Langerhans cell histiocytosis (LCH), formerly referred to as histiocytosis X, can be divided into three categories: eosinophilic granuloma, Hand-Schüller-Christian disease and Abt-Letterer-Siwe disease [1]. Clinically it is rarely possible to allocate patients to these subcategories, and often the disease is divided into local and generalized form. About 1200 new cases are annually registered in the U.S., giving an incidence rate of 3-4 in 1,000,000, with a predominance of males [2].

The disease is most common in infants and younger children, but cases where histiocytosis occurs in adults, even the elderly, are not infrequent [3]. Sometimes this is due to diagnostic difficulties, so that the appropriate diagnosis is made in an adult patient. Most scientific reports concern patients aged below 21 [4-6].

The aetiology of the disease is unclear. In pathogenesis a key role is played by Langerhans cells (LC), which are structurally and functionally different from those cells in healthy subjects. An important phenomenon in the pathogenesis of the disease is uncontrolled, monoclonal proliferation of LC, which leads to eosinophil infiltration in tissues and organs [7]. Cytokines and prostaglandins secreted by these abnormal histiocytes can damage organs involved in the disease process, or even to systemic consequences such as anaphylactic shock [8]. Abnormal immunoregulation due to abnormal release of cytokines as well as unidentified infectious agents are considered among the causes of the disease [9]. Due to the fact that the inflammatory infiltrate of histiocytes leads to destruction of the structure of the affected tissue and the disease can progress from a limited to generalized form, some researchers categorize LCH as a borderline disease between inflammatory changes and cancer. The method of treatment of histiocytosis confirms this thesis, as in addition to the commonly used steroids, methods reserved for cancer patients such as surgical excision, radiotherapy or chemotherapy are successfully applied [7].

Symptoms of the disease vary greatly and depend on which organs were infiltrated. The diagnosis of histiocytosis is determined by the characteristic image of histopathological material obtained by biopsy. The earlier the stages of the disease are, the easier it is to identify Langerhans cells, due to fibrosis granulomas which occur in the course of the disease. Then immunohistochemical markers such as S-100 protein, ATPase, alpha-mannosidase, lecithin, and vimentin can be useful, although they are not very specific and serve only as a complement to histopathology. Definitive diagnosis in doubtful cases may be obtained by observing the presence of Langerhans granules (X-body, Birbeck granules) in the electron microscope or the presence of CD1 proteins on the cell surface [10].

Treatment depends on the experience of the institute and in the case of local lesions most often is limited to surgery and/or irradiation. The dose range used in radiotherapy is 2.5-120 Gy (median 10.3 Gy) [10]. In the generalized form steroids are used, often in combination with chemotherapy. First-
line chemotherapy is mainly used in monotherapy within 3-6 months [11]. In case of failure (relapse, progression of the disease), multidrug therapy is applied [7].

Prognosis depends on the extent of the lesion. In the case of limited form the pathological process involves a single organ, most often bones (40-78%). The effectiveness of treatment reaches 97% and spontaneous remissions occur in patients who are not treated [10]. Other common locations of localized form are lymph nodes and skin. For the generalized form the prognosis is worse. It mainly occurs in infants or children under 3 years old and shows multiple organ involvement, leading to their insufficiency [12]. Lesions are mainly localized in the lungs, liver, spleen and central nervous system (usually manifesting as pituitary insufficiency) [13].

**Forms of the disease**

**Osseous Langerhans cell histiocytosis**

The most common symptom is a well-localized bone pain (90%) with tender oedema of the surrounding soft tissue. Pain occurs both day and night [13]. The most frequent sites of granulomas in the skeletal system are the skull (27%), proximal femur (15%) and ribs (10.2%). Bone lesions can be detected by bone scintigraphy or X-ray applied directly to the lesion. Bone infiltration in the X-ray is seen as a sharply defined area of a round or oval shape. Sometimes it is necessary to differentiate from Ewing’s sarcoma. The most common method of treatment is surgical excision of granuloma combined with complementary radiotherapy. Surgical treatment and irradiation are also applied as stand-alone methods. Chemotherapy is used very rarely, when there are many lesions in the skeletal system. The effectiveness of treatment reaches 97% in isolated LCH bone lesions and 90% in the case of LCH involvement of other systems [10]. In the event of local recurrence after surgery, second-line treatment is usually radiotherapy. Olschewski et al. analysed the largest cohort so far in this disease unit, comprising 98 patients with osseous LCH. The study included both patients with isolated and those with multi-focal bone lesions. Mean radiotherapy doses were 2 Gy in a single fractional dose and 24 Gy/g in the total dose. Local control was achieved in the irradiated site in 91%, while complete remission, involving the disappearance of lesions in all systems, was reported in 69% of patients. In 9% of cases there was a recurrence at the irradiated site [14]. The results of various studies confirm the high effectiveness of teleradiotherapy in osseous LCH [15]. In the case of multi-focal bone lesions and multi-system disease it is recommended to combine radiotherapy with systemic treatment, i.e. bisphosphonates, steroids or chemotherapy (indomethacin, vinblastine, methotrexate) [7]. Steroids are also used locally, by injection into the tumour [16].

**Pulmonary Langerhans cell histiocytosis**

This form of the disease often affects adults (90% of cases in patients aged above 15 years). The disease is initially asymptomatic, and later dominated by gradually worsening shortness of breath, general weakness and chronic cough. Sometimes spontaneous pneumothorax occurs in the course of the disease. 90% of pulmonary LCH patients are cigarette smokers [17, 18]. Like osseous LCH, pulmonary LCH often occurs as an isolated system LCH, but in about 40% of cases other organs are involved, most commonly bone, skin and pituitary [10]. First-line therapy for pulmonary LCH is prednisone [18,19]. In case of lack of response to such treatment, chemotherapy (methotrexate, vincristine, cyclophosphamide, etoposide) may be considered [18]. In rare cases, in a well-demarkated mass, lung lobe resection is successfully used. The effectiveness of treatment of this form of histiocytosis is about 85%. Refractory cases end in death due to extensive pulmonary fibrosis with subsequent pulmonary hypertension. Sometimes pulmonary LCH coexists with cancer (most commonly adenocarcinoma of the lung) [20].

**Mucocutaneous Langerhans cell histiocytosis**

The most frequent mucous membranes involved are genitalia and oral mucosa. By principle, it coexists with LCH involving other organs (bones, lungs, pituitary gland, lymph nodes). Mucosal lesions appear as ulcerations, and skin histiocytosis manifests as a maculopapular rash. The most common treatment is radiation as a stand-alone therapy or in combination with surgery or chemotherapy, depending on the severity of extrasosseous lesions [10].

**Pituitary-thalamic axis Langerhans cell histiocytosis**

The disease is manifested as diabetes insipidus. Practically all patients have some other organ involved, most often bone, skin, lungs, or lymph nodes [10]. Due to the multifocality of the lesions, primary treatment is chemotherapy, which is often supplemented with radiotherapy for the pituitary tumour area. If the lesions are limited to the pituitary gland surgery may be considered, usually followed by tumour bed irradiation. All patients with this form of the disease require permanent supplementation of vasopressin. This carries some risk in the form of central pontine myelinolysis resulting from too rapid changes in sodium concentration [21]. Minehan suggests that the effectiveness of radiation therapy increases with the size of the total dose and the response rate is greater when the dose was 15 Gy or more [22].

**Lymph node Langerhans cell histiocytosis**

Infiltration of histiocytes mostly concerns lymph nodes of the head and neck region. This form of the disease is rarely isolated and usually coincides with lesions in bone, skin or lungs. Treatment of the generalized form involves radiotherapy in combination with chemotherapy, whereas the localised form (lymph node lesions) is treated with surgery with supplementary irradiation. In individual cases, these methods were used separately [10].

**The role of radiotherapy**

The role of radiotherapy in the therapeutic process of this disease unit is not fully defined. Most authors recommend radiation therapy in the following cases: relapse or progression of disease, spinal cord compression, pain and the risk of breaking bones, exophthalmos and localized lesions which are nonsurgical due to either cosmetic reasons or an excessive risk of loss of organ function. Presumably, these recommenda-
tions could be extended by using modern methods of radiotherapy, such as intensity modulated radiotherapy (IMRT), but so far no cases treated with this technique have been described. There has been a report of a case of histiocytosis of the temporal bone pyramid treated with radiosurgery, where the tumour was irradiated with 10 Gy/isodose 85% and there was no recurrence of the disease within two years of follow-up [23]. Clinical studies show high radiosensitivity observed in LCH lesions and a favourable tumour response to low total dose [24]. However, optimal irradiation doses have not been determined yet. In the available publications, there is a large range of fractional (0.5-6 Gy/fr.) and total doses (5-50 Gy/h) [25]. Most authors claim that the total dose of 10 Gy/h may be effective and provides good local control, because in 90% of cases it cures single system disease [10, 25]. At the same time, it does not cause such side effects as secondary malignancies, abnormal bone growth or chronic otitis media, which we are particularly concerned about in the case of children [10]. The most important scientific reports on radiotherapy in histiocytosis are listed in Table 1.

**Summary**

Due to the rarity of LCH and the variety of symptoms of the disease, doctors encounter a number of diagnostic and therapeutic difficulties. The implementation of effective treatment is further hindered by the lack of clear standards for the treatment of this disease unit. Moreover, so far there have been no randomized trials which would demonstrate the optimal treatment of histiocytosis [8]. Radiotherapy in histiocytosis seems to be an effective therapeutic option, either as a stand-alone therapy or in combined treatment. It gives a high response rate and good local control, and helps reduce discomfort. This publication aims to draw attention to the need for individualization of radiotherapy in LCH, because there are still no standard algorithms for the use of ionizing radiation in this disease unit. Studies on histiocytosis are in progress. The Histiocytosis Association of America formed in the United States develops methods of treatment, but they mostly concern chemotherapy. Currently irradiation of histiocytosis patients still remains casuistic.

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Number of patients</th>
<th>Age</th>
<th>Location</th>
<th>Radiotherapy</th>
<th>Other treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minehan et al. 1992 [22]</td>
<td>28</td>
<td>no data</td>
<td>hypothalamus, pituitary</td>
<td>total dose 2.14 – 30 Gy</td>
<td>(on average 11.2 Gy)</td>
<td>22% complete remission (CR) 14% partial remission (PR)</td>
</tr>
<tr>
<td>Palmieri et al. 1989 [26]</td>
<td>1</td>
<td>54 years</td>
<td>hypothalamus</td>
<td>total dose 45 Gy/h</td>
<td></td>
<td>CR month after treatment and lasting 12 months</td>
</tr>
<tr>
<td>Ober et al. 1989 [27]</td>
<td>1</td>
<td>18 years</td>
<td>suprasellar area</td>
<td>total dose 22 Gy/10 fr.</td>
<td></td>
<td>CR</td>
</tr>
<tr>
<td>Anonsen and Donaldson, 1987 [29]</td>
<td>24</td>
<td>6 months – 36 years</td>
<td>head and neck</td>
<td>total dose 9-16 Gy, fractional dose 2 Gy</td>
<td>treatment combined with chemotherapy</td>
<td>CR in 67% (6-year follow-up period)</td>
</tr>
<tr>
<td>Cheung et al. 2006 [30]</td>
<td>1</td>
<td>20 years</td>
<td>orbit</td>
<td>30 Gy in divided doses</td>
<td></td>
<td>no recurrence after a 2-year follow-up period</td>
</tr>
<tr>
<td>Stromberg et al. 1995 [31]</td>
<td>1</td>
<td>16 years</td>
<td>sinus sphenoidal</td>
<td>10 Gy/h in 5 fr.</td>
<td></td>
<td>2 months after completion of radiotherapy complete remission of the tumour</td>
</tr>
<tr>
<td>Das et al. 2009 [32]</td>
<td>2</td>
<td>7 years and 8 years</td>
<td>orbit generalised form with orbital involvement</td>
<td>15 Gy/3 fr. 10 Gy/2 fr.</td>
<td>combined with vinblastine dose 6 mg/m² (due to extra orbital involvement)</td>
<td>without evidence of recurrence spleen reduction, reduction in solid lesions in orbital bone (5-year follow-up period)</td>
</tr>
<tr>
<td>Selch and Parker 1987 [33]</td>
<td>22</td>
<td>1-42 years</td>
<td>bones soft tissue of limbs mammary gland suprasellar area</td>
<td>6-15 Gy 15-18 Gy 20 Gy</td>
<td>10-25 Gy</td>
<td>local control in 82% (better in bones – 88%, worse in soft tissue – 69%) median follow-up period 4.5 years</td>
</tr>
<tr>
<td>Selch and Fu 1987 [34]</td>
<td>1</td>
<td>28 years</td>
<td>forearm</td>
<td>10 Gy (electron radiotherapy)</td>
<td></td>
<td>CR (3-year follow-up period)</td>
</tr>
</tbody>
</table>
References


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