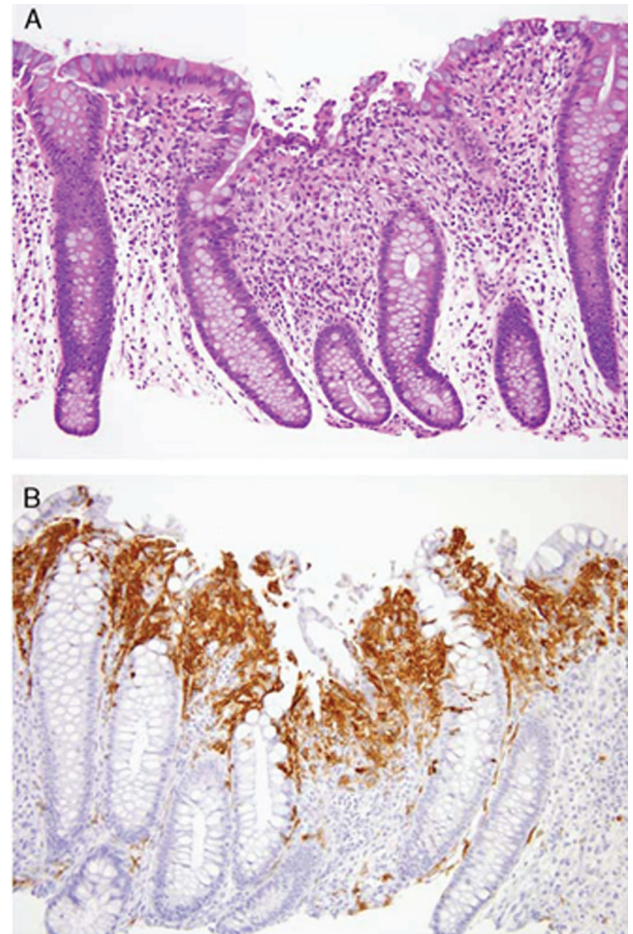


Figure 2 A: The colonic biopsy showed Langerhans cell histiocytosis which expanded to the lamina propria, separating the crypts. B: Immunohistochemistry staining of the colon mucous membrane showed infiltration of CD1a-positive histiocytes.

The child received nutritional support with total parenteral nutrition (TPN) to improve her nutritional status. Chemotherapy was started promptly. She was started on induction chemotherapy (weekly intravenous vinblastine 6 mg/m² day, Etoposide 150 mg/m²/day, daily oral prednisolone 40 mg/m²). After 6 weeks of induction, the patient was asymptomatic and there was no active

disease in the GIT and skin. TPN feeding was stopped and she could tolerate oral feeding. She was treated further with maintenance therapy (continuous daily oral 6-mercaptopurine 50 mg/m², prednisolone 40 mg/m² for 5 days every 3 weeks, and vinblastine 6 mg/m² and etoposide 150 mg/m²/day every 3 weeks) for 6 months and she was good response to chemotherapy protocol. Now, she is in clinical remission for about 5 years from the end of treatment. Her clinical status is normal development for age and her body weight is 20 kg (50th percentile), height is 106 cm (10th percentile).

Discussion

GIT involvement in LCH is exceedingly rare with an incidence of 9 in 348 patients (2.6%) from the French Langerhans Cell Histiocytosis Study Group between 1983 and 1994.⁴ We also reviewed a Medline literature search from 1966 to 2019 and were able to identify only a total of 68 pediatric cases of well-defined LCH with GIT involvement over nearly a 55-year period. Only 58 cases were reviewed from 1966 to 2010 and 10 more reported cases from 2010 to 2019 that included our case.^{2,5-10}

In this article we described an infant who initially presented with symptoms of chronic mucous bloody diarrhea for a 3-month period without any specific signs and then subsequently developed generalized skin rash. In this setting, a diagnosis of LCH was missed. It is possible that patients with GIT involvement of LCH are being missed because of uncommon GIT involvement and a wide spectrum of clinical presentations. GIT involvement in LCH may manifest as chronic mucous bloody diarrhea, hematochezia, constipation or protein losing enteropathy and can range in severity from mild to life-threatening.

Usually, the GI symptoms are preceded by or associated with the characteristic LCH rash in 86.0% of the patients. From a study of 9 patients from the French Langerhans Cell Histiocytosis Study Group, about 5 in 9

(55.6%) patients had a gap in time between the onset of skin manifestations and GI symptoms of 2–11 months and only 4 in 9 (44.4%) had simultaneous onset.¹¹ These clinical settings can guide a diagnosis to infective or allergic gastroenteritis that results in a delay to diagnose LCH. From a literature review, about 9 in 18 cases (50.0%) of patients with GIT involvement of LCH were initially diagnosed as allergic or infective gastroenteritis, inflammatory bowel disease or immunodeficiency.²

Patients with LCH and GIT involvement tend to present at a very young age. The majority of reported patients (86.0%) were under 1 year of age and 95.0% of the patients presented before 18 months of age.^{1,3}

It is apparent that the prognosis of LCH with GIT involvement is relatively poor. Sixty-one percent of the patients died within 24 months of diagnosis, whereas only 14.0% of the patients achieved complete remission.² The mortality rate of LCH patients with GIT involvement is about 55.0%.³ This is in contrast to LCH mortality rates in general which have a 7.0% mortality rate for single-system and a 39.0% mortality rate for multisystem disease.¹² It remains unclear if age at onset, severity of symptoms, timing of diagnosis or nutritional status contributes to the outcome. The majority of the patients with LCH and GIT involvement had poor nutritional status such as hypoalbuminemia and failure to thrive and most patients were diagnosed in their infancy period. These two factors may have an effect on the outcome.

There have been many regimens for treating LCH with GIT involvement which depend on the treatment center although the optimal approach to treatment remains unclear. Standard treatment includes corticosteroids, antimetabolites, vinca alkaloids, and cytotoxic agents. Treatment outcomes vary because only case reports are published in the literature. For our patient, we considered the two issues of age and nutritional status and decided to use the standard regimen for systemic LCH. She

received chemotherapy as scheduled without any serious side effects and tolerated the side effects until she completed the chemotherapy regimen. She was still alive and in clinical remission about 5 years after the diagnosis.

On the other hand, Choi, et al.¹³ reported that treatment with 2-chlorodeoxyadenosine and high dose cytarabine could achieve a durable response. The French langerhans cell histiocytosis study group concluded that any GIT involvement with LCH warrants aggressive evaluation and treatment. GIT involvement of LCH should be treated as a multisystemic disease irrespective of the patient's clinical status.¹¹

We need to observe and follow-up the number of patients with GIT involvement of LCH to determine the optimal regimen of chemotherapy. We should balance between the complications or side effects of aggressive chemotherapy with the survival rate which depends on several factors such as nutritional status and age of the patient. If we use aggressive chemotherapy for young infants who have failure to thrive or malnutrition status, the patient may get worse from the treatment.

Conclusion

We suggest that GIT involvement of LCH be considered on the list of the differential diagnosis for patients with chronic mucous bloody diarrhea who are unresponsive to amino acid-based formula or other treatments. Careful examination of the systemic manifestations such as skin rash or recurrent dermatitis can provide a guide in the diagnosis. The optimal treatment regimens might result in a durable long-term remission or cure.

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Conflict of interest

Nothing to declare

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