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Clinical Features and Management of Langerhans Cell Histiocytosis: A Case Series

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Abstract

Background: Langerhans histiocytosis (LCH) is a rare hematopoietic disease characterized by clonal expansion of myeloid precursors differentiating into CD1a+/CD207+ histiocytes infiltrating different organs. The study aimed to report the clinical features such as the onset presentation and systemic lesions of LCH among Tunisian adult patients and the therapeutic management of the disease with onboard medications.

Methods: A descriptive, retrospective and monocentric study taking place in the internal medicine department of Rabta University Centre.

Results: The study included eight patients. The median age at the diagnosis was 35 years. The mean duration between the first symptoms and the diagnosis was 17 months. The first most consulted doctors were neurologists. The revealing symptoms were neurological in five cases including headaches, paraplegia or walking trouble. Bone pain was the first symptom in three cases and in one case cervical adenopathy was the first manifestation. Bone involvement was the most frequently found (N=6). Four patients had central nervous system lesions. PLCH was observed in four cases and only one patient was a smoker. Two patients had lymphadenopathy. Retroperitoneal fibrosis and abdominal aortitis were found in one case. Skin involvement was found in one case and was associated with a multisystem LCH form. We observed one case of orbital involvement with optical canal infiltration. In all cases, the diagnosis of LCH was established based on histological features. Seven patients received a treatment with prednisone. Vinblastine was used in six cases.

Conclusion: Langerhans cell histiocytosis is a rare disease with different facets and heterogenous initial presentation. Patients with LCH would usually see different doctors and would have misleading signs with a variety of differential diagnoses before recognizing LCH.

Keywords: Langerhans cell histiocytosis • Oncology • Hematology

Introduction

Background

Langerhans histiocytosis (LCH) is a rare hematopoietic disease characterized by clonal expansion of myeloid precursors differentiating into CD1a+/CD207+ histiocytes infiltrating different organs, with large oval or round cells without the branching that characterizes inflammatory CD1a+ and coffee-bean nuclear groove surrounded by an inflammatory milieu [1]. The immunostaining features are CD1a, CD207 (langerin) and S100 [2]. The proliferation is driven by molecular alterations and genetic mutations activating the mitogen-activated protein kinase (MAPK) pathway that were found in nearly 90% of the LCH lesions in [3] series Recurrent BRAF and MAP2K1 mutations are the most common alterations and their identification helps choose targeted therapy which seems efficient, especially in refractory multisystemic forms [4]. LCH affects children more often [5] and the exact incidence of adult LCH remains unclear. The incidence of adult disseminated LCH has been reported to be 0.07 per million per year [6]. LCH has a wide spectrum of clinical presentation, different onset manifestations and multiple diagnostic circumstances with, sometimes, long diagnostic delays. Longer duration to diagnose the disease was noted in patients with single organ lesions, mainly bone lesions, whereas, patients with a multisystem disease had a shorter diagnostic delay because of their rapid deterioration [7]. Therefore, suspecting the disease, since the initial symptoms, is important to halt the evolution, using the right therapy. Osseous involvement is the most common [8]. Extraosseous involvement includes skin, central nervous system, lung, liver, spleen and lymph nodes. To unify the definition of the disease and its extent as well as to guide the treatment, a recent classification of adult LCH has been proposed. It subdivides the disease into four groups: unifocal, single-system pulmonary, single-system multifocal and multisystem [9]. The treatment approach depends on the extent of lesions. It might need multidisciplinary collaboration. Local therapy like surgical excision or radiation may be curative in some cases of the unifocal disease. However multifocal disease requires systemic therapies such as immunosuppressive agents, corticosteroids, bisphosphonates and chemotherapy agents [9]. Targeted therapy such as BRAF and MEK inhibitors is an interesting option in critical organ involvement [9].

Objective

The study aimed to report the clinical features such as the onset presentation and systemic lesions of LCH among Tunisian adult patients and the therapeutic management of the disease with onboard medications.

Methods

A descriptive, retrospective and monocentric study taking place in the internal medicine department of Rabta university centre. The study included adult patients with a medical history of Langerhans cell histiocytosis.

Results

Demographic data

The study included eight patients: Five men and three women (gender ratio= 1.6:1). The median age at the diagnosis was 35 years [8] (Figure 1). The study included only one pediatric case. At the time of diagnosis, no other comorbidities

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were found in seven patients. However, one female patient developed systemic lupus erythematosus (SLE) eight years after being operated on an intracranial unifocal LCH. No family history of LCH was found. Only two men admitted smoking.

Initial symptoms

The duration between the first symptoms and the diagnosis ranged from one month to five years with a mean of 17 months. The first consulted doctor was a neurologist in four cases, a gynecologist, an ophthalmologist, an orthopedist and an oto-rhino-laryngologist each in one case.

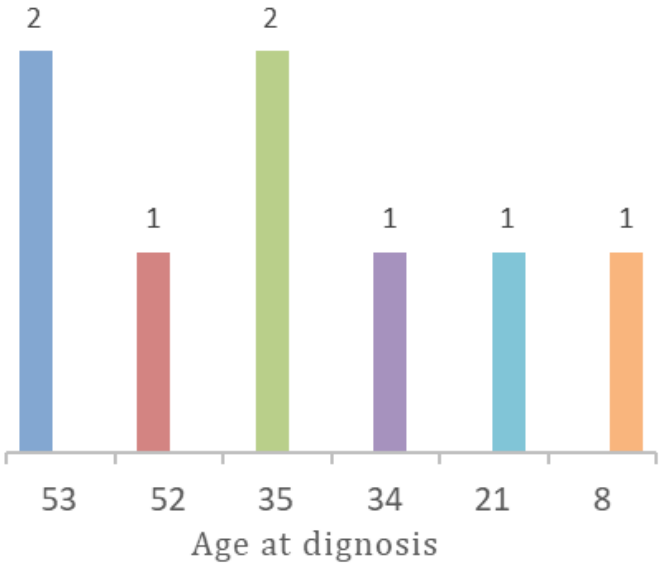

Figure 1. Age distribution in the study group.

The revealing symptoms were neurological in five cases including headaches, paraplegia or walking trouble (Table 1). Bone pain was the first symptom in three cases and in one case cervical adenopathy was the first manifestation. In one case back pain was the first symptom neglected by the patient who eventually presented to the emergency room with spinal cord compression and was operated on immediately. However, in all other cases, no emergency room visit was noted (Table 2).

Clinical presentation and different categories of the disease

LCH was unifocal in two cases: one patient had a central nervous system involvement and the other had one osteolytic lesion in the frontal bone. In the rest of the cases, patients had a multisystem disease with two organs involved in two cases, three involved organs in two cases and four organs involved in one case as well as one case of five involved organs.

Organ involvement

Osseous LCH: Bone involvement was the most frequently found (75%, N=6). In four cases bone lesions were single bone and unifocal: In two cases patients had a solitary osteolytic lesion in the frontal bone, in one case a woman had one osteolytic lesion in the iliac bone and one man had a unique lesion in the 11th thoracic vertebrae. On the other hand, two patients had multiple lesions in different bones including the mandibula (Figure 2) and long bones (humerus, tibia, femur). The standard radiographs showed lytic lesions in all cases. Bone scintigraphy was conducted in three cases and it showed in all of them an increased tracer uptake regarding the metaphysis and diaphysis extremities of the femur, tibia and humerus. In two cases the lesion had an extension to surrounding tissues: Intracanal extension with spinal cord compression (N=1) (Figure 3) and optic canal infiltration.

Central nervous system involvement: Four patients had central nervous system lesions: one patient had spinal cord involvement where the magnetic resonance imaging (MRI) showed aT2 hyper signal in the spinal cord regarding T11 with peri-vertebral extension, while the other three had a brain localization:

Table 1. The onset of the disease.

First Symptoms	Number of Patients (N)	First Consulted Doctor	Diagnostic Delay (month)
Headache	N=2		
Frontal lobe	N=1	Ophthalmologist	1
Unilateral fronto-temporal	N=1	Neurologist	2
Bone Pain	N=3		
Back pain then paraplegia with a T11 sensory level (spinal cord compression)	N=1	Neurologist (Emergency room)	9
Shin pain with leg swelling and impotence	N=1	Orthopedist	12
Pelvic bone pain	N=1	Gynecologist	3
Progressive walking and balance problems, polyuria-polydipsia syndrome	N=1	Neurologist	60
Cervical adenopathy	N=1	Oto-rhino laryngologist	36
Neurological impairment	N=1	Neurologist	Not mentioned

Table 2. Organ involvement.

	Organ Involvement	Cases
Bone involvement	Long bones (tibia, femur, humerus)	2
	Frontal bone	2
	Mandibula	2
	Iliac bone	1
	Thoracic vertebrae	1
Pulmonary involvement	Micronodules	4
	Emphysema	1
	Cystic lesions	1
Central nervous system involvement	Brain	3
	Spinal cord	1
	Pituitary involvement (diabetes insipidus)	1
Lymph nodes	Cervical	1
	Inguinal/retroperitoneal	1
	Orbital (Optic canal infiltration)	1
	Aorta	1
	Retroperitoneum	1

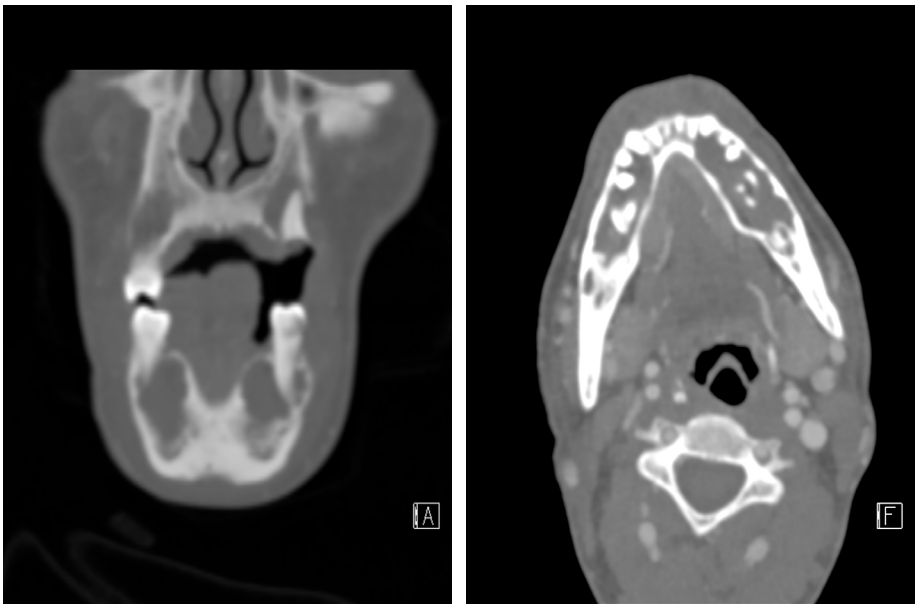

Figure 2. CT bone window **(A)** Coronal and **(B)** Axial views demonstrate irregular radiolucent areas mostly involving superficial alveolar bone with « floating tooth » appearance in an adult patient with Langerhans cell histiocytosis.

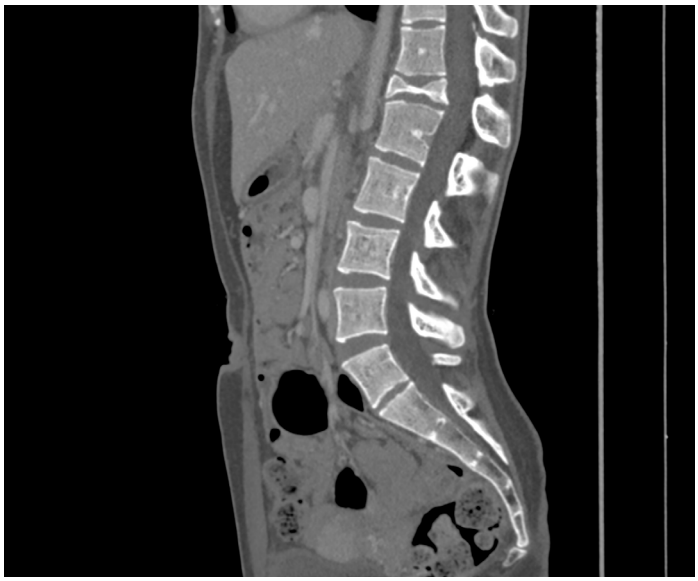

Figure 3. CT bone window sagittal view of lumbar spine shows a T12 vertebra plana.

one in the cerebellar peduncle, a cranial base tumour-like, and in one case in intraventricular mass lesion (Figure 4). These lesions had T2 hyper signal on MRI. One patient had a history of diabetes insipidus five years before the diagnosis and the brain MRI showed the absence of a bright spot in the posterior pituitary (Figure 5). This latter had a coexistence of two types of lesions: pituitary and cerebellar.

Pulmonary involvement: All patients had standard chest radiographs as a first-line assessment tool for pulmonary LCH (PLCH) which was afterwards confirmed with computed tomography. PLCH was observed in four cases and only one patient was a smoker. No isolated PLCH was found, instead, they were part of a multisystemic form of the disease. All patients were asymptomatic (no dyspnea, nor cough), and the chest tomography showed micronodules and nodules in three cases, bilateral reticulonodular pattern with centrilobular emphysema in one case and cystic lesions in none case. No patient underwent lung biopsy or bronchoalveolar lavage.

Lymphadenopathy: Two patients had lymphadenopathy: cervical and axillary in one case and retroperitoneal in another. This latter was associated with retroperitoneal fibrosis and abdominal aortitis. Lymph node involvement was not isolated in either case.

Cutaneous involvement: One patient had a pruriginous rash with hyperpigmented papules on the scalp, thorax and abdomen. In this case, skin involvement was associated with a multisystem LCH form.

Orbital/ optic canal involvement: We observed one case of orbital involvement with optical canal infiltration of an LCH lesion on the cranial base symptomatic of visual acuity loss. None of our patients had a risk of organ involvement.

Diagnostic tools and histological features

In all cases, the diagnosis of LCH was established based on histological features. In eight cases the biopsy was taken from bone while in one case it was a lymph node biopsy and in another, it was from craniotomy of a tumour-like tissue in the brain. In one case the patient had a skin biopsy of the xanthelasma-like lesions. The main histological pattern found in all biopsies was the dense inflammatory milieu rich in lymphocytes and eosinophilic infiltrate with foamy histiocytes in half of the cases. Immunostaining was positive for CD1a in all cases. PS100 immunostaining was positive in three cases and CD68 was positive in one case.

Treatment

Seven patients received a treatment regimen with prednisone at a dose

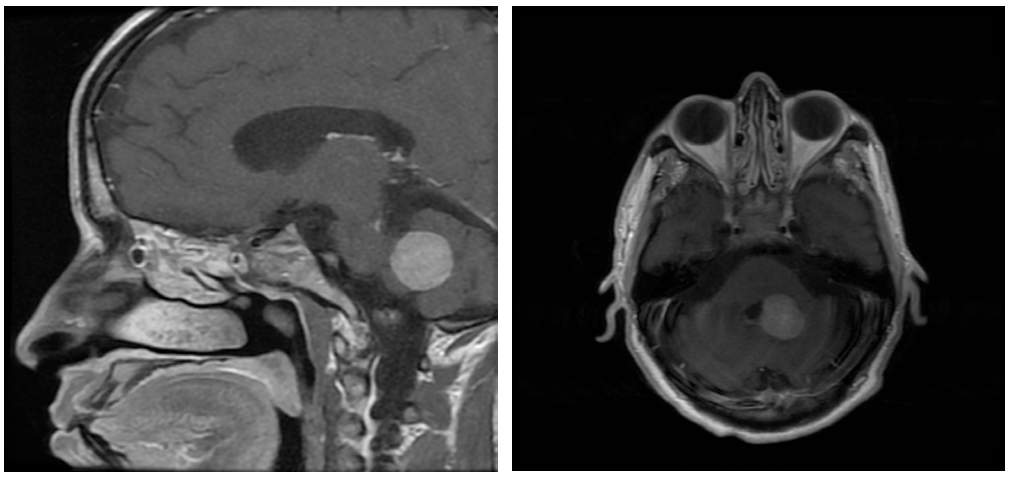

Figure 4. (A) Sagittal and **(B)** Axial post contrast T1-weighted MRI images show an enhanced intraventricular mass lesion.

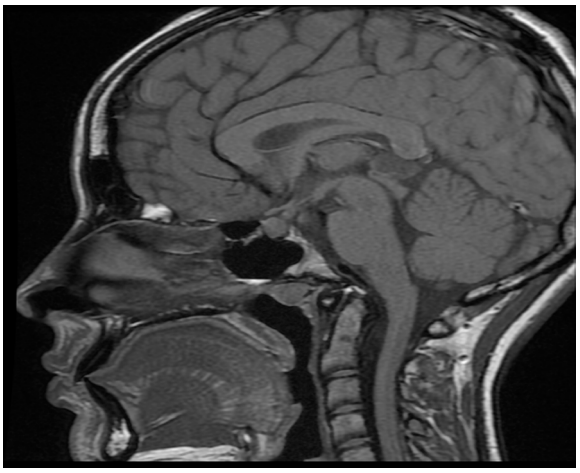

Figure 5. Sagittal T1-weighted image demonstrates a lack of T1-weighted high intensity of the posterior pituitary with associated thickening of the infundibulum.

of 1 mg/kg/day. Vinblastine was used in six cases: the regimen of vinblastine perfusion included induction therapy (6 weekly pulses of 6mg/m^2, followed by a maintenance treatment every 3 weeks). The mean number of perfusions was 7 [5-10] depending on the response. In one case a patient had a surgical removal followed by corticosteroid treatment for the residual tissue. In one case the disease was cured with surgical removal of the tumour-like brain lesion. It should be noted that in one case of unifocal frontal bone disease, the patient had systemic treatment with corticosteroids and vinblastine perfusions. Etoposide was used as a rescue therapy besides decompressive radiotherapy of a spine lesion that was unresponsive to prednisone and vinblastine perfusions. The patient received five perfusions and did not come back to the 6th perfusion.

Outcome and follow-up

In the case of patients who received corticosteroids with vinblastine (N=6), four had clinical and radiological improvement attested by the regression of the lesion extent on control scans. The patient with aortitis and retroperitoneum involvement had a radiological improvement after two months of corticosteroids and vinblastine treatment. In two cases, the neurological state deteriorated and patients needed surgical intervention. Among them, one had severe unresponsive neurological impairment despite the use of prednisone+ vinblastine+ etoposide+ surgical and radiotherapy decompression. One patient died from infectious pneumonia after being on corticosteroids for two months and five vinblastine perfusions. The mean follow-up duration was 22 months [2]. Remission of the disease was achieved after one induction course of vinblastine followed by maintenance treatment and no patient needed a second induction course.

Discussion

In the literature, there is a slight male predominance in LCH with a male-to-female ratio of 2 to 3:1 [5-10]. In the current study, the gender ratio was 1.6:1 which is the same ratio as in a large Korean study [11]. Our study included seven adult patients and one pediatric case that was revealed at history taking, due to inclusion bias since the study took place in the internal medicine department of adult patients. The median age at diagnosis was 35 years, similar to the median age of adult-LCH patients reported in study [12].

In one case, unifocal pediatric LCH was revealed posteriorly at history-taking based on histological proof. The patient was admitted to the internal medicine ward for the management of a systemic lupus erythematosus flare that ensued eight years after the LCH diagnosis and treatment with no relapses in the meanwhile nor afterwards. The coexistence of LCH and SLE was found in a case report by Robak T, et al. [13] it is different from ours since LCH occurred after SLE. The relationship between auto-immune diseases (SLE in particular) and neoplasms has been for a long-discussed and the physio-pathological link between the two remains unclear and needs more studies [14]. In Atsumi Y, et al. [7] study, more than 70% of patients had initial symptoms related to bony lesions that were painful in more than half of patients, especially in long bones and vertebral bodies. Even though in the current study, five of our patients reported pain as the first manifestation, which was related to bone involvement, the site of pain was often misleading and misinterpreted. Therefore, the most frequent initial symptoms were found to be neurological: whether they were headaches or sensory and motor deficiency.

Thus, the first most consulted doctors were neurologists. This study showed that doctors of different fields and specialities can be confronted with patients with LCH. Painful lesions often lead to a more rapid diagnosis which corroborates the findings in Atsumi Y, et al [7] study. In the latter study, the median time between the first symptoms and the diagnosis was 44 days with a range from 11 days to more than four years. While in our study the median diagnostic delay was 17 months [1]. An explanation for this delay is the variety of initial symptoms that are sometimes neglected by patients who seek medical help at the aggravation of their symptoms. The last diagnostic delays were found in the case of headaches.

Bone involvement is commonly observed in adult LCH patients reaching up to 80% [15].

In the current study, it was the most frequent involvement (75%) and it was unifocal in four cases and multifocal in two cases. Osseous involvement in our series was found in a variety of sites. As described in the literature [16], the skull was the most affected (frontal bone and mandible), other less common sites like long bones, vertebrae and pelvic bones were also found. We also observed extension and CNS infiltration due to "CNS risk bones" involvement [16], leading to orbital infiltration with visual disturbance and spinal cord compression secondary to vertebral lesions. The radiological aspect is usually osteolytic in standard radiographs and is an accessible diagnostic tool. Bone scintigraphy is also interesting in the assessment of osseous involvement but it lacks sensitivity, however, fluorodeoxyglucose (FDG) positron emission tomography is better in the assessment of the disease activity and treatment response [17].

CNS involvement in LCH ranges from 3.4 to 57% according to different series [18] and it is divided into focal mass lesions and lesions associated with progressive neurodegeneration. Mass lesions are commonly situated in the hypothalamic-pituitary region, resulting in diabetes insipidus which represents the most frequent initial sign of CNS-LCH [19]. Diabetes insipidus occurred in one case, five years before the diagnosis of LCH which is in line with the literature [20,21]. Intraparenchymal masses were described in three cases in this study. They are rare, and magnetic resonance T2 hyperintense and T1 hypointense signals can be seen in the cerebellar grey matter, cerebral peduncle, and basal ganglia [20]. Albeit pulmonary involvement is known to occur mostly in active or former smokers at the time of diagnosis of PLCH and 60% of patients with systemic LCH have a history of smoking [22], in the present study, only two men admitted exposure to cigarettes smoke and only one of them had pulmonary lesions. PLCH was never isolated in our study, instead, it was associated with other organ involvement and it was asymptomatic in all cases. The systematic screening of pulmonary involvement using plain chest X-rays at first then chest computed tomography in case of abnormalities revealed the lung involvement and since it was part of a multisystemic disease with easier biopsy sites, no patient underwent lung biopsy.

Lymph node involvement was reported in 5 to 10% of LCH patients [20]. Noteworthy, one patient had a lymphadenopathy in the retroperitoneum associated with retroperitoneum fibrosis and aortitis which are both unusual manifestations of LCH and rarely reported [20-23] and they were associated with a histologically confirmed LCH bone involvement (CD1a +, S100+). In front of such case, mixed histiocytic disorder including Erdheim-Chester disease and LCH was highly suspected. However, the patient did not undergo further biopsies of the retroperitoneum or lymph nodes and she actually, improved within two months of a treatment regimen of prednisone and vinblastine. Each case in the presented study was histologically confirmed with typical histopathological features and immunostaining. Molecular analysis for MAPK pathways mutations was, unfortunately, not conducted due to its high expense and unavailability in public laboratories.

The recently suggested treatment approach takes into consideration the extent of the disease and whether it's unifocal or multifocal in one organ or multiorgan. Regarding unifocal LCH we found our series in line with the suggested therapy [9] such as surgical excision in unifocal CNS LCH with no recurrence of the disease after eight years. In the meanwhile, another patient with a single frontal bone lesion had a systemic treatment since a curative surgical removal of the lesion was not possible. For multisystem disease, combo therapy of prednisone and vinblastine therapy was the go-to option. Based on Goyal G, et al. [9] and Tazi A, et al. [24] study, this treatment regimen was an efficient and well-tolerated first-line therapy except for pulmonary involvement with impaired lung function. Etoposide was only used once in our study group as a rescue therapy. The patient noted no improvement and abandoned treatment and follow-up after the fifth perfusion.

The strengths of the study were that it is presenting a wide spectrum of clinical presentations of adult LCH which is a rare disease, with some unusual manifestations along with treatment options in low-income countries and the different outcomes. The study is eye-opening for the diagnostic challenge of LCH in front of non-specific and luring first symptoms to which, physicians of several specialities can be confronted. The study limitations are the retrospective design; hence we are aware of some limited information including initial presentations in one case and the small study group with just one pediatric case since it was a monocentric study.

Conclusion

Langerhans cell histiocytosis is a rare disease with different facets and heterogenous initial presentation. Patients with LCH would usually see different doctors and would have misleading signs with a variety of differential diagnoses before recognizing LCH. Therefore, clinicians should be aware of this entity and should think of this diagnosis at the right time to start the treatment before the occurrence of irreversible complications. Since molecular analysis is out of reach in low-income countries and the same for targeted therapies, a good clinical and radiological assessment along with the typical histopathological features is crucial to establish the diagnosis of LCH. More multicentric studies are required nation-wise.

Conflict of Interest

Authors declare no conflict of interest.

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