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Monosystem Multifocal Langerhans Cell Histiocytosis (Multifocal Eosinophilic Granulomas of the Bone) in a 36-Year Old Patient: Case Report, Therapeutic Doubts and Review of Literature

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A B S T R A C T

Our aim is to provide review of available studies on Langerhans cell histiocytosis (LCH) and discuss treatment for polyostotic monosystem form of disease based on our clinical experience. LCH is an enigmatic disease with insufficiently understood etiology, pathophysiology, and variety of clinical presentations ranging from solitary eosinophilic granuloma to severe multisystem disease. It is marked by formation of granuloma in practically any organ. We present rare case of multifocal bone disease in 36-year old patient without visceral involvement. Treatment protocols for adult LCH patients, especially for uncommon form in our case have not yet been defined. Our therapeutical trial with corticosteroids showed limited success with numerous side-effects. We conclude that LCH treatment can commence only after diagnosis and staging of the disease. Other factors like patient's age, comorbidity, general condition, severity of symptoms and contraindications for therapy modalities should also be considered. In our experience expectative approach has better clinical outcome than immunosuppressive therapy in patients suffering from polyostotic multifocal form LCH with mild symptoms.

***Key words**: Langerhans cell histiocytosis, eosinophilic granuloma, corticosteroids, polyostotic, treatment*

Introduction

Langerhans cell histiocytosis is a rare disease with mostly unexplained etiology and pathophysiology characterized by pathological accumulation of Langerhans cells in various body organs. Recent findings classify it as a histiocytosis – a group of proliferative disorders of monocyte-macrophage system cells. Other members of this group are insufficiently understood macrophage disorders: hemophagocytic lymphohistiocytosis, Castleman and Rosai-Dorfman disease[1]. Langerhans cell histiocytosis (LCH) is traditionally divided into three clinical entities: Abt-Letterer-Siwe disease (fulminant disseminated form, predominant in children under age 2), Hand-Schüller-Christian disease (chronic disseminated form with involment of bone and internal organs) and eosinophilic granuloma (chronic localized bone disease)[2]. Practically every organ can be involved. Significant overlapping has been observed studying three disease presentations mentioned above. For instance, patient presenting with solitary eosinophilic granuloma can gradually evolve into multisystem form involving internal organs. Therefore new classification was developed with much greater emphasis on treatment and prognosis of LCH dividing it into monosystem and multisystem form. Monosystem form is further subdivided into unifocal and multifocal (monostotic and polyostitic in case of bone affection)[3].

First records of LCH date from 1893 when 3-year old boy with diabetes insipidus, exophtalmus, hepatosplenomegaly, bronze dry skin and petechiae was described[2]. Lichtenstein recognized these three seemingly separated clinical entities as parts of unique disease and named it histiocytosis X (X stands for unknown cause)[1]. In 1973 it was discovered that Langerhans cells are responsible for

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histiocytosis X. Langerhans cell histiocytosis has been the most frequently name used in medical terminology since then[4].

Epidemiological data on LCH are very sparse due to low incidence and the fact that clinicians rarely consider it as a differential diagnosis. More than 50% of described cases affect children. We still lack sufficient data on adult patients; incidence is estimated by some authors as 1 to 2 cases per million with most patients presenting with multisystem form of disease (69%). Median of incidence in children with monosystem form is between 5 and 15, and 2 years for multisystem form of disease[5]. Pulmonary LCH is more prevalent among smokers, therefore many cases of remission have been described after quitting[1,4]. There is a slight predominance among male patients in osseus disease, but all other forms are more prevalent among women[5,6].

Etiology is also mostly unknown. There are two confronted theories. Some authors explain cell proliferation as a malignant neoplastic process supported by finding of monoclonal Langerhans cells in lesions. Another group considers proliferation as an augmented immune system response to enviromental antigens which are yet to be identified. Finding of Glotzebecker et al. identified human herpes virus type 6 (HHV6) in 71% of examined eosinophilic granulomas. This makes HHV6 a possible pathogen[4]. Diniz et al. described eosinophilic granuloma as an inflammatory reaction to periapical tooth infection which lends support to the theory of LCH as a cytokine network malfunction disorder. Smoking is widely accepted as a risk factor for pulmonary LCH[1,4]. Hereditary factors might be involved because 1% of patients reported positive family history and identical twins show 86% concordance[1]. Etiology is yet to be clarified but it is most probably a consequence of innate immune system predisposition to react to some enviromental antigen with an abnormal proliferation of Langerhans cells.

Pathological finding is uniform regardless of disease manifestation. Lesions comprise of activated Langerhans cells surrounded by interdigitating cells, macrophages, T lymphocytes, multinuclear histiocytes and eosinophils. Besides characteristic morphology, Langerhans cells are further identified histochemically by the presence of Cd1a and S-100 surface markers and electromicroscopically by the presence of Birbeck granules[1,2]. Above mentioned pathological findings are obligatory for diagnosis.

Clinical presentation is extremely diverse since LCH can involve virtually any organ leading to the delay in correct diagnosis of approximately 4 months. Most of the clinical data have been acquired among children, with only few studies describing disease in adults[4]. LCH is more likely to occur in tissues with abundant reticuloendothelial system. Bones are affected in 70% of patients, predominantly skull, pelvis, proximal femur, ribs and mandibule (common disease localization in adult patients)[2]. Rarely, eosinophilic granulomas can be found in vertebrae. Most clinical reports found solitary bone lesions, but affected bones can be a part of multisystem disease. Reports on polyostotic monosystem LCH without visceral involment are very sparse, mostly as case reports or minor group of patients in retrospective studies. Some bone lesions are asymptomatic, others present with localized pain in 90% of affected patients. Chronic otitis media, sinusitis, mastoiditis and pathological fractures have also been described. Cranial base involment can cause diabetes insipidus, the most common endocrinopathy in LCH patients. 20% of pediatric cases of diabetes insipidus are caused by histiocytosis with increasing incidence in adult population. Other organs can be involved solitary or as a part of multisystem disease. Granulomas can be found in liver, spleen, bone marrow (associated with unfavorable prognosis), central nervous system, digestive tract (causing malapsorption in children), skin (seborrheic intertriginous exanthema) and lymph nodes. Peculiar site is a female genital tract because lesions can mimic some sexually transmitted diseases[1,6]. Pulmonary LCH is commonly decribed as a separate entity causing interstitial lung disease which can lead to irreversible pulmonary fibrosis[4]. Multisystem form of LCH can begin insidiously with general symptoms such as low grade fever, malaise, myalgia and the loss of appetite. Clinical presentation is more acute in younger patients. The most fulminant disease form occurs in children under age 2, sometimes with lethal outcome.

After establishing clinical indication, diagnosis is determined by imaging techniques and confirmed pathohistologically by finding of atypical Cda1+ and S100+ Langerhans cells with Birbeck granules[1]. Conventional radiograph can diagnose most lesion as osteolytic areas surrounded by reactive sclerosis which can also be found in numerous malignant bone conditions, e.g. osteosarcoma[2]. Spread of the disease is estimated by bone radionuclide scan and positronic emission tomography (PET) while computed tomography (CT) and magnetic resonance imaging (MRI) assess granuloma relation to surrounding anatomical structures. High resolution CT (HRCT) is a preffered test for the assessment of pulmonary LCH and MR is more convenient to show soft tissue involment (especially brain). Laboratory investigations in every patient should include complete blood count, blood urea nitrogen, electrolytes, liver and renal function tests, erythrocyte sedimentation rate, alkaline phosphatase, serum and urine osmolality.

Differential diagnosis is extensive and depends on clinical form of LCH and patient's age. In adult patients with bone involment it should include bone metastases, plasmocytoma, primary bone tumors, fibrous dysplasia and ameloblastoma[7].

Case Report

36-year old male came to his physician and was complaining of right hip pain, headache, tinnitus and hearing loss in his right ear. Family history was unremarkable. In childhood he had suffered from bilateral congenital hip dysplasia. He was previously diagnosed with psoriasis vulgaris. The patient smokes one pack of cigarettes a day while the rest of history is unremarkable. During workup for tinnitus multiple lytic areas on calvaria cranii were spotted using craniogram (Figures 1a and b). Since MRI of head showed them as multiple soft tissue forma-

tions, clinical suspicion of LCH was established. Further imaging (CT of the head) located one of those lesions on tip of the pyramid pressuring vestibulocochlear nerve and thus explaining patinent's audiological symptoms.

Frontal bone biopsy confirmed the diagnosis of eosinophilic granuloma. Further radiological and laboratory workup (ultrasound of abdomen, lymph nodes and heart, chest and bone X-rays, bone marrow biopsy) determined spread of disease. Multiple bone granulomas (on humerus, scapula, ribs, skull, proximal femur and pelvis) were identified without any internal organs involved. Bone marrow biopsy excluded malignant proliferation. Due to intensive pain and patient's history of hip dysplasia additional pelvic CT was ordered showing significant hip destruction caused by eosinophilic granulomas combined with consequences of delayed treatment of hip dysplasia.

Current symptoms and possibility of disease progression compeled us to start a treatment with metilprednizolon 1 mg/kg/day, gradually reducing dosage combined with prophylactic bisphosphonate treatment. After 7 months of treatment there was no improvement in patient's condition and PET-CT of affected regions indicated neither disease progression nor regression (Figures 2a and b). However, patient developed characteristic corticosteroid therapy adverse effects: cushingoid ap-

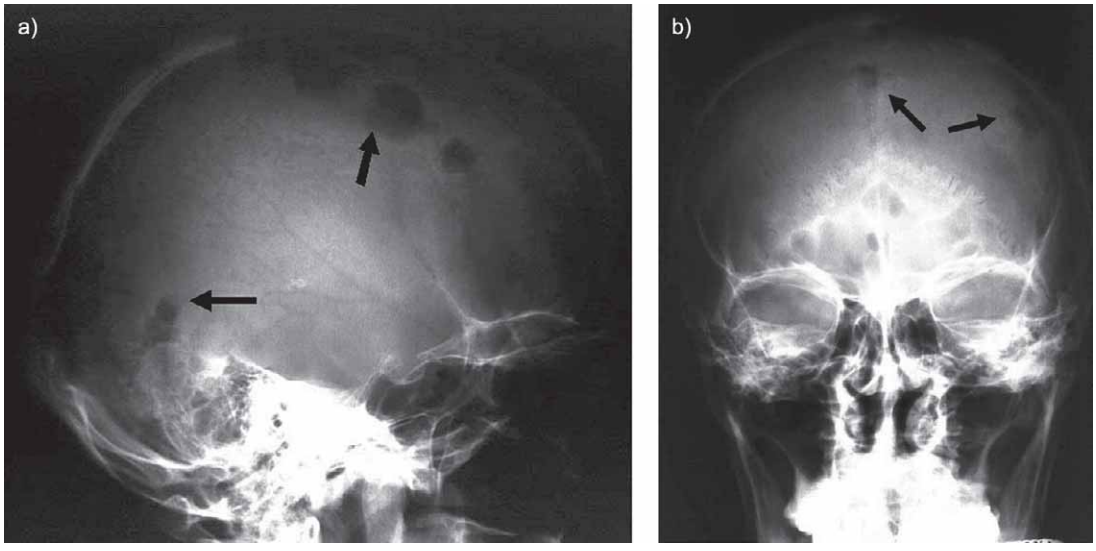

Fig. 1. a) Craniogram (lateral projection) showing multiple lytic areas in frontal, parietal and temporal bones marked by arrows. b) Anteroposterior projection.

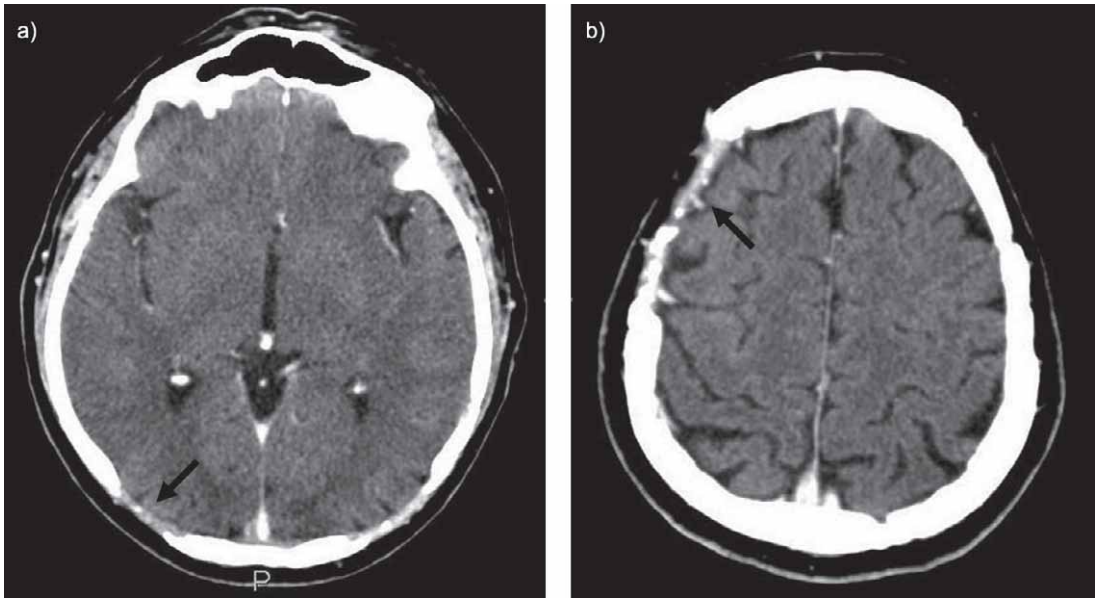

Fig. 2. a) PET-CT showing persistent confluenting lesions of calvariae cranii after 7 months of corticosteroid therapy (arrows). b) Extensive destruction of frontal bone

pearance and diabetes mellitus. Repaglinid was proscribed with unsatisfying result in controlling glycaemia. Therefore it was soon replaced by roziglitazon. During rutine checkup patient complained of calf swelling. Repeated workup excluded organ infiltration that would explain oedema (heart and kidneys). Afterwards we found that patient took significant amount of over-the-counter non-steroidal anti-inflammatory drugs which (combined with roziglitazon) caused fluid retention and oedema. Oedema withdrew after removing these drugs from therapy. Corticosteroids were abandoned and bisphoshonates were continued. Patient was ordered on often chekups and reffered to orthopedic surgeon to consider hip replacement surgery. He was also encouraged to abstine from smoking.

Discussion

Decision about treatment is made after final diagnosis and disease staging (monosystem or multisystem). We are confronted with two difficult doubts: should adult patients with mild to moderate symptoms receive any systemic treatment in paucity of clinical guidelines on conducting that treatment. Many cases of spontaneous disease remission have been described (even in multisystem form) contributing to unpredictability of LCH clinical course[1]. Most authors agree that expectative approach can be applied in patients with solitary eosinophilic granulomas if they cause no pain, deformity or loss of function.

Otherwise there are multiple treatment modalities: solitary, easily accessible lesions can be surgically extirpated, intralesional corticosteroid application and radiotherapy are also possible[1,2,6]. Although clinical guidelines are still under development, chemotherapy is widely used in treating multisystem form of LCH[6]. Two clinical studies exist for children[8,9] and there are two more under way. First randomized controlled study in adult patients started in 2004. First of the above mentioned studies showed similar outcomes in children treated with vinblastin or etoposide, with higher rate of etoposide toxicity[8]. Second study showed better results combining etoposide or vinblastin with prednisone. Ongoing adult patients study implements 6 or 12 month protocol of combined vinblastin and predisone treatment with addition of 6-mercaptopurine. Former protocol is used to treat polyostotic monosystem disease and granulomas in high-risk locations (e.g.anterior and middle cranial fossa) due to posibility of spread to the brain and high relaps rate if treated with monotherapy. Complete remission in those patients was usually achieved after second cycle of treatment[6].

Some children with chemotherapy resistant multisystem form of disease benefit from alogenic bone marrow transplantation[10]. Most authors concur that corticosteroids and smoking cessation are reasonable first line treatment for pulmonary LCH. Lung transplantation is also an option for refractory cases[1,4].

Disease course and response to therapy are highly unpredictable. Solitary bone lesions generally have an excellent prognosis with complete remission in 90% of cases[2]. Prognosis of multisystem and polyostotic form of LCH depends of several factors. Children under age 2 and patients with unfavourable sites (bone marrow, liver, spleen and lungs) are considered high risk patients[1]. Response to therapy after 6 weeks has recently been identified as the most important prognostic factor[8,9]. Involvement of 3 or more bones is associated with unfavorable prognosis in adults. Complications of LCH are disease and therapy related. The most frequent are diabetes insipidus, skeletal deformities, hearing loss and neurological deficits. Main causes of mortality are development of chronic cor pulmonale, chemotherapy adverse-effects and heart failure. Increased incidence of malignant disease was also observed among LCH patinents[6]. Rigorous clinical and radiological follow up is essential because disease can relapse at any age.

Conclusion

Presented case is interesting in several ways. LCH is extremly uncommon disease rarely considered in differential diagnosis. Clinical data on adult patients treatment is sparse bacause all clinical forms of LCH mostly occur in children. Besides that, multifocal eosinophilic granulomas disease form is not as frequent as solitary form and is usually accompanied by visceral manifestation, which is not the case with our patient. Defining universal therapy guidelines is troublesome due to low incidence and insufficient data from clinical studies. Radiotherapy, surgical extirpation and corticosteroid infiltration were not the option for our patient due to dissemination and localization of granulomas. Most studies recommend chemotherapy only in cases of viceral involvement and severe symptoms. Additionally, current protocol used in clinical trial for adult LCH (LCH-A1) is under scrutiny due to high incidence of vinblastin-induced polyneuropathy. In our experience long-term corticosteroid therapy results in minor clinical and radiological improvement in disease natural course, but causes multiple adverse effects, especially steroid diabetes. Therefore current treatment without unique guidelines should be strictly individual, following pathohistological diagnosis and detailed staging. Patient's age, general condition, comorbidity, severity of symptoms and contraindications for some therapy modalities should also be considered. Only after assessment of above parameters we can decide between expectative approach with rigorous checkups and active treatment by means of surgery, radiotherapy, immunomodulation or chemotherapy. Our experience advocates expectative approach in patients with monosystem polyostotic form of LCH.

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MONOSISTEMSKI MULTIFOKALNI OBLIK HISTIOCITOZE LANGERHANSOVIH STANICA (VIŠESTRUKI EOZINOFILNI GRANULOMI KOSTIJU) KOD 36-GODIŠNJEG BOLESNIKA: PRIKAZ SLUČAJA, TERAPIJSKE DVOJBE I PRIKAZ LITERATURE

SAŽETAK

Cilj našeg istraživanja je dati pregled dostupne literature o histiocitozi Langerhansovih stanica (LCH) te razmotriti liječenje poliostotskog monosistemskog oblika bolesti na temelju našeg kliničkog iskustva. LCH je bolest nerazjašnjene etiologije i patofiziologije s heterogenom kliničkom slikom; od solitarnih eozinofilnih granuloma sve do teških multisistemskih oblika bolesti. Obilježava je stvaranje granuloma sistemski, u organima. Predstavljamo rijedak slučaj multifokalnog koštanog oblika bolesti kod 36-godišnjeg bolesnika bez zahvaćanja unutarnjih organa. Protokoli liječenja LCH kod odraslih bolesnika, posebno rijetkog oblika u našem slučaju još uvijek nisu definirani. Pokušaj liječenja kortikosteroidima nije donio značajno poboljšanje na štetu nuspojava. Liječenje LCH može započeti tek nakon dijagnoze i procjene proširenosti bolesti. U obzir treba uzeti i ostale čimbenike – dob pacijenta, opće stanje, ostale bolesti te kontraindikacije za pojedine oblike liječenja. Prema našem iskustvu kod bolesnika s poliostotskim monosistemskim oblikom bolesti sa blagim simptomima ekspektativni pristup daje bolje rezultate od imunosupresivnog liječenja.