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RESEARCH ARTICLE

NEUROHISTIOCYTOSIS: TWO CASES OF A RARE DISEASE

Aballa L.[1], Bentahar H.[1], Hocar O.[2], Traore A.[1], Chraa M.[1,3], Kissani N.[1,4] and Louhab N.[1]

1. Neurology Department, Mohammed VI University Hospital, Faculty of Medicine and Pharmacy, Cadi Ayyad University, Marrakech, Morocco.
2. Dermatology department, Mohammed VI University Hospital, Faculty of Medicine and Pharmacy, Cadi Ayyad University, Marrakech, Morocco.
3. Physiology laboratory, Faculty of Medicine and Pharmacy, Cadi Ayyad University, Marrakech, Morocco.
4. Neuroscience Research Laboratory, Faculty of Medicine and Pharmacy of Marrakech, Cadi Ayyad University, Marrakech, Morocco.

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Abstract

Histiocytosis is a rare systemic disease, with heterogeneous and diverse clinical and radiological presentations. Diagnosis can therefore be intriguing. Several consensus recommendations have emerged in recent years, particularly with the advent of targeted therapies, changing the management and prognosis. The authors present two cases of neurohistiocytosis. The case of Langerhans cell histiocytosis was about an adolescent with polyuria-polydipsic syndrome in whom a cerebellar biopsy was inconclusive. The patient was lost to follow-up for one year and then returned with a multisystemic neurological, bone, and dermatological presentation. The diagnosis was confirmed based on skin biopsy results. The patient's condition rapidly deteriorated after chemotherapy with vinblastine and corticosteroids, leading to his death. The case of Erdheim-Chester disease was about a 53-year-old man who presented with cerebellar syndrome. His biological and radiological workup showed neurological, endocrine (diabetes insipidus) renal (hairy kidney), and bone (fibrosis) involvement. The diagnosis was confirmed by femoral biopsy and the patient was treated with Cladribine with an excellent evolution with an 18-month follow-up. This manuscript aims to report our personal experience and underline the entity's heterogeneity, non-specificity, and repercussions.

Introduction:-

Histiocytosis is heterogeneous hematopoietic diseases characterized by the accumulation of cells thought to be derived from dendritic cells or macrophages [1]. The annual incidence is less than five cases per million populations and it may affect a unique or multiple organs [2]. Thus, the diagnosis is challenging and often delayed or missed. The infiltration of the nervous system and adjacent structures is frequent and may be life-threatening [3]. More than 100 different subtypes have been described and recently gathered in five groups [1]. The most reported forms are Langerhans cell histiocytosis LCH and Erdheim Chester Disease (ECD) in L group, RosaiDorfman Disease (RDD) in R group, and hemophagocyticlymphohistiocytosis (HLH) in H group [4]. We present two cases of the L-group:

Corresponding Author:- Aballa L.
Address:- Neurology Department, Mohammed VI University Hospital, Faculty of Medicine and Pharmacy, Cadi Ayyad University, Marrakech, Morocco.

LCH ECD. The aim of this manuscript is to report our personal experience and especially to underline the heterogeneity and non-specificity of the entity and its repercussions.

Case presentation:

First Case:

A 17-year-old male patient, not previously known to have any medical history, complains of polyuria-polydipsia syndrome and vomiting. Encephalic Magnetic resonance imaging (MRI)showed nodular lesions in the entire brainstem and snowflake hypersignals in thetemporal and occipital lobes (figure 1). Cerebral spinal fluid (CSF) cytochemical examination, culture, cytopathology and protein electrophoresis remain normal. Thoracic, abdominal, and pelvic computed tomography (CT)also came back normal. The anatomo-pathological study of one of the cerebellar lesions was inconclusive. The patient was lost to follow-up for two years then presented with statokinetic cerebellar syndrome, bone pain and brownish scaly skin lesions in the axillary, inguinal folds and scalp (figure2). A new brain and spinal cord MRI showed a stable aspect of the previous lesions, and the appearance of new lesions at the spine cord, with infiltration of the hypotalamo-pituitary axis (HPA) (figure 3). Endocrine evaluation objectified central diabetes insipidus (DI) associated with stature and puberty delay. Skin biopsy with immunohistochemical study confirmed the diagnosis of Langerhans cell histiocytosis (figure 4). A treatment based on chemotherapy, vinblastine (6 mg/m², six courses weekly) and corticosteroid (1mg/kg/day for six weeks) was initiated. The patient died of septic shock three weeks after induction of chemotherapy.

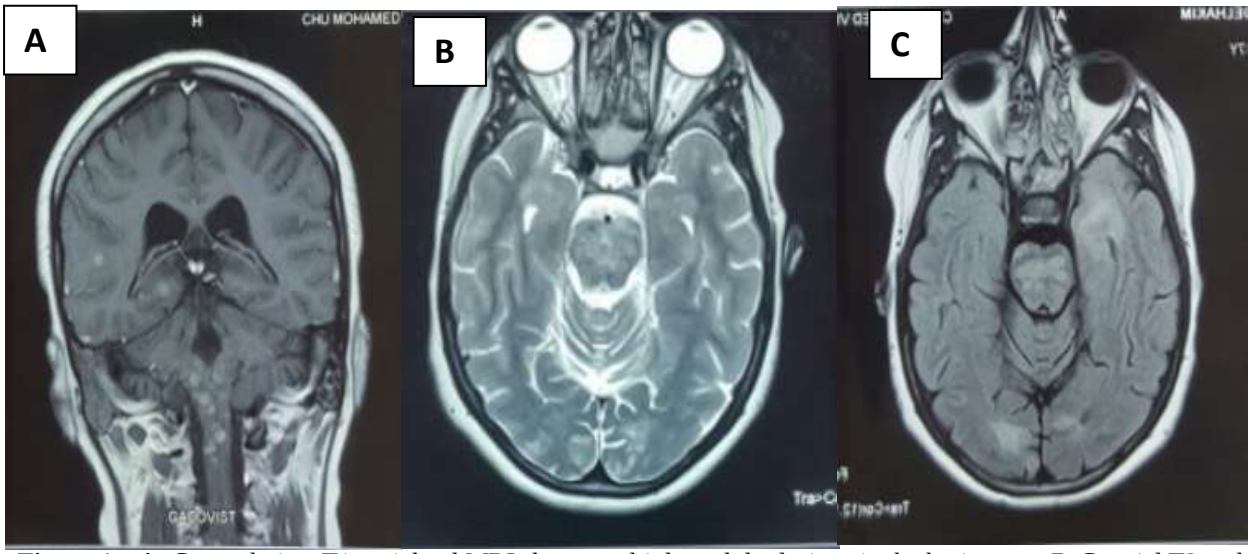


Figure 1:- A: Coronal view T1-weighted MRI shows multiple nodular lesions in the brainstem. B-C: axial T2 and FLAIR MRI showing temporal, occipital and midbrain snowflake hypersignals.

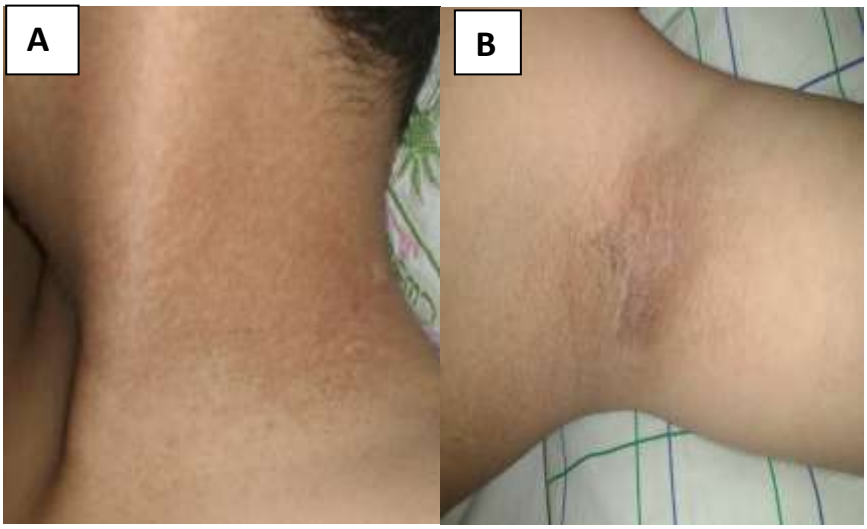


Figure 2:- Brownish scaly dermatological lesions on the neck (A), and in the axillary hollow (B).

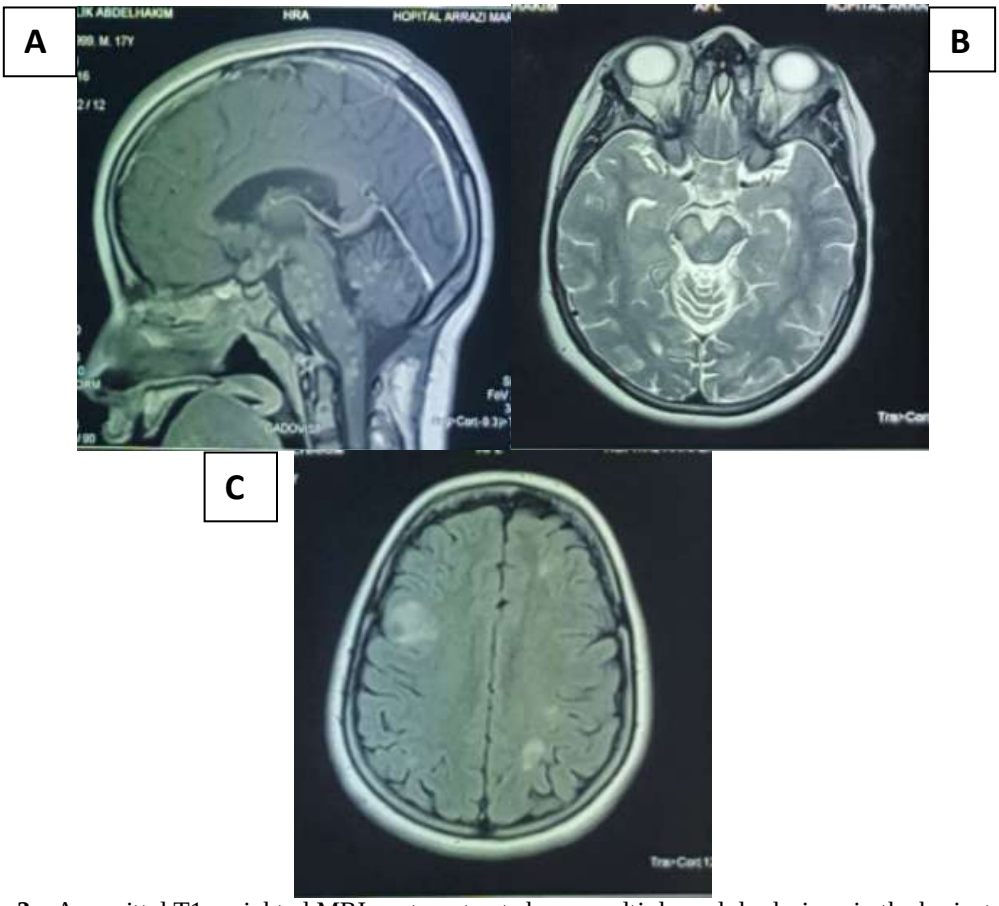


Figure 3:- A- sagittal T1-weighted MRI post contrast shows multiple nodular lesions in the brainstem, the cerebellum and the cervical spinal cord. B-C: axial T2 and FLAIR MRI showing cerebral cortical and subcortical lesions, and at midbrain.

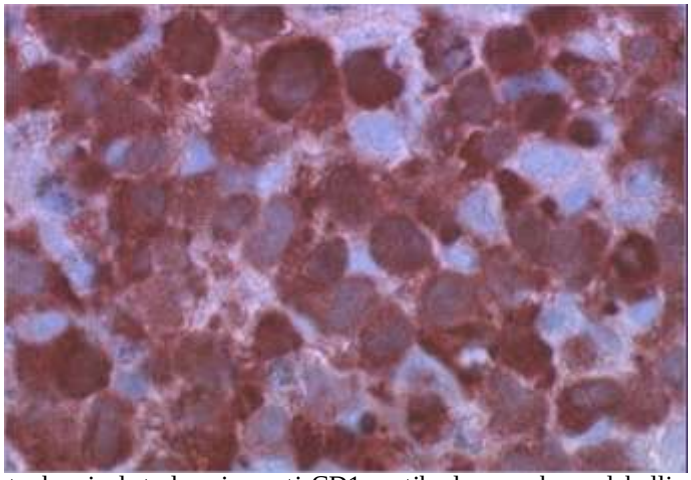
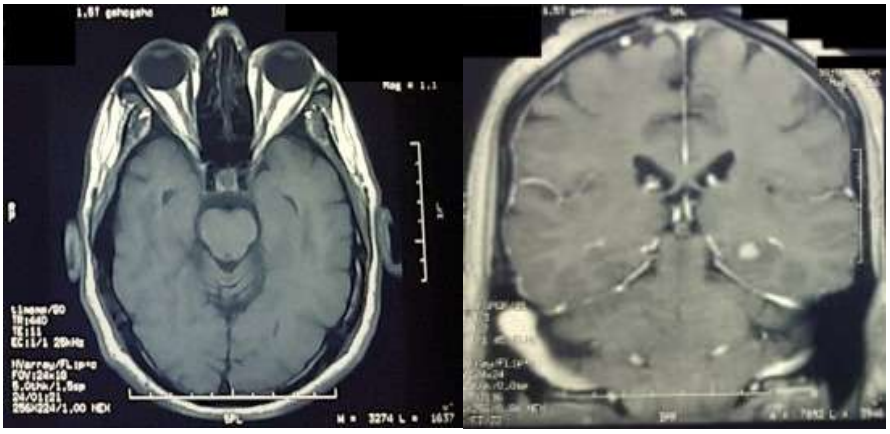


Figure 4:- Immunohistochemical study using anti-CD1a antibody: membrane labelling of Langerhans cells.

Second Case:

A 53-year-old man, with recent type-1 diabetes for a year presented complaining of progressive balance disorder and dysarthria for three years. His family history was negative for neurologic pathologies. The patient's overall condition was preserved. Neurologic examination found a stato-kinetic cerebellar syndrome with cerebellar ataxia, hypermetrydyschronometry, and adiadochokinesia. Brain MRI showed left temporal nodular lesion with gadolinium enhancement and vermian T2-Flair hyperintensities(figure 5).Biological paraclinical examinations objectified normal blood count, sedimentation rate,ionogram, renal and hepatic functions. Viral serologies (HIV, B and C hepatitis and syphilis) were negative and vitamin E dosage was normal. However, CRP was at 53g/L and fasting glycemia at 1.7g/L. Onconeural antibodies were negative. Thoracic, abdominal, and pelvic CT- scan revealed retroperitoneal fibrosis with bilateral Hairy Kidney sign (figure 6). Complementary CT of the lower limbs was requested and objectified bone fibrosis. Femoral bone biopsy was performed and showed bone infiltration by a histiocyte population expressing anti-CD68 antibody.BRAF-V600E mutation testing and other genetic studies in this setting weren't available. The patient received symptomatic treatment and balance and speech rehabilitation. A cladribine-based treatment protocol was administered. He received 6 cycles of 14mg/kg/day from D1 to D5 every 28 days. The evolution was marked by a regression of the cerebellar and biological inflammatory syndromes and a balancing of the diabetes. The control CT scan at the end of the treatment showed a regression of the peri-renal infiltration with persistence of a slight maxillary and femoral osteocondensation. The patient is currently under clinical and biological surveillance and has been stable for more than a year.



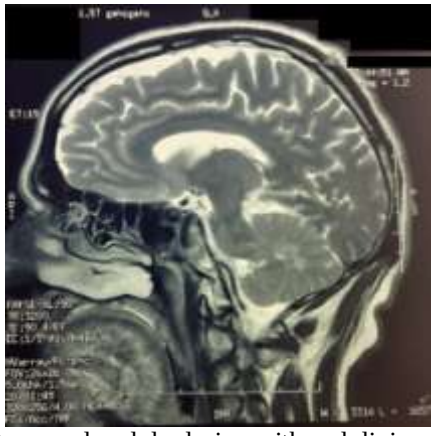


Figure 5:- Brain MRI showed left temporal nodular lesion with gadolinium enhancement and vermian T2-Flair hyperintensities.

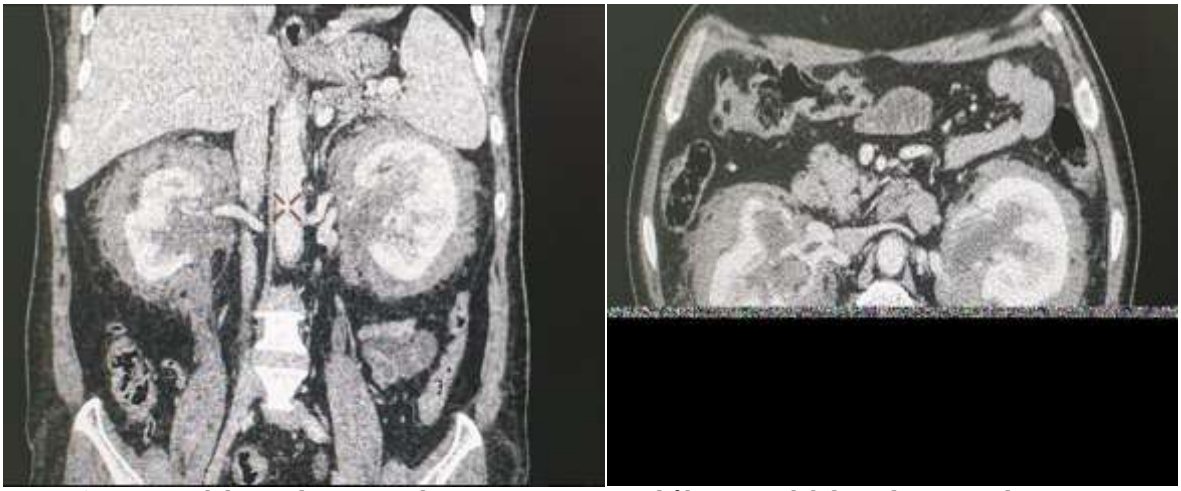


Figure 6:- Abdominal CT-scan showing retroperitoneal fibrosis with bilateral Hairy Kidney sign.

Discussion:-

Both LCH and LCD can involve a single or multiple organs. They may be associated with similar clinical complications such as DI and/or neurodegenerative disease [1]. In our two patients, diabetes was diagnosed at the onset of the symptomatology, which was multisystemic for both. In the first case, the clinico-radiological presentation was purely neurological for more than two years, which were quite challenging since the non-specificity of the entity and especially after the inconclusive biopsy.

LCH may be seen in all ages [2]. The disease is more frequent in children younger than 15 years and rare cases of familial LCH have been reported [1]. LCH is classified in four subtypes: unifocal (Solitary lesion involving any organ), Single-system pulmonary (Isolated lung involvement), Single-system multifocal (>1 lesion involving any organ) and Multisystem (>2 organ/system involvement) [5]. The diagnosis is challenging, based on the combination of clinical, radiological and histopathological findings, and Molecular analysis of tissue for BRAF and MAPK-ERK mutations is highly recommended to support the diagnostic [5, 6]. The most affected organs are the bones (80%) and the disease may be bone limited in 38% cases [1, 2]. The skullis the most commonly involved bony site (60%). Patients usually present with bone pain, fractures, or cord compression [6].LCH is characterized by an aggressive lytic pattern with a typical moth-eaten appearance that can progress to laminar periosteal reaction and cause fractures. Positron emission tomography–computed tomography (PET-CT) is globally superior to the conventional imaging except for subtle vertebral lesions in witch MRI is in advance [2].In children, Skin changes are the second more frequent sign, then lymph nodes, liver, spleen, oral mucosa, and lung. However, in adults infiltration of the lungs seems to be more frequent, then skin, liver or spleen, and lymph nodes [2, 7].In our first patient, the cerebellar biopsy was inconclusive and the appearance of skin signs and their biopsy made the diagnosis possible. LCH affects

the CNS in 10-25% of cases for both children and adults [3]. Neurological involvement in LCH has been classified as tumorous/granulomatous lesions, non-tumorous/ nongranulomatous lesions (neurodegenerative changes) and atrophy [8]. This classification is not perfect and overlaps may exist between the three groups, sometimes all found in the same patient [4]. Tumorous LCH affects mostly the hypothalamic-pituitary axis HPAcausing DI in 30% of adult patients or less frequently deficiency of anterior pituitary hormones. Parenchymal lesions typically affects the brainstem and cerebellar peduncles[1, 3, 6]witch explain the frequency of cerebellar ataxia and bulbar deficits, like presented in our two cases. MRI features of histiocytosis are non-specific. HPA involvement is characterized by loss of normal signal in the posterior pituitary gland on T1- weighted image, often associated with thickening and gradual enhancement of the pituitary stalk that may progress to a pituitary and hypothalamus mass. In our case, despite the revelation by DI, no lesions were detected in the HPA at the beginning. The lesions were probably discrete and therefore not detected on the 1.5T MRI. Histiocytic parenchymal masses are frequently (74%) T2-hyperintense and markedly enhanced on Gadolinium. However, areas of T2-hypointensity were also reported, corresponding to elevated ADC values [9].Neurodegenerative changes can present as symmetric T1 and T2-hypersignals in the dentate nucleus of the cerebellum, basal ganglia and the protuberance. Atrophy is usually limited to cerebellum, midbrain, supratentorial structures and is often associated with progressive neurodegeneration [4].Baseline full-body PET/CT, including the distal extremities, is recommended to define the extent of disease and biopsy is mandatory in all cases, even when clinical and imaging features are suggestive of the disease[5].

There are no standard therapies for adult LCH. Treatment modalities depend on LCH subtype [10]. For unifocal LCH (except DI), local therapies are recommended at first. Surgical excision, intralesionalsteroids, or radiation are here the main modalities. When unifocal LCH involve risk organs such as nervous system, systemic treatment should be administered. However, if the solitary lesion involves the HPA, systemic treatment is controversial and is recommended in cases with symptoms that are recent-onset or when a radiologic lesion is present. For multisystem LCH, systemic chemotherapy agents like cladribine, cytarabine, or vinblastine and prednisone are recommended. For LCH involving the brain parenchyma, chemotherapy with cladribine or cytarabine is first-line recommended treatment [5].

ECD mainly occurs in young adults with a median age around the 5th decade (46-60years)[11].The male-to female ratio is around 3:1 [12]. ECD rarely affects children and it mostly consists of mixed ECD+ LCH histiocytoses [13, 14]. It is very heterogenous and can involve almost any organ but it mainly affects bones, retroperitoneum (including kidney) and respiratory, cardiovascular and central nervous systems (including HPA) [11]. Unlike LCH, The hallmark of the disease is long-bone osteosclerosis, reported in 80% to 95% cases, typically in the distal femurs and the proximal and distal tibias. It is symptomatic in 38% of patients [15, 16]. The anomalies can be detected by radiological imaging or bone scintigraphy 99Technetium [99Tc], but PET-CT far exceeded standard investigations and detectsavid FDG uptake in the legs in about 95% of patients. PET scans are also remarkably informative of ECD activity and therapeutic responses [17]. It was widely conceived that urological ECD infiltration is distinctively symmetric and bilateral. This infiltration has characteristic CT aspect, known as a hairy kidney [18]. This sign found in our patient, was strongly orienting. Respiratory and cardiovascular involvement is mostly asymptomatic and can be life-threatening. Thus, it has been suggested that all new diagnosed patients should have PET/CT including distal extremities (vertex-to-toes), Cardiac MRI, and brain MRI with contrast [11]. Intracranial ECD is posterior-fossa predominant but it can occur throughout the neuraxis. Neurological manifestations depend on the site of involvement. Cognitive impairment, ataxia, peripheral neuropathyand headaches are the most reported signs [15, 16, 17, 19]. These anomalies often demonstrate gadolinium enhancement, contrasting with LCH and may rarely present with atrophy of brainstem and cerebellum [19].As for LCH, Tissue biopsy is mandatory, to confirm the diagnosis and identify associated mutations for therapeutic purposes. BRAF-V600E mutation testing should be pursued for all patients. If not detected, alterations in other genes of the MAPK-ERK and PI3K-AKT pathways must be tasted [11].The presence of these mutations support the diagnosis of a histiocytic neoplasm despite the specific histology [2]. Except for asymptomatic patients for whom close monitoring may be sufficient, treatment should be offered on a routine basis. Targeted therapies may be used as a treatment of choice for patients with BRAF-V600E ECD. For patients without access to mutation screening or targeted therapies may be treated withpegylated interferon-α (IFN-α/PEG) or cladribine [11], as in the case of our patient.

Conclusions:-

Neurohistiocytosis is a rare, intriguing, and potentially life-threatening disease. Phenotypes are very heterogenous and overlapping. Diagnosis can be delayed or missed, particularly when the disease is limited to one organ, the nervous system in particular. Biopsy of the nervous system is sometimes delicate and inconclusive. consequently,

genetic study, which now plays a major role in diagnosis and treatment through targeted therapies, is of great interest but is not accessible in all countries, especially developing ones. This gap is not without consequences in a disease that is potentially fatal.

List of abreviations:
LCH: Langerhans cell histiocytosis
ECD: Erdheim Chester Disease
RDD: RosaiDorfman Disease
MRI: Magnetic resonance imaging
CSF: Cerebral spinal fluid
CT: computed tomography
HPA: hypotalamo-pituitary axis
DI: diabetes insipidus
PET-CT: Positron emission tomography–computed tomography
IFN-α/PEG: pegylated interferon-α

Declaration

Ethical Approval And Consent To Participate

It is a retrospective report and the authors respected the anonymity of the patient and his archived medical file. Consequently, only the agreement of the head of the department (KN) was required and obtained.

Consent For Publication

Not applicable.

Competing Interests

The authors declare no potential conflicts of interest.

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Authors' Contributions

All the authors took part in the patient's care and support for his family throughout the hospitalization. They all contributed to the drafting of the manuscript. CM, KN and LN approved the final version.

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