

# Langerhans-Cell Histiocytosis In Children: A Bicentric Study From Tunisia

## Histiocytose Langerhansienne pédiatrique: Étude bicentrique tunisienne

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### ABSTRACT

Langerhans cell histiocytosis (LCH) is the most common form of histiocytosis in children, characterized by clonal proliferation of CD1a+ and CD207+ dendritic cells. This retrospective study aimed to evaluate the clinical characteristics, treatment response, and progression of LCH in children diagnosed between January 2010 and July 2023 at two Tunisian referral centers. Forty-three patients were enrolled with a median age at diagnosis of 3 years. Multisystem LCH with risk organs involvement was the most common group (44%), followed by single-system LCH (37%). Bone, skin, and liver were the most frequently affected organs. Central nervous system tumorous lesions were observed in five patients. The BRAF-V600E mutation was identified in eight of nine tested cases. Thirty-four patients received a vinblastine-based first-line therapy; six patients (18%) showed no response after two courses of vinblastine induction. Two patients received a combination of Cytarabine and Cladribine, with a favorable outcome in one case. BRAF inhibitors were used in four cases, with a favorable response in two. Reactivations occurred in 28% of patients, and 23% experienced at least one permanent consequence. Overall survival (OS) and disease-free survival (DFS) rates were 93% and 63%, respectively. Risk organs involvement and poor response to vinblastine induction were associated with worse outcomes.

**Key words:** Pediatric, Langerhans cell histiocytosis, overall survival, disease-free survival, LCH reactivation

### RÉSUMÉ

L'histiocytose des cellules de Langerhans (LCH) est la forme la plus courante d'histiocytose chez les enfants, caractérisée par la prolifération clonale des cellules dendritiques CD1a+ et CD207+. Cette étude rétrospective visait à évaluer les caractéristiques cliniques, la réponse au traitement et la progression de la LCH chez les enfants diagnostiqués entre janvier 2010 et juillet 2023 dans deux centres de référence tunisiens. Quarante-trois patients ont été inscrits avec un âge médian au diagnostic de 3 ans. L'HCL multisystémique impliquant les organes à risque était le groupe le plus courant (44 %), suivi par l'HCL monosystémique (37 %). Les os, la peau et le foie étaient les organes les plus fréquemment touchés. Des lésions tumorales du système nerveux central ont été observées chez cinq patients. La mutation BRAF-V600E a été identifiée dans huit des neuf cas testés. Trente-quatre patients ont reçu une thérapie de première ligne à base de vinblastine ; Six patients (18 %) n'ont montré aucune réponse après deux cycles d'induction de vinblastine. Deux patients ont reçu la combinaison de Cytarabine et de Cladribine, avec un résultat favorable dans un cas. Les inhibiteurs BRAF ont été utilisés dans quatre cas, avec une réponse favorable dans deux cas. Les réactivations ont eu lieu chez 28 % des patients et 23 % ont subi au moins une conséquence permanente. Les taux de survie globale (OS) et de survie sans maladie (DFS) étaient respectivement de 93 % et 63 %. L'implication des organes à risque et une mauvaise réponse à l'induction de la vinblastine ont été associées à de pires résultats.

**Mots clés:** Pédiatrie, Histiocytose des cellules de Langerhans, Survie sans maladie, Tunisie, Analyse de la survie

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## INTRODUCTION

Langerhans cell histiocytosis (LCH) is an inflammatory myeloid neoplasm characterized by clonal proliferation of pathological CD1a, CD207+ dendritic cells and their accumulation in various organs(1). The clonal nature of LCH is now well established with the identification of mutually exclusive somatic mutations in mitogen-activated protein kinase (MAPK) pathway genes in most cases, resulting in constitutive extracellular signal-regulated kinases (ERK) activation (1). BRAF-V600E is the most common activating mutation, identified in approximately 60% of cases. LCH is the most common of histiocytic disorders in children, with an annual incidence of 2.6 to 8.9 cases per million children younger than 15 years (1). Clinical presentations vary widely, and treatment is tailored according to disease severity (2). The risk of disease reactivation and long-term sequelae primarily determines prognosis. In Tunisia, data on LCH in the pediatric population are lacking. A study of clinical and therapeutic characteristics would help develop locally adapted treatment protocols suited to national healthcare conditions. For example, Japanese protocols differ from Western approaches, highlighting the importance of tailoring management strategies to the local context.

The study aimed to describe the clinical characteristics, treatment outcomes, and disease progression of LCH in patients under 18 years of age.

## METHODS

### Patients

A retrospective study enrolled all pediatric patients (aged 0-18 years) diagnosed with LCH between January 2010 and July 2023 who were followed at two referral centers in Tunis: the Pediatric Hematology Department at the Bone Marrow Center and the Pediatric Oncology Unit at the Children's Hospital. The diagnosis of LCH was established based on clinical, radiological, and histological criteria, and was confirmed by DC1a expression(1). Cases without histological and immunohistochemical confirmation or with missing data were excluded from analysis.

### Methods

#### LCH Classification

Patients were retrospectively classified into single-system LCH (involving one organ or system, with uni- or multifocal lesions) and multisystem LCH (involving two or more organs). Risk organs included the bone marrow, liver, and spleen. Patients were stratified into two groups: RO+ (with involvement of one or more risk organs) and RO- (without involvement of any risk organs) (3).

#### LCH treatment

The 2010 French guidelines and, more recently, the 2021 recommendations were adopted for LCH management (4). These recommendations align with

the international guidelines established by the Histiocyte Society(3). Systemic chemotherapy was administered in cases involving risk organs, bone involvement with functional risk, refractory skin lesions, mass lesions in the central nervous system (CNS), and in cases of pulmonary condensations and nodular lesions. First-line chemotherapy consisted of induction with six weekly pulses of Vinblastine combined with prednisone at 40 mg/m<sup>2</sup>/day for four weeks, then gradually tapered over the following two weeks. Therapeutic response was evaluated using the Disease Activity Score (DAS) and other scoring systems outlined in the French guidelines(4). Maintenance therapy included Vinblastine administered at 6 mg/m<sup>2</sup> every three weeks, with prednisone given at 40 mg/m<sup>2</sup>/day for days 1 through 5 every three weeks. Mercaptopurine (6MP) was added for hematopoietic system involvement. Second-line therapy was aligned with the French guidelines when suitable molecular agents were available: a combination of 2-chlorodeoxyadenosine (2CDA) and cytarabine was indicated for refractory LCH with risk organ involvement, particularly in cases with refractory hematological involvement. Vinblastine was administered every two weeks in cases of symptom recurrence during maintenance therapy. In addition, corticosteroids were replaced with a longer course of 6MP, especially in the presence of diabetes insipidus (DI). Recently, targeted therapy has been used in selected cases(4).

#### Response to treatment

Treatment response to systemic chemotherapy was assessed according to the international LCH study group criteria (5) and disease activity score (4). Disease was classified as a non-active disease (NAD; no symptoms persisted), active disease (AD)-better (regression of signs or symptoms), AD-intermediate (persistence of signs or symptoms, unchanged disease), AD-worse (progression of signs or symptoms and/or appearance of new lesions) (5). Disease evaluation occurred at the seventh week during vinblastine induction or after two cycles of cladribine (2CDA) administration.

Reactivation was defined as the reappearance of disease activity following complete disease resolution (non-active disease)(6). Permanent Consequences (PC) were defined as any form of permanent or irreversible physical or neuropsychological handicap, attributable to the disease itself and developing at any time during the disease course(6). In our study, DI without evidence of tumor in the hypothalamic-pituitary axis was not considered reactivation.

Non-response was defined as disease progression (AD/worse) or lack of response (AD/intermediate) after each induction, or as death within 12 weeks of treatment initiation. A good response was defined as partial or complete disease resolution (NAD or AD-better).

#### Statistical analysis

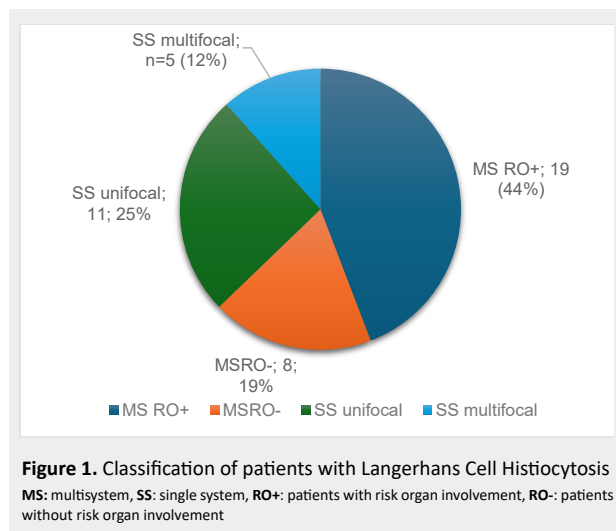
Overall survival (OS) and disease-free survival (DFS) were estimated with the Kaplan–Meier method. Disease-free survival was defined as the time from diagnosis to the

last assessment indicating the absence of active disease. Reactivation incidence was estimated using the Kaplan-Meier method. The last follow-up was on July 30<sup>th</sup>, 2024.

## RESULTS

### Patients' characteristics

Over 13.5 years, 46 patients were diagnosed with LCH. Three children were excluded due to loss of follow-up or lack of immunohistochemical confirmation; two had multifocal bone involvement, and one had pituitary involvement. Thus, 43 patients were included in the study, 21 boys (49%) and 22 girls (51%), yielding a sex ratio of 0.95. The median age at diagnosis was 3 years (interquartile range [IQR]: 1.5–6 years), ranging from 36 days to 14 years. Fourteen patients (33%) were under 2 years of age. Patients with MS LCH were significantly younger than those with SS LCH (median age 2.3 [IQR 1.3–3.5] vs. 6.7 years [IQR 2.5–9.2],  $p = 0.003$ ). The median time between symptom onset and diagnosis was 2 months (IQR: 0.25–7 months). Among the patients, 16 (37%) were diagnosed with single-system (SS) LCH, and 27 (63%) had multi-system (MS) LCH. Within the MS LCH group, eight patients (19%) were classified as MS RO-, and 19 patients (44%) as MS RO+ (Figure 1).



Molecular analysis identified a BRAF alteration in all tested patients: the BRAF V600E mutation in 8 of 9 cases and a BRAF c.1457\_1471del, p.(486\_490del) deletion in one case. The bone was the most affected organ (77% of cases). Skull lesions were present in 56% of patients, with 6 cases showing exophthalmos and 5 cases exhibiting extension into the endocranium. At diagnosis, pituitary stalk lesions were present in 5 cases, and mass lesions affecting the pineal gland, meninges, and intraparenchymal regions were observed in 4 patients. Lung involvement was observed exclusively in patients with MS LCH. Systematic chest radiography was performed, and chest computed tomography (CT) was conducted in 21 cases, particularly in the presence of clinical abnormalities or abnormal findings on chest X-ray. Chest CT abnormalities were found in 11 cases (26%),

including nodular and micronodular lesions in 9 cases, a cystic pattern in 2 cases, and pulmonary consolidations in 3 cases (Table 1).

**Table 1.** Patient's characteristics at Langerhans cell histiocytosis diagnosis

| Patient's characteristics                            | Number (%) |
|------------------------------------------------------|------------|
| <b>Number of patients</b>                            | 43 (100)   |
| <b>SS LCH number, (%)</b>                            | 16 (37)    |
| Unifocal                                             | 11 (25)    |
| Multifocal                                           | 5 (12)     |
| <b>MS LCH number, (%)</b>                            | 27 (63)    |
| RO+                                                  | 19 (44)    |
| RO-                                                  | 08 (19)    |
| <b>Organ involvement at diagnosis number, (%)</b>    |            |
| Liver                                                | 19 (44)    |
| Hematopoietic system                                 | 03 (7)     |
| Spleen                                               | 12 (28)    |
| Lungs**                                              | 11 (25)    |
| Skin                                                 | 20 (46)    |
| Bone                                                 | 33 (77)    |
| Ear/mastoid                                          | 7 (16)     |
| Pituitary tige                                       | 05 (12)    |
| Tumorous central nervous system ***                  | 04 (09)    |
| <b>Disease activity score (DAS) (Median and IQR)</b> | 3 (1-6)    |
| <b>Patients with DAS &gt;6 (number, %)</b>           | 10 (23%)   |

IQR= Interquartile range, MS= multisystem, SS= single system, RO= risk organ

\*\* : cases with radiological abnormalities observed on the chest CT scan

\*\*\*: Extra-pituitary tumor lesions

### Outcome and treatment response

#### First-line treatment

In our study, nine patients did not receive systemic chemotherapy. Among these, seven had single-system involvement with isolated skin or bone lesions, and one patient with MS RO+ LCH died before the initiation of the treatment. One patient with MS RO+ LCH, initially misdiagnosed as Evans syndrome with a negative antiglobulin test, was treated with corticosteroids and Sirolimus. This treatment resulted in a remission that lasted for 44 months. However, the patient later experienced a reactivation of the disease with CNS involvement, including neurodegenerative LCH and a focal mass lesion in the meninges.

Thirty-four patients received vinblastine-based first-line therapy. Seventeen of these patients had MS RO+ LCH, two had pulmonary LCH, one had a CNS tumor located in the pineal gland, and fourteen had bone involvement associated with functional risk. One patient with a tumour lesion in the pineal gland that did not improve after treatment with vinblastine and two courses of 2-CDA was later reclassified as a cystic lesion and was not evaluable for response to chemotherapy. After the first course of vinblastine induction, 22 out of 33 evaluable patients (67%) exhibited either non-active disease or AD better state. Non-response was noted in eleven cases (33%): eight patients had AD intermediate, and three patients experienced disease progression (Figure 2). Median disease activity score after first induction was 1 (IQR=0-3). Nineteen patients underwent a second Vinblastine-

based induction, including 11 patients with non-response to the first induction and eight with AD better state. After the second induction, three patients continued to exhibit disease progression, three had unchanged disease, eight had active better disease, and five had non-active disease. Two of the patients with disease progression after two inductions died. One achieved remission after second-line therapy combining Cladribine and Cytarabine. Seven patients proceeded to a third induction.

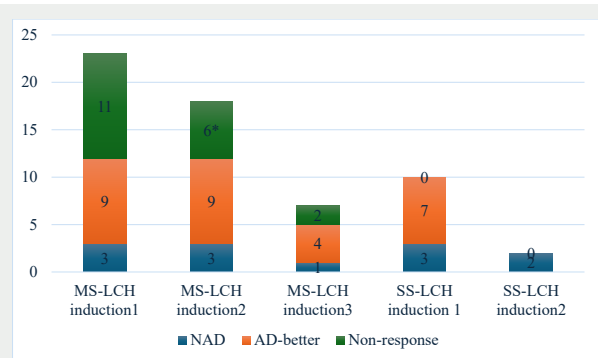


**Figure 2.** Response to vinblastine-based induction(s)

\*: MS LCH who received second induction: All patients with non-response to induction 1 and six patients with AD-better status after induction 1.

LCH: Langerhans cell histiocytosis, MS: multisystem, SS: single system, NAD: non-active disease, AD-better: active disease better.

Thirty-two patients underwent maintenance therapy. Six patients received an intensified regimen involving a biweekly vinblastine pulse due to the accordion effect or partial response of LCH lesions observed during the maintenance period (Figure 3). The median time of the initial maintenance therapy was 13 months (interquartile range: 12-25 months), with a range from 6 to 33 months.

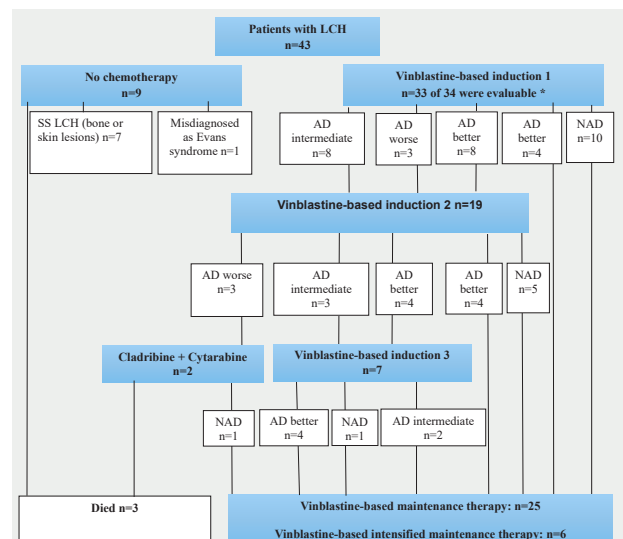


**Figure 3.** Flowchart of frontline therapy in the entire cohort

(AD)-better= active disease better, AD-intermediate= active disease intermediate, AD-worse= active disease worse, NAD= Non active disease.

\*: Cystic nature of the lesions made it impossible to evaluate the treatment response.

### Second-line therapy:

In our cohort, seven patients received second-line therapy, consisting of three cases of Cladribine (2Cda)-based chemotherapy and four cases of targeted therapy with vemurafenib. Indications for second-line therapy included refractory MS RO+ LCH in three patients, vinblastine intolerance in one patient, and neurodegenerative LCH in one patient. One patient in the second-line chemotherapy group achieved remission, while two out of four patients in the targeted therapy group achieved remission (Table 2).

**Table 2.** Second line therapy of patients with Langerhans cell histiocytosis

|      | LCH-classification | Age at diagnosis (months) | Indication for second-line therapy                    | Second-line therapy*   | Time from onset (months) | Evolution                       |
|------|--------------------|---------------------------|-------------------------------------------------------|------------------------|--------------------------|---------------------------------|
| P 1  | MS RO+             | 36                        | Progression of RO involvement                         | Cytarabine +Cladribine |                          | Sustained remission             |
| P2   | MS RO+             | 24                        | Progression of RO involvement                         | Cytarabine +Cladribine |                          | Died                            |
| P3** | MS RO-             | 42                        | Tumor in pineal gland                                 | Cladribine (2 courses) |                          | Unchanged cystic lesion         |
| P 4  | MS RO+             | 6                         | Neurodegenerative LCH                                 | Vemurafenib            | 19                       | unchanged neurodegenerative LCH |
| P 5  | MS RO+             | 28                        | Spleen involvement                                    | Vemurafenib            | 9                        | Remission                       |
| P 6  | MS RO+             | 5                         | Multiple reactivations                                | Vemurafenib            | 4                        | Remission                       |
| P 7  | MS RO+             | 19                        | RO involvement with neuropathy induced by Vincristine | Vemurafenib            | 1                        | ***                             |

LCH: Langerhans cell histiocytosis, MS: multisystem, SS: single system, RO: risk organ

\*: All patients undergoing targeted therapy are receiving the treatment at last follow up

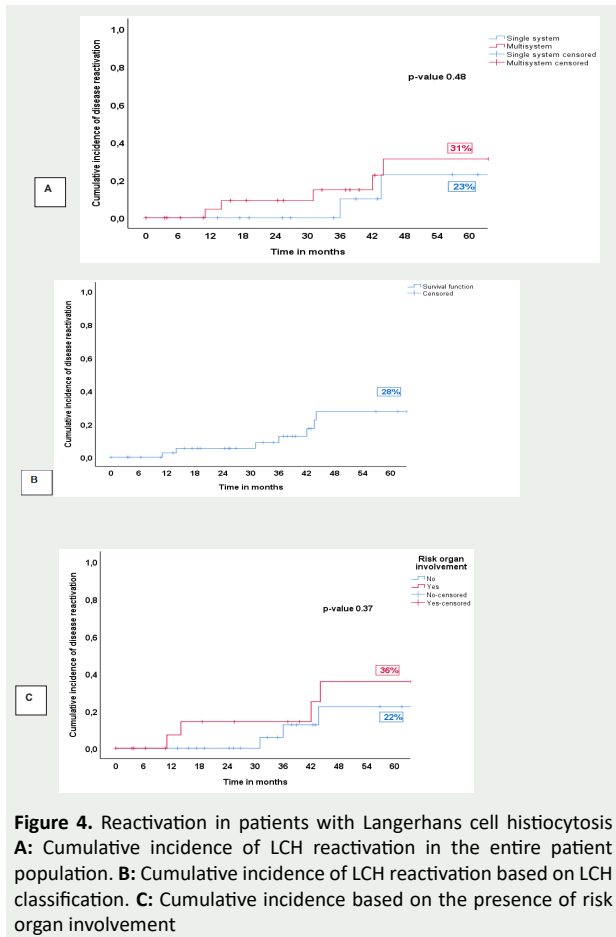
\*\* : A patient with tumorous lesion in the pineal gland that not improved with vinblastine and two courses of 2-CDA, the lesion was subsequently reclassified as a cystic lesion.

\*\*\*: Not yet evaluable

### Reactivations:

Three patients experienced disease progression and subsequently died, while three others did not achieve remission and were thus excluded from the reactivation assessment. Among the 37 evaluable patients, seven experienced at least one reactivation. Of these, five had multisystem LCH, and two had single-system bone LCH. Reactivation occurred during maintenance therapy in two cases. The median reactivation time was 22 months

(IQR: 13-36 months) from diagnosis. The cumulative incidence (CI) of reactivation at 3 years and 5 years was, respectively, 13% and 28% (Figure 4). Cumulative incidence of reactivation was higher in multisystem LCH and in risk organ involvement without significant difference, estimated at 31% and 36 % at 5 years, respectively (Figure 4).



Bone was the most involved organ during relapse, as observed in six cases. Neurological tumoral lesions were identified in two patients, and skin involvement was also noted in two patients. One patient experienced a multisystem relapse with hematological, splenic, hepatic, and digestive involvement.

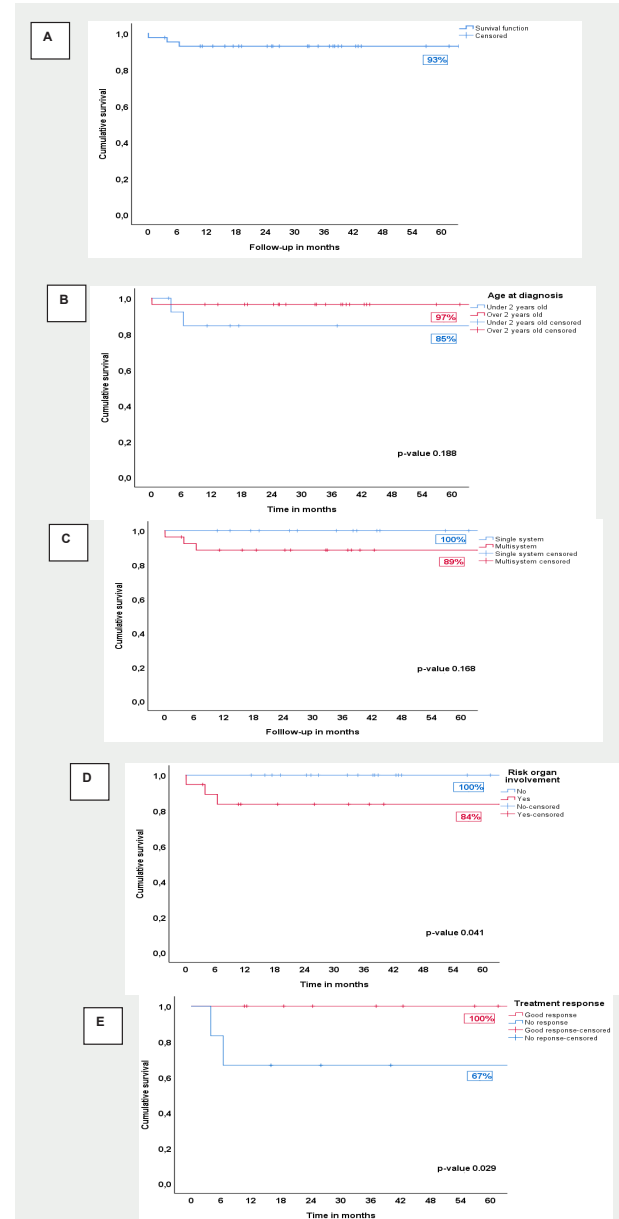
#### Permanent consequences:

At the last follow-up, ten patients (23%) had at least one permanent consequence (Table 2). Diabetes insipidus was the most common, affecting eight patients (19%), all of whom were treated with anti-diuretic hormone (ADH); among these, two had associated anterior hypopituitarism. Neurodegenerative LCH was observed in one patient 44 months after the onset of LCH symptoms. Two patients had cystic bilateral pulmonary lesions without any clinical respiratory complications. One patient (2%) developed sclerosing cholangitis, complicated by cirrhosis and portal hypertension. Hearing loss was reported in one case, and dental instability in two cases. Survival:

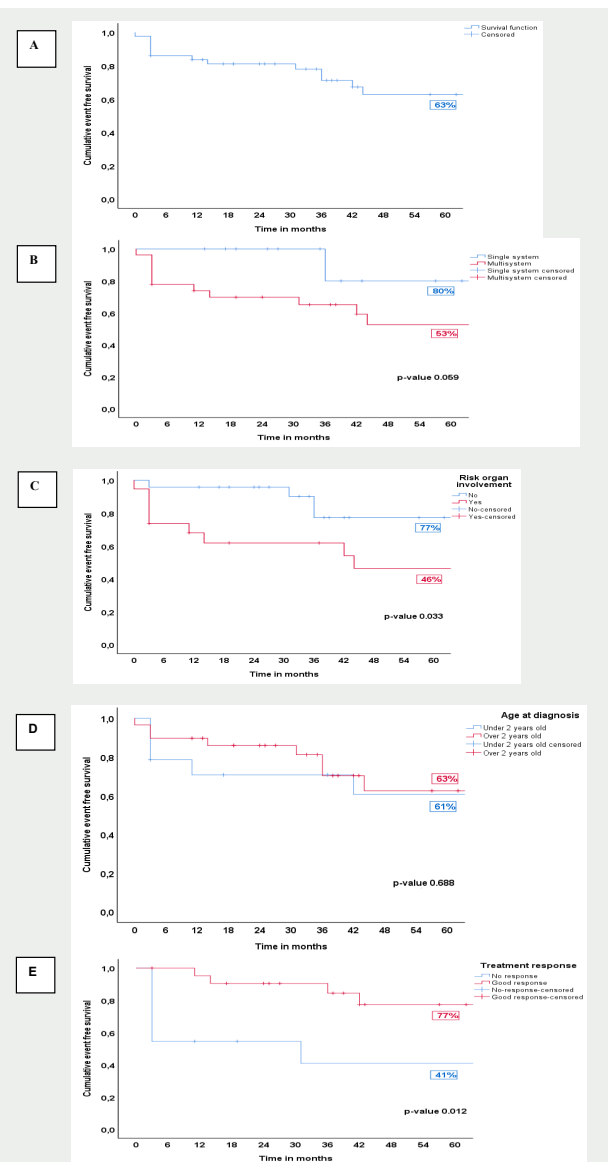
After a median follow-up of 39 months (IQR = 19-69 months), the OS and the DFS at five years were 93% and 63%, respectively. Three patients with RO+LCH died: one patient died before the initiation of chemotherapy, and two patients experienced disease progression following two courses of vinblastine induction. One of these patients subsequently received a combination of Ara-C and vinblastine.

In univariate analysis, factors influencing OS at 5 years

included the presence of RO involvement. The 5-year OS was 100% in patients with RO- LCH compared to 84% in those with RO+ LCH ( $p=0.04$ ). In addition, response to vinblastine induction was significant, with a 5-year OS at 100% in NAD and AD-better versus 76% in non-responders ( $p=0.003$ ) (Figure 5).



Similarly, RO involvement and response to vinblastine induction influenced DFS: the 5-year DFS was 77% in patients with RO- LCH compared to 46% in those with RO+ LCH ( $p=0.03$ ). In addition, response to vinblastine induction was significant, with a 5-year OS rate of 77% in NAD and AD-better versus 41% in non-responders ( $p=0.01$ ) (Figure 6).



**Figures 6.** Disease-free survival curves, **A:** Disease-free survival, **B:** Disease-free survival by disease classification, **C:** Disease-free survival according to risk organ involvement, **D:** Disease-free survival according to age at diagnosis, **E:** Disease-free survival according to treatment response after vinblastine-based induction.

## DISCUSSION

### LCH epidemiological and clinical features

This study investigated the clinical features, therapeutic responses, and survival of 43 pediatric patients with LCH treated at two reference centers in Tunisia over 13.5 years. The median age at diagnosis was 3 years. Patients with multisystemic LCH were significantly younger than those with single-system LCH. The most common group in our cohort was MS RO+ LCH, accounting for 44% of cases. The epidemiological characteristics of our cohort are not fully representative of the broader population of patients with LCH. Data from LCH registries and reviews showed an annual LCH incidence of 2.6 to 8.9 cases per one million children per year (7). Single-system and multisystem diseases accounted for approximately half of the patients each. Among the patients with multisystem disease,

approximately 15% of them had involvement of a risk organ (2,8). The predominance of multisystem LCH with risk organ involvement (MS RO+) in our cohort is due to our status as a tertiary referral center; single-system LCH may be less frequently referred or likely underdiagnosed. Bone involvement was the most prevalent, occurring in 77% of patients, followed by skin involvement in 46% and liver involvement in 44%. As shown in our cohort, the median age at diagnosis is around 3 years, with patients with MS RO+ LCH being younger (2,8). Bone lesions are present in approximately 80% of patients with LCH, and in half of them, lesions are single. The most common site of bone involvement is the skull, followed by the spine, limbs, and pelvis (2,8).

Neurological involvement manifests primarily in two forms: focal mass lesions and neurodegenerative lesions (9). Neurodegenerative CNS (ND-CNS) involvement is characterized by distinct cognitive, psychological, and radiological abnormalities. In our study, neurodegenerative LCH was identified in one case of multisystem disease with a positive BRAF V600E mutation, giving an incidence of 2.2%. Tumorous lesions were found in five cases (17%), which is in line with the literature, which suggests that long-term neurodegenerative LCH occurs in 1.9% to 11% of cases, while tumorous lesions are reported in 10% to 15% (7,9,10). Recognized risk factors for neurodegenerative lesions include diabetes insipidus, skull base involvement, and the presence of the BRAF V600E mutation (7,9,10).

In our cohort, BRAF mutation analysis was performed in nine patients with refractory or relapsed LCH. The BRAF V600E mutation was identified in eight cases. The constitutive activation of the MAPK pathway, resulting from RAS–RAF–MEK–ERK mutations, had a central role in the pathogenesis of LCH. The BRAF V600E mutation is identified in 50–60% of LCH cases, with MAP2K1 mutations occurring in 10% to 30% of cases. The BRAF V600E mutation is associated with more severe patterns of the disease. Moreover, the detection of circulating cell-free BRAF V600E levels has demonstrated potential as a marker for therapeutic response (7,9–11).

### LCH treatment and outcome

Among patients, 34 received Vinblastine-based first-line therapy. At the 12-week mark, 27 of 33 evaluable patients (82%) showed either no evidence of disease or an improvement in disease status. Six patients (18%) showed no response, including two patients who died. These results are consistent with the existing literature (8,12,13). Patients with LCH are categorized for treatment planning based on the disease extent (MS vs SS) and the presence of risk organ involvement or CNS risk lesions. Single-system LCH without special site involvement or functional impairment requires local therapy or observation. Current frontline therapy for multisystem LCH and single-system LCH with special site or CNS risk lesions is a 12-month regimen of vinblastine and prednisone, as established by the results of the LCH III trial, with the potential addition of mercaptopurine for RO+ LCH (2,4,9). The LCH III trial concluded that

prolonging intensive therapy with a second induction in patients with a poor response improved survival. Extending the duration of treatment from 6 months to 12 months reduced reactivation rates in RO patients, and no benefit with methotrexate added (4,5,9,12).

The 5-year survival rate was 93%. Cumulative incidence of reactivation was 28 %, and DFS at 5 years was 63%. RO involvement and non-response to vinblastine-based induction influenced significantly OS and DFS. The OS of LCH patients improved with this risk-adapted management, exceeding 90% at five years, even in RO+ LCH (12). According to the results published in 2016 from the French registry, the five-year survival rate was 98.7%

for all patients, 91.7% for those with RO+ LCH after 1998, and 100% for SS and MS RO- LCH over time(8,14,15). This improvement is attributed in part to the introduction of the 2-CdA+Cytarabine combination therapy for refractory MS RO+ patients (8). However, LCH reactivation remains a significant concern with an incidence of approximately 30% (2,8,16). The reactivation rate was also high with the Japan LCH protocol (JLSG-02) based on intensified and prolonged therapy comprising cytarabine, vincristine, and prednisolone, which demonstrated high response and survival rates, but reactivation incidence was still high (17.9 % of RO+ patients and 20.6 % of RO- patients) (17).

**Table 3.** Treatments and Follow-Up of Patients with Multisystem Langerhans Cell Histiocytosis

|     | Age at diagnosis | RO | DAS * | Response to first-line therapy ** | Reactivation | Second-line therapy | Follow-up time months | State at the last follow-up                                            |
|-----|------------------|----|-------|-----------------------------------|--------------|---------------------|-----------------------|------------------------------------------------------------------------|
| P1  | 4.3              | +  | 8     | Not received ≠                    | Yes          | Target therapy      | 69                    | Target therapy for 19 months, Neurodegenerative LCH, DI                |
| P2  | 1.6              | +  | 8     | Good response                     | Yes          | Target therapy      | 11                    | Target therapy for 1-month Active better disease, DI                   |
| P3  | 0.4              | +  | 6     | Good response                     | Yes (3)      | Target therapy      | 89                    | Target therapy for 4-months, DI, dental instability, NAD               |
| P4  | 2.3              | -  | 1     | Good response                     | No           |                     | 24                    | No treatment, NAD, DI                                                  |
| P5  | 3.5              | -  | 0     | Non-response≠#                    | No           | 2CDa (Cladribine)   | 38                    | No treatment, NAD, DI                                                  |
| P6  | 3                | +  | 4     | Non-response                      | No           |                     | 40                    | Under an intensified-vinblastine regimen, active orbit involvement, DI |
| P7  | 2.5              | +  | 3     | Intensified regimen               | Yes          |                     | 69                    | No treatment, NAD, DI, anterior hypopituitarism                        |
| P8  | 6.9              | +  | 3     | Good response                     | No           |                     | 11                    | Under maintenance therapy, NAD, DI                                     |
| P9  | 0.6              | +  | 7     | Good response                     | No           |                     | 166                   | No treatment, NAD, sclerosing cholangitis                              |
| P10 | 2.2              | -  | 2     | Good response                     | No           |                     | 72                    | No treatment, NAD, hearing loss                                        |
| P11 | 1.3              | +  | 14    | Good response                     | No           |                     | 107                   | No treatment, NAD                                                      |
| P12 | 2.4              | +  | 4     | Good response                     | Yes          |                     | 33                    | No treatment, NAD, without sequelae                                    |
| P13 | 2.3              | +  | 10    | Partial response≠##               | No           | Target therapy      | 19                    | Under treatment, NAD, without sequelae                                 |
| P14 | 2                | +  | 18    | Non-response                      | No           | 2CDa+Aracytine      | 6                     | Death                                                                  |
| P15 | 3                | +  | 14    | Non-response                      | No           | 2CDa+Aracytine      | 85                    | No treatment, NAD, without sequelae                                    |
| P16 | 6                | -  | 2     | No treatment                      | No           |                     | 33                    | No treatment, NAD, without sequelae                                    |
| P17 | 4                | +  | 1     | Good response                     | No           |                     | 64                    | No treatment, NAD, without sequelae                                    |
| P18 | 0.1              | +  | 1     | Good response                     | No           |                     | 4                     | Under maintenance therapy, lost follow-up                              |
| P19 | 1                | +  | 5     | Good response                     | No           |                     | 84                    | No treatment, NAD, without sequelae                                    |
| P20 | 4.6              | -  | 1     | Good response                     | No           |                     | 42                    | No treatment, NAD, without sequelae                                    |
| P21 | 1.5              | -  | 5     | Good response                     | No           |                     | 64                    | No treatment, NAD, without sequelae                                    |
| P22 | 1.5              | +  | 11    | 3 inductions/intensified regime   | No           | NO                  | 90                    | No treatment, NAD, without sequelae                                    |
| P23 | 3.4              | +  | 18    | No treatment                      | No           |                     |                       | Death before chemotherapy initiation                                   |
| P24 | 4                | +  | 5     | Non-response intensified regimen  | No           |                     | 26                    | Continued to exhibit active disease under intensified regimen          |
| P25 | 1.2              | +  | 6     | Good response                     | No           |                     | 37                    | No treatment, NAD, without sequelae                                    |
| P26 | 0.8              | +  | 3     | Non-response/ intensified regimen | No           |                     | 16                    | Lack of improvement on chest CT scan                                   |
| P27 | 1.8              | +  | 20    | Non-response                      | No           |                     | 4                     | Death                                                                  |

NAD: non-active disease, DI: diabetes insipidus, DAS\*= disease activity score at diagnosis, RO= Risk organ,

\*\*=: response to vinblastine-based therapy, either complete or partial, ≠: misdiagnosed as Evans syndrome, ##: " evaluation of the response to vinblastine cannot be performed due to the cystic nature of the lesion." ###: Improvement of hepatic involvement, resolution of cutaneous lesions, disappearance of lymphadenopathy and fever, but persistence of splenomegaly

Second-line therapy for refractory or relapsed LCH is also risk-adapted but is not yet defined. For high-risk patients with refractory RO+LCH or relapse with RO involvement on therapy or shortly after treatment discontinuation, Cladribine and Cytarabine combination therapy and hematopoietic stem cell transplantation with reduced intensity conditioning regimen showed efficacy and improved prognosis, although toxicity remains a concern. In our cohort, Cladribine and Cytarabine combination was used in two cases, with a favorable outcome in one case; however, delayed administration contributed to death in the other case.

Recently, targeted therapies have demonstrated rapid efficacy with limited toxicity. Our experience with targeted therapies is still evolving. Vemurafenib was used in four cases, including two with refractory and relapsed RO+LCH. All patients were still on therapy at the last follow-up and exhibited favorable results. Donadieu and al reported the results of the Vemurafenib study, including 44 children with LCH, of which 34 had RO+LCH. At 8 weeks, 38 complete responses and 16 partial responses had been achieved. However, 24/30 patients rapidly experienced reactivations after Vemurafenib discontinuation. The reactivation rate was higher for RO-

positive patients and for those with circulating free cell BRAF-V600E positive(18).

Efficacy and short-term tolerance were demonstrated in other studies, but long-term safety remains unknown, and reactivations after therapy discontinuation were high (19). Therefore, the association of target therapy (vemurafenib) with chemotherapy was evaluated in a multicenter study including seventeen children with LCH. Vemurafenib was added either from the start or on maintenance therapy. Results were promising with relapse-free survival among the 15 patients who discontinued treatment after a response reaching 73.3% at a median follow-up of 34 months (20). Nevertheless, the sample size and follow-up are insufficient to draw definitive conclusions.

Treatment of central nervous system (CNS) involvement depends on the type of lesion. For tumorous lesions, vinblastine, prednisone, and cladribine may be used as frontline therapies. In cases of neurodegenerative LCH, clinical and radiological stabilization has been observed in patients receiving immunoglobulin infusions, cytarabine and Rituximab, and favorable outcomes were reported in a few cases with targeted therapies (7,21,22).

**Table 4.** Follow-up of patients with single-system Langerhans cell histiocytosis

|     | Age at diagnosis (years) | Involved organ | Unifocal or multifocal involvement | Response to treatment | Reactivation | Follow up time (months) | State at the last follow up                                |
|-----|--------------------------|----------------|------------------------------------|-----------------------|--------------|-------------------------|------------------------------------------------------------|
| P1  | 6.5                      | Bone           | Multifocal                         | Good response         |              | 62                      | No treatment, NAD, no sequelae                             |
| P2  | 12                       | Bone           | Multifocal                         | Good response         |              | 25                      | No treatment, NAD, no sequelae                             |
| P3  | 2.4                      | Bone           | Multifocal                         | Good response         | Yes          | 44                      | No treatment, NAD, no sequelae                             |
| P4  | 9                        | Bone           | Multifocal                         | Good response         |              | 77                      | No treatment, NAD, no sequelae                             |
| P5  | 2.2                      | Bone           | Multifocal                         | Good response         |              | 39                      | No treatment, NAD, no sequelae                             |
| P6  | 14                       | Bone           | Unifocal                           | No                    | Yes          | 38                      | Bone reactivation in shoulder, treatment not yet indicated |
| P7  | 6                        | Bone           | Unifocal                           | No                    |              | 35                      | No treatment, NAD, no sequelae                             |
| P8  | 3                        | Bone           | Unifocal                           | No                    |              | 13                      | No treatment, NAD, no sequelae                             |
| P9  | 0.6                      | Skin           | Unifocal                           | No                    |              | 69                      | No                                                         |
| P10 | 8                        | Skin           | Unifocal                           | No                    |              | 72                      | No treatment, NAD, no sequelae                             |
| P11 | 9.4                      | Bone           | Unifocal                           | No                    |              | 19                      | No treatment, NAD, no sequelae                             |
| P12 | 0.8                      | Bone           | Unifocal                           | Good response         |              | 17                      | No treatment, NAD, no sequelae                             |
| P13 | 8                        | Bone           | Unifocal                           | Good response         |              | 57                      | No treatment, NAD, no sequelae                             |
| P14 | 3.1                      | Bone           | Unifocal                           | Good response         |              | 43                      | No treatment, NAD, no sequelae                             |
| P15 | 9.3                      | Bone           | Unifocal                           | Good response         |              | 27                      | No treatment, NAD, no sequelae                             |
| P16 | 4.7                      | Bone           | Unifocal                           | Good response         |              | 127                     | No treatment, NAD, no sequelae                             |

NAD: non active disease

## CONCLUSIONS

The overall survival of LCH patients has improved with the risk-adapted management. The involvement of risk organs and non-response to vinblastine induction may worsen the prognosis. Concerns persist regarding the potential risk for reactivation and permanent consequences.

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