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CASE REPORT

Clinical and Radiological Features of Childhood Langerhans Histiocytosis: First Tunisian Case Series

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ABSTRACT

BACKGROUND

Langerhans cell Histiocytosis (LCH) is a rare proliferating disorder of CD1a Langerhans cells for which the etiology and pathogenesis remains largely unknown. The signs and symptoms of LCH vary widely among affected people ranging from spontaneously regressing single lesions to multisystemic life threatening disorder. Given the multitude clinical and radiological presentations of LCH the differential diagnosis can be quite extensive. A definitive diagnosis remains however consistent with identical histopathologic features by demonstration of CD1a on the lesional cells.

OBJECTIVES

There are few clinico-epidemiologic studies of such disease in North Africa. Our study was designed to look at the clinico-radiological features and outcomes of patients with LCH in Tunisia.

METHODS

We conducted a retrospective study from 2011 to 2020 involving 10 patients with histologically confirmed LCH. A review of medical records and imaging was performed.

RESULTS

They were 9 males and 1 female, with a mean age of 3 years and 4 months. Fever was the commonest presentation, alongside torticolis, perianal lesions, dyspnea and polyuria. Clinical manifestations ranged widely from unifocal bone lesions (1 case) to multisystemic disease (9 cases). Skeletal, liver and spleen were the most involved systems

(60%). The treatment was based on combination of surgery and chemotherapy in all cases. Clinical and follow up data showed a variable prognosis, particularly a poor response to treatment in multisystem form of the disease.

CONCLUSION

This report outlined polymorphous clinical and radiological features of LCH. Recognizing diagnostic pitfalls and providing a long term follow up is crucial for paediatricians to avoid long term sequelae and improve patient's life quality. Although considered a benign and curable pathology, treatment is still controversial and should be monitored by paediatric oncologist. A national registry collecting the several cases could be a major contribution in knowledge regarding the underlying clinical presentations, therapy, and outcome.

KEYWORDS

Langerhans cell histiocytosis; Central diabetes insipidus; Surgery; Chemotherapy

ABBREVIATION

LCH: Langerhans Cell Histiocytosis; CDI: Central Diabetes Insipidus; DDAVP: Desmopressin Test; SC: Sclerosing Cholangitis; 2 CDA-ARA: 2-Chloro Deoxyadenosin; GHD: Gonadotropin Deficiency

1. INTRODUCTION

Langerhans Cell Histiocytosis (LCH) is a rare group of disorders without a well-understood etiology [1]. It is a multi-systemic pathology with a large clinical spectrum ranging from single bone involvement to a systemic disease-causing substantial morbidity and mortality. The new trend is divided into three groups on the basis of the number of LCH lesions and systems involved and include unifocal form, multifocal unisystem, and multifocal multisystem [2]. Its diagnosis is based on association of different clinical and radiological signs and confirmed by histological and immune-histochemical examination [2]. There is a high incidence in males, which becomes less obvious with increasing age and most common in whites of northern European descent [3].

To our knowledge, a little is known about different forms of LCH in North Africa and especially in Tunisia where children with LCH are still treated in pediatric department. We report in this study the first Tunisian series of LCH in children.

Our purpose is to describe various clinical and radiological aspects as well as different evolutionary modalities of patients in a country with limited therapeutic ways.

2. METHODS

A retrospective chart review was performed between 2011 and 2020 at a single tertiary care children's hospital. All pediatric patients (age <16 years) with a final diagnosis of LCH were eligible for the study. Ten patients were identified with a diagnosis of LCH. The following parameters were retrieved from the medical files: Gender, symptoms at initial presentation, known chronic diseases, biological and radiological data.

3. RESULTS

Nine boys and one girl were identified with final diagnosis of LCH. The mean age at the time of diagnosis was 3 years and 4 months [Range: 11 months - 14 years]. All children were symptomatic at the time of diagnosis.

Fever was the most frequent mode of revelation (5 cases). The Other signs observed were torticollis (one case), perianal lesions (one case), dyspnea (two case). Polyuria and polydipsia were the first symptoms in one case.

The clinical examination revealed cutaneous involvement, in 5 children. They were preferential lesions of the scalp (crusted lesions were present in 4 patients), palms and plants (Figure 1A), onychodystrophy, onycholysis (Figure 1B) and perianal lesions were observed.

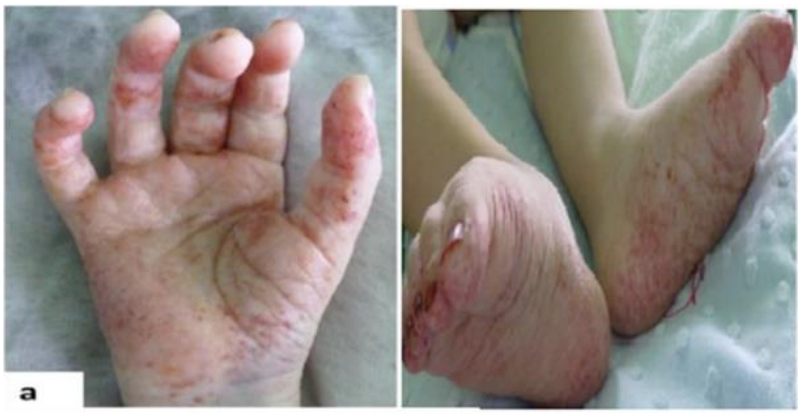

Figure 1A: Scamous lesions of palms and plants.

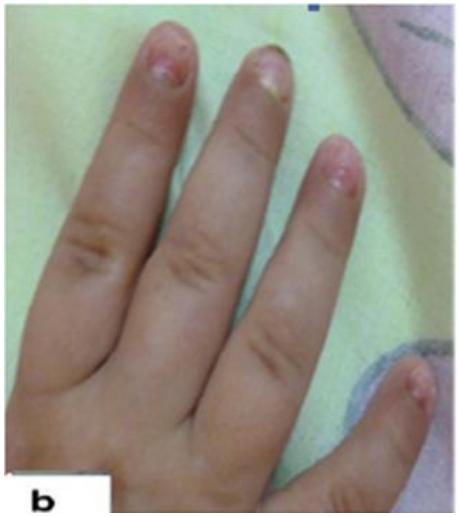

Figure 1B: Fingers onychlysis.

Hepatomegaly and splenomegaly were found in 6 cases, cervical lymphadenopathy in 5 cases and axillary one in 2 cases. In three cases, the disease had affected only one organ. Persistent ear infections and dyspnea were observed in five cases. Table 1 summarizes the different clinical data.

The biological assessment revealed Central Diabetes Insipidus (CDI) confirmed by the desmopressin test (DDAVP), in 3 cases on the presence of polydipsia and polyuria with inappropriate dilute urine. Cholestasis and a cytolysis were found in 3 cases, pancytopenia in only one case and anemia in six cases.

One patient had a single system bone disease, and 5 had bone lesions as part of multisystem disease. Skull x-rays performed in 4 patients showed lytic pictures related to geodes. A mastoid lysis revealed on cerebral CT in four cases (Figure 2) and a C2 tooth lysis on CT of the cervical spine in one case.

Table 1: Summary table of the different clinical signs, different affected organs and evolutionary aspects of our patients.

	Sex	Age at Diagnosis	COD	Associated Symptoms and Signs	Associated Delete Organs	Evolution
Case 1	M	4 Years	Torticollis	Torticollis	Bone	Favorable
Case 2	M	15 Months	Postoperative Mediastinitis	Cutaneaous signs, Respiratory signs HMG, SMG, Cervical and Axillary LAD	Skin/lung/Lymph Node Involvement (LNI)/Hepatoslenic impairement (HSI)	Death
Case 3	M	11 Months	Paleness Chronic Fever	Cutaneous signs, Otitis, LAD, HMG, SMG	Skin/Otorhinolaryngologic (ORL) involvement/LNI/HSI Bone marrow	Complications: Vasculitis, BCGitis
Case 4	F	28 Months	Earache Abdominal pain Jaundice	Otitis, HMG, SMG	ORL/HIS/Bone marrow/Bone	Death
Case 5	M	24 Months	Mastoid Swelling Chronic Fever	Bone Involvement (Mastoid) Otitis/LAD	Bone	Favorable
Case 6	M	16 Months	Abdominal Mass	Cutaneous Signs/ Bone Involvement/ (Mastoid), HMG, SMG. Respiratory Signs	Skin/Bone/HSI/ORL/Lung	Liver failure
Case 7	M	14 Years	Bilateral PNO	Cutaneous Signs, Otitis, Dyspnea	Skin/ORL/Lung/Central Nervous System	Slight Improvement
Case 8	M	30 Months	SMG, Paleness, Scalp Swelling, Fever	Cutaneous Signs, Bone Involvement (Skull) HMG, SMG	Skin/Bone/HSI/Central Nervous System/Bone Marrow	Neurological Sequelae DI
Case 9	M	18 Months	Hepatomegaly PUPDS	Bone Involvement (Subclinical) Cutaneous signs HMG, SMG	Bone, Skin, HIS, Central Nervous System	Lost View
Case 10	M	42 Months	Swelling of the Mandibular Angle	Bone Involvement (Mandibular) -LAD	Bone	Favourable

Note: M: Male; F: Female; COD: Circumstances of Discovery; Fig: Figure; PNO: Pneumothorax; PUPDS: Polyuro-Polydipsic Syndrome; SMG: Splenomegaly; HMG: Hepatomegaly; LAD: Lymphadenopathy; LNI: Lymph Node Involvement; HSI: Hepatosplenic Impairment; DI: Diabetes Insipidus; Cs: Corticosteroid.

Hypothalamo-hypopituitary axis involvement was confirmed in 3 cases on brain MRI showing a thickening of the pituitary stalk associated with post-pituitary signal suppression (Figure 3). A white matter involvement associated to lesions of the serrated nuclei, cortical and cerebellar involvement was found in only one case with a secondary growth hormone deficiency.

Sclerosing cholangitis (SC) was confirmed in 2 cases using needle liver biopsy and MR cholangiography (Figure 4).

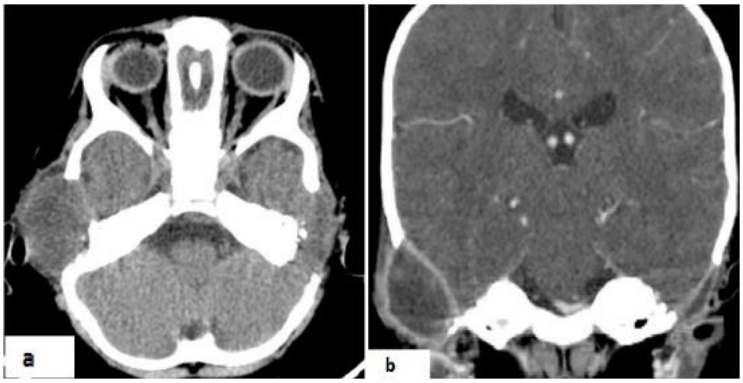

Figure 2: (A) Brain CT scan: non enhanced axial (a) and enhanced coronal (b) and axial (B) MPR thin slice images: Bilateral temporal bone osteolysis and mastoid collections with peripheral enhancement.

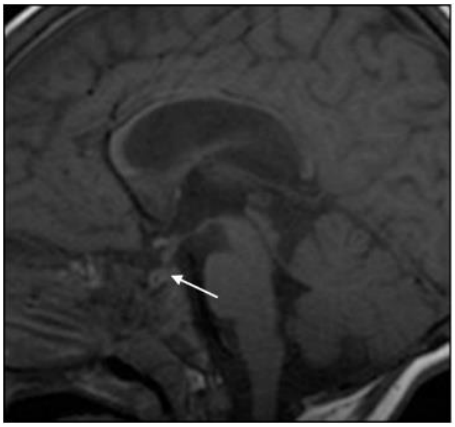

Figure 3: MR imaging of the pituitary region: A: SE T1sagittal image: Lack of the normal T1 high signal intensity of the posterior pituitary.

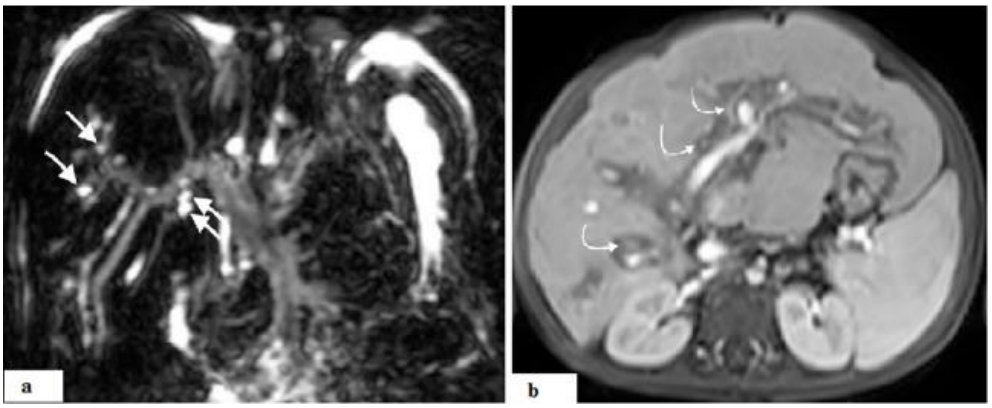

Figure 4: Typical pattern of sclerosing cholangitis: MRCP with MIP 5 mm slice image and postcontrast T1 image: Several images of intra hepatic bile duct dilatation and stenosis (white arrows). Peri portal enhancement consistent with fibrosis (curved arrows).

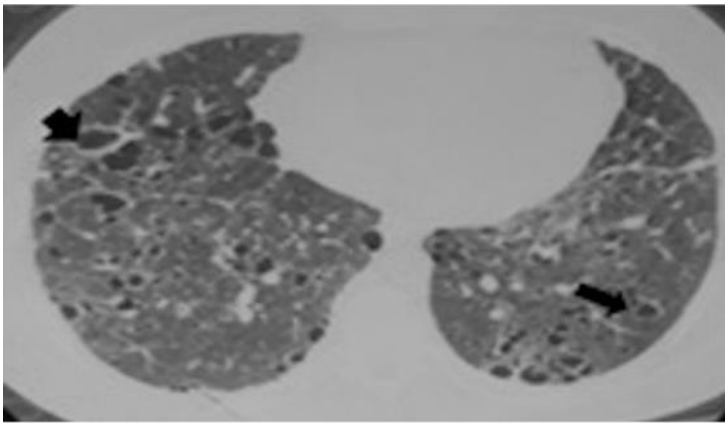

Figure 5: Pulmonary CT scan: axial thin slice image: Ground glass opacities with septal thickening and multiple thin wall parenchymal cavitation's consistent with cysts (black arrows).

The pulmonary involvement was radiologically manifested by bilateral symmetrical and diffuse interstitial syndrome in 4 cases and pneumothorax in 1 case. Chest CT was performed only in two cases showing air cavities of varying size and thickness in one case and alveolar damage with a frosted glass appearance in the second case (Figure 5).

The diagnosis was confirmed on pathological examination in all patients, showing positive histiocytic population for S-100 and CD1a.

The treatment was based on chemotherapy with combination of Vinblastine and corticosteroid therapy in 9 cases with induction and maintenance phase. Only one patient benefited of second-line chemotherapy with aracytin and 2-chloro deoxyadenosine (2 CDA-ARA), which was stopped because of haemato-toxicity.

Only one patient underwent surgical treatment alone (bone curettage in a case of mandibular eosinophilic granuloma). A C1-C2 arthrodesis for a cervical eosinophilic granuloma ended in definitive stiffness and limitation of lateral movements of the head for another patient.

Neurological sequelae (mental retardation and cerebellar ataxia) were observed in only one patient with brain lesions. Patients' CDI continues to be well-managed with desmopressin (DDAVP). Three patients with systemic LCH died.

4. DISCUSSION

LCH is a rare idiopathic disease characterized by a disorder of the reticuloendothelial system [1], secondary to proliferation and accumulation of a deficient phenotype of langerhans cells whose maturation stopped at an early stage [1]. Its exact etiology is unknown, and the heterogeneous illness make the different clinico-radiological spectrum helpful in clinical decision-making [2].

The disease affects mainly children with a frequency peak between 1 years and 3 years [4]. A slight male predominance was described in several series [2, 4-6] and was found in our study (sex ratio equal to 9/1).

A clinical diversity was described; therefore, the circumstances of discovery are variable. Miiller et al. [7] have described in their series the various symptoms that led to discover the disease and were dominated by local masses and cutaneous involvement.

A clinical polymorphism was described by several authors [8-11] ranging from simple bone involvement with self-involution to multi-systemic lesions. In our series, although the patients' number is reduced, the cases are distinguished by the diversity and singularity of the circumstances of discovery. The perianal lesions found are an exceptional and atypical cause of LCH discovery. Very few similar cases in children have been reported in the literature [12-17]. Torticollis in a 3-years-old child is one of the rarest manifestations leading to the diagnosis of localized LCH, only fifteen observations have been reported [18].

Bone is the most commonly injured organ (80%). The bone involvement may be asymptomatic, the anomaly is fortuitously discovered in this case on systematic examination or as part of an extension assessment. In our series, 30% of patients had asymptomatic bone involvement. Standard radiographs, first-line requested, show evocative osteolytic lesions, producing bone deficiencies known as "geography maps" or "cookie cutters" [19, 20]. CT scan confirm the osteolysis and appreciate the importance of cortical rupture and periosteal reaction. Currently it is largely supplemented by PET scan which is more sensitive than X-rays to detect lesional healing earlier [21-23].

Cutaneous lesions affect mainly the trunk, the scalp, the seat, and the inguinal folds [24]. Nail damage, possible but not very specific, evolving towards onychodystrophy [25], was present in 2 patients of our series. An otitis objectified in 15 to 61% of the patients according to several series [26], had affected half of our patients. The outer, middle, and inner ear can be reached simultaneously or separately. The involvement of the inner ear can cause deafness or behavioral problems in young children [27].

Central nervous system involvement is also rare and divided into three groups [28]. Lesions of the hypothalamic-pituitary axis are the most frequent affecting 15% to 35% of the patients according to many series [29-31]. The thickening of the pituitary stalk visible on MRI is the most common abnormality generally responsible for CDI. Other endocrine abnormalities, far rarer but may be associated with DI. The most common is Gonadotropin Deficiency (GHD) [11,32]. In our series, 3 patients with a multi-systemic form developed CDI (patient 7, 8, 9). A Delayed neuro-psychomotor development seen in only one patient is due to pontocerebellar symptoms (abnormal reflexes, ataxia, intellectual impairment, or dysarthria) [33].

Pulmonary involvement is highly variable, clinically manifested by progressive dyspnea or recurrent broncho pneumopathies, lung biopsy is the best way to confirm the diagnosis [34]. In our series, only one patient underwent a pleural biopsy (patient 7) following a recurrent pneumothorax, thus representing a rare manifestation in children. Standard radiographs show diffuse, bilateral, symmetrical reticulonodular interstitial syndrome resulting from the fusion of nodules and thin-walled cysts [35-37]. The presence of multiple small bilateral nodules, with early signs of excavation or cysts with varying thickness, preferentially located in the upper or middle lobe, on chest CT scan, was found in 2 of our patients [38,39].

In multisystemic forms, the liver is most often affected, children under 5 years are the most affected [40,41]. Hepatomegaly with smooth edge is present in 9 of our patients. The chronic form typically consists of SC was confirmed in two of our patients (patient 6 and 9). The initial presentation with CDI, SC as a clue to find LCH, described in only one patient, is exceptional [42].

The prognosis of hepatic involvement and particularly SC is reserved [43,44]. Resistance to first-line chemotherapy associated with corticosteroid therapy is frequent. Our two patients developed liver failure. A liver transplantation is very discussed as the last line therapy.

The first-line treatment of multi-visceral forms is mainly based on vinblastine and steroids [45,46]. Nine of our patients benefited from this association. Only one patient was treated with 2-chloro deoxyadenosine and cytarabine, lately complicated by severe aplasia.

The evolution of the disease is very variable and unpredictable at the time of diagnosis. It is eminently capricious, ranging from spontaneous regression to rapid progression that can sometimes lead to death [47].

CDI can be the only sign that triggers the explorations leading to the diagnosis of LCH but also a quasi-definitive sequel [48]. Many other sequelae have been described in some series. However, 50% of patients can have an impact on quality of life [8,49]. The vital prognosis can also be impaired [5]. Three of our patients with a multisystemic form have died.

5. CONCLUSION

As clinical presentation is extremely heterogenous, a prompt diagnosis may be challenging, to avoid a misdiagnosis. LCH, although considered a benign and curable pathology, can cause sequelae in the different affected tissues which require a long term follow up.

Since chemotherapy is the cornerstone of the treatment of multisystem disease, which is by far the most common form, LCH should be under supervision of pediatric oncologists.

Collection of cases through a national registry should be evocated to enable better assessment of this condition and thus better improving of surviving rates and quality of life.

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