

Langerhans cell histiocytosis of bone – a case report and review of the literature

Ewa Wasilewska-Teśluk¹, Zbigniew Szutkowski², Andrzej Kawecki²

Langerhans cell histiocytosis (LCH) is a rare disease. Bones are the most frequent site of this disorder. We report the case of LCH of the skull in stage Ia. A 21-year-old man presented with painful, sharply demarcated, filled-in soft masses defect of the right fronto-temporal region of the skull. The osteolytic lesion was found in this region both in plain radiograms and CT scans. Bone scintigraphy showed increased uptake in that site. Curettage of the lesion of bone and infiltrated meninges was performed revealing a LCH. He received post-operative radiotherapy of 12 Gy in 6 fractions. 5 years after treatment the patient is asymptomatic, with good local control, without any signs of the dissemination of the disease.

We review the literature, present the natural course of disorder and discuss the treatment modalities and results.

Zmiany kostne w histiocytozie komórek Langerhansa - opis przypadku i przegląd piśmiennictwa

Histiocytoza komórek Langerhansa (LCH) jest rzadkim, histologicznie łagodnym schorzeniem, którego istotą jest proliferacja komórek Langerhansa. Kości są najczęstszą lokalizacją zmian. W artykule przedstawiono przypadek histiocytozy w obrębie kości czaszki w stopniu zaawansowania Ia. U 21 letniego mężczyzny stwierdzono w prawej okolicy czołowo-skroniowej bolesny, ostro odgraniczony ubytek, wypełniony miękką patologiczną masą. W wykonanym zdjęciu RTG i KT głowy opisano osteolityczną zmianę tego obszaru. Badanie scyntygrafii kości wykazało wzmożone gromadzenie znacznika w tym rejonie. Wyłęczkowano naciezoną kość i zajęta przez ciągłość oponę twardą. W badaniu histopatologicznym rozpoznano LCH. Chorego napromieniono pooperacyjnie. Otrzymał 12 Gy w 6 frakcjach. W 5 letnim okresie obserwacji po leczeniu stwierdzono dobrą kontrolę miejscową oraz nie wykazano cech rozsiewu choroby.

W przeprowadzonym przeglądzie piśmiennictwa przedstawiono przebieg schorzenia oraz omówiono metody, wskazania do leczenia oraz jego rezultaty.

Key words: histiocytosis, Langerhans cell, bone, treatment modalities

Słowa kluczowe: histiocytoza, komórka Langerhansa, kość, metody leczenia

Introduction

Langerhans Cell Histiocytosis (LCH) is a rare disease with unknown etiology. The incidence of LCH is estimated to be 0.2-0.5 cases per 100.000 per year. Bone is the most frequent site of this disease. It is usually considered to be a disease of childhood. Many patients are 1-15 years old, however the diagnosis frequently is made in adults and many cases of childhood onset progress into adult life. LCH has a widely variable disease course and clinical presentation with the capacity for spontaneous remission or chronic disease. There is persistent controversy surrounding the terminology of histiocytic disorders. Illnesses characterized by clonal

proliferation of histiocytes in various tissues were traditionally labeled eosinophilic granuloma of bone, Hand-Schuller-Christian syndrome, and Letterer-Siwe disease. Lichtenstein integrated these entities under the title histiocytosis X [1]. The Histiocyte Society now recommends the term Langerhans Cell Histiocytosis to unify this disparate group of disorders. The staging system proposed by Greenberger et al. [2] is applied in many reports.

The relative rarity of LCH has meant that treatment and outcome data have been based largely on small case series and single case reports. No prospective controlled studies have been performed so the choice of the most appropriate treatment in everyday clinical practice may be difficult. We report the case of Langerhans cell histiocytosis in stage Ia according the staging system by Greenberger [Table I] and review the literature of treatment modalities in stages Ia and Ib to make therapeutic decisions easier.

¹ Public Hospital of Pulmonology and Oncology in Olsztyn

² Head and Neck Department

The Maria Skłodowska-Curie Memorial Cancer Center and Institute of Oncology, Warsaw, Poland

Table I. The staging system proposed by Greenberger et al.1981 [2]

Stage I	a) Single monostotic bone lesion b) Multiple lesions in one or multiple bone
Stage II	>24 months of age at diagnosis and having one or more of the following systems involved: diabetes insipidus, teeth, gingivae, lymph nodes, skin, mild lung involvement (i.e., infiltrates seen on chest radiograph without pulmonary symptoms or gross consolidation), focally positive bone marrow
Stage III	a) Age <24 months at diagnosis with any of the systems involved in stage II b) Age >24 months with involvement of liver and/or spleen, massive nodal involvement (nodes > 5 x 5 cm in several sites above or below diaphragm), honeycomb lung (major involvement in all areas with apparent fibrosis), bone marrow packed
Stage IV	Spleen > 6 cm (palpable below costal margin) and fever >1 month with or without any or all of the above systems involved
Stage V	"Special" monocytosis in peripheral blood > 20% of differential cell count, in addition to stage III or IV

Case report

A 21 year-old male patient was referred to the Centre of Oncology in September 1997. He complained of 2 months of stubborn pain of the skull in the right fronto-temporal region. At first this pain occurred during pressure, then it became constant, with site- swelling. There was no history of trauma of this region. In clinical examination a defect of 5 cm, sharply demarcated, was palpable in the right frontal region. The lesion was filled with soft masses. The patient had no neurological symptoms. An osteolytic lesion in right frontal bone was found in radiograms. A CT scan of the head revealed a large, irregular destructive lesion of the right frontal and partially temporal bone, which was filled with abnormal masses. There was no sign of brain tissue involvement. Bone scintigraphy showed increased uptake in this region. The blood tests all were in normal range.

Two weeks later an open biopsy with curettage of the affected bone with part of the roof of the orbit was performed. The infiltrated part of the meninges was also curetted. Pathologic examination of the involved bone by routine hematoxylin and eosin morphology revealed Langerhans cell histiocytosis (eosinophilic granuloma – diagnosis was confirmed by Professor Mioduszevska). Four weeks later the patient still complained of pain in this region and persistent disease within the meninges was also suspected and therefore postoperative radiotherapy was performed. The patient received a total dose of 12 Gy to the affected area, 2 Gy per fraction, using 4 MV photons. Three-dimensional treatment planning was used. The irradiated volume included the post-operative bed with a 1 cm margin.

A CT scan obtained 3 months later did not show any signs of progression, CT scans performed during follow-up period were also normal. For 5 years now the patient is in a good performance status, asymptomatic, with good local control. No signs of dissemination are

observed. He has no late post- irradiation complications and no neurological abnormalities.

Discussion

The staging system of Langerhans cell histiocytosis proposed by Greenberger et al [2] has classified lesions primary limited to the bone as stage Ia or Ib (Table I). About 80% of patients show bone lesions at diagnosis and about 40% of them have the disease limited to the bones [3].

The lesions are benign in their histology, but with respect to their osteolytic character lead to the destruction of bone. LCH has a predilection for specific bones. The flat bones are involved most frequently and among them the skull is commonest. The other sites frequent reported are: mandible, maxilla, femur, scapula, ribs, vertebrae, pelvis (Table II). It remains unclear why the skull is so favored by this disease. These tumors rarely appear in the small bones of the hand and foot. The multifocal form of LCH is uncommon.

Table II. Anatomic distribution and frequency of bone lesions in LCH

Parietal	18.1%
Frontal	9.5%
Occipital	9.5%
Temporal	7.5%
Sphenoid	2.8%
Maxilla	0.9%
Mandible	13.3%
Scapula	1.9%
Clavicle	1.9%
Humerus	2.8%
Ribs	4.7%
Spine	14.2%
Pelvis	5.7%
Femur	6.6%

Pain is the most common presenting symptom in pediatric and adult patients. Children more commonly develop localized soft tissue swelling than do adults. The sharply demarcated bone defect is often palpable. Patients with mandibular or maxillary involvement usually seek medical attention for loose teeth and /or oral ulcers. Otitis media and diminished hearing are common presenting symptoms in patients with mastoid lesions. Fractures of the affected bones can appear as a first sign of the disease.

The presented patient had typical signs of disease but all of them are non-characteristic. Also additional studies are non-specific for the diagnosis of LCH [4]. Bone lesion is often detected by plain-film radiography and characterized by a lytic defect without evidence of reactive sclerosis [3]. Biopsy of the lesion is necessary to establish the diagnosis.

Pathology demonstrates infiltration of bone by clusters of characteristic histiocytes with admixture of morphologically related giant cells, eosinophils and lymphocytes. Specific Langerhans granules (Birbeck's

granules) can be identified in the histiocytes by electron microscopy. Immunohistochemistry shows strong S-100 protein, HLA-DR and CD-1a surface antigen positivity by the histiocytosis X cells [5, 6]. The necessity of the immunohistochemistry or ultrastructural examination for the diagnosis of LCH is controversial. Many authors believe that definitive diagnosis can be established by routine hematoxylin and eosin morphology especially when correlated with radiological and clinical data [8]. When immunohistochemistry or ultrastructural analysis is used as definitive tool for establishing a pathologic diagnosis it can lead to misdiagnosis [7, 8]. Use of the histopathologic parameters to predict prognosis in LCH has produced conflicting results. Some studies report significant eosinophilia as a favorable prognostic indicator [9] but the others show no feature correlated with survival [4].

The treatment of LCH is usually reserved for the patients with symptomatic lesions [10]. Asymptomatic patients should be observed because some lesions appeared to resolve spontaneously [11, 12]. The lesion responds well to the most treatment modalities e.g. curettage, excision, irradiation and infrequently resulted in functional impairment [13-20]. Therapeutic strategy depends on the size, localization of the lesion and age of the patient. There is no objective indication that the kind of therapy effectively altered the course of disorder or prevented its progression [3, 4, 21].

The generally accepted treatment of choice for solitary bone lesions, especially for these affecting calvaria, is surgical excision when the lesion is readily accessible. Data of many authors indicate that surgical curettage is a very successful treatment. If necessary, excision is combined with concurrent bone grafting. However some authors report the higher risk of local recurrence after surgery alone [2, 22]. Persistence symptoms of disease, or expansion of the lesion after surgical intervention, may respond to the subsequent radiotherapy [23]. In presented case we doubted whether curettage of the meninges was a sufficient procedure, while the persistent pain was also alarming. For these reasons it was decided that surgery should be followed by irradiation.

Primary radiotherapy in LCH of bone is recommended in the following cases: symptomatic, with lesions large in size, with strong pain, potential for fracture, multifocal in one bone and in circumstances in which surgical resection might result in significant functional or health risk [3, 13, 16, 18-20, 23-25]. Modern radiation modalities, such as stereotactic radiotherapy, can be useful especially in cases with intracranial base lesions if there is incomplete resolution of the symptoms after stereotactic biopsy or during recurrence [26-27]. This method allows to use sufficient doses of radiation to the target volume with sufficient precision to avoid vital structures at cranial base. Because there are no large prospective series with adequate follow-ups on the effectiveness or possible complications of stereotactic

radiotherapy for this lesion such a modality must be used cautiously, especially in children.

Doses of radiotherapy recommended in literature range from 2 Gy to 30 Gy in conventional fractionation schedule [2, 18, 24, 25, 28]. Greenberger et al. report 95% local control using total dose 4-20 Gy [25, 28]. Similar results are reported by Anonsen et al. [24] where total doses of 6-20 Gy allow to obtain a local control of 88%. According to these reports we delivered 12 Gy to the surgical bed. Acc. to some authors [3, 13, 16] the dose of radiotherapy depends on the age of the patient. In the group under 10 years of age it has been observed that lesions are very radiosensitive and the recommended dose range from 6-10 Gy. It is also reported that patients aged over 18 do not achieve such good results of radiotherapy as children (local control 72% vs 100%, respectively). The total dose in this group of the patients should be over 20 Gy, but in these reports the number of reported adult cases was very small and the results have not been confirmed by other investigators on larger number of the patients [4].

The morbidity of radiation therapy is rather slight because of the low dose of irradiation but in the child group it is extremely important to remember that disturbances in bone growth are observed [11, 13]. Also cases of scoliosis are described after radiotherapy of the vertebral column. It is difficult to state whether this complication is associated with irradiation or with surgery or both [13]. Some authors report secondary malignancies in field, related with low dose of radiotherapy [29]. In the reported case we do not observed any late effects of radiotherapy.

The treatment of LCH primary limited to the bone with chemotherapy is associated with poor results (only 25% responders) and after this adjuvant radiotherapy is recommended in normal doses [30, 31]. Chemotherapy based on multidrug programs is used rather for disseminated disease or in cases with recurrent disease with progression from solitary to multifocal bone lesions [18, 29]. Recent literature supports the idea that steroid injection with 50-150 mg of methylprednisolon is effective in the management of recurrent or expansive lesions [32, 33].

Results of treatment are good. Local control of 85-100% of bone lesions and overall survivals of 90-100% after radiotherapy or surgery is reported with a median follow-up of 10 years [3, 13, 18, 29]. Control of the bone lesions required: resolution of pain, absence of uptake on radionuclide scan and reconstruction of bone shadow on plain radiography. Reports in the literature [23, 33] describe post irradiation bony healing at an average 8 months (range 6-34 months).

Prognosis in LCH is different in relation to the extension of the disease and is favorable with only one site of the disease and in patients over 2 years of age, while it is the best in patients with solitary bone lesions [4, 18]. Kilpatrick et al. report that even in case of multifocal bone lesions some 80% of patients achieve long disease free survival after treatment but they have a higher risk of

internal organ involvement in the future [4, 18, 34]. The presented patient remains in the most favorable group, however in adults new bone lesions appear more frequently (15%) than in children (5%) during the follow-up period [4]. Most of the skeletal recurrences occur within 2 years of the previous diagnosis. The jaw and mastoid bones are the most common sites of skeletal recurrences. The interval between the original diagnosis and recurrence ranged from 2 months to 13 years, also completely new bone lesions, solitary or multiple, can occur from 1 month to 33 years. Because of that long-term follow-up is recommended in LCH [13, 18, 19]. The 5-year follow-up free of recurrence in our case is insufficient to state that the patient is already cured. Several authors [23, 35] have reported excellent results when a second course of irradiation is applied to recurrent or persistent bone lesions, but in those series the initial dose was inadequate. Others [12] maintain that re-irradiation proved to be of little benefit. Progression from Ia and Ib stage to the disseminated disease is observed in 30% of the patients.

Conclusion

The treatment result of the presented case of LCH of bone is good in a 5-year follow-up, but long-term follow-up is necessary. Although the bone lesions in LCH respond well to most treatment methods, optimal therapy is still unknown because no prospective controlled study has been performed. No current modality treatment does effectively alter the course of the disorder or prevents its progression.

Ewa Wasilewska-Teślak MD

Public Hospital of Pulmonology and Oncology in Olsztyn
10-357 Olsztyn, str. Jagiellońska 78
ewawt@maxi.pl

References

- Lichtenstein L. Histiocytosis X. *J Bone Joint Surg [Am]* 1964; 46: 76-90.
- Greenberger JS, Crocker AC, Vawter G. Results of treatment of 127 patients with systemic histiocytosis Letterer-Siwe syndrome, Schuller-Christian syndrome, multifocal eosinophilic granuloma. *Medicine* 1981; 60: 311-38.
- Selch MT, Parker R. Radiation therapy in the management of Langerhans cell histiocytosis. *Med Pediatr Oncol* 1990; 18: 97-102.
- Kilpatrick SE, Wenger D. Langerhans cell histiocytosis (Histiocytosis X) of bone. *Cancer* 1995; 76: 2471-84.
- Eriksen B, Janinis J. Primary histiocytosis X of the parieto-occipital lobe. *Hum Pathol* May 1988; 19: 611-4.
- Ladisch S Langerhans cell histiocytosis. *Curr Opin Hematol* 1998; 5: 54-8.
- Malone M: The histiocytoses of childhood. *Histopathology* 1991; 19: 105-19.
- Gonzales CL, Jaffe ES: The histiocytoses: clinical presentation and differential diagnosis. *Oncology* 1990; 4: 47-60.
- Risdall RJ, Dehner LP. Histiocytosis X: prognostic role of histopathology. *Arch Pathol Lab Med* 1983; 107: 59-63.
- Chu T. Histiocytosis syndromes in children. *Lancet* 1987; 2: 208-9.
- Muller P, Alleman J Spontaneous remission in histiocytosis X with lung and bone involvement. *Schweiz Med Wochenschr* 1991; 121: 1140-4.
- Broadbent V, Pritchard J. Spontaneous remission of multi-system histiocytosis X. *Lancet* 1984; 1: 253-4.
- Wiegel T, Sommer K Radiotherapy of the solitary and multiple eosinophilic granuloma of the bone (stage I). *Strahlenther Onkol* 1991; 167: 403-6.
- Bayazit Y, Sirikci A. Eosinophilic granuloma of the temporal bone. *Auris Nasus Larynx* 2001; 28: 99-102.
- Greis PE, Hankin FM. Eosinophilic granuloma. The management of solitary lesions of bone. *Clin Orthop* 1990; 257: 204-11.
- Cassady JR. Current role of radiation therapy in the management of histiocytosis X. *Hematol Oncol Clin North Am* 1987; 1: 123-9.
- Gulam I, Pegan B. Langerhans cell granulomatosis in an adult: a 22-year follow-up. *Eur Arch Otorhinolaryngol* 2001; 258: 203-7.
- Howarth DM, Gilchrist GS. Langerhans cell histiocytosis: diagnosis, natural history, management, and outcome. *Cancer* 1999; 85: 2278-90.
- Rawlings CE Wilkins RH. *Neurosurgery* 1984; 15: 155-61.
- Appling D, Jenkins HA. Eosinophilic granuloma in the temporal bone and skull. *Otolaryngol Head Neck Surg* 1983; 91: 358-65.
- Womer RB, Beverly R. Healing rates of treated and untreated bone lesions in histiocytosis X. *Pediatrics* 1985; 76: 286-8.
- Marinez F. Solitary eosinophilic granuloma of the pediatric skull and spine. The role of surgery. *Child Nerv Surgery* 1991; 7: 448-51.
- Pereslegin IA, Ustinowa U. Radiotherapy of eosinophilic granuloma of bone. *Int J Radiat Oncol Biol Phys* 1981; 7: 317-21.
- Anonsen CK, Donaldson SS. Langerhans cell histiocytosis of the head and neck. *Laryngoscope* 1987; 5: 573-78.
- Greenberger JS, Cassady JR. Radiation therapy in patients with histiocytosis: management of diabetes insipidus and bone lesions. *Int J Radiat Oncol Biol Phys* 1979; 5: 1749-55.
- Brisman J, Feldstein N. Eosinophilic Granuloma of the clivus: case report, follow-up of two previously reported cases, and review of the literature on cranial base eosinophilic granuloma. *Neurosurgery* 1997; 41: 273-8.
- Dunbar SF, Tarbell NJ. Stereotactic radiotherapy for pediatric and adult brain tumors-preliminary report. *Int J Radiat Oncol Biol Phys* 1994; 30: 531-9.
- Chowdhury AD, Nagappan R. Eosinophilic granuloma of mandible in an adult (case report). *Australas Radiol* 1989; 33: 406-8.
- Willis B. Disease course and late sequel of histiocytosis 25-year experience at the university of California. *J Clin Oncol* 1996; 14: 2073-82.
- Oberman HA. Idiopathic histiocytosis. A clinicopathologic study of 40 cases and review of the literature on eosinophilic granuloma of bone. *Pediatrics* 1961; 38: 307-28.
- Shelby H, Sweet R. Eosinophilic granuloma of the temporal bone: medical and surgical management with special reference to dose levels employed. *South Med J* 1983; 76: 65-70.
- Cohen M, Zornoza J. Direct injection of methylprednisolone in the treatment of solitary eosinophilic granuloma of bone: a report of 9 cases. *Radiology* 1980; 136: 289.
- Capanna R, Springfield DS Direct cortisone injection in eosinophilic granuloma of bone: a preliminary report on 11 patients. *J Pediatr Orthop* 1985; 5: 339.
- Heyd R: Radiotherapy in Langerhans cell histiocytosis. 2 case reports and review of the literature. *Rontgenpraxis* 2000; 53: 51-61.
- Slater JM, Swarm OJ: Eosinophilic granuloma of bone. *Med Pediatr Oncol* 1980; 8:151-4.

Paper received: 11 November 2002

Accepted: 16 January 2003