Langerhans cell histiocytosis of the parietal bone with epidural and extracranial expansion – case report and a review of the literature

Histiocytoza komórek Langerhansa kości ciemieniowej z ekspansją nadtwardówkową i zewnątrzczaszkową – opis przypadku i przegląd piśmiennictwa

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Abstract

Langerhans cell histiocytosis is a rare neoplasm that belongs to the histiocytic and dendritic cell neoplasm group according to the 2008 WHO classification. It has been defined as neoplastic proliferation of Langerhans cells that express CD1a and S-100 proteins and have Birbeck granules on the ultrastructural examination. Clinical presentation and behaviour are heterogeneous and can range from a solitary lytic bone lesion with a favourable course to a fatal disseminated leukaemia-like form, with a wide spectrum of intermediate clinical presentations between these two extremes. Here, we present a case report of a solitary calvarial lesion in an adolescent boy along with a review of the literature. Presenting features, initial diagnostic evaluation and treatment protocol of a unifocal monosystemic calvarial location of LCH are presented.

Key words: Langerhans cell histiocytosis, case report, treatment protocol.

Streszczenie

Histiocytoza komórek Langerhansa to rzadki nowotwór należący wg klasyfikacji WHO z 2008 r. do grupy nowotworów komórek histiocytarnych i dendrytycznych. Jest ona definiowana jako nowotworowy rozrost komórek Langerhansa wykazujących ekspresję białek CD1a i S-100 oraz obecność ziarnistości Birbecka w badaniu ultrastrukturalnym. Klinicznie jest schorzeniem heterogennym obejmującym szerokie spektrum pacjentów, poczynając od chorych z pojedynczym ogniskiem osteolitycznym i korzystnym rokowaniem aż do chorych ze źle rokującym rozsiewem ogólnoustrojowym przypominającym białaczkę. Poniżej zaprezentowano opis pojedynczego ogniska osteolitycznego w kościach sklepistości czaszki obejmujący obraz kliniczny, zakres zalecanych badań diagnostycznych oraz schemat postępowania w przypadkach pojedynczych ognisk osteolitycznych kości czaszki wraz z przeglądem piśmiennictwa.

Słowa kluczowe: histiocytoza komórek Langerhansa, opis przypadku, schemat postępowania.

Introduction

The first clinical description of "Langerhans cell histiocytosis" (LCH) was published in 1895 by Thomas Smith. He described a case of a four-year-old child who died from pertussis and whose autopsy revealed erythematic changes on the skin and a few osteolytic foci in the calvaria [1]. Three years later, Paul Langerhans described epithelial cells with long, dendrite-like processes. Each cell may have several processes and no pig-

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ment. Langerhans suggested that they might originate from bone marrow and be a part of the immunological system [1,2]. It is well established now that Langerhans cells reside mainly in the epidermis (3-8% of epithelial cells), and sparsely in the main skin, digestive system and genital epithelium. Dendritic Langerhans cells along with B type lymphocytes and macrophages are responsible for antigen presentation to T lymphocytes [3]. Upon contact with an antigen, they are activated and moved to a regional lymph node where specific clones of T lymphocytes are generated [3]. Langerhans cells play an important role in hypersensitivity induction present in contact dermatitis.

Lichtenstein named Langerhans histiocytosis as histiocytosis X (or less commonly as Langerhans granulomatosis) in 1953. The letter "X" emphasized the unknown aetiology of diseases such as acidophilic granulomatosis, Hand-Schüller-Christian or Abt-Letterer-Siwe disease [4]. In 1987 the Writing Group of the Histiocyte Society replaced the name "histiocytosis X" with the current term "Langerhans cell histiocytosis" [5].

Currently, Langerhans histiocytosis belongs to the histiocytic and dendritic cell neoplasm group, according to the 2008 WHO classification of lymphoid and haematopoietic tumours. It has been defined as neoplastic proliferation of Langerhans cells that express CD1a and S-100 proteins and have Birbeck granules on the ultrastructural examination [6].

According to ICD-O (International Classification of Diseases – Oncology) Langerhans cell histiocytosis has several subtypes:

1. Langerhans histiocytosis NOS (not otherwise specified) (SNOMED: 9751/1).
2. Langerhans histiocytosis, unifocal (SNOMED: 9752/1) formerly called acidophilic granulomatosis – the most common form of LCH. Most of the cases were described in bones and lungs; infrequently it can develop in the digestive system, salivary glands and thymus. Usually present in older children and adults, carries best prognosis [7-10].
3. Langerhans histiocytosis, multifocal (SNOMED: 9753/2), formerly Hand-Schüller-Christian disease – usually present in 2-to-5-year-old children, common symptoms include multiple granulomas in the calvaria, jaw and mandible (less often in other bones), exophthalmos due to granulomas in the orbital bones and retrobulbar space and diabetes insipidus resulting from pituitary/hypothalamus dysfunction attributable to histiocytic infiltrations [7-10].
4. Langerhans histiocytosis, diffuse (SNOMED: 9754/3), formerly Abt-Letterer-Siwe disease – the rarest form of LCH, first presentation usually in newborns and young children; changes are present in multiple organs, patients promptly develop respiratory distress syndrome, anaemia, leucopenia, haemophilia; prognosis is poor [7-10].

LCH is a rare disease; annual morbidity averages 2 to 5 cases per 1 000 000 children [2,3,7,9,11]. Annual incidence of unifocal form of the skeletal system averages 2 cases per million [8]. Eighty percent of cases appear among the Caucasian race, the disease being infrequent among Africans [1,2,7,9,11]. The incidence is much higher among males (M : F ratio up to 6 : 1) [2,9,11,12].

LCH occurs at all ages from infancy up to senility with the peak incidence between 2 and 4 years of age [3,9,12]. It has been estimated that 75% of LCH cases are younger than 20 years of age [8].

LCH can develop in tissues of various origins [9]. The disease usually involves the skeleton, skin, lymph nodes, lungs, liver, spleen, thymus, and central nervous system [2,10]. Approximately 60-70% of cases appear on the head and neck [10] and 70% of cases involve the skeleton [13]. LCH foci can be present in any bone but calvaria, mandible, ribs and pelvis are the most common [2, 12, 13]. Presence in the long bones, usually tibia, brachial bone and femur, has been described as well [1,11].

Case report

A 14-year-old boy, a secondary school student, noticed a tender tumour in the left parietal region while washing his head. He was admitted to the Department of Neurological Surgery four weeks later in a very good condition. According to the patient and his parents, the tumour had enlarged over this period. In the left parietal region there was a palpable bone defect approximately 3 cm in diameter. It was painful at palpation. No neurological deficits were observed, and no significant medical history, including head trauma, was reported. Family history was non-significant. On skull plain X-ray, a sharply demarcated osteolytic lesion with a mean diameter of 3 cm in the left parietal bone was discovered. Multidetector computed tomography (CT, GE Healthcare, Milwaukee, WI, USA) examination was then performed.

CT examination confirmed a sharply emarginated osteolytic lesion of the parietal bone (Fig. 1). There were

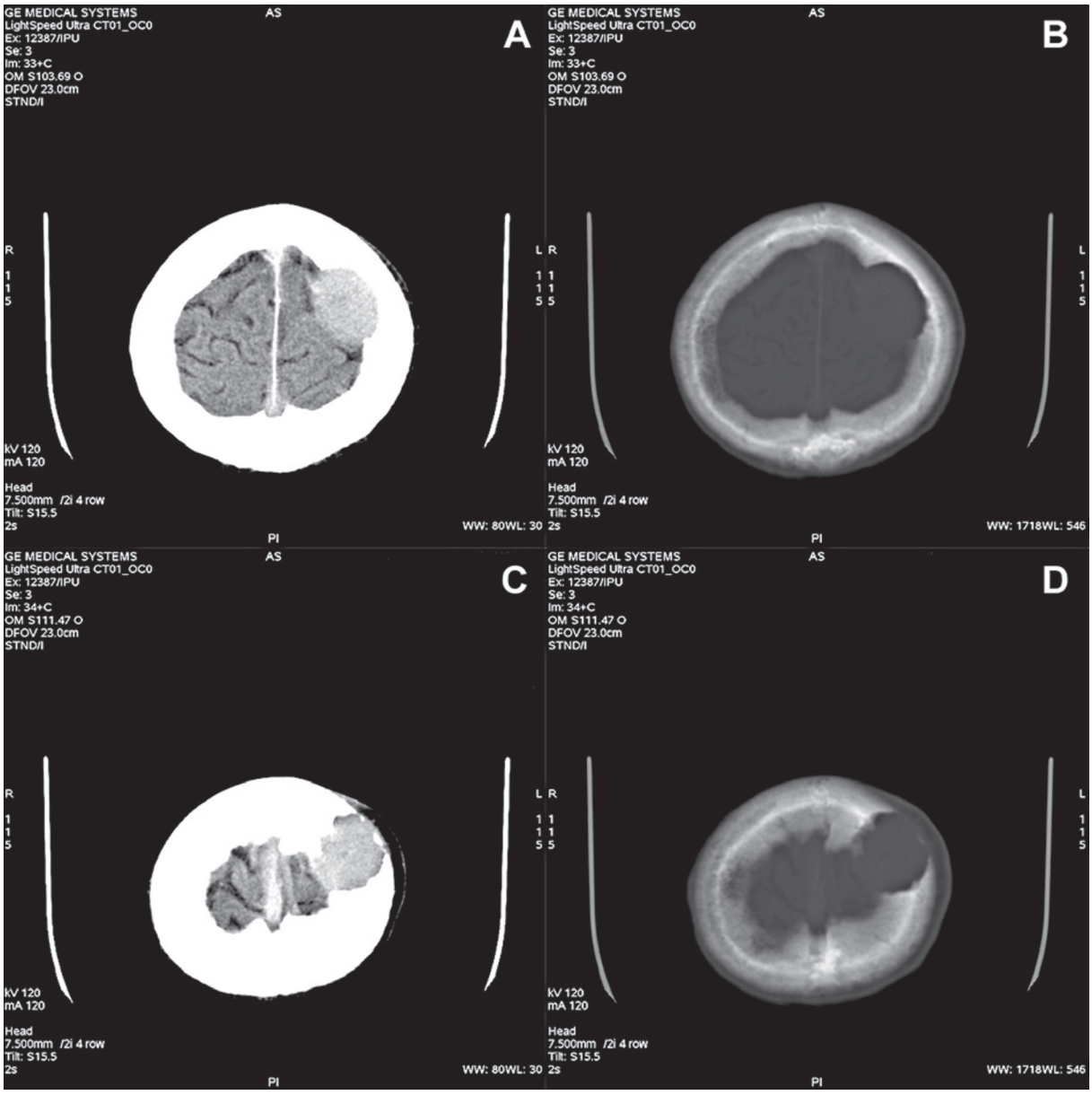

Fig. 1. Langerhans cell histiocytosis lesion of the parietal bone as seen in a soft tissue (A, C) and bone (B, D) window. Changes in the adjacent brain and round pathological contrast enhancement patterns are present. Sharply demarcated osteolytic changes without surrounding bone reaction are also evident

no other signs of bone disease in the entire skull. Cortical and subcortical bone structure was unchanged. No periosteal reactions were noted.

On contrast-enhanced CT scans there were signs of brain compression seen as a round lesion of pathological enhancement pattern, but no brain oedema.

Based on the described radiological features of the bone deficit, an initial diagnosis of LCH with rare extra- and intracranial expansion was proposed. The entire panel of laboratory tests, i.e. blood, urine and coagulation analysis along with biochemical serum analyses (electrolytes, protein levels, urea, creatinine, glucose, cholesterol and liver enzymes), was normal. Chest X-ray was described as normal. The patient underwent surgical treatment. Under general anaesthesia a grey-red tumour of approximately 3.5 × 2.5 × 3 cm was removed. It had destroyed the bone, with bilateral, extra- and intracranial expansion. The tumour was easy to dissect from the skin, soft and fragile, extensively bleeding. On the dural side this tumour was much sturdier and

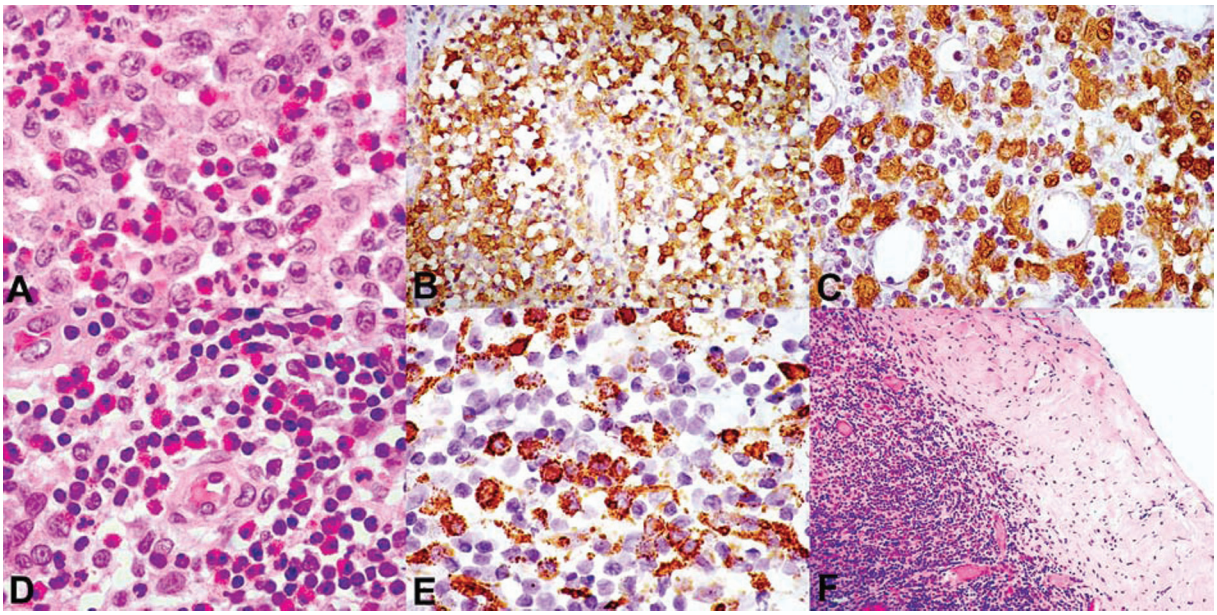

Fig. 2. Histopathological samples show distinct features of Langerhans cell histiocytosis. Langerhans cells with characteristic folded and indented nuclei and blurred nucleoli, hardly copious and sparsely eosinophilic cytoplasm (A), positive membrane staining for CD1a (B) and S-100 (C) are present. On top of Langerhans cells inflammatory cell infiltration that consists mainly of eosinophilic granulocytes, small lymphocytes and to a smaller extent neutrophilic granulocytes, plasmocytes and macrophages, including single polynuclear granulocytes, is present (D). Diffused macrophages show positive cytoplasmic reaction with CD68 antibody (E). Histiocytosis infiltration reaches the dura but does not penetrate it (F)

had a visible capsule. It compressed the dura, but still it was easy to detach from it. Macroscopically the dura was not infiltrated by the tumour. In a 2-cm zone around the tumour the bone was grey, soft and bleeding. Surgical removal included a 1-cm margin of healthy bone. The resulting deficit was approximately 7 cm in diameter. Cranioplasty was performed with a Codubix® plate.

Samples for intraoperative examination were collected during surgery. Subsequently they were frozen at –22°C, sectioned into 8-μm thick sections and stained with haematoxylin and eosin (H&E). Postoperative samples were fixed in 10% buffered formalin and processed for paraffin embedding. Next, 3-μm thick sections were cut and stained with H&E or immunohistochemistry for CD1a, S-100 and CD68 using Dako-Cytomation antibodies (M0721, 1 : 50; Z0311, 1 : 400 and M0876, 1 : 50, respectively) and the EnVision visualization system.

Intraoperative examination revealed presence of cells with Langerhans cell morphology with inflammatory infiltration made up of acidophilic granulocytes and lymphocytes. Afterwards, the pathologist suggested Langerhans histiocytosis. Postoperative histopathological examination confirmed the initial diagnosis. It disclosed focal presence of Langerhans cells with characteristic folded and indented nuclei and blurred nucleoli. Cell cytoplasm is hardly copious and sparsely eosinophilic (Fig. 2A). On top of Langerhans cells infiltration of inflammatory cells, mostly acidophilic granulocytes, small lymphocytes and to a lesser extent neutrophilic granulocytes, plasmocytes and macrophages with single polymorphonuclear cells were present (Fig. 2D). Histiocytosis permeation was adjacent to the dura but did not penetrate it (Fig. 2F). Langerhans cells showed positive membrane staining for CD1a (Fig. 2B) and nuclear staining for S-100 (Fig. 2C). Disperse macrophages revealed a positive cytoplasmic reaction with CD68 antibody (Fig. 2E). Histology samples from macroscopically invaded bone that surrounded the tumour revealed bone tissue architecture.

Six days after surgery the patient was discharged in a good condition. The consulting paediatric oncologist found no other LCH foci. Frequent check-up and observation was recommended. Currently, the patient feels well 3 years after treatment; he attends school and enjoys sport activities. On follow-up CT examination which was performed after 3 years, there was no evidence of new osteolytic foci in the entire skull, and also the brain adjacent to the bone lesion was without evidence of pathology (Fig. 3).

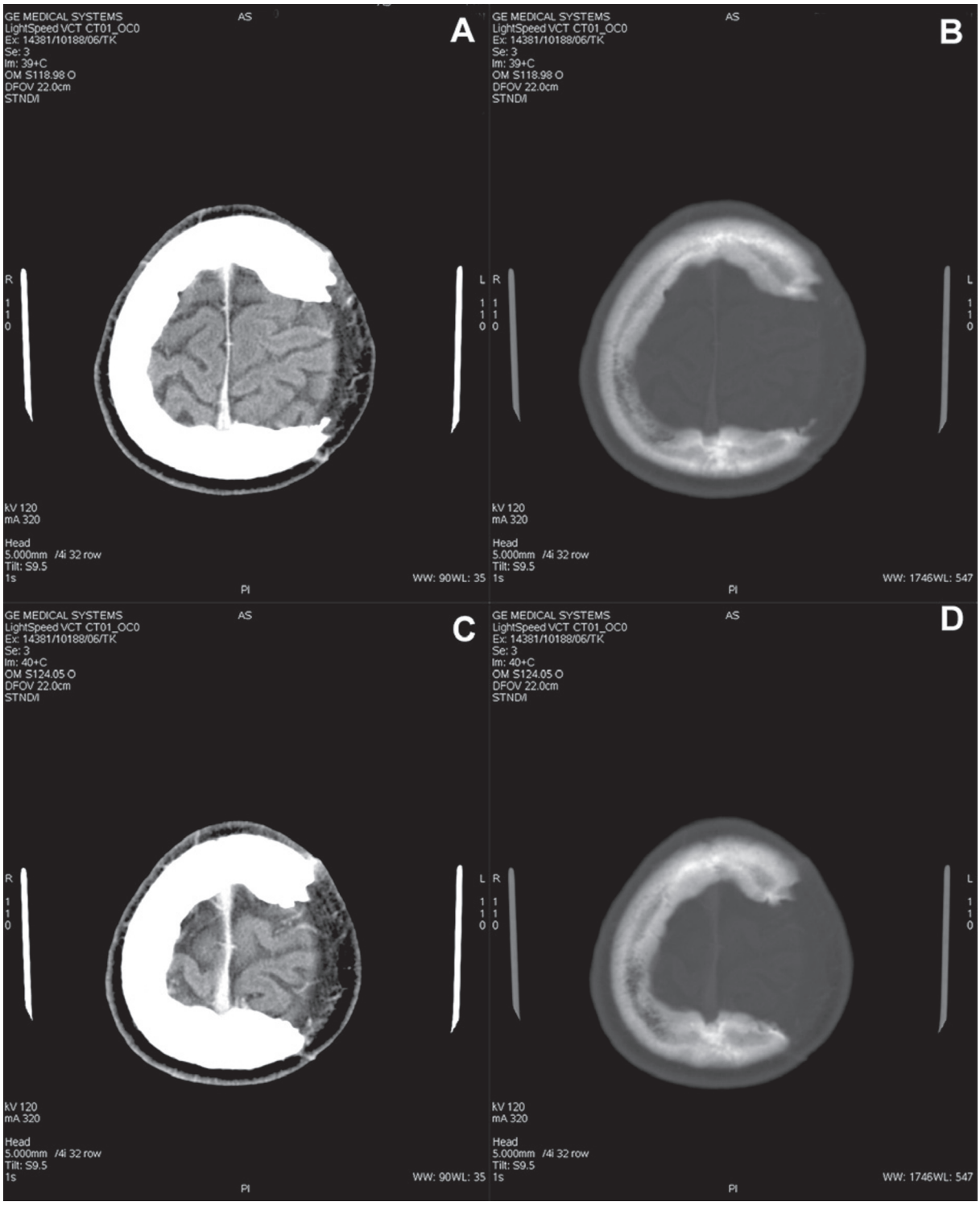

Fig. 3. Post-operative follow-up scans in bone window (B, D) demonstrate no evidence of disease in the vicinity of the previous lesion. The Codubix plate, visible as a thin object of very low density, can be seen in the left parietal bone. Soft tissue window (A, C) scans present normal structure of adjacent brain

Discussion

LCH aetiology is still unclear, and abnormal proliferation of Langerhans has been attributed variously to neoplastic propagation, immunological defect or viral infection [1,3,12,14]. LCH rarely, if ever, reveals mitotic figures [3].

One of the hypotheses links LCH development with cytokine activity. Cytokines produced by lymphocytes and monocytes influence cell proliferation and differentiation into immunocompetent or haematopoietic lines. Overexpression and/or deficient cytokine activation control may play a role in the pathogenesis of LDH. Data exist showing that tissues involved in LDH have higher levels of cytokines [3]. It has been proven that GM-CSF and TNF-α play an important role in the generation of Langerhans cells from haematopoietic stem cells [15].

Viral aetiology of LCH is suggested by often diffuse growth and described spontaneous remissions of the disease. Ebstein-Barr virus and human herpes virus 6 and 8 (HHV6 and 8) [1] as well as cytomegalovirus, adenoviruses, papovaviruses, human T-cell leukaemia type 1 and 2 viruses and HIV infections have been accused [16]. Higher incidence of LCH has been described in populations of patients with infectious disease history in early childhood, after exposure to chemical solvents and with family history of thyroid diseases [1,17]. Rare cases of familiar LCH have also been described [18]. Additionally, a relationship between diffuse form of Langerhans histiocytosis and acute lymphoblastic leukaemia and malignant lymphomas has been proven. A strong association with tobacco and marihuana addiction has been found [16]. Data exist showing a relationship between head trauma and LCH in 33 to 50% of cases. However, a direct causal link has not been proven yet [19,20]. Importantly, the medical history of our patient in this aspect was negative.

The most common clinical symptoms of LCH of the skeletal system are pain and oedema. Other symptoms depend on the bone involved. In the case of the temporal bone clinical signs suggest middle ear infection or mastoid process infection. Presentation with mandible and jaw involvement usually entails disengagement of the teeth and their loss. Compressive fractures are the most frequent sign in LCH with vertebral body involvement [21]. The clinical symptoms presented by our patient – expanding, painful tumour of the skull – are analogical to those previously described for this location [1,3,19,20,22]. Asymptomatic cases of LCH with bone involvement have been described, mostly in children younger than 15 years [1].

On radiological examination, sharply demarcated punch-out osteolytic lesions in the skull are characteristic. They are of various diameter (typically several cm), and sometimes reactive osteosclerosis of the margins is visible [1,7]. Changes in the skull bone are sometimes described as a hole in a hole, since both lamina are non-homogeneously affected [21]. Endosteal erosion is common, as is a linear periosteal reaction. Such lesions may simulate infection or low-grade neoplasms and early biopsy is advisable, as the diagnostic histological features are often obscured by healing [23].

Very helpful in the diagnosis of the disease is computed tomography examination in thin slices, in a bone reconstruction kernel, especially when small osteolytic foci are suspected, since they might not be visible on standard plain skull X-ray [1].

A few similar cases have been described previously. Fujimura *et al*. [22] described a case of a 15-year-old boy with LCH that led to occipital bone destruction and intracranial penetration with dura compression. No extracranial component was present. Lee *et al*. [14] presented a case of an 8-year-old boy who was admitted to hospital with symptoms of increased intracranial pressure after head injury. CT examination revealed epidural haematoma over an occipital lobe overlaid by an osteolytic area with extracranial expansion of abnormal tissue. Mut *et al*. [20] treated a 9-year-old boy for headaches with nausea and vomiting. Skull X-ray disclosed the presence of a well-demarked osteolytic region in the left occipital region overlaying the transverse sinus while subsequent CT proved the presence of bilateral epidural haematomas in occipital regions with a solid tissue mass both intra- and extracranially. Despite the aforementioned relationship between LCH and head trauma, the acute presentation of a solitary LCH lesion of the skull with an epidural haematoma is extremely rare and only five cases have been reported in the literature. The causes of epidural haematoma in these cases were suggested to be a rupture of the tumour cyst communicating with the epidural vein and the sinus, intratumoural bleeding rupturing into the epidural space, or tumour-related erosion of the sinus [20].

The study by Rawlings *et al*. [19], one of the largest series of eosinophilic granulomas ever published (26 cases), described intracranial expansion only in one case. Basic laboratory tests for our patient were normal. Accordingly, Rawlings *et al*. reported [19] that only one patient out of 26 described had a higher fraction of acidophilic granulocytes.

Final LCH diagnosis is possible based only on histopathology. The most important step involves identification of Langerhans cells. They are usually 10-15 μm in size with characteristically folded or multilobular nuclei with typical grooves. Chromatin is delicate with absent nucleoli and slight membrane. Eosinophilic or light cytoplasm has a variable number of lysosomes [15,22]. In bone histiocytosis, Langerhans cells usually form groups, rarely present as diffuse architectonic configurations [21]. Langerhans cells are mixed with inflammatory cells, predominantly acidophilic granulocytes. Small lymphocytes, plasmocytes and neutrophils are also present [1,12,18]. Early changes usually have large numbers of Langerhans cells while late changes have fibrosis and foam macrophages. Osteoclast-type polynuclear macrophages might be present focally [12,15,16]. Birbeck cytoplasmic granules with their typical tennis racket-like shape are a characteristic feature of Langerhans cells [1,18,22]. It has been suggested that they originate from cell membrane [16]. They are present in 1 to 75% of Langerhans cells in a given change. Early changes usually have more Birbeck granules [15].

Atypical nuclei with variable numbers of mitotic figures are sometimes present [12]. Ki67 proliferation index averages 10% (2-25%) [15].

In LCH diagnostics immunohistochemistry is helpful. Diagnosis in our patient was made based on characteristic morphology and confirmed with positive stains for CD-1a, S-100 and CD68. Neoplastic Langerhans cells morphologically as well as immunophenotypically resemble healthy, epidermal Langerhans cells (antigen presenting cells) but are not identical. Normal Langerhans cells in contrast to neoplastic cells are negative for PLAP (placental alkaline phosphatase) [15].

LCH treatment has been significantly modified over the last few decades towards less aggressive therapeutic modalities which can be attributed to the increasing number of publications describing the benign character of the disease. Nonetheless, various clinical scenarios of LCH should be considered, from a rapid evolution of clinical signs with unfavourable outcome in case of systemic involvement up to a very slow, benign progression. Although it is very rare, spontaneous LCH regression has been described in several case reports [3,12,17,19]. Recurrences sometimes occur, even after surgical removal of bone foci [19]. Therapeutic modalities include surgery, radiotherapy, chemotherapy and hormone therapy. These methods may be used separately or in combination [13,24].

Surgical treatment, successful in our case, is advocated for isolated changes, where total surgical removal is feasible [12,24]. Intervention was undertaken based not only on rapid progression of the tumour but also on the increased risk of expansion towards the midline and parietal part of the superior sagittal sinus along with the possibility of seizures and left-sided hemiparesis resulting from parietal lobe compression due to the intracranial pathological mass.

Presently, the importance of surgical removal of macroscopically changed bone adjacent to the LCH focus is unclear since local management has been proven to be effective [8]. Some argue, however, that non-radical resection might result in higher incidence of relapses and advocate extensive surgery with healthy bone margin removal [10,23,24]. In our opinion all feasible cases should be treated with extensive tumour dissection along with healthy bone margin due to the low risk of recurrence.

Non-surgical cases that include non-accessible or multifocal lesions are treated with local management modalities that involve local steroid injections and radiotherapy as well as systemic chemotherapy. Local methylprednisolone injections have proved to be an efficient treatment for relatively small lesions not feasible for surgery or multiple circumvent lesions, which has been documented by multiple case reports or small series of patients. To our best knowledge, no systematic analysis of treatment results has been carried out, however. Radiotherapy is restricted to cases where local administration of steroids is not feasible. The suggested dose varies from 5.5 to 6 Gy. Severe complications may be related to this treatment – secondary tumours and encephalomalacic changes after head irradiation have been reported [3]. Chemotherapy is restricted to diffuse cases of LCH, usually after local steroid administration. Chemotherapeutics used in LCH treatment include vincristine, methotrexate, mercaptopurine and etoposide [3,24].

It has been three years since our patient's surgery. He is in a very good condition, continuing his education, and control CT scans have not revealed any new foci. Single, surgically accessible bone changes have been described in the literature as those with the best prognosis [13].

Disclosure

Authors report no conflict of interest.

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