Langerhans cell histiocytosis in adults

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Summary: Langerhans cell histiocytosis in adults is a rare disease with potential involvement of all organs with or without organ dysfunction. In our single institution, 95 patients with histologically confirmed LCH were treated. At time of diagnosis, more than 1/3 of the patients had shown multi-system disease. Reactivations of LCH occurred in about 1/4 of the patients within a median of 6 years, especially in other individual organs. For staging and determination of organ dysfunction extensive diagnostic is necessary. There are a lot of treatment options in relation to isolated organ involvement or systemic disease. It makes sense to approach the disease in a multidisciplinary way.

Key words: Langerhans cell histiocytosis

Histiocytóza z Langerhansových buněk u dospělých

Souhrn: Histiocytóza z Langerhansových buněk u dospělých je vzácným onemocněním, které potenciálně může postihovat všechny orgány nebo při kterém může toto multiorgánové postižení chybět. Na našem pracovišti bylo léčeno 95 pacientů s histologicky potvrzenou LCH. V době stanovení diagnózy mělo onemocnění u více než 1/3 pacientů multisystémový charakter. Aktivita LCH se u přibližně 1/4 pacientů obnovila do 6 let (medián), obzvláště v dalších jednotlivých orgánech. Pro určení stupně závažnosti choroby a stanovení orgánového postižení je potřebná rozsáhlá diagnostika. K dispozici je řada léčebných možností, jak při postižení jednoho orgánu, tak pro léčbu systémové formy onemocnění. Je smysluplné toto onemocnění řešit interdisciplinárně.

Klíčová slova: histiocytóza z Langerhansových buněk

Introduction

In adults, Langerhans cell histiocytosis (LCH) is a rare disease with a predominantly good prognosis. But consequences of the non-malignant proliferations of Langerhans cells in organs can be dysfunctions up to organ failures. Manifestations of LCH can vary from single organ involvement, usually of lungs, bones or skin, to multiple organ involvement. So, LCH is divided into a single-system disease and into a multi-system disease. The symptoms are related to the organs affected. Risk organs in adults are not yet defined [1]. Only a few cases of malignant courses are described [2]. Langerhans cell sarcoma can occur as well de novo as from an antecedent LCH [3].

Exact incidence and prevalence of LCH in adults are not known. There is an estimation of one to two new manifestations per million population per year [4]. An immune defect is presumed as the likely cause of the disease. Additional influences of environment, for example smoking, were widely discussed [5]. Women are more frequent affected than men. The preferred age of manifestation is in the third to fourth decade. Accumulations in families are described.

There seems to be an association between LCH and malignant tumours. In most cases, LCH occurs before or concurrently with the associated neoplasma. The histopathology of ma-

Tab. 1. Characteristics of patients with LCH.

Patients (gender)	95	(57 women, 38 men)
Age at diagnosis (years)	median 35	[childhood (3 patients) – 75]
Follow-up (months)	median 78	(2–488)
Deaths	2	(suicide, liver failure by sclerosing cholangitis)
Single-system disease	79	(lungs 35, skeleton 28, skin 7, central nervous system 4, colon 2, lymphnodes 1, kidney 1, eye 1)
Multi-system disease	16	
Isolated pulmonary manifestation and smoking	35/35	(2 patients waiting for a lung transplantation)
Partial or complete diabetes insipidus	16/95	
Coexisting (semi-)malignant tumours	9/95	(breast cancer 3, colorectal cancer 2, renal cell cancer 1, acute lymphoblastic leukemia 1, Non-Hodgkin-lymphoma 1, basalioma 1)

Tab. 2. Reactivations of LCH in adult patients.

Patients	Single-system disease	Multi-system disease
n = 73	n = 64	n = 9
Within the same organ	1	
In a other single-system	10	
Multi-system disease	6	2

Follow-up: median 72 months

lignant neoplasms are especially malignant lymphomas or solid tumours [6].

Patients and course of disease

From October 2000 until May 2010 95 patients with histologically confirmed LCH were treated in our single institution. Characteristics of patients are shown in tab. 1. Isolated lung manifestation only occurred in patients smoking or having smoked. At time of diagnosis, more than 1/3 of the patients had been suffering from multi-system disease.

The course of LCH is variable with spontaneous remissions up to 70% in cutaneous manifestations and up to 50% in pulmonary disease. Osseous manifestations are difficult to measure. In active disease there are the categories regression, stable disease and progression. In non-active disease reactivations are possible.

In 2008, we evaluated our patients with regard to reactivations (tab. 2). Reactivations of LCH in adults occurred in about 1/4 of the patients within a median of six years of follow-up, especially in other individual organs. Eight patients have shown two to four further reactivations in course.

Diagnostic evaluation

For staging and determination of organ dysfunction an extensive diagnostic is necessary. The evaluation should embrace history and physical examination, especially inspection of skin and mucous membranes. Moreover, technical investigations are necessary: ultrasound of neck with thyreoid gland, abdomen and pelvis, X-ray and if need be CT scans of thorax, CT scan or NMR of skeleton, NMR of head, blood measurements and status of urine. Further investigations can be scintigraphy

Tab. 3. Treatment options in adults.

Isolated pulmonary involvement (symptomatic nodular form): smoking cessation			
Systemic	Prednisone	1 mg/kg/d po	Tapered over 6 mo
Isolated cutaneous involvement:			
Topical	Glucocorticoid ointment, Tacrolimus ointment PUVA-therapy		
Systemic	Methotrexate	20 mg/m^2/w po	6 mo
	Thalidomide	200 mg/d po	12 mo
Isolated osseous involvement:			
Monostotic	without risk of fracture		Glucocorticoid instillation
	with risk of fracture		Surgical resection and spongiosa reconstruction
	impending neurological deficit or high surgical risk		Radiotherapy 16–30 Gy
Monostotic involvement with risk of CNS involvement, polyostotic involvement or multisystem involvement:			
Initial treatment	Prednisone	1 mg/kg/d po	6 w
	Vinblastine	6 mg/m^2/w iv	
Maintenance treatment	Prednisone	1 mg/kg/d 1–5 po, q 3 w	6 or 12 mo
	Vinblastine	6 mg/m^2 iv d1, q 3 w	
	Mercaptopurine	30 mg/m^2/d po	
Patients with a poor prognosis or early recurrence	Cladribine	0.14 mg/kg/d iv d 1–5, q 4 w or	
	Cladribine	5 mg/m^2/d sc d 1–5, q 4 w and	
	Cytarabine	1000 mg/m^2 iv d 1–5, q 4 w or	
	Etoposide	100 mg/m^2 iv d 1–3, q 3 w	
Supportive treatment	Bisphosphonate in polyostotic involvement		12 mo

of bones, PET-(CT) scan, bone marrow biopsy and other investigations because of specials symptoms, for example measurements of hormones. An experimental approach is the measurements of cytokines to correlate with the activity of the disease. Typical manifestations of LCH are shown in fig. 1–5.

Treatment options and discussion

An optimal therapy for LCH in adults has not been established. But there are

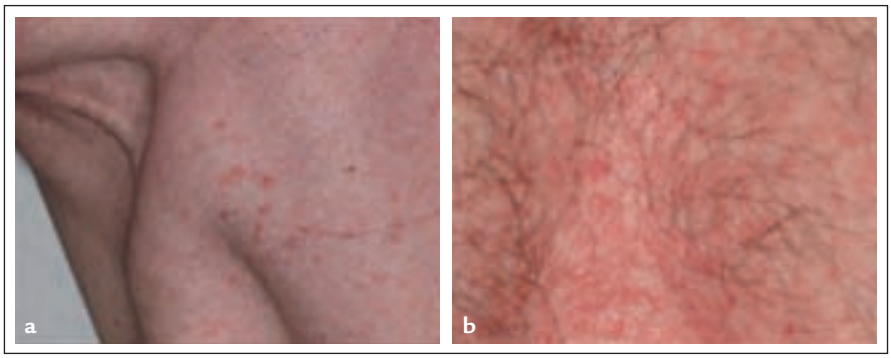

Fig. 1a, 1b. Cutaneous manifestations of LCH: disseminated brown papules on regions of increased sweating.

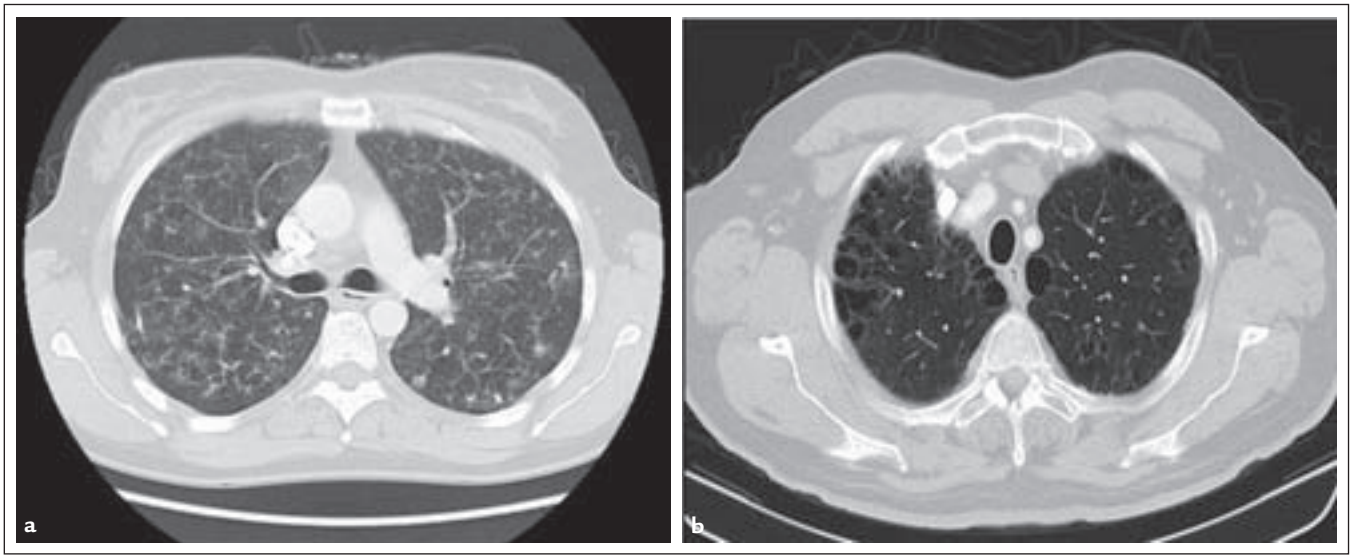

Fig. 2a, 2b. Pulmonary manifestations of LCH: computerized tomography of the chest with multiple nodular foci and cystic changes of the lungs.

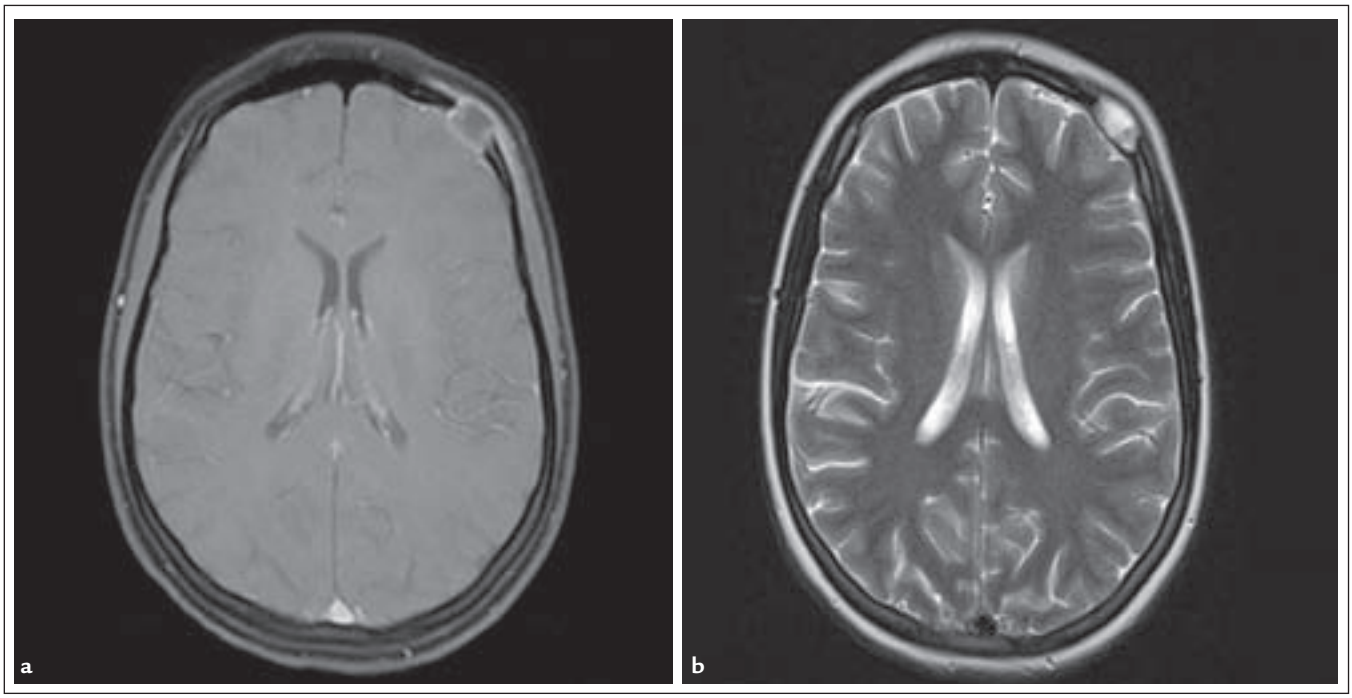

Fig. 3a, 3b. Osseous manifestation of LCH: nuclear magnetic resonance tomography of the head with an eosinophilic granuloma of the skull.

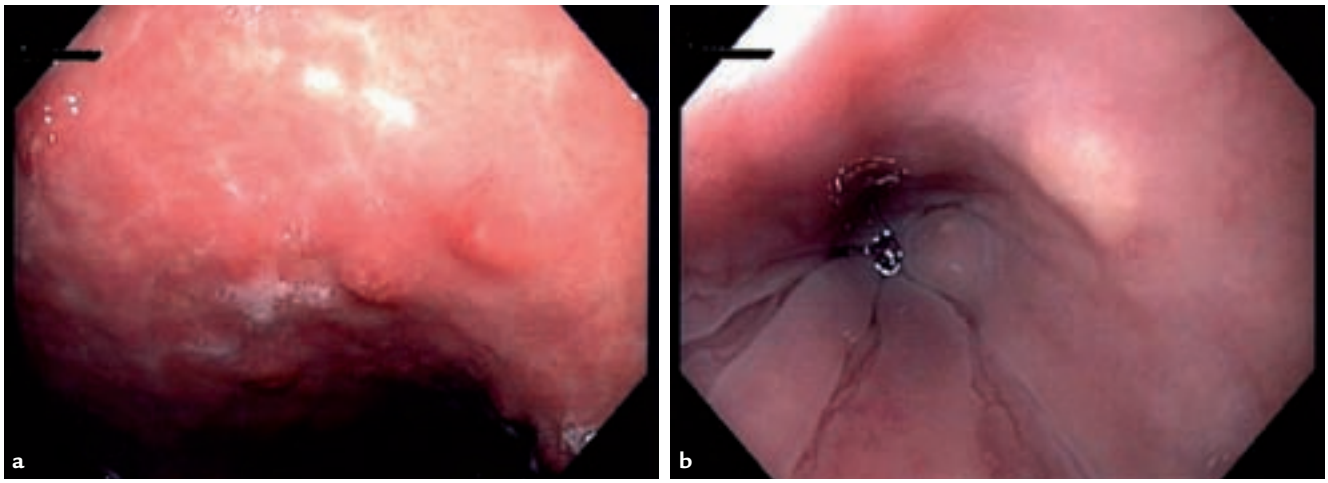

Fig. 4a, 4b. Gastrointestinal manifestations of LCH: granulomatous lesions of the mucous membrane of the stomach and the esophagus in an endoscopic view.

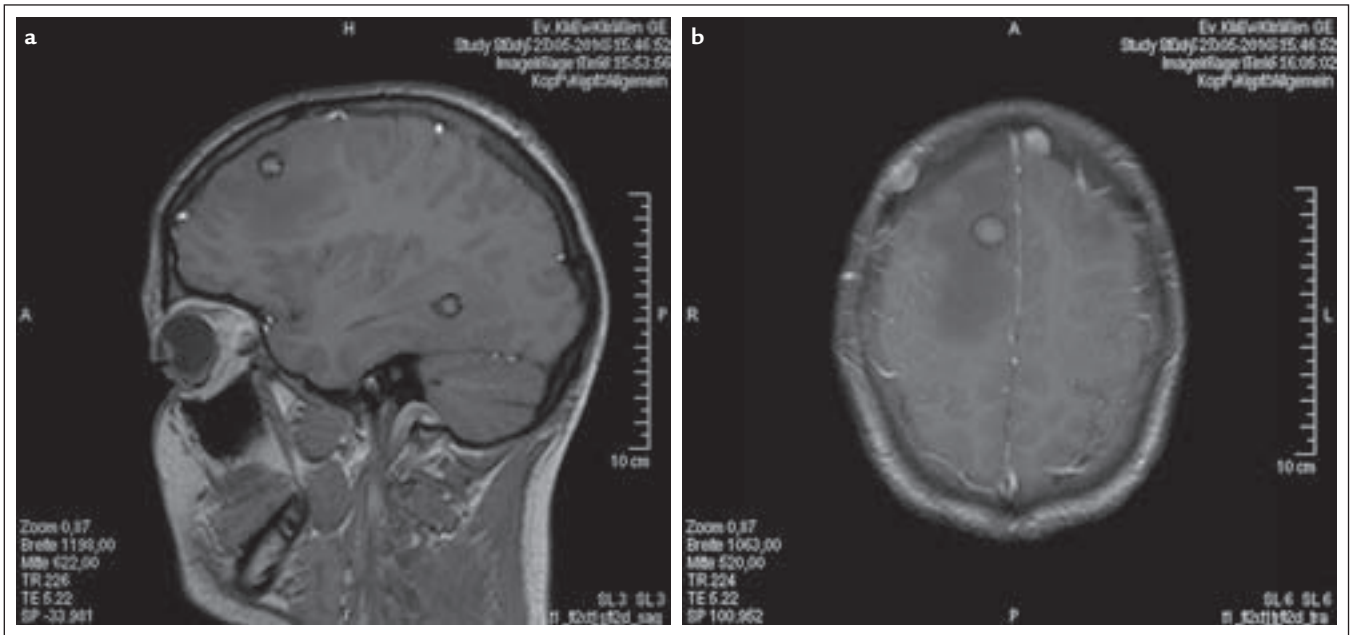

Fig. 5a, 5b. Manifestations of LCH in central nervous system: magnetic resonance tomography of the head with metastases-like lesions in cerebrum.

a lot of treatment options in relation to isolated organ involvement or systemic disease with or without organ dysfunction (tab. 3). Up to now, no controlled therapeutic studies have been performed in adults. So, approaches of therapy are following the experiences in children or take experimental results into consideration. Factors with unfavorable prognosis are advanced age, extensive organ involvement, number of organs affected, organ dysfunction and poor response to therapy. In cases of organ dysfunctions, supportive therapy is crucial.

Further options of therapy seemed to be an immunomodulatoric therapy with cyclosporine or interferon, the use of monoclonal antibodies like CD1a- or CD52-antibodies, and treatment with TNF-α-inhibitors like etanercept or infliximab. The results of these approaches were disappointing or of questionable success. In a few patients with chronic active course of LCH, an anti-inflammatoric and angiostatic therapy with rofecoxib, pioglitazone and trofosfamide resulted in long-lasting non-active disease [7]. Autologous or allogenic stem cell transplantation can lead to healing of the disease, but is fraught with high morbidity and mortality [8]. Advanced organ failure can only be treated with transplantation, for example of liver or lung, but LCH may reappear in the transplanted organ [9]. A new promising approach is the treatment with an aggressive chemotherapy resulting in long-lasting regressions [10].

Because of missing studies, the treatment of Langerhans cell sarcoma has to be individual. There are a lot of open questions. For answering these questions, further studies are warranted.

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Doručeno do redakce: 9. 9. 2010

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