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# Langerhans Cell Histiocytosis with Multisystem Involvement in a Young Woman: A Case Report and Literature Review

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**Abstract**

Langerhans Cell Histiocytosis (LCH), also known as Histiocytosis X (HX), is a group of hyperplastic cellular diseases of unknown causes. LCH could affect bones, lungs, central nervous system, liver, thymus, skin, and also lymph nodes. The diagnosis of LCH is difficult to enforce and rarely found in adults, with just about 5 cases per million per year. The present study reports the case of a young woman with LCH with multisystem involvement, including that of the bone, orbit, pulmonary system and central nervous system. The patient received chemotherapy for 6 months and exhibited rapid improvement in the involved systems. The last PET/CT showed metabolic activity in the right iliac bone. One year after completion of the therapy, the patient returned to the hospital showing deteriorating health. The clinical case is interesting not only because of the registered clinical, morphological, and imaging data of histiocytosis but also because of the unclear prognostic and diagnostic importance of this phenomenon.

**Keywords:** Langerhans cell histiocytosis • PET/CT • Multi-organ involvement

## Introduction

Histiocytosis X, which was renamed by the Society of Histiocytosis to Langerhans Histiocytosis (LCH) in 1987, is a clonal neoplastic proliferation of Langerhans cells [1]. Although LCH can affect any age group, it primarily impacts children of 1-4 years of age. The annual incidence of LCH in adults is about five cases per population of a million, and at a male to female ratio of 3.7:1, it predominately appears in males [2]. The disease is common in Caucasians of northern European descent and rare in blacks populations. In addition, rare cases can be associated with follicular lymphoma [3,4]. According to last literature data primary lung LCH is almost always a disease of smokers [3]. The aetiology of the disease remains unknown. With the development of modern molecular biology and genetics, as well as in-depth clinical research, it is considered a type of reactive hyperplastic disease. The timing and development of LCH are closely related to chromosomal instability and gene mutation. Because cellular tissues in LCH exhibit the character of clonal proliferation, the native lesion of the disease is a tumour [5]. Some scientists also believe that LCH is associated with cytokine mediation, immunological disorders, viral infections and other issues [6].

The disease can be localized in one place, may occur in many areas within one system (usually bone) or can be more widespread and affect multiple systems [2]. In its solitary form, the dominant sites of involvement include the bones and adjacent soft tissues. When the disease affects multiple systems, the primary sites of involvement include the skin, bones, liver, spleen and bone marrow. The diagnosis of LCH depends on the disease's clinical manifestation, the histopathology of the lesion. Langerhans cells accumulate in the epidermis under light microscopy. The gold standard for diagnosing LCH is to find a Birbeck particle by electron microscopy, but this examination is rarely performed in a clinic [7]. The main immunohistochemical manifestations of LCH are S-100 protein and CD1a (+). Langerin (CD207), a novel monoclonal antibody to the LC-specific C-type lectin, has been associated with Birbeck particle formation [10]. Its specificity is higher than CD1a in Langerhans cells. In addition to typical histopathological evidence, cases have also expressed CD1a, CD68 and S-100. Taken together, this evidence shows a clear and specific diagnosis. In sum, the clinical manifestation of LCH varies widely due to differences between the age of onset, the rate at which Langerhans cells proliferate and the affected tissues and organs [8].

## Case Presentation

Presented in this study is a 66-year-old female with clinically significant pre-existing conditions. Her complaints began 1 year ago, with a sudden onset of severe headache in the right part of the skull and visual disturbances resembling coloured spots and double images. She also reported reduced hearing and purulent flow from both ears. She was hospitalised in a neurosurgery department. A CT scan and Magnetic Resonance Imaging (MRI) of the brain were performed there, showing tumour formation in the right part of the skull. Biopsy performed on a brain tumour formation with subsequent histological and immunohistochemical examination revealed a morphological image of LCH (Figure 1). Histopathology revealed hypercellular discohesive singly scattered Langerhans cells which are having abundant eosinophilic cytoplasm with characteristic retiform, convoluted nuclei with distinct longitudinal grooves. Also seen are binucleated and multinucleated cells with similar nuclear features. Immunohistochemical examination of histiocytes in LCH showed positive marking for CD1a, langerin S100 and CD45.

The patient then was transmitted to the Clinic of Hematology at the University Hospital St. Marina-Varna. Physical examination of the patient

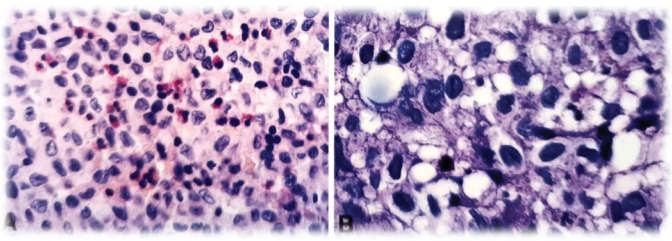

**Figure 1.** Histological preparation from lymph node with damaged architectonics, massive sinusoidal dilation with presence of histiocytes, lymphocytes, plasma cells and Langerhans cells.

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revealed conjunctivitis and otitis externa, no lymphadenomegaly and no organomegaly. Hematological investigations showed mild-grade anemia (Hemoglobin 116 g/L) and normal leukocyte and platelet count. The chemistry panel showed no deviations. PET/CT of the body revealed multiple soft tissue density lesions with irregular and punched out bony destruction noted involving left mandibular, left side of occiput, sphenoid bone, zygomatic bone, lateral wall of right orbit, right maxillary and right temporal bone. Also the PET/CT shows metabolic activity of right iliac bone, sella turcica, thyroid nodule of the left lobe of gland and lung involvement, so called "LCH with multisystem involvement and high CNS risk" (Figures 2 and 3).

Spirometry revealed the following: FVC\ Forced vital capacity\-2.93, FEV\Forced expiratory volume \-2,93, FEC1\First Forced expiratory volume \-2,47, FEV1/VC-76,6%, FEV2\Second Forced expiratory volume\ 5%-5,42, FEV-50%- 3,68 and mild obstruction. Approximately 2 weeks after diagnosis was made, a treatment regimen was initiated with corticosteroids and chemotherapy which included the following: Etoposide 200 mg/d D1-D5, D22, D29, D36, D63, D84, D105, D126, D168, Vinblastin 10 mg/day D15, D22, D29, D36, D63, D84, D105, D126, D147, D168, D189, D252, D294, Purinetol 100mg/day D42-D364, Prednisolone 40 mg/m$^2$ D1- D28, D63-D67, D84-D88, D105-D109, D126-D130, D168- D172, Zolendronic acid 4 mg/day D1. Her complaints exhibited clinical improvement. The control PET/CT after the last chemotherapy shows metabolic activity of right iliac bone (Figure 4). The patient received maintenance therapy with methotrexate and 6-MP\ 6- Mercaptopurine\. Approximately 1 year later, the patient returned to the hospital in deteriorating health, exhibiting progressive dyspnoea, visual disturbance and 15 kg of weight loss for this period. Following this, progression of the disease was registered, and the patient ultimately died.

## Discussion

LCH is easy to misdiagnose clinically. The gold standard for the diagnosis is histopathological and immunohistochemical examination. It is quite important to differentiate LCH from other diseases such as juvenile xanthogranuloma, Rosai-Dorfman disease, malignant melanoma and etc. The prognosis of LCH is closely related to the age of onset, number of involved organs and degree of functional lesions. The prognosis of single-organ involvement is better than that related to multiple-organ involvement, and the latter has a higher case-fatality rate. The prognosis is poor when the patient has lung, liver, spleen and bone marrow damage or a bad response to the early treatment [9], while it is good when there is only skin and bone infringement. Treatments for LCH include surgery, radiotherapy, local, systemic chemotherapy and combination therapy. The specific treatment depends on the following factors: the classification, focal or general systematic disease, dysfunction of the mainly affected organs and age [10].

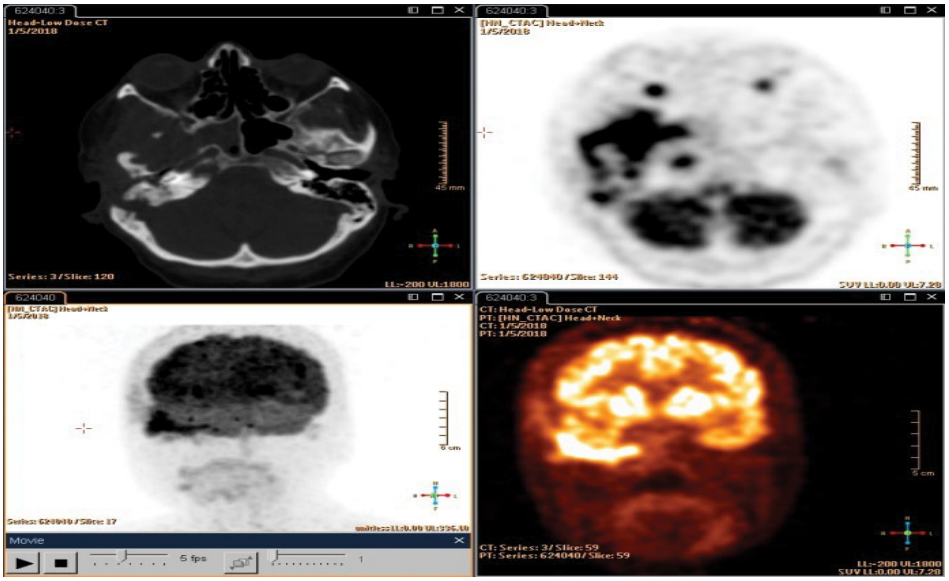

**Figure 2**. PET\CT revealed multiple soft tissue density lesions involving left mandibular, left side of occiput, sphenoid bone, zygomatic bone, lateral wall of right orbit, right maxillary and right temporal bone.

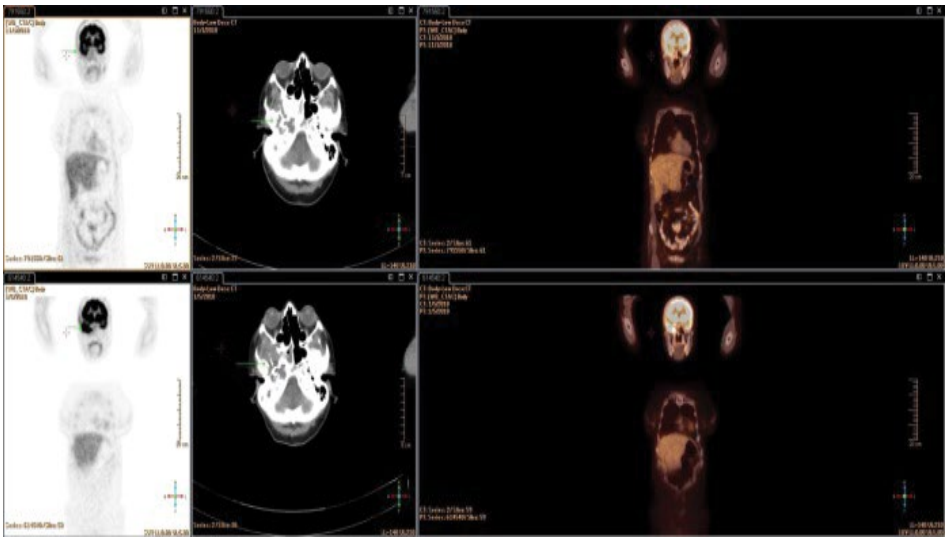

**Figure 3**. PET/CT of body, revealed metabolic activity of right iliac bone, sella turcica, thyroid nodule of the left lobe of gland and lung.

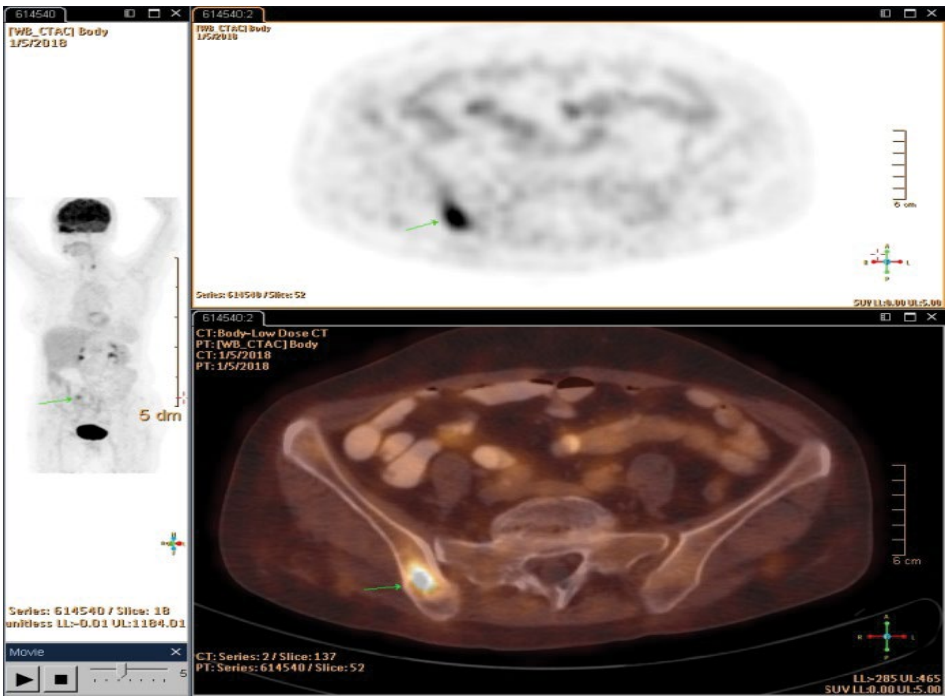


**Figure 4.** The control PET/shows metabolic activity of right iliac bone.

## Conclusion

The patient in this case was treated with systemic chemotherapy and oral corticosteroids due to the multisystem damage. After a year's follow-up, it turned out that the treatment had a considerable effect. However, LCH relapse easily occurs and may accompany malignant tumour, so it is still necessary to carry out long-term follow-up and observation. The prognosis depends chiefly upon the involvement of multiple organ systems, organ dysfunction and the patient's response to chemotherapy during the initial 6 month of treatment.

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