Langerhans Cell Histiocytosis of the Gastrointestinal Tract: Evidence for Risk Organ Status

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Objective To investigate the "risk status" of Langerhans cell histiocytosis (LCH) of the gastrointestinal tract.

Study design Outcomes from 43 published cases of patients with LCH and gastrointestinal tract involvement were matched to 43 patients with LCH without gastrointestinal tract involvement cared for at our institution. Comparisons were made of the 5-year overall survival rates determined from Kaplan–Meier survival curves for the entire cohort of patients, as well as subgroups defined by lack of risk organ involvement and later era of treatment (to control for temporal changes in LCH treatment regimens). In addition, an association between LCH–gastrointestinal tract and risk organ involvement was investigated.

Results The 5-year overall survival for children with LCH–gastrointestinal tract (45.3%) was significantly worse than for those without gastrointestinal tract involvement (94.6%; $P = .001$). This difference remained significant after we excluded risk organ involvement (53.6%% vs 100%; $P = .001$), and analyzing subjects diagnosed after 2000 (75% vs 100%; $P = .012$). A 4-fold increase in risk organ involvement with LCH–gastrointestinal tract was observed (OR 4.359; 95% CI 1.75-10.82, $P = .001$).

Conclusions This limited retrospective study suggests that patients with LCH–gastrointestinal tract involvement may have decreased survival, independent of risk organ involvement, and provides evidence to support a prospective study to evaluate risk organ status of LCH–gastrointestinal tract. LCH–gastrointestinal tract may be associated with a 4-fold risk for risk organ involvement. Attention to gastrointestinal symptoms and LCH–gastrointestinal tract in young children diagnosed with LCH is warranted. *(J Pediatr 2019;212:66-72)*.

Langerhans cell histiocytosis (LCH) is a disorder of abnormal proliferation of dendritic myeloid cells known as histiocytes.[1] LCH primarily affects young children, has an incidence of about 4-5 cases per million, and symptoms at diagnosis vary.[2] In general, risk-adapted chemotherapy has led to excellent outcomes in patients with LCH, with a reported 5-year overall survival of 99%.[3] Patients who meet criteria for high-risk LCH have lower survival rates and more chronic sequelae.[4]

Various studies have established that involvement of certain organs is associated with worse outcomes, and these are termed "risk organs" (risk organ). Although patients with pulmonary involvement previously were considered to be high risk, evidence that lungs are not a risk organ comes from a review that demonstrated no impact on mortality with pulmonary involvement.[5] Another study found the cause of death in patients with pulmonary LCH frequently was not attributable to disease progression but instead from unrelated complications.[6] Thus, pulmonary LCH in isolation no longer makes a patient high risk. At present, the organ systems that are associated with increased mortality in LCH, and so considered risk organs, include the liver, spleen, and bone marrow.[7] One study of patients with multisystem LCH found that risk organ involvement was associated with a 5-year overall survival of 69%, compared with 100% in those without risk organ.[4] Therefore, precisely determining which organ systems contribute to high-risk status is important in the clinical care of patients diagnosed with LCH.

LCH involving the gastrointestinal tract (LCH–gastrointestinal tract) is rare, occurring in only 2%-4% of patients with LCH.[8] Classic signs and symptoms of LCH–gastrointestinal tract are bloody diarrhea, malabsorption, failure to thrive, and anemia. The diagnosis of gastrointestinal tract involvement by LCH is established by endoscopy and tissue biopsy. At present, LCH–gastrointestinal tract is not considered to be high-risk organ involvement, and so evaluation in newly diagnosed patients is not emphasized.[4] However in a case series of 9 patients with LCH–gastrointestinal tract, more than one-half (56%) died, inconsistent with standard risk disease.[9] Another series describes 12 patients with histologically diagnosed LCH–gastrointestinal tract and found that although adult patients have a clinical course that is different than children (they often had minimally symptomatic single nodular disease), multisystem disease with

LCH	Langerhans cell histiocytosis
LPCH-S	Lucile Packard Children's Hospital-Stanford
UCSF	University of California San Francisco

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LCH−gastrointestinal tract was associated with death in 2 young children (4 months and 2.3 years of age).[10] The high mortality rate described in these published cases of LCH−gastrointestinal tract has not been well studied and has been attributed to simultaneous risk organ involvement. The current study was performed to investigate the impact that LCH−gastrointestinal tract at diagnosis has on clinical outcome and whether that warrants consideration of independent risk organ status.

Methods

Datasets from relevant patients with LCH were developed to determine the 5-year overall survival in multisystem LCH with LCH−gastrointestinal tract (Figure 1, A and B). Because disease progression, disease activity, and organ involvement are subjective and rely on the clinical experience of medical providers, they were not used as study endpoints. Because death is an unambiguous endpoint, and poor survival is used in defining risk organ status, 5-year overall survival was used as the outcome measure for this study. In addition, this study examined if LCH−gastrointestinal tract is associated with risk organ involvement.

Because lung involvement and young age at diagnosis previously were considered risk factors, subjects with LCH of the pulmonary system were excluded. Datasets were compared for all patients with LCH−gastrointestinal tract, and after exclusion of patients over 2 years of age. The institutional review boards at participating centers approved this study before its conduct. Data were retrospectively collected in a deidentified manner and stored within a secure and encrypted electronic study database.

Patients

Group A. To identify a cohort of LCH−gastrointestinal tract subjects with available clinical data, a search using the diagnostic code for LCH, the procedure codes for endoscopy and colonoscopy, and the clinical term gastrointestinal tract was conducted through the electronic medical record systems (Epic Systems Corp, Verona, Wisconsin) of the Bay Area Consortium for Histiocytosis. This consortium includes 3 clinical pediatric Hematology/Oncology programs: Lucile Packard Children's Hospital-Stanford (LPCH-S), University of California, San Francisco (UCSF) Benioff Children's Hospital Oakland, and UCSF Benioff Children's Hospital San Francisco. In addition, a literature search of 3 search engines (PubMed, Google, and Medline) was performed to identify published cases of LCH−gastrointestinal tract, using the key words "Langerhans cell histiocytosis," "gastrointestinal tract," "colitis," "protein-losing enteropathy," and "histiocytosis X." Only cases with demographic, clinical, radiographic,

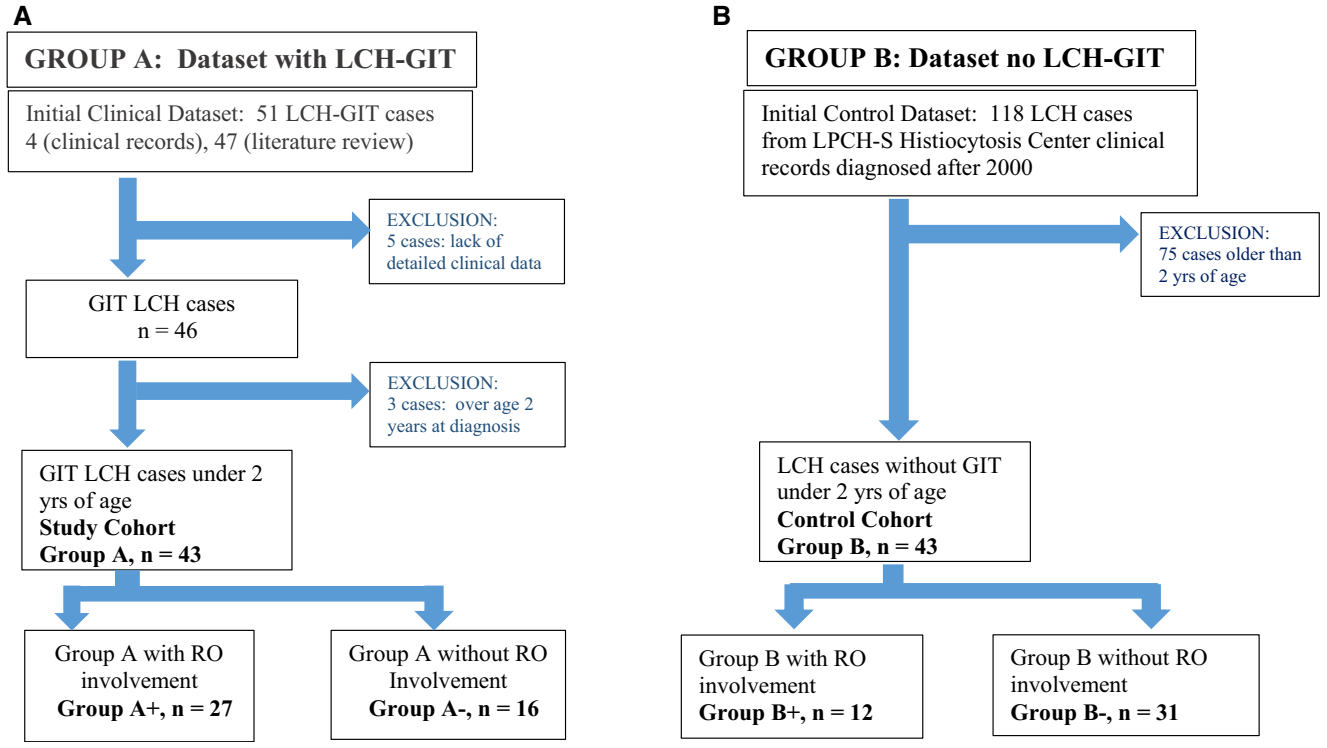

Figure 1. **A,** Diagram of formation of study dataset (Group A) of patients with LCH and gastrointestinal involvement. Group A includes patients all with LCH−gastrointestinal tract, no subjects with pulmonary LCH included. **B,** Diagram of formation of study dataset (Group B) of patients with LCH and no gastrointestinal involvement. Group B includes patients all with LCH−gastrointestinal tract, no subjects with pulmonary LCH.

laboratory, endoscopic and histologic findings, treatment data, and corresponding dates, along with health status at last follow-up were included. Finally, causes of death were determined from the published reports. The clinical data from these cases were combined to form a cohort of subjects with LCH-gastrointestinal tract (Group A) (Figure 1, A).

Group B. The LPCH-S Histiocytosis Clinical Program maintains a clinical database for the care and case management of patients. This database was used to identify age-matched patients with LCH without gastrointestinal tract involvement. Demographic, clinical, radiographic, laboratory, treatment data, endoscopic and histologic findings, and corresponding dates of evaluation, along with health status at last follow-up, and causes of death if applicable, were recorded to form a control dataset of patients with LCH without LCH−gastrointestinal tract (Group B) (Figure 1, B).

Statistical Analyses

Datasets were summarized and compared with clinical descriptions in the literature to assess relevance with other LCH populations. The 5-year overall survival was calculated from date-of-diagnosis to date-of-death from any cause; patients with no events were censored at the date of last follow-up. The Kaplan−Meier method was used to generate survival curves and estimate the 5-year overall survival. The Kaplan−Meier survival curves between Groups A and B were compared with the log rank and Cox proportional hazards tests. To minimize the impact of confounding risk organ involvement, the 5-year overall survival also was compared between Groups A and B after exclusion of subjects with risk organ involvement. Also, to minimize the possible effect of variations in treatment, the 5-year overall survival of Groups A and B, including only subjects diagnosed after 2000 (introduction of LCH-III, risk adapted, standardized treatment protocol), was compared.[3] To evaluate whether treatment era affected outcome, 5-year overall survival of Group A subjects diagnosed before and after 2000 was compared. Finally, a χ^2 test determined the significance of the association between LCH−gastrointestinal tract and other risk organs by comparing percent of patients in Groups A and B with concomitant risk organ involvement. All analyses were performed using SPSS software version 24.0 (IBM Corp, Armonk, New York), and P values less than 5% (<.05) were considered significant.

Results

Group A: LCH−Gastrointestinal Tract (N = 43)

Four patients with biopsy-proven LCH−gastrointestinal tract were identified from the local clinical programs (3 subjects from LPCH-S, and 1 subject from UCSF Benioff Children's Hospital Oakland). We identified and reviewed 47 published cases of LCH−gastrointestinal tract, of which 42 had sufficiently detailed clinical information (Figure 1, A). Data from 4 patients and the 42 published cases were combined, and 3 subjects over 2 years of age at diagnosis were excluded (ages 3, 12, and 16 years). The final dataset (Group A) from 43 patients with LCH−gastrointestinal tract involvement is summarized in Table I.[9-33] Group A had a median age at diagnosis of 5 months (range: birth to 2 years), one-third (15/43, 35%) were male, 98% had multisystem disease, and risk organ involvement was observed in 27 patients (62.8%). Twenty patients (46.5%) died, and 90% of deaths occurred within 18 months of diagnosis at a median follow-up period of 14 months (Table II; available at www.jpeds.com).

Group B: Control Dataset, Non-gastrointestinal Tract LCH (n = 43)

Forty-three cases with histologically confirmed LCH, and no symptoms of gastrointestinal tract involvement in patients who were <2 years of age at diagnosis were identified from the LPCH-S clinical database (Figure 1, B). The median age at diagnosis was 12 months, with 63% (27/43) male. Risk organ involvement was seen in 27.9% (12/43) and 6.9% (3/43) died, with a median follow-up period of 79 months (Table I).

5-Year Overall Survival Analysis

The 5-year overall survival for Group A (n = 43) was 45.3% and for Group B (n = 43) was 94.6%, a difference that is statistically significant ($P < .001$; Figure 2, A). Among Group A patients who died, disease progression was the cause for the vast majority (16/20, 80%); 4 patients died from non-LCH causes (2 from sepsis, 1 from hemorrhage, and 1 from mechanical pulmonary failure) (Table I). In Group B, 3 patients died, 2 from disease progression and 1 from pulmonary failure attributable to pre-existing bronchopulmonary dysplasia resulting from premature birth.

The analyses suggest an independent association of LCH−gastrointestinal tract with decreased 5-year overall survival. The 5-year overall survival after the exclusion of patients with risk organ involvement (Groups A− and B−) was calculated and compared: Group A− (n = 16) had an overall

Table I. Demographics and characteristics: Group A and Group B

Characteristics	Group A (n = 43)	Group B (n = 43)
Age at diagnosis, mo Median (range)	5 (at birth-2 y)	12 (5 d-2 y)
Sex Male/female	15/28	27/16
Risk organ involvement at diagnosis	27 (62.8%)	12 (27.9%)
Follow-up time Median (range)	1 y 2 mo (1 mo-10 y 3 mo)	6 y 5 mo (1 mo-17 y 11 mo)
Death	20 (46.5%)	3 (6.9%)

Group A: cases younger than 24 months of LCH with gastrointestinal tract involvement in literature. Group B: cases younger than 24 months of LCH without gastrointestinal tract involvement in Stanford Bass Center Histiocytosis Clinical Database.

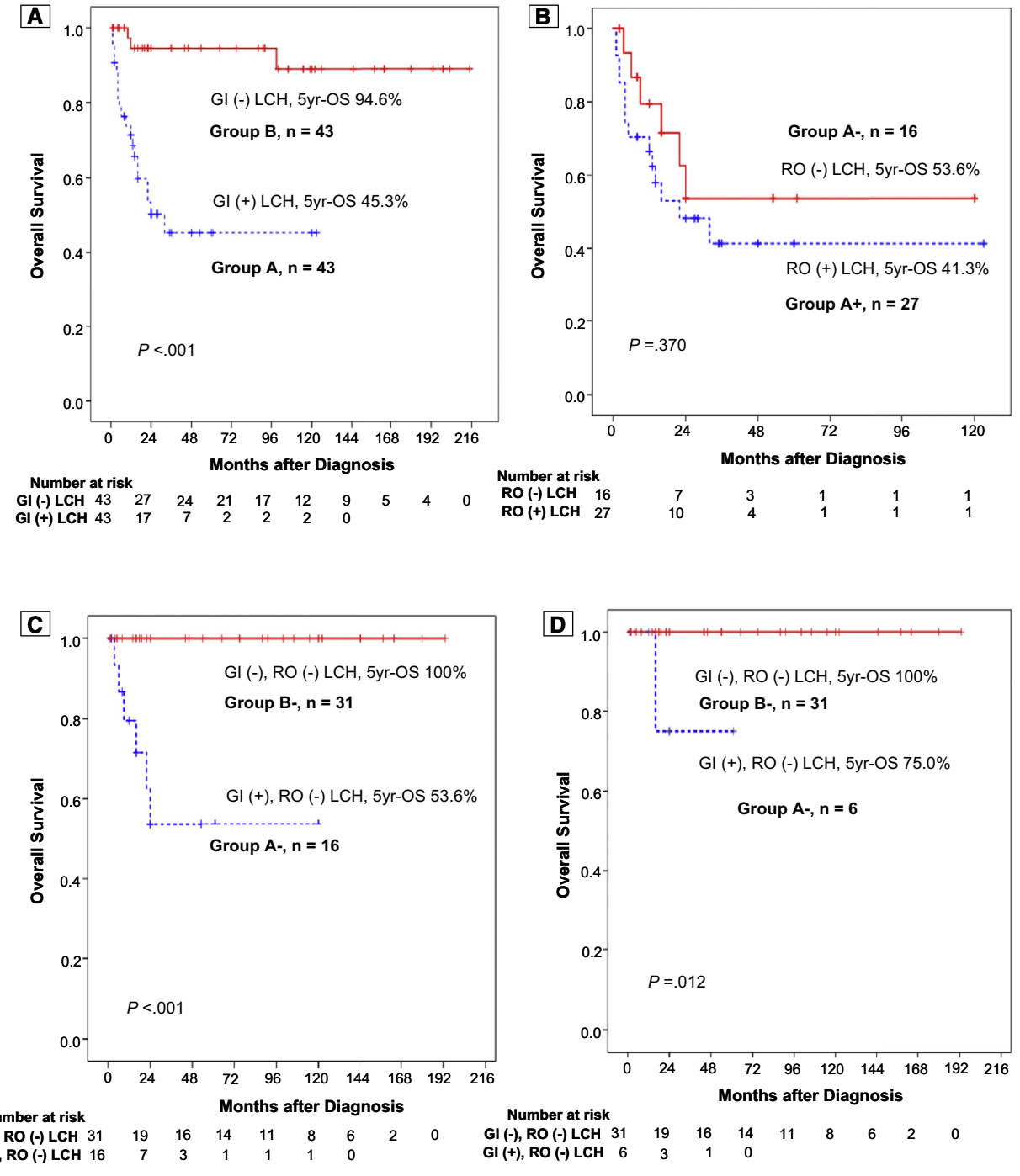

Figure 2. **A,** Comparison of 5-year survival between subjects with LCH−gastrointestinal tract (Group A) with those LCH and no gastrointestinal tract involvement (Group B). **B,** Comparison of 5-year survival between subjects with LCH−gastrointestinal tract involvement with and without risk organ from Group A (risk organ + vs risk organ−) evaluates the additive effect of LCH−gastrointestinal tract with risk organ involvement. **C,** Comparison of 5-year survival between groups after excluding all subjects with risk organ involvement (Group A− vs Group B−). This analysis evaluates the independent LCH−gastrointestinal tract impact on survival. **D,** Comparison of 5-year survival between subjects diagnosed after 2000 without risk organ involvement with LCH−gastrointestinal tract (Group A−) and without LCH−gastrointestinal tract (Group B−). This analysis minimizes the impact of variability of treatment.

survival of 53.6%, and Group B− (n = 31) of 100%, which was statistically significant (P = .001; Figure 2, C). Finally, to minimize the impact of treatment variability as a cause for the difference in survival, we further excluded patients diagnosed before 2000. The 5-year overall survival in patients diagnosed after 2000 was 75% in Group A− and 100% in Group B−, which also was statistically significant (P = .012) (Figure 2, D).

The 5-year overall survival within Group A patients diagnosed before and after 2000 were compared to determine whether more contemporary treatment regimens improved outcome. The 5-year overall survival was 31.1% for pre-2000 patients and 61.6% for those diagnosed after 2000, which was statistically significant (P = .008). In the past, poor outcomes from LCH−gastrointestinal tract was attributed to simultaneous involvement of other risk organs. To determine whether an association exists between LCH−gastrointestinal tract and other risk organs, we compared the frequencies of risk organ involvement between the groups: 62.8% (27/43) of subjects in Group A and 28% (12/43) in Group B had risk organ involvement, an OR of 4.359 for risk organ involvement when LCH−gastrointestinal tract was present. This is a significant association (95% CI 1.75-10.82, P = .001).

Discussion

Published studies indicate that LCH−gastrointestinal tract is rare and occurs in about 2%-4% of patients with LCH,[8] which is consistent with our findings: the query of the clinical records database (LPCH-S Histiocytosis Program) found LCH−gastrointestinal tract in 2.5% of patients (3 of 118). In addition, LCH−gastrointestinal tract usually is diagnosed in children <1 year of age, with 74% of our LCH−gastrointestinal tract cohort diagnosed before 1 year of age. The decision to exclude patients >2 years of age at diagnosis was based on age <2 years was previously considered a risk factor, and the suggestion that older patients with LCH−gastrointestinal tract may have a very different clinical course compared with younger children.[10,34] Of note, an analysis that included patients >2 years of age showed that the difference in overall survival between the groups maintained clinical significance.

Almost all patients with LCH−gastrointestinal tract involvement (93%, 40/43) exhibited a rash, consistent with LCH of the skin. Published studies have observed that LCH−gastrointestinal tract precedes skin lesions in >80% of newly diagnosed patients.[9,27] A possible mechanism to explain why some patients exhibit LCH−gastrointestinal tract comes from a study in which the LCH cells in both skin and gastrointestinal tract biopsies of patients with LCH−gastrointestinal tract stained positively with ACT-1, an antibody against the mucosal adhesion receptor $\alpha 4\beta 7$ integrin. This marker was not present in normal epidermal Langerhans cells nor in the majority of skin lesions from LCH patients without LCH-gastrointestinal tract.[9]

Histologic biopsy results from endoscopy were available in 35 of 43 (81%) patients in Group A. LCH was found histologically in the small intestine in 54% (n = 19), colon in 49% (n = 17), rectum in 43% (n = 15), stomach in 23% (n = 8), and perianal skin tag in 3% (n = 1). About 63% (n = 22) had LCH lesions in more than 1 section of the intestine. A similar distribution of disease sites within the gastrointestinal tract was reported in a small series of 9 patients: the small intestine was most commonly involved (89%), then the colon (33%), and stomach (11%), and about one-half of patients (45%) had multisite disease. Hait et al reported that duodenal biopsy demonstrated histologic evidence of LCH in 89% of newly diagnosed patients with LCH, including patients without upper gastrointestinal tract symptoms.[28] Thus, the location, distribution of disease, the endoscopic findings, and histology seemed to be generally consistent with the available information from published, small cases series. The findings of frequent skin disease and the distribution of disease in the gastrointestinal tract in our study cohort may be expected.

Patients with isolated gastrointestinal disease typically are adults, who are often found incidentally during colon cancer screening to harbor an asymptomatic solitary LCH polyp.[34] In contrast, children commonly present with gastrointestinal symptoms such as failure to thrive, bloody and non-bloody diarrhea, vomiting, and abdominal pain. In our study, hypoalbuminemia was found in 63% of the LCH−gastrointestinal tract cohort, with a median albumin level of 2.2 g/dL (range 1.2-2.9 g/dL) in our study (Table II). This observation is expected, as publications report that a majority of young patients with LCH−gastrointestinal tract involvement present with protein-losing enteropathy, with frequencies as high as 77%.[13,18,20,29]

Treatment has been reported to be ineffective in some cases of LCH−gastrointestinal tract,[30] and the poor outcomes were blamed on delayed diagnosis. Thus, in our current study, we attempted to evaluate the effect of evolving treatment strategies on LCH−gastrointestinal tract. In general, the standardization of treatment appeared to improve outcomes for patients with LCH−gastrointestinal tract, with the 5-year overall survival improving from 31% to 62% when comparing patients diagnosed before and after 2000, a time point for implementation of standardized modern treatment regimens. The strategy of grouping subjects by time periods has been used previously to assess chemotherapy response by LCH in other publications, with some using 1998 as the pivotal year.[35] The 5-year overall survival for high-risk patients in our study is lower than the approximately 75% overall survival in patients with multisystem and risk organ disease reported in the literature (Figure 2, A-D).[7] These previously published studies report that rapid response to initial therapy is associated with improved outcomes. We did not incorporate the evaluation of response to therapy in our dataset, which may explain why we observed a much lower 5-year overall survival in each of our analyses. Finally, LCH−gastrointestinal tract without risk organ involvement did not have a significantly different 5-year

overall survival when compared with LCH−gastrointestinal tract with risk organ involvement. The 5-year overall survival for risk organ− was 53.6% and for risk organ+ was 41.3% (P = .370; **Figure 2**, B). These different analyses suggest that there may be an independent impact of LCH-gastrointestinal tract at diagnosis on 5-year overall survival.

Currently, a patient with LCH−gastrointestinal tract but without other risk organ involvement would be considered standard risk. This classification is inconsistent with the high mortality rate of published cases.[30] A significantly lower 5-year overall survival among patients with LCH−gastrointestinal tract was observed in our study, which is inconsistent with its designation as a standard risk organ. However, there are several other possible explanations for this discrepancy. First is the potential that patients with LCH−gastrointestinal tract involvement with poor outcomes are more likely to be reported in the literature than patients with LCH−gastrointestinal tract involvement who do well. Other possible explanations for the apparent high mortality rate reported among patients with LCH−gastrointestinal tract involvement include the fact that the low incidence of gastrointestinal tract disease may not allow for adequate comparison between groups, and that gastrointestinal tract involvement tends to be seen more often in younger patients. Previously, the increased mortality rate in LCH−gastrointestinal tract was attributed to an association with other risk organ involvement.[30] Although we did find a 4-fold increase in risk organ involvement among patient with LCH−gastrointestinal tract compared with control patients, the overall survival for patients with LCH−gastrointestinal tract involvement remained significantly lower even after the exclusion of all risk organ patients.

The retrospective nature of our study also imposes several limitations. Our small subject numbers and the stratification of patients by time periods could lead to incorrect representation of the natural history of LCH−gastrointestinal tract. Finally, the reported clinical data may be incomplete or inaccurate The selection of death as an unambiguous study endpoint and analysis of 5-year overall survival are factors that strengthen our findings and observations. In addition, we found similar differences in survival when comparing various subgroups of patients, which we feel further supports the finding that LCH−gastrointestinal tract is associated with increased mortality.

In conclusion, the presence of LCH−gastrointestinal tract should be considered in children newly diagnosed with LCH, especially those with skin lesions and nonspecific gastrointestinal symptoms such as failure to thrive, diarrhea, vomiting, and abdominal pain. It also appears that more intensive combination chemotherapy improve overall survival for these patients. ■

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Table II. Group A dataset cases of LCH with gastrointestinal tract involvement

Case	Author	Year	Age	Sex	Symptoms	Biopsy sites	Laboratory findings	Other organ involvement	Risk organ	Treatment*	Outcome	Cause of death (if dead)
1	Keeling et al[12]	1973	2 mo	F	PLE, diarrhea, rash	Small intestine Bx: LCH+	Hypoalbuminemia	Skin, LN, lung, liver	+	A	Died at 3 mo (1 mo after Dx)	Sepsis, lung infection
2	Tamura et al[13]	1980	1 d	M	Rash, PLE	Skin Bx: LCH +	Thrombocytopenia, hypoproteinemia, anemia	Skin, BM, liver, spleen, lung, LNs, adrenal glands, thymus	+	E	Died at day 46 (1 mo after Dx)	Disease progression
3	Hyams et al[14]	1985	3 mo	M	Bloody diarrhea, otitis media, petechia	Rectal suction Bx: LCH +	Anemia, hypoalbuminemia	Pulmonary infiltration	+	D	Died at 5 mo (2 mo after Dx)	Pulmonary failure
4	Stephe et al[15]	1986	18 mo	F	Diarrhea, intestinal perforation	Ileum Bx: LCH+	N/A	No	–	A	Alive at CR at 5 y of age	N/A
5	Egeler et al[11]	1990	5 mo	M	Bloody diarrhea, vomiting, edema, rash	Sigmoid, Skin Bx: LCH+	Anemia, hypoalbuminemia	Liver, Spleen, skin	+	A	Alive in second CR at 1 y f/u	N/A
6	Egeler et al[11]	1990	4 mo	M	FTT, vomiting, diarrhea, rash	Duodenum, skin Bx: LCH+	Anemia, hypoalbuminemia	Skin	–	A	Died at 18 mo (14 mo after Dx)	Disease progression
7	Egeler et al[11]	1990	10 mo	F	FTT, vomiting, rash	Duodenal, jejunal, LN, and skin Bx: LCH	Hypoalbuminemia	Liver, spleen, skin, mesenteric LNs	+	A + D	Died at 16 mo (6 mo after Dx)	Disease progression
8	Lee et al[16]	1990	1 wk	F	Bloody diarrhea, rash	Rectal, skin Bx: LCH+	NA	Skin, bone	–	E	Died at 16 wk (4 mo after Dx)	Disease progression
9	Lee et al[16]	1990	2 wk	F	Bloody diarrhea, rash	Rectal, skin Bx: LCH+	N/A	Skin, bone	–	A	Died at 10 mo (9 mo after Dx)	Disease progression
10	Patel et al[17]	1991	4 mo	F	Bloody diarrhea, obstruction	Laparotomy, Bx site?	N/A	BM, bone	–	E	Alive at CR (2-y f/u)	N/A
11	Boccon-Gibod et al[18]	1992	At birth	M	FTT, rash	Duodenal, rectal, liver Bx: LCH+	Anemia, thrombocytopenia, hypoalbuminemia, hyperbilirubinemia	Liver, skin	+	A + D	Died at 16 mo (16 mo after Dx)	Disease progression
12	Boccon-Gibod et al[18]	1992	16 mo	F	Bloody diarrhea, fever, hepatosplenomegaly, rash	Stomach, duodenal, sigmoid Bx: LCH+	Anemia, thrombocytopenia, hypoalbuminemia	BM? Skin, LNs	+	A	Alive at CR (4-mo f/u)	N/A
13	Gillmore et al[19]	1993	16 mo	F	Diarrhea, vomiting, fever, rash, hepatosplenomegaly	Duodenal, colonic, skin, BM Bx: LCH+	Pancytopenia	BM, Skin	+	A + D	Alive at CR (long-term f/u unknown)	N/A
14	Geissmann et al[9]	1996	3 mo	F	Bloody diarrhea, hypoproteinemia, 17rash	Duodenal, gingival, skin Bx: LCH+	Hypoproteinemia	Skin, gingiva	–	A + B + D	Alive at CR at 10-y f/u	N/A
15	Geissmann et al[9]	1996	2 mo	M	Diarrhea, anemia, hypoproteinemia, rash	Duodenal, rectal, skin Bx: LCH+	Hypoproteinemia, anemia	Skin	–	A + D	Died at 2 y (22 mo after Dx)	Disease progression
16	Geissmann et al[9]	1996	7 mo	F	FTT, vomiting, anemia, hypoproteinemia, rash	Duodenal, skin Bx: LCH+	Hypoproteinemia, anemia	Skin	–	A + B	PR at 4.5-y f/u	N/A
17	Geissmann et al[9]	1996	16 mo	F	Bloody diarrhea, FTT, anemia, hypoproteinemia	Stomach, duodenal, colonic, skin Bx: LCH+	Hypoproteinemia, anemia	Skin, BM	+	A + D	Died at 32 mo (16 mo after Dx)	Disease progression
18	Geissmann et al[9]	1996	At birth	M	Vomiting, hypoproteinemia, anemia, rash	Colon, rectal, skin Bx: LCH+	Hypoproteinemia, anemia	Skin, liver	+	A + D	Died at 4 mo (4 mo after Dx)	Disease progression

(*continued*)

Table II. Continued

Case	Author	Year	Age	Sex	Symptoms	Biopsy sites	Laboratory findings	Other organ involvement	Risk organ	Treatment*	Outcome	Cause of death (if dead)
19	Geissmann et al[9]	1996	At birth	F	Vomiting, hypoproteinemia, anemia, rash	Colon, rectal, skin Bx: LCH+	Hypoproteinemia, anemia	Skin	–	A + D	Died at 3.5 mo (3.5 mo after Dx)	Disease progression
20	Geissmann et al[9]	1996	2 mo	M	FTT, vomiting, diarrhea, anemia, hypoproteinemia,	Stomach, colon, rectal, skin, gingival Bx: LCH+	Hypoproteinemia, anemia	Skin, gingiva, bone, liver	+	A	Alive at CR (5-y f/u)	N/A
21	Geissmann et al[9]	1996	2.5 mo	F	FTT, bloody diarrhea, vomiting, hypoproteinemia, anemia, rash	Stomach, duodenal, skin Bx: LCH+	Hypoproteinemia, anemia	Skin	–	A	PD at 8 mo	N/A
22	Geissmann et al[9]	1996	0.5 mo	M	FTT, anemia, hypoproteinemia, rash	Stomach, duodenal, colon, skin Bx: LCH+	Hypoproteinemia, anemia	Skin, liver, lung	+	A + C	Died at 22 mo (13 mo after Dx)	Disease progression
23	Santos-Machado et al[20]	1999	24 mo	F	Diarrhea, PLE, fever scalp ulcer, petechial, hepatosplenomegaly	Skin, BM: LCH+	Pancytopenia, hypoalbuminemia, hyperbilirubinemia	Skin, BM	+	A	Died at 26 mo (2 mo after diagnosis)	Disease progression
24	Santos-Machado et al[20]	1999	24 mo	M	Diarrhea, PLE, weight loss, fever, hepatomegaly, rash, diabetes insipidus	Palatal Bx: LCH+	Hypoalbuminemia, hyperbilirubinemia, low PT activity	Skin, liver	+	A + D	Died at 29 mo (5 mo after diagnosis)	Hemorrhage, from liver failure coagulopathy
25	Damry et al[21]	2000	9 mo	F	Diarrhea, FTT, rash	Bone Bx: LCH+, radiograph with barium (abnormal jejunum)	Hypoalbuminemia, anemia, thrombocytopenia	Skin, BM, bone, liver, spleen	+	A	Alive at CR (2-mo f/u)	N/A
26	Stein et al[22]	2001	1 mo	F	Bloody diarrhea, rash	Skin Bx: LCH+	?	Skin, bone	–	A	Alive at CR (4-y f/u)	N/A
27	Levy et al[23]	2001	9 mo	F	Diarrhea, rash, otitis media, scalp dermatitis	Gastric, duodenal, colonic, skin, bone Bx: LCH+	NA	Skin, bone	–	A + D	Achieved PR, but long-term f/u not known	N/A
28	Akkari et al[24]	2003	8 mo	M	GI involvement present but details not known	Not known	NA	BM, liver, spleen, skin	+	A + D + C (auto)	Died at 30 mo (4 mo post HSCT, 22 mo after Dx)	Disease progression post-HSCT
29	Akkari et al[24]	2003	5 mo	F	GI involvement present but details not known	Not known	NA	BM, lung, skin	+	A + B + C (allo)	Died 37 mo after 23 mo post-HSCT (sepsis) 32 mo after Dx	Disease progression post-HSCT
30	Akkari et al[24]	2003	12 mo	F	GI involvement present but details not known	Not known	NA	BM, lung, bone, skin	+	A + D + C (allo)	Alive at CR (28 mo after Dx)	N/A
31	Choi et al[25]	2003	7 mo	M	FTT, bloody diarrhea, vomiting, fever, rash	Stomach, duodenal, colonic Bx: LCH+	Hypoalbuminemia, anemia, thrombocytopenia	Skin, liver, spleen	+	A + B	Alive at CR (35 mo after Dx)	N/A
32	Usmani et al[26]	2003	12 mo	M	FTT, fever, constipation, hepatomegaly, perianal rash, bony lump	Colonic, rectal Bx: LCH+	Pancytopenia,	BM, liver, lung, bone, skin, retroperitoneal LNs	+	A + D	Died at 26 mo (14 mo after Dx)	Disease progression
33	Sabri et al[27]	2004	3 y	M	Oral ulcers, gingival hyperplasia, constipation, perianal skin tag	Oral cavity, stomach, perianal skin tag Bx: LCH +	anemia	No	–	A	Alive at CR (3 mo after Dx)	N/A

(*continued*)

Table II. Continued

Case	Author	Year	Age	Sex	Symptoms	Biopsy sites	Laboratory findings	Other organ involvement	Risk organ	Treatment*	Outcome	Cause of death (if dead)
34	Hait et al[28]	2006	2 d	F	Bloody stool, rash	Stomach, rectal, skin Bx: LCH+	No specific findings	Skin	–	A + C	Died at 16 mo (16 mo after Dx)	Sepsis secondary to conditioning regimen chemo
35	Shima et al[29]	2010	11 mo	F	Diarrhea, vomiting, bloody stool, edema	Colonic, skin Bx: LCH+	Hypoproteinemia	Skin, lung, liver, spleen, BM, mesenteric LNs	+	A + B	Alive at CR (disease free for 24 mo)	N/A
36	Yadav et al[30]	2010	22 mo	F	FTT, vomiting, diarrhea (often bloody), fever, PLE, anasarca	Duodenal, colonic, BM Bx: LCH+	Anemia, hypoalbuminemia	BM, liver	+	A	Alive at CR (24 mo of f/u)	N/A
37	Yadav et al[30]	2010	17 mo	F	FTT, diarrhea, fever, hepatosplenomegaly	Duodenal, colonic, skin, Bx: LCH +	Thrombocytopenia	Bone, skin, liver, spleen	+	A + B	PR, considered for SCT (8 mo of f/u)	N/A
38	Singhi et al[10]	2011	4 mo	M	Bloody diarrhea, FTT	Duodenal, colonic, skin, BM Bx: LCH+	Anemia	Skin, BM	+	E	Died at 16 mo (12 mo after dx)	Disease progression
39	Wiliamson et al[31]	2012	6 mo.	F	Rash, bloody diarrhea, bilious vomiting, FTT, lump	Small intestine, skin Bx: LCH+	Anemia, Thrombocytopenia, high ESR, hypoalbuminemia	Skin, bone, LNs, spleen	+	A	Alive at CR (3-y f/u)	N/A
40	Adion et al[32]	2015	4 mo	F	Rash, delayed growth, hematochezia	Colorectal, skin, Bx: LCH +	NA	Skin	-	A	Alive at CR (10 mo after completing the treatment) 1 y therapy	N/A
41	Adion et al[32]	2015	12 y	F	Polyuria, polydipsia (no GI symptoms)	Duodenal Bx: LCH+	NA	Pituitary gland	–	A	Alive at CR (2 y after the end of treatment)	N/A
42	Zei et al[33]	2016	16 mo	F	Emesis, poor weight gain, rash	Duodenal, colonic, skin Bx: LCH +	Hypoalbuminemia	Skin, bone	–	A	Alive at CR (1 y after the end of therapy)	N/A
43	Yoon (current)		6 wk	M	Bloody stool, FTT, rash	Duodenal, rectal, colon Bx: LCH +	Hypoalbuminemia, anemia, high ESR	BM, liver, spleen, skin	+	A	Alive at CR (at 2 y, 32 mo after the end of therapy)	N/A
44	Yoon (current)		6 mo	F	Bloody stool, FTT, rash	Colonic Bx: LCH +	Hypoalbuminemia, high ESR	Bone, skin	–	A + B	Alive at CR (at 10 y, 72 mo after the end of therapy)	N/A
45	Yoon (current)		3 mo	F	Bloody diarrhea, rash, splenomegaly	Bx done, but not available	Hypoalbuminemia, anemia, high ESR	Liver, spleen, skin	+	A	Alive at CR (at 21 mo after the end of therapy)	N/A
46	Yoon (current)		16 y	F	Diarrhea, constipation, abdominal pain, rash	Upper and lower GI tract, skin Bx: LCH+	High ESR, hypoalbuminemia	Bone, skin, CNS	–	A + B + D	Alive at CR (at 107 mo after the end of therapy)	N/A

BM, bone marrow; *Bx*, biopsy; *CNS*, central nervous system; *CR*, complete remission; *Dx*, diagnosis; *ESR*, erythrocyte sedimentation rate; *F*, female; *f/u*, follow-up; *GI*, gastrointestinal; *FTT*, failure to thrive; *HSCT*, hematopoietic stem cell transplantation; *M*, male; *N/A*, not available; *LN*, lymph node; *PD*, progressive disease; *PLE*, protein-losing enteropathy; *PR*, partial remission.
*Treatment: A (vinblastine, steroids, and/or etoposide, 6 mercaptopurine); B (2 CDA and/or cytarabine and/or cyclophosphamide); C (stem cell transplant); D (radiotherapy, CD1 antibody, interferon, ATG); E (not known); *allo*, allogenic; *auto*, autologous.