Langerhans Cell Histiocytosis: Its Oral and Maxillofacial Dimension

SUMMARY

This paper reviews clinical, histological and pathological characteristics of Langerhans Cell Histiocytosis (LCH) in relation to its oral and maxillofacial interest. For purposes of better examination, LCH is differentiated into 3 syndromes: Hand-Sculler-Cristian (HSC) disease, Letterer-Siwe (LS) disease and Eosinophilic Granuloma (EG). Abnormal proliferation of histiocytic cells with Birbeck granules is found in all 3 of them.

The cause of LCH is related to abnormal proliferation of Langerhans Cells (LCs) which are mononuclear phagocyte system cells concentrated in oral gingival sulcular and junctional epithelium. LCH appears to attack patients of any age, especially young children. Its predilection sites are the maxilla and the mandible. In LS disease, ulceration of oral mucosa, premature loss of teeth, suppurative or haemorrhage, all are common symptoms. Moreover, in HSC soreness, generalized stomatitis and bone destruction are found. EG preserves all the above characteristics and underlines a delayed healing after extraction and pathologic fractures. The diagnosis is served by radiographic images, which show solitary intraosseous lesions, defined periphery and multiplicity of alveolar bone lesions, bone sclerosis or root resorption. Early diagnosis improves the prognosis and effectiveness of the treatment. The weapons against LCH are: surgery, corticosteroids and alkylating agents.

Keywords: Langerhans Cell Histiocytosis; Hand-Sculler-Cristian Disease; Letterer-Siwe Disease; Eosinophilic Granuloma; Alveolar Bone; Bone Destruction

Introduction

The term Histiocytosis X was introduced by Lichtenstein in 1953 for a group of diseases that produce 3 syndromes with similar clinical and histopathological features1: Hand-Sculler-Cristian (HSC) disease, Letterer-Siwe (LS) syndrome and Eosinophilic Granuloma (EG). Since all 3 diseases have an abnormal proliferation of histiocytic cells with characteristic Birbeck granules, a differentiation between them has been abandoned and the term “Langerhans Cell Histiocytosis” (LCH) is commonly used nowadays2.

LCH develops in childhood as well as in adulthood3. It can involve many organ systems but primarily affects bone, skin, lymph nodes, lung, liver and spleen, endocrine glands and nervous system4.

Its dental interest derives from its special histopathological characteristics referring to the oral and maxillofacial region, as well as its relationship to certain dental pathologies. This comprises the reason of a review of all the aforementioned syndromes, which can be proven useful either for general dentists or for specialized ones.

Role of Langerhans Cells in Oral Pathology

Langerhans Cells (LCs) are bone marrow derived cells that belong to the mononuclear phagocyte system and (or) dendritic system5. In gingiva they are present in 3 areas: (1) the oral gingival epithelium; (2) the sulcular...
epithelium; (3) the junctional epithelium. They are located in the suprabasal and spinous layers of the oral gingival and sulcular epithelium. In the junctional epithelium, 2 types of Langerhans cells can be observed. The first type with a spherical morphology possesses a few short dendrites and is weakly stained for Castleman’s Disease (CD) 1a Thymocyte (T) 6 antigen. The other type exhibits dendrites of moderate length and number with varied fluorescence intensity against CD1a T6 antigen. These heterogeneities could represent different stages of a dynamic process leading to an accumulation in number of LCs.

Much experimental evidence has shown that there are differences both in LC numbers and in surface antigen expression between healthy and diseased gingiva. Consequently, LC could represent “key” cells in pathogenesis and development of periodontal disease. Moreover, the relationship between an increased number of LCs and plaque accumulation was demonstrated in men during experimental gingivitis. More LCs were found in the inflamed gingiva in comparison to healthy gingiva from the same patients. Many studies also suggested an increase of the LCs in moderate gingival inflammation, but a decreased number of LCs in periodontitis compared with the controls. The numerical diminution of LCs in the passage from gingivitis to periodontitis reveals an important role of these cells in the pathogenesis of gingival disease.

In contrast to gingivitis and periodontitis, a satisfactory explanation of the proliferation of LCs in the lesions of LCH is still missing, although its appearance is definitely related to this proliferation.

**Histology (Microscopy)**

For purposes of a better examination of the histology of the disease, its differentiation into the 3 syndromes we mentioned in the introduction could be critical. Consequently:

1. **Hand-Schuller-Cristian disease (chronic disseminated)** comprises of multiple lesions in the bones and soft tissues initially, with some visceral lesions developing later. Except of the skin lesions, which are typical nodules in flexures, a crusted scalp rash mimicking seborrheic dermatitis may also be seen. Oral lesions include gingivitis, ulcerations and destructive granulomas involving the mandible and the maxilla. Gingival tissue shows a dense infiltrate (histiocytic) throughout most of the connective tissue. The nuclei of the histiocytes are, for the most part, regular with some vacuolisation. There is a significant number of eosinophils scattered throughout much of the infiltrate.

2. **Letterer-Siwe disease (acute disseminated):** It demonstrates an excessive proliferation of histiocytes that accumulates in tissues. It can also include nodular foci. Oral manifestations such as gingivitis and ulcers as well as oral bleeding and eventual loss of teeth are present.

3. **Eosinophilic granuloma of bone (chronic focal):** It can be solitary or multifocal.

LCs are associated with eosinophils and often other types of granulocytes in variable number. LCs have pale, vesiculated, weakly eosinophilic cytoplasm and nuclei that appear folded or lobulated. Mitotic activity is typically absent. Eosinophils may be scattered among the LCs or histiocytes. By electron microscopy, Birbeck granules may be seen in LCs. They appear as lamellar plates with a central striated line. They occasionally have a terminal vesicular dilatation giving them a racquet shape.

**Incidence and Dental Predominant Sites**

LCH is considered a childhood disease, but the diagnosis is often made in adults as a likely evolution of the juvenile form. It seems to be more frequent in males than in females, with a reported ratio ranging from 1:1 to 4:1. In adults, there is a much greater variation with a slight predominance of female patients. It is very interesting to notice that in a review of 1120 patients, Hartman reported oral involvement in 10% of the cases.

a. **LS disease:** There is no special information about the incidence of the LS disease. It particularly affects infants or young children, under the age of 2 years, predilection sites being the alveolar parts of the maxilla and the mandible;

b. **HSC disease occurs mainly in children or adults. The maxilla and the mandible may be the first structures to show signs of this condition.** It commonly affects older children, between ages of 5 and 10, but may be seen in any group;

c. **EG constitutes about 50% to 60% of all Histiocytosis X cases.** It is a disease with an incidence of 1 new case/350000-2 million per year. Approximately 75% of all patients are below 20 years of age. Predominant locations are the flat bones, with frequent involvement of the mandible in patients less than 20 years old. Individuals over the age of 50 are uncommonly affected.

**Oral Manifestations**

In case of the LCH, the first manifestations and symptoms occur in the mouth and identification is necessary for the diagnosis of the disease. The leading
symptom of the LCH within mandibular and maxillary bones is pain, which sometimes is misdiagnosed as a marginal infection\(^2\). There is also loosening of teeth, as common presenting complains of the patients, as well as necrotising and ulcerating defects of the mucosa and jaw swelling\(^3\). The ulcerations are accompanied by granulomatous exophytic tissue in the areas of the attached gingiva in the maxilla, extending to the palate anteriorly and posteriorly\(^4\).

In clinical cases without bone involvement, palatal, lingual and vestibular bilateral ulcerations were recorded in molar maxillary and mandibular regions. Submucosal nodules were also recorded in the superior and inferior frontal gums\(^5\). Except from pain,, a burning sensation and spontaneous and mechanically induced bleeding during oral hygiene procedures were noticed. The upper and lower third molar regions were more inflamed and painful\(^6\).

More specifically referring to each entity of the disease separately, we can look into the following signs and symptoms of oral involvement of the LCH:

1. The LS syndrome - ulcers of oral mucosa, diffuse destruction of bone, premature loss of teeth, haemorrhage, foul breath, suppuration;  
2. The HSC disease - generalised stomatitis, soreness, haemorrhage, foul breath, ulceration and necrosis of the oral mucosa, progressive bone destruction of the alveolar process, loosening and premature loss of teeth, facial asymmetry;  
3. The EO - periodontitis localised in an otherwise healthy dentition, loss of alveolar bone with the area of destruction replaced by soft tissue, extending to the palate anteriorly and posteriorly\(^7\).

In the EO, pathologic fractures may occur especially in the long bones\(^8\). It is also useful to underline the fact that in the HSC disease, typical lesions of the disease involve the cranial bones, the eyes (exophthalmia) and the pituitary gland (diabetes insipidus), whereas in the LS disease, the syndrome is characterised by lymph node, spleen and liver involvement, with a severe clinical course\(^9\).

**Diagnosis - Radiographic Image**

An effort to find out the diagnosis of LCH would be surely incomplete and insecure without taking into consideration the radiographic image of the disease. LCH presents as localised punched out radiolucencies with no calcification and no sign of sclerosis or reaction at the borders. There may be severe alveolar bone resorption producing an appearance of teeth “floating in space”. Panoramic radiograph and computerised tomography is used for this purpose\(^10\). Moreover, in the EO of the jaws, the borders of the lesions are mostly well delineated, whereas in the HSC disease the lesions appear as round, oval or irregular areas with sharp margins. In the jaws, these areas look like cysts.

Concentrically, several studies showed at least 7 radiographic characteristics occurred frequently with LCH of the jaws, such as the solitary intraosseous lesions that are located outside the alveolar process, the multiplicity of “alveolar bone” lesions or the well defined periphery. The periphery of the lesions of LCH in the jaws is considered to be well defined but uncorticated.

Another radiographic characteristic is the scooped out shape. This occurs because bone destruction starts below the crest of the alveolar process. Usually, a portion of the superior aspect of the crest of the alveolar bone is maintained at the mesial and distal margins of the area of destruction and produces the scooped out appearance. Bone sclerosis is a common observation in inflammatory lesions of the jaws, and the fact that it appears frequently in the alveolar bone lesions might be explained by communication of the lesions with the oral cavity, that results in a superimposed infection. Periosteal new bone is observed in intraosseous lesions. The identification of the presence of this thin layer of bone is highly dependent on the projections available for study. Finally, root resorption associated with lesions of the LCH is always very slight\(^11\).

It is necessary to notice the need of biopsies along with immunohistochemistry to confirm the diagnosis of the LCH and ascertain the nature of cells involved in the lesions detected\(^12\). The infiltration cells in LCH are S-100, CD1, CD4 and Human Leukocyte Antigen (HLA)-DR positive. Electron microscopy will also detect the presence of Birbeck granules\(^13\).

**Differential Diagnosis**

The puzzle of a successful diagnosis is completed by the fulfilment of the differential one: clinically, the LCH is difficult to be distinguished from bone metastases, osteomyelitis or even malignant tumours. The final diagnosis of the LCH can be made only by histology. Morphologically, the cells are characterised by lobulated nuclei, basophilic nuclei and eosinophilic cell plasma. By immunohistochemistry, tumour cells usually express S-100 and CD-1a. The detection of cytoplasmic inclusion bodies known as Birbeck-Breastman granules is a typical characteristic of the LCH\(^14\). Besides histopathologic diagnosis, a bone scintigraphy is mandatory to exclude or to detect additional lesions. A common extraosseous manifestation can be found in the lungs\(^15\).

The clinical appearance and course of the presenting lesions usually suggest a differential diagnosis including other causes of chronic ulceration, such as trauma, necrotizing sialometaplasia, tuberculosis or deep fungal.
infection. Although T-cell lymphoma might manifest as an ulcer, growth is very rapid and progressive, with destruction of underlying bone. In contrast, in the LCH, the ulcer may maintain the same appearance for months.

Another differential diagnostic possibility is melanoma, although the presence or not of pigmentation allows clinically to distinguish it from the LCH.

As mentioned above immunohistochemistry is very useful to confirm diagnosis. S-100 positivity might prove sufficient, in the appropriate light microscopic setting and with negative immunohistochemical studies for Human Melanoma Black (HMB)-45, leukocyte common antigen (LCA) or CD30.26.

**Prognosis**

Generally, the prognosis for patients with the various forms of LCH has improved steadily with the advent of an early and successful diagnosis and the evolution of a more effective treatment. However, clinical prognosis of patients will become worse with the growing number of involved organs, with growing number of oral dysfunctions, with rapid disease progression, with limited treatment response and decreasing age of the first disease manifestation.22

Early onset is associated with bad prognosis. In younger children, before the age of 3, the disease progresses rapidly and is fatal. Late onset is associated with milder forms of the disease. Prognosis is excellent in isolated EO of bone, which may heal spontaneously. There is a 90-95% recovery. Prognosis is also good to very good in multiple EO’s restricted to bone.15 Moreover, soft tissue involvement is associated with bad prognosis.

In bone and soft tissue involvement, the mortality rate is 50%. In HSC disease the mortality rate has been estimated to be 30%. In LS disease the outcome is usually fatal. Death usually ensues within 1-3 years from bone marrow depletion, toxicity, sepsis and exhaustion. In HSC death usually ensues from opportunistic infections, intracranial extension and anaemia. Long survival is an exception in LS disease. In infants, it is very acute and rapidly fatal.

**Treatment**

The treatment of LCH is dependent on the lesion size and the degree of tissue involvement, and thus differs from unifocal or multifocal (monostotic or polyostotic) presentations.28 Surgery, in particular for solitary bone lesions, is still the treatment of choice. Following radiation therapy, patients frequently experience pain relief; however a complete remission is seldom achieved.29 In some large or multifocal lesions, it is necessary to follow surgical curettage with radiation therapy.

Oral lesions are treated by topical corticosteroids (betamethasone dipropionate 0.05% and sometimes in combination with topical antifungals (miconazole oral gel) to avoid oral Candida infections. The patient undergoes frequent oral professional hygiene sessions to minimize mucosal and periodontal damage.

Particularly, in the LS disease with a poor prognosis, therapy consists of steroids used in conjunction with a cytotoxic drug. Alkylating agents provide a more definite suppressing action. Vinblastin has proved to be a medication of value. Moreover, in recent years, drug treatment, especially in cases of multiorgan involvement, gains more and more importance. Such drugs are 2-deoxycoformin, etoposide, vinblastin, mercaptopurine, methotrexate, predisolone, interferon, and interleukin.14

**Concluding Remarks**

As it is well understood, the most important parameter in the analysis of a disease as a scientific issue is its cure. Generally speaking about cure of the LCH, not only in jaws but as a multi-system threat, very interesting questions are born such as: is LCH a malignant or an inflammatory disorder? Should all LCH patients receive therapy?

Concerning the first question, clinical data is ambiguous. Clonal expansion of LC, but not lesional T-cells, was defined by the human androgen receptor (HUMARA) DNA assay as well as T-cell receptor analysis.32 These findings have led many aficionados of LCH to strongly state that it is a malignant proliferation. Given certain CGH/LOH results from clonal versus nonclonal LCH, the controversy on the malignant nature of the LCH seems far from settled.33,34

About the second question (whether should all LCH patients receive therapy), the studies show distinct conclusions. The simple answer is no when including single skull lesions in the frontal, parietal or occipital areas and other skeletal lesions. However, it would be a mistake to say that LCH is a slowly progressive disease in which a “wait and see” approach should be adopted. This is especially true of pulmonary, jaw and skin disease of adults. Smoking cessation may be effective in some patients with lung disease, but they need to be monitored carefully since the insidious progression of cystic changes and fibrosis can rob the patients of vital lung function.

Heroic surgery for jaw disease results in disfigurement and loss of teeth, whereas a 6 month course of viblastine and prednison can cure the disease and allow reformation of the bone with no loss of dentition. Finally, painful and disturbing perineal ulcers...
of LCH in women are best treated with chemotherapy or thalidomide, not radiation. This whole description reveals the importance of the existence of such questions as the above. These prove to be the basis of further evolution of scientific studies about certain subjects of great medical concern.

References


Correspondence and request for offprints to:

Petros Papadopoulos
Th. Sakellaridi 25a
542 48 Thessaloniki, Greece
E-mail: peterpap77@yahoo.gr