Journal of Cranio-Maxillo-Facial Surgery 42 (2014) 93–100

Contents lists available at SciVerse ScienceDirect

Journal of Cranio-Maxillo-Facial Surgery

journal homepage: www.jcmfs.com

Case report

Langerhans cell histiocytosis in childhood – Review, symptoms in the oral cavity, differential diagnosis and report of two cases☆

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ARTICLE INFO

Article history:
Paper received 27 February 2013
Accepted 25 March 2013

Keywords:
Langerhans cell histiocytosis
Infants
Dermatitis
Bone lesions
Granulomatous gingivitis
Periodontitis

ABSTRACT

Background: Langerhans cell histiocytosis is a rare disease characterized by monoclonal proliferation and migration of special dendritic cells. This disease primarily affects bones, but occurs less frequently in other organ systems or may manifest as a multisystem disease.
Case reports: Extraoral and intraoral symptoms of Langerhans cell histiocytosis are described in a 13-month-old female and a 5-month-old male infant.

Dermatitis was found on the scalp, abdomen, flexures and in intertrigineous areas in both patients. The intraoral examination of the 13-month-old infant showed premature eruption of all maxillary deciduous molars, loosening and significant damage of periodontal tissues (gingivitis with bleeding, swelling of palatal mucosa, periodontal pockets) resembling severe periodontitis.

In the oral cavity of the 5-month-old predentate infant bilateral swellings of maxillary alveolar mucosa with deep ulcerations were seen.

The oral and skin symptoms in both infants were indications for biopsy. Langerhans cell histiocytosis was confirmed histologically and immunohistochemically.
Conclusion: Oral findings in Langerhans cell histiocytosis may be the only clinical symptom of the disease; therefore the role of dentists in establishing diagnosis is very important.

1. Introduction

Histiocytic diseases originate from mononuclear histiocyte cells of the macrophage system (Huang and Arceci, 1999). Under normal conditions, histiocytes are a part of the reticuloendothelium. Proliferation of their precursors in bone marrow causes monocytic leukaemia, proliferation of immature histiocytes in tissues is typical for histiocytic medullary reticulosis, and proliferation of mature histiocytes was called histiocytosis X (Lichtenstein, 1953). This term was introduced by Lichtenstein in 1953, who characterized the disorder as proliferation of histiocytes of unknown aetiology. The term "histiocytosis X" expresses its unclear aetiology and whether this disease should be classified as neoplastic, inflammatory, or fall among the lipid thesaurismoses. Lichtenstein also stated that these are three clinical entities with identical histologic characteristics. In the past, a number of terms were used for the disease. Apart from the already mentioned histiocytosis X those are also eosinophilic granuloma, Letterer–Siwe disease, Hand–Schuller–Christian syndrome, Hashimoto–Pritzker disease, self-healing histiocytosis, skin histiocytosis, Langerhans cell granulomatosis, Langerhans cell eosinophilic granulomatosis, II type histiocytosis, or non-lipid reticuloendotheliosis (Larralde et al., 1999). The current term used for the disease is Langerhans cell histiocytosis (LCH), and the origin of the disease is explained as arising from monoclonal neoplastic proliferation and migration of special dendritic skin cells that were first described by Paul Langerhans in 1868 and are called

☆ The study was not supported by research grants or any other sources.
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http://dx.doi.org/10.1016/j.jcms.2013.03.005

Langerhans cells after him (Leonidas et al., 2003). The most recent research supports the concept of immunological aberrations (Hicks and Flaitz, 2005; Abla et al., 2010). Langerhans cells are an important part of the immune system. They originate in bone marrow, are derived from CD 34+ stem cells and are transported by blood into the skin, lungs, thymus, lymph nodes and the gastrointestinal tract mucosa (Kilborn et al., 2003). The typical histopathological feature of Langerhans cells is the presence of Birbeck granules in the cytoplasm that were discovered a century after the cells themselves. According to the WHO classification (Favara, et al., 1997), Langerhans cell histiocytosis falls among the group of malignant histiocytic diseases.

LCH is a disease affecting primarily bones, less frequently it occurs in other organ systems or manifests as a multisystem disease. LCH may manifest as a solitary bone or lung lesion, its symptoms may be limited to skin (Lau et al., 2006), or it may be a life-threatening disease involving many organs (skin, bones, lymph nodes, lungs, liver, spleen, endocrine glands, and central nervous system) (Larralde et al., 1999).

The cause of LCH is unclear (Weitzman and Egeler, 2008). Among possible aetiological factors are neonatal infections, a skipped vaccination during childhood, exposure to the effect of solvents, and thyroid diseases. The disseminated form of the disease is related to acute lymphoblastic leukaemia and malignant lymphomas. The lung form in adult patients is almost always linked to tobacco or marijuana smoking. There is a rare congenital form and genetic influence is also considered.

LCH is found in both children and adults. Its is most frequent in children between 1 and 3 years of age but it can be found in newborns as well as in the 9th decade of life (Broadbent et al., 1994; Henter et al., 2004; Minkov et al., 2009). In older children between 5 and 15 years of age it usually manifests as an isolated bone lesion. The incidence of LCH is 0.4 in 100 000 children up to 15 years of age. Boys are affected twice as often as girls; in adults, the ratio is reversed (Broadbent et al., 1994).

Currently, LCH is classified, according to the spread of the disease, into the unifocal and multifocal form (Pritchard and Broadbent, 1994; Huang and Arceci, 1999; Satter and High, 2008). The unifocal form is usually benign, affects older children and adults and is characterized by a solitary bone lesion, usually in the skull or vertebrae (Weitzman and Egeler, 2008). Less frequently, this form affects lymph nodes, skin, or lungs. According to the older terminology, the unifocal form corresponds to eosinophilic granuloma. The multifocal form of LCH (earlier called Hand–Schüller–Christian disease) is more aggressive, affects infants and is characterized by multiplex bone lesions and the involvement of the adjacent soft tissues. The disseminated form of multifocal and multisystem LCH (previously Abt–Letterer–Siwe disease) carries an unfavourable prognosis and affects infants, manifesting itself in skin, lymph nodes, gastrointestinal tract, bones, and less frequently in the central nervous system. The disseminated form of LCH usually presents clinically as a lack of appetite, a failure to thrive in children, or weight loss, tiredness, high temperature, upper respiratory tract infections, and middle ear infections (Skoulakis et al., 2008). Other symptomatology depends on which organs have been affected. The multisystem form of LCH is currently divided into high-risk diseases when vital organs (i.e. the spleen, lungs, liver, and the haematopoietic system) are involved and low-risk diseases without vital organ impairment.

The first manifestations of LCH are often skin changes (Broadbent et al., 1994; Weitzman and Egeler, 2008; Bashir et al., 2011). Typical is seborrhoea-like dermatitis in the scalp and dermatitis on the body, which manifests as skin erythema, infiltration, and the formation of yellow-brown desquamating papulae (Satter and High, 2008). Rarely, LCH may manifest in newborns only as skin lesions spontaneously disappearing within weeks or months (Lau et al., 2006). Rarely dermatitis connected with dystrophic changes of nails has been described (Mendes et al., 2006).

LCH most often affects the skull and the jaws, the long bones of the upper extremities, ribs, the pelvic bones and vertebrae (Glotzbecker et al., 2002). The involvement of bones is usually followed by swelling and pain in the affected area, however it may also be asymptomatic (Broadbent et al., 1994). If the lesion is located in the wall of the orbit, it may cause exophthalmos, in the middle ear it leads to deafness (Surico et al., 2000; Jalil and Hin-Lau, 2009). Osteolytic lesions in the jaws occur mostly in the mandibular molar region, where they may be followed by soft tissue swelling, pathological jaw fractures and excessive teeth mobility. The typical radiographic changes caused by LCH are osteolytic lesions with irregular borders that may be single or multiple (Mitomi et al., 2005). The bone defects may have sclerotic margins.

Bone marrow involvement may cause pancytopenia, which is usually followed by hepatosplenomegaly and indicates a serious prognosis of the disease. The pulmonary form of LCH manifests by tachypnoea, spontaneous pneumothorax and in later phases even emphysema may occur. Diabetes insipidus, growth disorders, and central nervous system damage symptoms are other LCH manifestations (Glotzbecker et al., 2002).

The diagnostic of the disease is based on the typical clinical symptoms, on clinical imaging and on biopsy of the pathologically altered tissues (Azous et al., 2005; Kaste et al., 2007; Minkov et al., 2009). Histopathologically, the typical finding is an infiltrate consisting of Langerhans cells, macrophages, lymphocytes, eosinophilic granulocytes and giant cells. Langerhans cells have quite large eosinophilic cytoplasm and the nuclei are of an irregular shape, often with a groove ("coffee beans") (Duda-Szymańska and Wiezchniewska-Lawska, 2009; Henter et al., 2004). Considering immunohistochemistry, it is possible to demonstrate CD1a antigen on the surface of Langerhans cells, the presence of S100 protein, and by means of electron microscopy the presence of Birbeck granules in the cytoplasm (Chu and Jaffe, 1994).

The treatment of LCH is based on chemotherapy, radiotherapy and the administration of corticosteroids (Henter et al., 2004). Isolated bone lesions are removed surgically. The prognosis of LCH depends especially on the number of organs involved and whether the spleen, lungs, liver, or the haematopoietic system are infiltrated. The patient's age is a less important prognostic factor (Kilborn et al., 2003).

2. Case report 1

In the spring of 2003, a 13-month old female toddler was referred to the Paediatric Dentistry Department of Faculty Hospital in Pilsen, Czech Republic, by a dental practitioner. There was no relevant family history. The child came from the second pregnancy, was born in the expected term and the delivery was without complications. The birth weight was 4300 g, the length was 51 cm. Since birth, there were evident skin changes in the child's perineal region, especially in cases of perspiration. Erythema and papoulopustulae appeared. From 1 month of age the child allegedly suffered from candidosis in the oral cavity and, since the fourth month, demonstrated failure to thrive. In the ninth month of age, a purulent exudate from the external auditory canal appeared due to an infection with *Pseudomonas aeruginosa*. The symptoms in the skin and oral cavity both worsened. The child was hospitalized in a local hospital and received both topical and systemic treatment with antimycotics and antihistaminics. During the hospitalization, the child was examined by a dental practitioner, who referred the patient to our department.