SYSTEMATIC REVIEW

Cutaneous neonatal Langerhans cell histiocytosis: a systematic review of case reports [version 1; peer review: 1 approved with reservations, 1 not approved]

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Abstract

Background: Cutaneous langerhans cell histiocytosis (LCH) is a rare disorder characterized by proliferation of cells with phenotypical characteristics of Langerhans cells. Although some cases spontaneously resolve, no consistent variables have been identified that predict which cases will manifest with systemic disease later in childhood.

Methods: A systematic review (Pubmed, Embase, Cochrane database and all published abstracts from 1946-2018) was undertaken to collate all reported cases of cutaneous LCH in the international literature. This study was registered with PROSPERO (CRD42016051952). Descriptive statistics and correlation analyses were undertaken. Bias was analyzed according to GRADE criteria.

Results: A total of 83 articles encompassing 128 cases of cutaneous LCH were identified. Multiple lesions were weakly associated with an increased length of survival ($R=0.304$ ($p<0.05$)), Worse prognosis was associated with internal organ involvement with a statistically significant chi squared statistic ($\chi^2=14.96$, 2DF $p<0.001$) and an elevated odds ratio ((OR)= 12.30 95% CI=2.67-56.74). Vesicular lesions (OR=10.8 95% CI=2.83-41.26), but not ulceration (OR=0.53 95% CI 0.12-2.05) were associated with greater risk of mortality.

Conclusions: Congenital and neonatal LCH most commonly presents as multiple lesions in multiple anatomical sites at birth. Significant differences, including the associations of mortality with lesion morphology and number were seen in this neonatal cohort compared to overall pediatric LCH. These findings require validation in a large prospective cohort.

Keywords

Histiocytic Disorders, Lumps/Bumps, malignant Neoplasms, benign Neoplasms, Skin signs of systemic disease

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Background

Cutaneous Langerhans cell histiocytosis (LCH) is a rare disorder manifest in the proliferation of cells with phenotypical characteristics of Langerhans cells which involves the cutaneous structures¹. We have used the term ‘cutaneous’ in this review to differentiate from ‘skin-limited’ which implies the absence of systemic disease involvement^{1,2}. The incidence of cutaneous LCH varies from two to nine cases per million children per year^{1,2}. Rarely, the disease is present at birth or in the neonatal period. A proportion of these cases spontaneously resolve however no consistent variables have been identified which provide predictive value as to which cases will resolve or remain skin-limited, and which will manifest with multisystem LCH later in life^{1,2}. The rate of progression of cutaneous LCH to other organs has varied widely in previous studies, from 0 to 60%¹. This lack of accurate and reliable data makes it difficult to provide information to patients regarding the risk of progression of disease and limits the development of evidence-based screening measures to identify the presence of systemic disease. Currently, consensus guidelines¹ state that most cases of cutaneous LCH spontaneously regress but some cases do progress to multisystem disease¹. It is unclear whether cutaneous LCH is merely clinically more easily identified and hence often precedes diagnosis of internal disease. This would also suggest that widespread screening of cases of cutaneous LCH may produce lead-time bias in the survival rates of individuals with multisystem LCH with cutaneous involvement, an issue which to date has not been explored. Currently, in cases of cutaneous LCH screening is considered mandatory^{1,2}.

Regarding identified risk factors for disease progression and mortality, overwhelmingly the data is sourced from cases of systemic LCH^{3,4}, which may or may not include cutaneous disease. Data from older children also far exceeds data from neonatal cohorts, limiting our knowledge of differences between presentations in the neonatal population and older pediatric age groups. Only one retrospective case series of 19 patients⁵ examined survival outcomes in infants diagnosed with cutaneous LCH within the first 4 weeks of life, with long-term follow-up beyond 10 years being limited to small case series of less than 10 patients⁶. In the setting of systemic LCH, inadequate response to initial therapy and risk organ involvement, (defined as bone marrow, liver, spleen and/or lung), are the currently associated with adverse clinical outcomes and mortality in LCH^{1,2}.

Isolated bone involvement portends significantly prolonged survival compared with other organ involvement^{3,4}. As expected, patients with multiple organ involvement have been found to have the highest risk of progression and mortality⁷. Detection of the BRAF-V600E mutation (often seen in systemic LCH but rarely in skin-limited LCH), has also been associated with increased risk of disease recurrence⁴.

Overall, given the reports (albeit uncommon) of progression of cutaneous LCH to multisystem disease, the identification of

clinical or histological predictive variables may reduce rates of unnecessary invasive screening in neonates with skin-limited LCH.

Objectives

To collate all published cases of cutaneous congenital/neonatal LCH.

To perform a descriptive analysis of cases and reviews to evaluate mortality risk and risk of progression to systemic disease.

To identify risk factors which may contribute to mortality risk and risk of progression to systemic disease.

Methods

This systematic review was registered with PROSPERO (Registration number [CRD42016041425](#)) and was conducted in line with the PRISMA statement⁸

Data sources

Information Sources for this review encompassed Medline (1946-March 1 2018), Embase (1980- March 1 2018) as well as “Epub ahead of print, and non-indexed citations” as shown in [Figure 1](#). The search strategy is presented in [Table 1](#). The databases searched were PubMed (National Library of Medicine), EMBASE, Cochrane Database of Systematic Reviews and published abstracts on Ovid Medicine (date limits for all: January 1 1980 to March 1 2018). The search terms used were: (Langerhans Cell Histiocytosis OR Hashimoto-Pritzker) AND (Congenital OR Birth OR Neonate) AND (Skin OR Cutaneous)

Study eligibility criteria

Eligibility criteria for this review included published case reports, case series and reviews with no restrictions of patient sex or ethnicity and language of publication. Eligible cases included:

- 1) Cases of histologically diagnosed LCH at birth (congenital) or within the first 4 weeks of life involving the skin.
- 2) Cases which report data pertaining to evidence of systemic involvement (clinical examination, skeletal survey etc.) and/or histological data (CD1a, eosinophil density etc.)
- 3) Cases with follow up data of any period.

Appraisal and synthesis methods

Data collection was performed independently by two independent authors (EH and EY), with any disagreements regarding inclusion of citations being referred to a third author (VV) for mediation. Information was collected using a standardized data collection form (available as [extended data on OSF](#)⁹) with the principal outcomes of interest being mortality, age at demise and length of follow up. Data not available from the published article was requested via email contact with the relevant corresponding authors.

Figure 1. PRISMA flow diagram of included studies.

Potential sources of bias in collating cases were acknowledged including publications bias and reporting bias regarding the overall incidence of congenital and neonatal LCH, therefore only cases with a diagnosis of cutaneous LCH at birth (congenital) or within the first 4 weeks of life (neonatal) were included, and no attempt to quantify the number of cases of systemic LCH with a “missed” diagnosis of self-resolving cutaneous congenital LCH was undertaken. Particular effort was made to include unpublished cases and cases presented as posters and abstracts in order to reduce the impact of publication bias in our analyses.

An exploratory univariate analysis (using Pearson correlation coefficients for categorical variables and chi-squared tests for binary variables) was undertaken to correlate mortality and the progression to systemic disease with the clinical and histological variables collated.

Results

Study selection

A total of 211 articles were identified in the literature review; 82 of these articles were removed upon review of titles and abstracts against eligibility criteria. Full-text review of 129 articles excluded 12 review articles, 1 duplicated case report and 33 articles (containing 42 cases) due to lack of follow up data. The remaining 83 articles^{5,10-91} containing 128 individual cases were used as the basis of this review.

Summary of findings

The summarized demographic data of the included cases is presented in [Table 2](#).

Univariate correlation analysis

The results of univariate correlation analysis are summarized in [Table 3](#). The presence of multiple lesions was associated with an increased length of survival ($r=0.304$ $p<0.05$), whilst the presence of systemic disease portends a worse prognosis, with a statistically significant chi squared statistic ($\chi^2=14.96$, 2DF $p<0.001$). Having lesions at birth had an odds ratio (OR) of mortality of 1.38, which did not reach statistical significance (95%CI=0.417-4.56). Individuals presenting with either weight loss, hepatosplenomegaly and internal organ involvement also had a worse prognosis and decreased overall survival (OR= 8.01 95% CI=2.07-30.86)

The presence of ulcerated lesions did not change risk of survival (OR=0.53 95% CI 0.11-2.05) Having less than 10 lesions increased the risk of mortality but not to a statistically significant degree (OR=1.77 95% CI= 0.76-17.30). Vesicular lesions were significantly more likely to be associated with mortality (OR=10.8 95% CI=2.83-41.26). Of 128 cases, 112 were screened for systemic involvement (87.5%). Of the screened cases, 66 were found to have cutaneous involvement only (51.6%). The mortality rate for those with identified systemic involvement

Table 1. Demographics and Descriptive Results from this review.

Characteristic	N=
Gender	
Male	63
Female	55
Missing	10
Number of Lesions	
Single	26
Multiple	72
Average Number of Lesions	30
Presenting Symptoms	
Skin	98
Bone	2
Fever	0
Internal Organ	20
Diabetes Insipidus	0
Hepatosplenomegaly	5
Weight Loss	2
Missing	1
Onset	
At Birth	87
In First 4 Weeks of Life	39
Missing	2
Description of Lesions	
Papules	31
Nodules	39
Seborrhea	7
Vesicle	11
Other	31
Missing	9
Ulceration	
Yes	23
No	93
Missing	12
Skin Site Involved	
Head and Neck	65
Trunk	60
Upper Limb	59
Lower Limb	57
Multiple Sites	63
Missing	0
Systemic Screening Undertaken	
Yes	112

Description of Lesions	
No	5
Missing	11
Systemic Involvement Identified	
Yes	54
No	66
Missing	8
Treatment	
None	56
Steroid	4
Akylating Agent	25
Topical	3
Antibiotic	6
Surgery	6
Missing	28
Av Length of Follow Up (Months)	23.89
Av Length of Survival (Months)	10.24
Alive at End of Follow Up	
Yes	104
No	17
Missing	7

was 27.4% (n= 17/62). The calculated OR for mortality based upon the presence of systemic involvement was 12.3 (95% CI). No statistically significant associations or OR were seen between histological markers and clinical outcomes including mortality or length of survival in the data examined. Given the heterogeneity of the sample, no multivariate analysis was performed on the collated data.

Discussion

Summary of evidence

The results of this systematic review of case reports of cutaneous neonatal LCH differ from the pre- existing literature in several areas. This may be because existing data includes all cases of pediatric LCH, as opposed to the congenital and neonatal cases focused on in this review. This highlights the need for recognition that congenital and neonatal LCH have inherently different clinical characteristics compared to other pediatric cases of LCH. Minkov *et al.*³ have reported that the trunk was the most common overall site of disease. However, our data suggest that a large proportion of congenital and neonatal cases involve multiple anatomical sites (n=65). No significant gender predominance was identified (males=63; females=55). A weak association was seen between a later onset of disease and a worse prognosis (r=0.263, p<0.05). This is in line with the literature with earlier onset disease significantly associated with spontaneous resolution^{92,93}.

Systemic disease was identified in 48.4% of cases (n=62) lower than the rates for the overall pediatric group at 59%³, and those

Table 2. Results of univariate analysis.

Variable 1	Variable 2	Statistical test	Correlation coefficient	Explanation
Age of onset (weeks)	Extent of Disease (Number of organ systems involved)	Pearson correlation coefficient	0.263 (p<0.05)	Weak correlation of worse disease in those presenting later in the neonatal period
Systemic involvement (Yes/No)	Mortality (Alive/Deceased)	Chi Squared	14.96 (p<0.0001)	Systemic involvement associated with mortality
Length of survival (Weeks)	Number of Lesions	Pearson's correlation coefficient	0.304 (p<0.05)	Survival better in those with multiple lesions

reported by Stein *et al.* (63.1%)⁵. In line with previous research and recommendations⁵, systemic disease was significantly correlated with mortality ($r=0.453$, $p<0.05$), with persistent cutaneous lesions associated with poorer outcomes^{3,75,92}. The overall mortality rate for all cases in the population of this review was 14.05%.

Previous studies have suggested high rates of spontaneous clinical remission (from 60%³ to 100%⁵) in skin-limited LCH, and 8% in multisystem disease⁹⁴. The accuracy of such figures is disputed due to the absence of systemic screening and long term follow up in these published reports. We attempted to identify cases of spontaneous remission (both clinical and biological) in the literature. Clinical remission was documented in 41/128 cases (32.1%); however, due to the high variability in length of follow-up and low rates of systemic screening post clinical remission, rates of biological remission could not be accurately established. We would suggest that long term prospective follow-up studies with systemic screening (both at diagnosis and post clinical remission) are required to accurately quantify rates of spontaneous biological remission in future studies.

Regarding lesion morphology, Battistella *et al.*⁹² suggest that single, necrotic, hypopigmented macules and distal topography (lesions present at a distal site) suggest a self-regressive form of disease⁹². This is still an area of contention with no reliable data from cohorts larger than 20 patients^{5,93,95–98}. We identified a weak correlation between skin lesion descriptors and overall mortality as well as length of survival in the neonatal and congenital LCH population. The presence of multiple lesions was associated with increased length of survival, although the presence of lead-time bias was likely given the non-significant differences in mortality between the two groups. Vesicular lesions were associated with increased mortality whereas no impact of survival was seen in the presence of ulcerated lesions. We anticipated that reporting bias would result in confirmation of an association between ulcerated lesions and mortality if one existed, although this has not been confirmed by our review. One explanation is that vesicular lesions commonly progress to ulceration during the stages of healing, thus emphasizing the need for consistent descriptors in case reports of LCH. Alternatively, ulcerated lesions might have an association with mortality but not in the congenital and neonatal LCH cohort.

Limitations

Most cases identified were congenital (67.9%; $n=87$), although some controversy exists regarding whether congenital cases exist at all⁹³. Morren states that LCH presents prior to 3 months of age but does not occur congenitally⁹³. Given the retrospective nature of our study, we were unable to shed further light on this debate as we were reliant upon multiple authors' observations and recordings.

Given the variability in patient follow-up in this review, the current estimates of mortality risk are only valid until 18 months of age (the mean length of follow-up). The lack of long-term follow-up is the major reason why data is lacking regarding long term recurrence rates in neonatal LCH and thus our review is limited to conclusions regarding short- and medium-term outcomes.

Future research should expand upon this by analyzing longer-term outcomes. Haupt¹ has recommended a long-term follow-up of 5 years for patients, mirroring that of childhood cancer survivors. This is applicable even to both skin-limited LCH and systemic disease. Progression of skin-limited LCH to multisystem involvement is documented in the literature^{1,5}.

We had a limited ability to identify statistically significant variables that contribute to LCH mortality due to limited follow-up in documented cases. The GRADE approach⁹⁹ to assessing the quality of evidence and strength of recommendations (available as [extended data on OSF](#)⁹⁹) shows the absence of control groups, and incomplete follow up. Long-term, prospective, multicenter collaborative studies needed to confirm the findings of this review and are important steps in characterizing the progression of neonatal LCH.

Conclusions

We present a systematic review of case reports of cutaneous congenital and neonatal LCH. The descriptive characteristics in this review significantly differ from descriptions of overall pediatric LCH, highlighting the clinical differences between these entities. Congenital and neonatal LCH most commonly presents in multiple anatomical sites at or shortly after birth, with the presence or absence of systemic involvement significantly impacting mortality. Further prospective, long-term multicenter collaborative studies are required to corroborate the results of this review.

Data availability

The Data Collection Proforma and GRADE Bias Assessment are available on OSF. DOI: <https://doi.org/10.17605/OSF.IO/TRX429>.

Data are available under the terms of the [Creative Commons Zero “No rights reserved” data waiver](#) (CC0 1.0 Public domain dedication).

Reporting Guidelines

A completed PRISMA Checklist for this study is available on OSF. DOI: <https://doi.org/10.17605/OSF.IO/TRX429>.

Grant information

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Dr. Venning and colleagues perform a review on neonatal and congenital cases of Langerhans cell histiocytosis (LCH) to examine predictors for progression to systemic disease. While this endeavour will help to risk-stratify patients, there are several issues that need to be addressed:

ABSTRACT

1. In the abstract, the text should make reference to congenital and neonatal onset LCH, as this is the focus of their research.
2. The title should be more specific as to the purpose of the review (i.e. that this is to look for variables the predict systemic involvement).

BACKGROUND

1. In the background, the authors state that "Currently, consensus guidelines state that most cases of cutaneous LCH spontaneously regress but some cases do progress to multisystem disease". However, the reference states that "progression to MS-LCH is common."
2. Throughout the manuscript, the discussion intermingles description of cutaneous LCH, skin-limited LCH and neonatal/congenital LCH. Since the focus appears to be on the progression of neonatal/congenital cutaneous LCH, the discussion and data collection should be focused on this. As well, it would have been helpful to have more background information as to the previously documented frequency of skin-limited LCH, as the paper doesn't clearly provide this (i.e. How common is skin-limited LCH that doesn't progress (or regresses)).
3. The authors mention the lung may be a high-risk organ. However, pulmonary involvement is no longer considered a risk organ, as Ronceray *et al.*¹ found it to have no significant impact on survival in a multivariate analysis.
4. The authors mention that "Overall, given the reports (albeit uncommon) of progression of cutaneous LCH to multisystem disease...". However, the study from Lau *et al.*² in 2006

demonstrated that 4/12 (33%) of patients with isolated skin LCH progressed to multi-system LCH.

METHODS

1. It is unclear if the the study eligibility criteria requires all 3 criteria to qualify. Please elaborate. As well, please document reasons for exclusion. I note that the study by Lau *et al.*² has data on patients but was not included.
2. It is unclear what the statement "no attempt to quantify the number of cases of systemic LCH with a "missed" diagnosis of self-resolving cutaneous congenital LCH was undertaken" means. Does this mean these cases were included or excluded?

RESULTS

1. Please define "multiple". Is this more than 1 lesion or 10 and why was this number chosen? As before, the distinction between skin limited LCH and cutaneous LCH should be clear.
2. Among the paper's objectives is: "to identify risk factors which may contribute to mortality risk and risk of progression to systemic disease.", however, when I finished reading the paper, I still did not have a clear idea of what risk factors contribute to the mortality and progression risk in the congenital/neonatal subset of LCH. In the conclusion they state that the presentation of congenital/neonatal LCH more often involves multiple sites compared to paediatric LCH, and that systemic involvement significantly impacts mortality. To me, the latter point holds in both paediatric and congenital/neonatal LCH and isn't new information, nor helpful in distinguishing the two.

LIMITATION

1. The statement "Morren states that LCH presents prior to 3 months of age but does not occur congenitally" is odd, as Morren's report lists 2 congenial cases³.

Overall, this is an interesting undertaking. However, methodologically, there a number of issue that should be examined.

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Are the rationale for, and objectives of, the Systematic Review clearly stated?

Yes

Are sufficient details of the methods and analysis provided to allow replication by others?

No

Is the statistical analysis and its interpretation appropriate?

No

Are the conclusions drawn adequately supported by the results presented in the review?

No

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Pediatric dermatology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

Reviewer Report 02 May 2019

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The authors clearly state their rationale for the review: to identify particular cutaneous presentations that are more frequently associated with progression to multisystem disease. In fact, the authors undermine their study's potential implications in only mentioning reduced invasive screening. Perhaps equally, if not more important, it can help guide management, decreasing the use of systemic therapy in cases that will likely regress while prompting the use of systemic therapy in patients with high-risk lesions. Nevertheless, while the objective stated by the authors was to identify risk factors which may contribute to mortality risk and risk of progression to systemic disease, this aspect was not adequately addressed in the paper (we do not think that collating published cases is the appropriate methodology for such a scientific question) and is not part of the conclusions.

More details of the methods and analysis are needed to allow for replication by others. A standardized data collection form (not received by reviewers) should accompany the article for readers to understand some of the statements that are not based on findings described in the section "Results". Furthermore, comparing single versus multiple lesions implies clear definitions for a skin lesion (at least for size and type), and the authors do not provide such definitions. For instance, multiple lesions may describe widespread rashes involving most of the body, two or three distinct nodules, or a rash covering a significant portion of the diaper area. Are these all

truly equivalent?

Certain components of the authors' interpretation need to be addressed. For instance, it is unclear why the authors preferred to study the influence of multiple lesions on length of survival, rather than on progression to systemic disease or mortality, especially considering the limitation of short follow-up period. Also, the authors conclude that the descriptive characteristics in this review significantly differ from descriptions of overall pediatric LCH. However, they do not provide a statistical comparison or clarification of the age range that they consider pediatric. It is also questionable whether meaningful analysis of the impact of lesions type can be performed considering that 31/128 (24%) of lesions were listed as "others" and another 9 were missing.

In the last paragraph of the results, the authors state that no statistically significant associations or OR were seen between histological markers and clinical outcomes. How could such a conclusion be drawn without central pathology review? In the view of the reviewers, such a correlation cannot be made based on a description of the pathology findings, regardless of how well and detailed they are described, but needs a review of the biopsy specimens by experienced pathologists in a structured way. Additionally, the authors report that they were unable to perform a multivariate analysis due to data heterogeneity. If by heterogeneous the authors were implying that the data was inconclusive and/or insufficient, then this poses questions to the findings of the univariate analysis either.

The following components should also be addressed:

In the 1st paragraph of the background, the authors write: "Cutaneous Langerhans cell histiocytosis (LCH) is a rare disorder manifest in the proliferation of cells with phenotypical characteristics of Langerhans cells which involves the cutaneous structures¹." However, it should be noted that Langerhans cells are dendritic cells of the skin and mucosa, and that despite their phenotypic resemblance to Langerhans cells (and shared immunohistochemical markers), the pathologic cells of LCH derive from immature myeloid precursor cells¹. Additionally, reference one used by the authors is a set of guidelines. Accordingly, the original studies should be cited when statistics are noted (i.e. the incidence of cutaneous LCH and rate of progression). The authors write: "Currently, consensus guidelines¹ state that most cases of cutaneous LCH spontaneously regress but some cases do progress to multisystem disease¹". Do they mean "skin-limited" rather than "cutaneous" according to the distinction made by the authors that "skin-limited" implies the lack of systemic involvement? Though spontaneous remission is the norm for "skin-limited" LCH, skin-limited disease is rare (2% of cases)². The authors write: "It is unclear whether cutaneous LCH is merely clinically more easily identified and hence often precedes diagnosis of internal disease". Actually, cutaneous disease is often misdiagnosed due to its resemblance to other more common conditions (i.e diaper dermatitis and cradle-cap)³. In addition to noting in the background section that screening for multisystem disease at the time of initial presentation is mandatory, the authors should also mention here the need for long-term follow-up due to the potential for disease reactivation following resolution or future progression to multisystem disease. The authors note this in the conclusion, but it should also be stated here. The authors only note one source in the conclusion giving this recommendation, which undermines its importance^{4,5,6}.

In the 3rd paragraph of the background, the authors write "Detection of the BRAF-V600E mutation (often seen in systemic LCH but rarely in skin-limited LCH), has also been associated with increased risk of disease recurrence⁴". Of note, BRAF-V600E mutations are not only associated with recurrence, but also with treatment-refractory disease and permanent sequelae. These

associations are observed in both isolated and disseminated LCH (and in disseminated disease are also associated with risk organ involvement)^{7,8,9}. Furthermore, Héritier's study in a cohort of 315 patients with determined BRAF status conflict with the statement that BRAF-V600E is rare in skin-limited disease. They report the presence of BRAF-V600E mutations in 87.5% of patients with multifocal single system cutaneous disease and in 80.2% of patients with multifocal cutaneous multisystem disease. What might also be of interest to the authors is that the mutation was absent in the 6 infants with solitary cutaneous lesions and single system disease¹⁰.

In the 4th paragraph of the background, the authors write: "Overall, given the reports (albeit uncommon) of progression of cutaneous LCH to multisystem disease, the identification of clinical or histological predictive variables may reduce rates of unnecessary invasive screening in neonates with skin-limited LCH". However, as we note above, multisystem disease in patients presenting with cutaneous involvement is the norm.

In the 1st paragraph of the discussion, the authors write: "This is in line with the literature with earlier onset disease significantly associated with spontaneous resolution^{92,93}". In contrast, because high-risk multisystem disease has been negatively correlated with age, younger age is associated with a worse prognosis¹¹. Subsequent to Minkov's findings, Gadner *et al.* reported no difference in treatment response between different age groups when correcting for the involvement of risk organ systems. Thus, the difference in prognosis between age groups is likely due to the higher prevalence of multisystem disease in younger patients¹². Similarly, in the 2nd paragraph, the authors write: "Systemic disease was identified in 48.4% of cases (n=62) lower than the rates for the overall pediatric group at 59%³, and those reported by Stein *et al.* (63.1%)⁵". However, in a retrospective analysis of 61 neonates with LCH, Minkov *et al.* note a higher prevalence of multisystem disease in neonates (ironically, 59%)¹¹.

The authors write in the 4th paragraph of the discussion: "The presence of multiple lesions was associated with increased length of survival, although the presence of lead-time bias was likely given the non-significant differences in mortality between the two groups". Despite the evolution in the classification system with increased recognition that the previously distinct categories have some overlapping features, it might still be worth mentioning. Specifically, Hashimoto-Pritzker disease (a.k.a congenital self-healing reticulohistiocytosis) was described as a widespread eruption of red-brown nodules presenting within the first few weeks from birth that resolve spontaneously with isolated cutaneous involvement¹³.

The authors acknowledge a number of limitations, but this does not compensate for them. As they note, limited follow-up prevented them from identifying statistically significant variables that contribute to LCH mortality. Though their stated objective of identifying particular cutaneous presentations that are more frequently associated with progression to multisystem disease and overall mortality is a good one, they were not able to identify any new prognostic factors that would contribute to the literature.

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Are the conclusions drawn adequately supported by the results presented in the review?

No

Competing Interests: No competing interests were disclosed.

We confirm that we have read this submission and believe that we have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however we have significant reservations, as outlined above.

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