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Langerhans Cell Histiocytosis: a Case Report

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Abstract

Langerhans cell histiocytosis is a disease which results from accumulation or proliferation of a clonal population of cells with the phenotype of Langerhans cells arrested at an early stage of activation that are functionally deficient. The etiology and pathogenesis of the disorder are still unknown. There are ongoing investigations to determine whether it is a reactive or a neoplastic disease. The fact is that neoplastic and reactive processes may have many clinical and pathological similarities. Some emphasize the role of "cytokine storm" in Langerhans cells. Further studies are necessary in all areas, from the etiology and pathogenesis to diagnosis and therapy.

Langerhans cell histiocytosis primarily affects bones, but less commonly it may involve other organ systems, or present as a multisystem disease. The clinical course is variable, from benign forms with spontaneous resolution, to chronic disseminated forms with fatal outcome.

This is a report of a 29-year-old man with Langerhans cell histiocytosis with an onset at the age of 8, which later progressed to a multisystem disease. Apart from lesions on the skin and exposed mucous membranes, the patient also presented with: diabetes insipidus, granuloma of the right femur and slight bulbar protrusion of the right eye. The patient experienced spontaneous pneumothorax on two occasions. The diagnosis of Langerhans cell histiocytosis was histologically confirmed using electron microscopy by presence of Birbeck granules in the histiocytes. A favorable therapeutic response was obtained after systemic corticosteroid therapy.

Key words

Histiocytosis, Langerhans-Cell; Diabetes Insipidus; Eosinophilic Granuloma; Pneumothorax; Treatment Outcome

Langerhans cell histiocytosis (LCH), also known as histiocytosis X, is a rare disease characterized by an accumulation of cells with Langerhans cell phenotype in a variety of tissues causing their damage (1). In 1987, the Writing Group of the Histiocyte Society defined it as "accumulation or proliferation of a clonal population of cells with the phenotype of Langerhans cells (LCs) arrested at an early stage of activation and functionally deficient" (2, 3). Other authors believe that LCH is caused by: primary antigen-presenting cells (4); oligoclonal accumulation of LCs (5), or phenotypically immature CD1a + LC (6, 7, 8).

LCH primarily affects bones, but rarely it may involve other organ systems as well (skin, lymph nodes, pituitary, nervous system, lungs, spleen), or it presents as a multisystem disease (9). The clinical course is variable, from benign forms with spontaneous resolution (10, 11), to chronic disseminated forms which may be aggressive with fatal outcome (12, 13). In 1987, the Histiocyte Society (2) classified histiocytoses into three major categories: 1. Langerhans cell histiocytosis (Letterer Siewe disease, Hand-Schuller-Christian disease, eosinophilic granuloma, congenital self-healing reticulohistiocytosis of Langerhans cells, and undetermined cell histiocytosis); 2. Non-Langerhans cell histiocytosis and 3. Neoplastic (malignant) histiocytoses.

In 1997, the Histiocyte Society revised the earlier classification. According to the revised classification, there are two categories: disorders of varied biological

behavior and malignant disorders. The first category included two groups of diseases: 1. Dendritic cell or related disorders (Langerhans cell histiocytosis, juvenile xanthogranuloma and related disorders, solitary histiocytoma with dendritic cell phenotypes and secondary dendritic cell disorders); 2) Macrophage or related disorders (primary and secondary hemophagocytic syndromes, Rosai-Dorfman disease, solitary histiocytoma with macrophage phenotypes, multicentre reticulohistiocytosis, generalized eruptive histiocytoma. The second category includes malignant disorders: monocytic leukemia, monocytic sarcoma, histiocytic sarcoma with dendritic cell phenotype and macrophage phenotype (14).

LCH commonly occurs in childhood. The annual incidence of LCH in Denmark is reported to be 5.4 per million children (15). The German Registry for Childhood Cancer shows that the incidence of LCH in Germany is 6.0 per million children (16), while the Hungarian National Cancer Registry shows an incidence of 2.2 per million individuals under the age of 18 years (17). The Manchester Children's Tumor Registry shows that 101 children have been treated for LCH during 45 years with an annual incidence of 2.6 cases per million children: in children under the age of 12 months the annual incidence was 9.0 and in children from 10 to 14 years of age it was 0.7 cases per million children (18). A French study showed an annual incidence of 4.6 cases per million children under the age of 15, ranging from 15.3 per million children under the age of 2, to 2.0 cases per million children over the age of 10 (19). The incidence of LCH among adult population has not been precisely defined: it is assumed that 30% of all patients are adults (20).

Case Report

A 29-year-old man, a traffic technician out of job and a father of two children, on his first visit complained about the following: increased fluid intake, constant thirst and frequent urination, pain in the muscles of the lower extremities and painfull and difficult walking. His history showed that at the age of 8 he noted excessive thirst and fluid intake, frequent urination and weight loss. At the age of 12 he presented with red squamous skin lesions on the scalp and had problems with fast tooth loss. He had spontaneous pneumothorax twice, at the age of 21 and 24, and was treated with pronisone and eutisone (supposedly due to sarcoidosis, but there is no written evidence about it). The skin lesions got worse and spread over the folds of large joints, chest and face. The patient's history shows that his father died of liver cancer and his father's sister had diabetes mellitus.

On his first visit the patient was in good general condition, presenting with skin and mucous membrane changes: erythematous infiltrated plaques partly covered with vegetant proliferative yellowish squames; dense erythematous papules, the size of a lens, somewhat eroded and covered with yellowish squames, were found on the face, mostly on the forehead (Figure 1), on the nasolabial folds, in the retroauricular region (Figure 2), on the chin (Figure

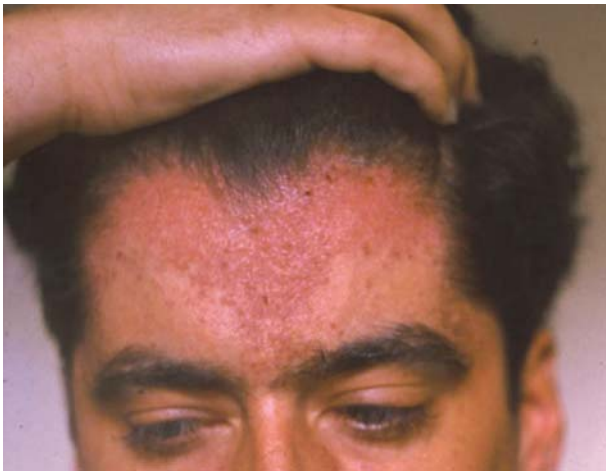

Figure 1. Great part of the forehead affected by erythema, eroded papules and squames

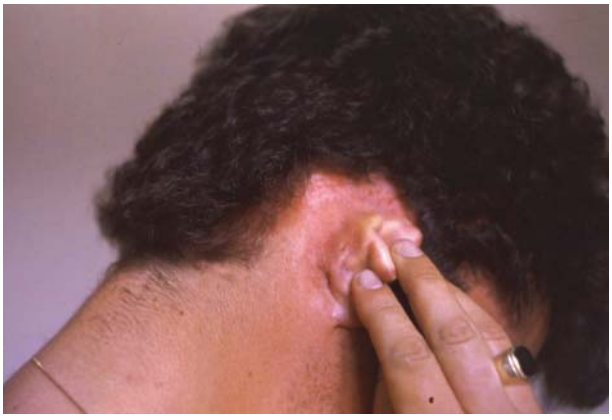

Figure 2. Retroauricular area with papular and squamous lesions on erythematous base

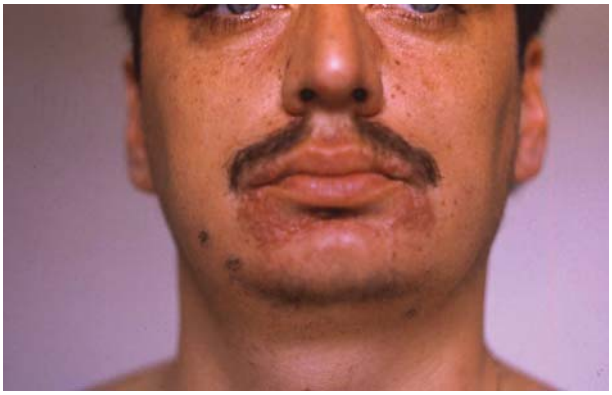

Figure 3. Lesions on the chin similar to those on the forehead

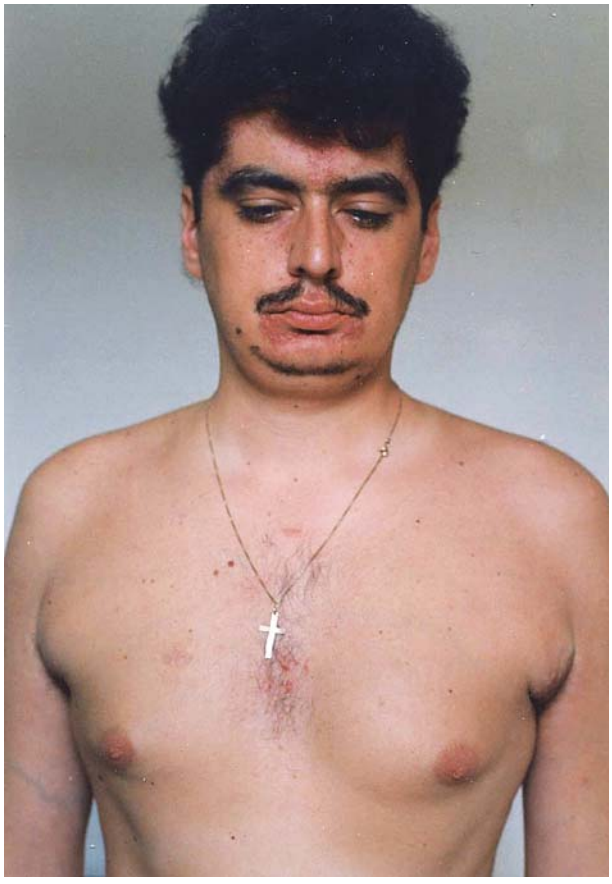

Figure 4. Presternal area with dense erythematous papules, the size of a lens, covered with yellowish squames; Plaques of partly eroded papules on the face

3), as well as on the trunk, especially on the presternal (Figure 4) and intercapular regions; erythematous vegetant proliferations with erosions and effusion of

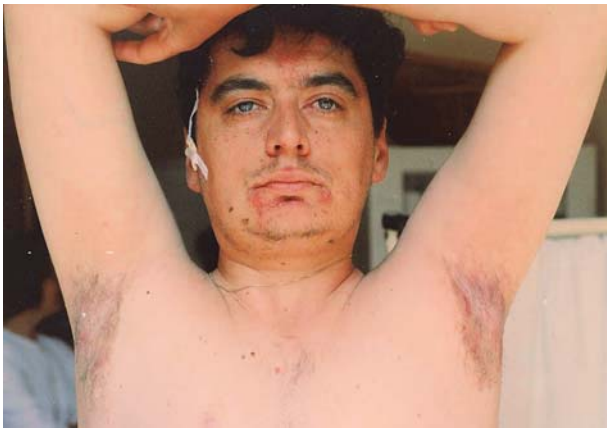

Figure 5. Axillary folds with vegetant erythemas and moist erosions

putrid, bad odor were found in the axillary (Figure 5), groin (Figure 6) and intergluteal areas; the intergluteal area presented with several wet fistula canals and macerated surrounding skin; protrusions about the size of a grain of rice were found on the hard palate mucosa; fibrinoid pseudomembranes were present in the hypertrophic gingival area; the teeth were affected by caries, a great number were missing; exophthalmos was noted in both eyes.

Laboratory test results, including erythrocyte sedimentation rate, complete blood count, basic biochemical, endocrinology and immunology tests, were within normal physiological limits.

Microbiology specimens were collected from the affected lesions and *Staphylococcus aureus*, susceptible to penicillin, erythromycin and ciprocinal, was isolated.

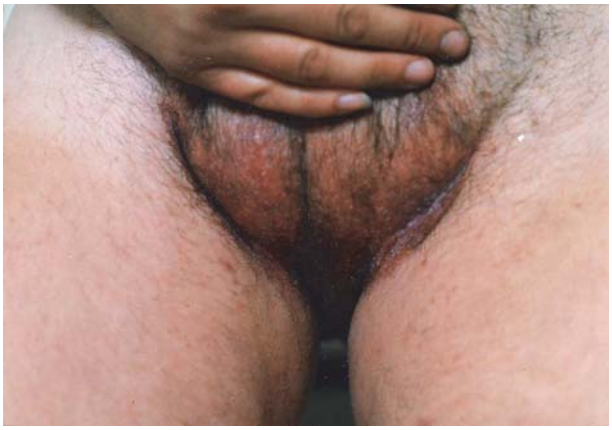

Figure 6. The groins and intergluteal folds affected by intensive exudation with a few fistula canals

Ultrasonography of the upper abdomen, thyroid gland and breasts showed no abnormalities.

X-ray of the heart and lungs showed no pathological findings. There were no osteolytic lesions on the bones of the head; sella turcica presented with normal physiological findings; paranasal sinuses showed no pathological changes. In the lower end of the right femoral diaphysis a small lytic lesion of irregular shape was found (Figure 7).

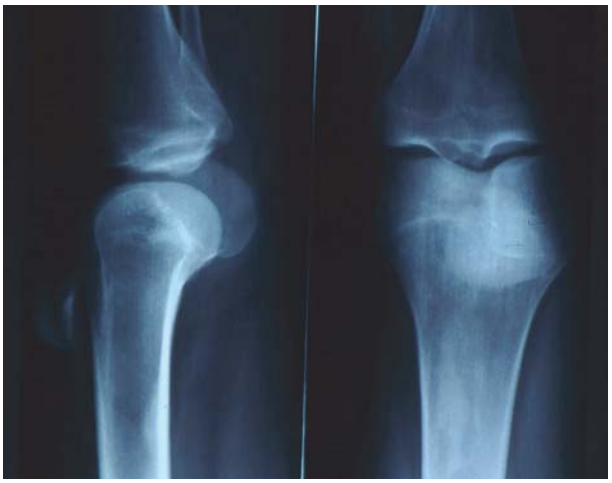

Figure 7. X-ray of the lower end of the right femur shows a lucent area of irregular shape

Static bone scintigraphy (anterior skull projection) showed a physiological distribution of radio-opacity (Figure 8). There was an increased focal accumulation in the lower end of the right femur (Figure 9).

Fistulography was carried out using a cannula and it revealed a great number of pseudofistulous canals with uneven walls and purulent discharge.

Histopathological analysis of skin biopsy specimens showed: severe epidermal atrophy; dense histiocyte infiltrations, sparse eosinophils and erythrocyte extravasation in the dermis invading epidermis on several sites; numerous sebaceous glands near the atrophic epidermis. These findings supported the conclusion about Hand-Schuller-Christian disease.

Electron microscopy analysis of skin biopsy showed Birbeck granules in histiocytes (Figure 10).

Specialist consultations established the following pathological conditions: borderline (partial) diabetes insipidus requiring no medication therapy;

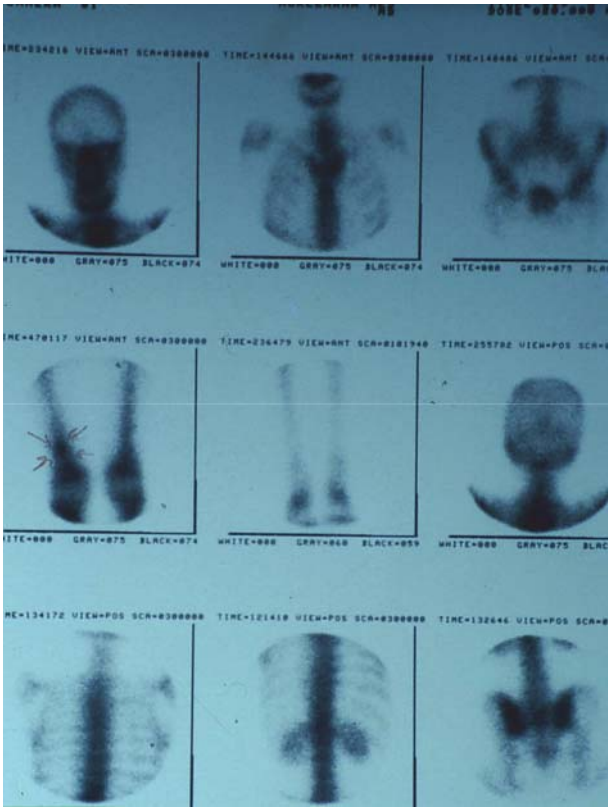

Figure 8. Static bone scintigraphy shows a physiological distribution of radio-opacity, except on the lower end of the right femur

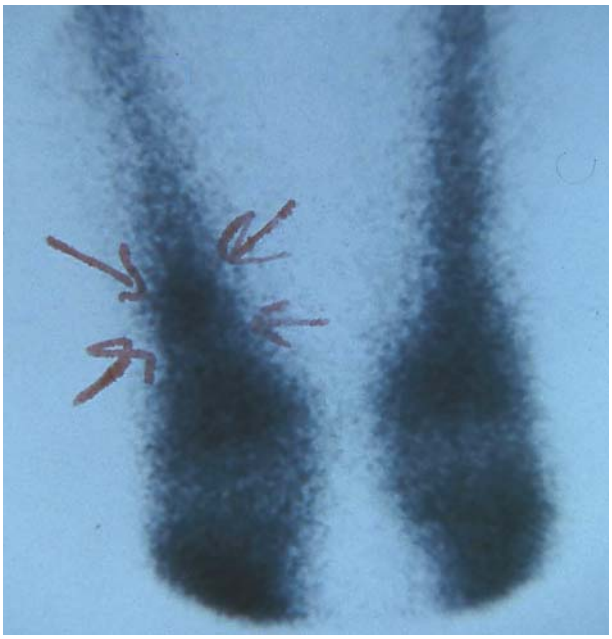

Figure 9. Increased focal accumulation in the lower end of the right femur

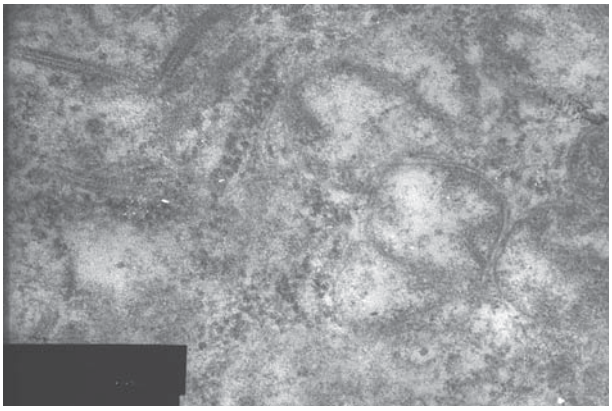

Figure 10. Electron microscopy shows Birbeck granules in histiocytes

periodontal disease; right eye protrusion (Hertel 110: OD 21, OS 19); nasal septal deviation.

The treatment started with systemic parenteral prednisone (initial dose of 1 mg/kg/bw per day, which was gradually reduced), systemic antibiotics, topical corticosteroid and antibiotic preparations and cryotherapy.

Discussion

Langerhans cell histiocytoses include a group of rare diseases that may develop at any age, most commonly in childhood. They are characterized by unpredictable course and variable prognosis, from self-healing to fatal outcome.

The etiology of LCH remains unknown (1) despite numerous studies over the past decades. Various factors have been indicated, such as tuberculosis, lipid metabolism disorders, infections and immunity disorders, genetic and environmental factors. Although some studies established an association between human herpesvirus type 6 (HHPV6) (21) and LCH, others failed to prove increased prevalence of HHPV6 in the tissues of patients with LCH in regard to healthy population (22). It was also found that there was no causal role for HHV8 in the etiology of LCH (23), as well as the other eight viruses (24): herpes simplex virus, cytomegalovirus, Epstein Barr virus, adenoviruses, T-cell lymphotropic type I and type II virus, human immunodeficiency virus (HIV) and parvovirus. Huang and Arceci (12) indicated authors who suggested that development of LCH was associated with several apparently unrelated factors, including maternal urinary infection and nutritional problems, use of medications, blood transfusion during the first six months of life (25). An association was also established with personal or family history of patients, thyroid disease and postnatal infection, vomiting, diarrhea and drug use (26).

The pathogenesis of the disease is also unclear. There is a long standing dispute whether LCH is a reactive or a neoplastic disorder (9, 13, 27, 28, 29). Egeler and associates (30) tried to elucidate this dilemma in their paper. The fact is that neoplastic and reactive disorders may have many clinical and pathological similarities, making their differentiation more difficult. Neoplasms are caused by proliferation of genetically abnormal progenitor cells, while in reactive disorders genetically normal cells multiply and accumulate under some other stimuli. Neoplastic processes are associated with inflammatory responses inducing accumulation of adjacent cells, and contrary to this, some reactive immune diseases are characterized by the accumulation and sequestration of activated white blood cells, which occasionally form lesions similar to neoplastic tumors. Some emphasize the role of "cytokine storm" in Langerhans cells (28). Cytokines provide an optimal microclimate for survival of interactive inflammatory cells by creating autocrine or paracrine mechanisms. They also affect differentiation of precursor cells. Some cytokines may stimulate development of macrophages, Langerhans cells and other types of dendritic cells from CD34+ stem cells, or by sequestrating of circulating (peripheral) monocytes from the blood to affected tissues. Arguments supporting the neoplastic or reactive process that results of numerous studies are given in Table 1 (30-37).

Given the existence of this dilemma, the third edition of the International Classification of Diseases for Oncology differentiates three groups of LCH: unifocal and multifocal variants which are considered to be neoplastic diseases, and disseminated LCH, considered as a malignant disease (19, 38). The most important characteristics of this disease are given in Table 2 (39, 40).

In our 29-year-old patient, the onset was at the age of 8, with symptoms of diabetes insipidus, associated with skin and oral lesions, involvement of lungs (spontaneous pneumothorax at the age of 21 and 24), whereas in the last 5 years the leading

Table 1. Langerhans cell histiocytosis: a neoplastic or reactive disease? [Adapted from Egeler et al, (30)]

Neoplastic	Reactive
Clonality of LC cells in all studied cases of non-pulmonary LCH	Non-clonality of pulmonary LCH, related to smoking
Recurrent genetic abnormalities, including deletion of chromosome segments in 7 patients	No gross genetic abnormalities observed in 72 patients No mutation in genetic master switch p53 gene
More extensive and higher-risk forms of LCH have evidence of more mutational events at tumor suppressor genes	
Rare cases of familial clustering with high concordance between monozygotic twins	Sporadic disease in vast majority of cases
Clinically aggressive behavior of some LCH forms	Indolent, clinically benign behavior of most LCH cases, sometimes involving: Spontaneous remissions; "Flare up" when patients develop a cold or other infectious process; Faborable response to antibiotic treatment
Apparent maturation arrest of LCH cells *in vivo*	Immature LCs may accumulate in inflammatory processes, e.g. in lymph nodes that drain chronically inflamed skin
	LCH cells cannot be maintained *in vitro* or *in vivo* in humanized mouse models
	LCH cells are cytologically benign
	Granulomatous compositions of apparently immune-activated cells

LCH, - Langerhans cell histiocytosis; LCs- Langerhans cells

symptoms included cutaneous-mucosal lesions. Right eye protrusion and right femoral granuloma developed as well. Histological examination showed histiocytic infiltration, and electron microscopy showed Birbeck granules in the histiocytes. The dominant clinical symptoms corresponded with those typical for Hand-Schuller-Christian disease and for eosinophilic granuloma, making differentiation between diseases difficult. Given that this is a common problem, all the above-mentioned diseases are grouped under the common term Langerhans cell histiocytosis, or after Lichtenstein, histiocytosis X (41). In 1997, authors from Novi Sad reported a case of a patient with hyperthyroidism and LCH, but also presenting with symptoms found in our patient: diabetes insipidus, pneumothorax and skin lesions (42). A retrospective study conducted by the Mayo Clinic included 265 patients with LCH aged from 2 months to 71 years demonstrated the following: the sex ratio was 1,6 : 1,0 in favor of male patients; the most common signs and symptoms were pain, bone defects, soft tissue swelling, tooth loss, oral ulcerations, and diabetes insipidus (43). One study of adult patients with LCH reported that the most common sites of involvement were skin, lungs and bones, and then the lymphoproliferative system (20). The disease may develop in the CNS

Table 2. Langerhans cell histiocytosis (LCH)

Characteristics	Letter-Siwe disease	Hand-Schuller Christian disease	Eosinophilic granuloma	Congenital self-healing histiocytosis	Undetermined cell histiocytosis
Onset	First year of life	Rare in childhood Adult	Older children Adult	At birth	Adult
Course	Acute (disseminated)	Acute-chronic to progressive	Chronic and localized	Subacute	Subacute
Prognosis	Unfavorable	Favorable	Good	Self-healing	Poor
Systemic symptoms	Septic fever Weight loss Limphadenopathy Hepatosplenomegaly Lungs Anemia Eosinophilia	Classical triad: lytic bone lesions, exopthalmos, diabetes insipidus Infantility Otitis media Lymphadenopathy, Hepatosplenomegaly Lungs	Bone tumors Lymphadenopathy Hepatosplenomegaly		No
Skin	Papulopustular lesions Papulovesicular lesions, Erosions Mucosal petichias	Papules Xanthomas	Granulomas	Papules Nodules Crater-shaped ulcers	Papules Nodules Tumors
Mucous membranes	Yes	Yes	Yes	Yes/No	Yes/No
Bone lesions	Sometimes	Multifocal	Solitary or sparce	No	No
Histology	Proliferative reaction Histiocytic LC infiltrations	Xanthomatous reaction	Granulomatous reaction	Proliferative reaction	Proliferative reaction
Antigenic markers	S-100+, CD1a+, Birbeck granules +	S-100+, CD1a+, Birbeck granules +	S-100 +, D1a+, Birbeck granules +	S-100+, CD1a+, Birbeck granules +	S-100+,CD1a+ Birbeck granules

LC - Langerhans cell

(4%), while diabetes insipidus in a wide range of 10 – 50% of patients (44, 45).

According to the International Langerhans Cell Histiocytosis-2 (LCH2) study, LCH has three stages: the first stage is unifocal, the second multifocal – without spleen, liver, lung or bone involvement in patients over the age of 2 years, whereas the third stage is characterized by involvement of the liver, spleen, lungs and bone marrow in patients under the age of 2 years (44).

The diagnosis is based on anatomical and pathological signs and symptoms. In 1987, the Writing Group of the Histiocytic Society identified three levels of confidence in the diagnosis of LCH (2): presumptive diagnosis is based on histological findings; the diagnosis is established when the histology is consistent with LCH and lesional cells are shown to express S 100 protein, peanut agglutinin and alpha-D-mannosidase activity; a definite diagnosis is made if the histology is consistent with the diagnosis of LCH and the lesional cells are shown to express CD1 complex or to have intracytoplasmic Birbeck granules on electron microscopy. In the early days, a definitive diagnosis was the ultrastructural proof of Birbeck granules (BGs), now it can immunohistologically be recognized by the expression of langerin in the histiocytic cells (46). Langerin (CD207 antigen) is a mannose-specific lecitin endocytic receptor that induces formation of Birbeck granules (47). The induction of BGs appears to be the consequence of antigen-capture function of langerin, allowing routing of antigen into these organelles. Langerin, as a type of transmembrane cell surface glycoprotein is involved in the formation of BGs by limiting cell membranes (48, 49, 50). Using langerin, BGs provide sequestrial selection of antigens, which may be important in migration of LC into epidermis (51). The significance of langerin in BGs is obvious from the definition of LCH as accumulation of langerin + dendritic cells (DCs) in the skin, bones and other tissues (52). Although langerin, as an intracellular component is associated with BGs in 100% of cases (52, 53), its diagnostic specificity has not been established yet, which points to the necessity of further investigations. Thus, langerin is an additional marker for identification of LCH (48).

Three types of histological reactions have been described in LCH: proliferative, granulomatous and xanthomatous (54, 55). These reactions may be considered *sui generis*; they may develop at sites of previous lesions, may simultaneously exist, or heal in any of these types. Various types of histological reactions may be found in one patient (56). No association has been established between the histological type and severity of illness, morbidity or mortality (1).

The differential diagnosis includes: seborrheic dermatitis, Darier's disease, Hailey-Hailey disease, purpura, scabies, cutaneous tuberculosis, hematological diseases, malignant neoplasms, leukemia, lymphomas, multiple myeloma, disseminated xanthomas with diabetes insipidus and non-Langerhans cell histiocytosis (57).

Therapeutic options depend on the clinical presentation of the disease (unifocal, multifocal, disseminated (19, 38), and the disease status (inactive or active) (58). LCH may be: inactive – if there is no evidence of the disease (due to resolution of all signs and symptoms) and active. The activity may lead into three directions: regression of signs or symptoms without new lesions; persistence of signs and symptoms without new lesions; progression of signs and symptoms and/or development of new lesions (58). Progression and reactivation of the disease indicate a chronic clinical course (59). There is a variety of therapeutic options: local curettage, radiotherapy, use of mechlorethamine (60), combination of mechlorethamine and PUVA (psoralen ultraviolet A) therapy (61), local corticosteroid therapy, antibiotics, systemic corticosteroids and cytostatic agents (methotrexate, cyclosporine, azathioprine), various protocols of chemotherapy and immunosuppressive treatment. According to LCH I protocol in the treatment of LCH, patients with multisystem disease receive vinblastine or etoposide during 6 months with an initial dose of methylprednisolone (62). Etoposide proved to be more effective than vinblastine (14, 63), but may induce significant leukemoid reactions (20, 64). According to LCH II protocol, vinblastine is combined with etoposide (65). The LCH-S-98 protocol includes 2-chlorodioxyadenosine (58). Immunotherapy is associated with bone marrow transplantation, and if the donor is not compatible, antithymocyte globulin + prednisone + cyclosporine A are used (66). Etanercept also proved to be successful in the treatment of multifocal LCH (67).

The course and prognosis depend on the age of patients, number of involved organs and the degree of organ dysfunction, as well as on the applied treatment. The prognosis is better if only the skin and bones are involved, and if the onset is from birth. The prognosis is favorable if there is bone involvement without diabetes insipidus. Diabetes insipidus in children is associated with high risk for chronic disease, but not for mortality. Permanent consequences

are rather common and they significantly reduce patients' quality of life (68, 69). A study conducted by 12 oncology centers and 9 institutions included 201 children with LCH. Endocrine problems were reported (diabetes insipidus in 24% and growth disorders in 9% of cases), neurological consequences in 11% (cerebellar symptoms and psycho-intellectual problems), orthopedic abnormalities in 20%, hearing loss in 13%, ophthalmological problems in 8%, skin problems in 2%, pulmonary fibrosis in 4%, secondary carcinoma in 4 patients: 3 cases with acute myeloid leukemia and 1 case with thyroid carcinoma (68).

Increased risk of mortality is associated with: early onset, hepatosplenomegaly, thrombocytopenia and polyostotic bone diseases (43). Disseminated forms may also be related to the development of lymphomas, leukemias and tumors. It is a fact that LCH may precede malignancies; the fact that it occurs simultaneously or after the development of malignancies, suggests the same etiological factors (20). Fatal outcome accounts for 10% of cases, remission occurs in 30%, while 60% of cases have a chronic course. However, with adequate treatment the survival rate is believed to be 80% (64).

Conclusion

In conclusion, this is a case report of a patient with a very rare disease, multisystem Langerhans cell histiocytosis, but with a relatively favorable course and good response to systemic corticosteroid therapy. Langerhans cell histiocytosis is a disease with many unknown factors which remain to be further studied in all aspects, from the etiology and pathogenesis, to diagnosis and therapy.

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Abbreviations

LCH - Langerhans cell histiocytosis
LCs - Langerhans cells
OD - oculus dexter
OS - oculus sinister
HHPV6 - human herpesvirus type 6
HIV - human immunodeficiency virus
BGs - Birbeck granules
DCs - dendritic cells
PUVA - psoralen ultraviolet A

Histiocitoza Langerhansovih ćelija – prikaz slučaja

Sažetak

Uvod: Histiocitoza Langerhansovih ćelija (eng. *Langerhans cell histiocytosis* – LCH) ili histiocitoza X (eng. *histiocitosis X*) bolest je koja se retko javlja i kod koje se ćelije sa fenotipom Langerhansovih ćelija (eng. *Langerhans cells* – LCs) akumuliraju u različita tkiva i izazivaju oštećenja tih tkiva. *Writing Group of the Histiocyte Society* je 1987. godine dala sledeću definiciju: „Akumulacija ili proliferacija klonalne populacije sa fenotipom Langerhansovih ćelija koje su zaustavljene u ranom stadijumu aktivacije i funkcionalno su deficijentne". LCH je bolest koja primarno zahvata kosti, ali u retkim slučajevima može takođe da zahvati i druge organske sisteme (koža, limfni čvorovi, hipofiza, nervni sistem, pluća, slezina), ili da se prezentuje kao multisistemska bolest. Kilnički tok je varijabilan, od benignih formi sa spontanom rezolucijom do hroničnih, diseminovanih formi, agresivne bolesti koja može imati smrtni ishod).
Prema klacifikaciji *Writing Group of the Histiocyte Socity* iz 1987. Godine, kod histiocitoza se razlikuju tri velike grupe bolesti: 1) histiocitoze Langerhansovih ćelija (*Morbus. Leterer Siwe*, *Morbus Hand-Schuller-Christian*, eozinofilni granulom, kongenitalna samozaceljujuća histiocitoza Langerhansovih ćelija i histiocitoza nedeterminisanih ćelija); 2) ne-X histiocitoze (histiocitoze ne-Langerhansovih ćelija) i 3) neoplastične histiocitose.
Prema studiji iz Francuske, godišnja incidencija LCH je 4,6 na milion dece mlađe od 15 godina i to 15,3 na milion pre prve godine do 2 na milion posle 10. godine života. Tačna incidencija među odraslima je nepoznata – pretpostavlja se da 30% svih obolelih čine odrasli.
Prikaz slučaja: Muškarac star 29 godina još u osmoj godini života primetio je da je često žedan, često mokri i gubi na težini. U 12. godini javile su mu se prve promene na koži u vidu crvenila i naslaga skvama u kosmatom delu glave. Od tada nastaju problemi sa

zubima (klate se, ispadaju, kariozni su). U 21. i 24. godini nastupio je spontani pneumotoraks. Promene na koži se šire i zahvataju lice, grudni koš i pregibe velikih zglobova.

Opšte stanje pacijenta na prijemu je bilo u fiziološkim granicama, bez limfadenopatije i hepatosplenomegalije. Od tegoba naveo je povećan unos tečnosti, učestalo mokrenje, bolove u listovima i butinama i kod jače izraženih promena u pregibima, smanjenu pokretljivost i bol.

Dermatološki status je ukazao na prisustvo: u kosmatom delu glave eritemne, infiltrovane, mestimično vegetantne plaže sa naslagama žućkastih skvama; na čelu, u nazolabijalnim brazdama, na bradi, retroaurikularno, presternalno i interskapularno gusto zbijene eritemne papule do veličine sočiva, mestimično erodovanih površina, pokrivenih žućkastim skvamama; u aksilama i preponama i interglutealno eritemne vegetacije, sa erozijama i vlaženjem, putridne; interglutealno vlaženje intenzivno sa nekoliko fistuloznih otvora; u predelu tvrdog nepca veći broj prominencija veličine zrna pirinča, gingive hipertrofične, pokrivene belim naslagama, zubi kariozni ili nedostaju; oči krupne, lako egzoftalmične. Laboratorijske analize uključujući hematološke, osnovne biohemijske i imunološke, kao i ehosonografski pregled gornjeg abdomena, štitne žlezde i dojki bili su u fiziološkim granicama. Sa promena na koži izolovan je *Staphylococcus aureus.*

Radiološki nalazi na plućima, srcu, prednjim paranazalnim šupljinama, kraniogram, kao i *sela turcica* u fizioloskim granicama. Rendgenografski pregled butne kosti otkriva u donjem okrajku desne butne kosti rasvetljenje nepravilnog oblika. Fistulografija ukazuje na prisutnu pseudofistulu.

Patohistološki nalaz isečka uzetog sa promenjene kože pokazao je atrofiju epidermisa, gust infiltrat sa mnoštvom histiocita, retkim eozinofilima i retkim ekstravazatima eritrocita u dermisu, koji na više mesta invadira epidermis. Zaključak, u preparatu ima mnogo elemenata koji ukazuju na Hant-Šiler-Kristijanovu bolest (*Morbus Hand-Schuller-Christian)*.

Elektronska mikroskopija ukazala je na postojanje Birbekovih granula u histiocitima. Statička scintigrafija kostiju (ciljano je rađena scintigrafija lobanje u anteriornoj projekciji) ukazala je na fiziološku distribuciju radiorazređivača, ali je na donjem okrajku desnog femura utvrđeno pojačano fokalno nakupljanje.

Na osnovu konsultativnih specijalističkih pregleda, utvrđeno je prisustvo graničnog (parcijalni) insipidnog dijabetesa (koji aktuelno nije zahtevao medikamentnu terapiju), paradontopatija, laka protruzija desne očne jabučice, devijacija nosne pregrade, hronični faringitis, u spoljnom ušnom kanalu promene kao na koži. Audiometrija je bila u granicama normale.

Lečenje je započeto sa parenteralnim davanjem prednizona u početnoj dozi od 1 mg/kg/TT dnevno, sistemskom primenom antibiotika i lokalnom primenom kortikosteroidnih i antibiotskih preparata uz krioterapiju.

Diskusija: Etiologija LCH je nerazjašnjena: navode se razni faktori kao što su tuberkuloza, lipidne abnormalnosti, infekcija, imunološki poremećaji, genetski i faktori okoline. Patogeneza bolesti takođe nije jasna. Vode se rasprave da li je to reaktivna ili neoplazijska bolest. Veliki značaj pridaje se „citokinskoj oluji“ u LCH ćelijama. Poznato je da neoplazijski i reaktivni poremećaji mogu imati mnogo kliničkih i patoloških sličnosti, što otežava njihovo razumevanje. Upravo zbog ove dileme, treća verzija *International classification of Diseases for Oncology* kodira tri glavna klinička podtipa LCH: unifokalna i multifokalna varijanta koja se smatraju neneoplastičnom/neoplastičnom reaktivnom bolešću i diseminovana LCH, označena kao maligna bolest. Najvažnije osobine ove grupe bolesti prikazane su u Tabeli 2.

Kod našeg 29-godišnjeg bolesnika bolest je počela u osmoj godini života simptomima insipidnog dijabetesa, potom su se javile promene na koži i u usnoj duplji, na plućima (spontani pneumotoraks u 21. i 24. godini), da bi poslednjih 5 godina vodeća bila kutano-mukozna simptomatologija. Došlo je do razvoja i lake protruzije desnog bulbusa i granuloma na desnom femuru. Histološki je u bioptatu uzetom sa promene na koži utvrđen histiocitni infiltrat a elektronskom mikroskopijom Birbekove granule u histiocitima. Istovremeno prisustvo simptoma i znakova tipičnih za Hant-Šiler-Kristijanovu bolest i eozinofilni granulom otežalo je kod bolesnika prikazanog u ovom radu, diferencijaciju prema jednoj od ovih bolesti. Kako je to česta pojava, sve navedene bolesti su obuhvaćene zajedničkim nazivom histiocitoza Langeransovih ćelija

ili po Lihtenstejinu, histiocitoza X.
Na osnovu podataka iz literature, LCH najčešće zahvata kožu, pluća i kosti, zatim limfoproliferativni sistem CNS u 4% slučajeva a u 10–50% slučajeva prisutan je insipidni dijabetes.
LCH je klasifikovana prema *International Langerhans Cell Histiocytosis* – 2 (LCH2) studiji u tri stadijuma: 1) unifokalni, 2) multifokalni bez zahvtanja slezine, jetre, pluća ili kostne srži kod osoba starijih od 2 godine i 3) diseminovani stadijum sa zahvatanjem jetre, slezine pluća i kostne srži kod osoba mlađih od 2 godine. Dijagnoza LCH se postavlja na osnovu kliničke slike i anatomopatoloških znakova. Prema Udruženju za histiocitoze, postoje tri nivoa dijagnostičke sigurnosti: 1) verovatni, kada je dijagnoza postavljena histološkim nalazom; 2) viši, ako se pomoću markera otkrije da su ćelije pozitivne na S 100 protein, aglutinin kikirikija i alfa D-manozidozu; 3) definitivan, ako ćelijske lezije produkuju CD1 kompleks ili se na elektronskom mikroskopu nađu Birbekove granule. I dok je u početku za definitivnu dijagnozu bio potreban ultrastrukturni dokaz Birbekovih granula (BG), sada se BG mogu demonstrirati imunohemijski ekspresijom langerina. Langerin (CD207) je manoza specifični lecitin, endocitni receptor, koji utiče na formiranje BG. Iako se langerin, kao intraćelijska komponenta, dovodi u vezu sa BG u 100% slučajeva pa se čak LCH definiše kao akumulacija langerina + dendritičnih ćelija u koži, kostima i ostalim tkivima, dijagnostička specifičnost langerina još nije utvrđena, što zahteva dodatna istraživanja. Tako je langerin samo dodatni marker za identifikaciju LCH.
Histološki se u LCH razlikuje nekoliko tipova reakcija: proliferativni, granulomatozni i ksantomatozni. Oni mogu nastati kao takvi, proisteći iz prethodnih, biti prisutni u lezijama drugih i zaceliti u bilo kom tipu.
Diferencijalna dijagnoza uključuje seboroični dermatitis, *Morbus Darier*, *Morbus Hailley-Hailey*, purpuru, skabies, kutanu TBC, hematološka oboljenja, maligne neoplazme, leukemiju, limfome, multipli mijelom, diseminovane ksantome sa insipidnim dijabetesom i kandidozu.
Izbor terapije zavisi od kliničkog oblika bolesti (unifokalni, multifokalni, diseminovani) i aktivnosti (neaktivna ili aktivna). Postoje različite mogućnosti lečenja od lokalne primene kiretaže, radioterapije, kortikosteroida, mehloretamina, kombinacije mehloretamina i PUVA terapije, po potrebi antibiotika, do sistemske imunosupresivne terapije primenom kortikosteroida i citostatika (metotreksat, ciklosporin, azatioprin).
Ishod bolesti zavisi od starosti bolesnika, broja zahvaćenih organa, stepena njihove disfunkcije i od primenjene terapije. Prognoza je bolja kada su zahvaćeni samo koža i kosti i kad bolest počinje od rođenja. Prisustvo insipidnog dijabetesa kod dece povećava rizik za hroničnu bolest, ali ne i smrtnost. Prognoza bolesti kod zahvaćenosti kostiju bez dijabetesa je izvrsna.
Trajne posledice su relativno česte, npr. endokrini problemi, neurološke konsekvence, ortopedske abnormalnosti, gubitak sluha, oftalmološki problemi, kožne promene, fibroza pluća, sekundarni kanceri (akutne mijeloidne leukemije i tiroidni karcinom). Faktori koji predstavljaju povećani rizik za smrtni ishod su: početak u prvim godinama života, hepatosplenomegalija, trombocitopenija i poliostitične promene na kostima. Kod diseminovanih formi postoji mogućnost nastanka limfoma, leukemija i tumora. Smrtni ishod nastaje u 10% slučajeva, kod 30% nastaje remisija a 60% slučajeva bolest dobija hronični tok.
Zaključak: U radu je prikazan bolesnik sa vrlo retkom bolešću, histiocitozom Langerhansovih ćelija, sa multisistemskim lokalizacijama, ali sa relativno povoljnim tokom bolesti i reakcijom na sistemsku kortikosteroidnu terapiju. Bolest podrazumeva postojanje mnogih nepoznanica koje zahtevaju dalja istraživanja na svim poljima, od etiologije i patogeneze do dijagnostike i terapije.

Ključne reči

Hisiocitoza Langerhansovih ćelija; Dijabetes insipidus; Eozinofilni granulom; Pneumotoraks; Ishod lečenja