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ORAL CAVITY AND SYSTEMIC DISEASES – LANGERHANS CELL HISTIOCYTOSIS

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ABSTRACT

Langerhans cell histiocytosis (LCH), previously known as histiocytosis X is a rare disease of unknown ethiology, characterized by intense and abnormal proliferation of bone marrow-derived histiocytes (Langerhans cells). It can present both local and systemic manifestations involving bone, skin and mucosal tissues and internal organs.

Oral manifestations could be the first or the only signs of this disease. The oral changes may be presented as single or multiple unspecific lesions –this is the reason for undetected symptoms in a lot of cases and the reason for the late diagnosis. Therefore early symptoms that are manifested on the oral mucosa and in jaw area can be first recognized by dental professionals.

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Introduction

Langerhans cell histiocytosis (LCH), formerly known as histiocytosis X, is a rare proliferative disease of histiocytes which may affect a single system at a single/multiple site or may be represented as a multisystem disease (17, 18, 19). The disease usually occurs during childhood and the incidence is 5 cases per 1 million children per year; it may also occur later in life: 1 or 2 persons per million with a slight predominance in men (12, 20).

The etiology is unknown and various theories have been proposed, e.g. a role for environmental, infectious, immunologic, genetic causes, and it has even been suggested that LCH is a neoplastic process (2, 15).

The clinical manifestation of LCH varies from a localized lesion to a systemic disease, divided into three basic clinical forms: Letterer–Siwe disease (subacute or acute disseminated form), Hand–Schüller–Christian disease (disseminated chronic form), and eosinophilic granuloma (localized chronic form). Eosinophilic granuloma (EG) is considered as the most frequent and benign of the three clinical forms of LCH. It can be solitary or multiple. It can affect bones without internal involvement. It seems to be more frequent in males than in females with a reported ratio ranging from 1.1:1 to 4:1 (2, 3, 5, 14).

Clinical symptoms of LCH in the oral cavity

Oral clinical symptoms are variable: patients suffer from teeth pains, swelling, dental hypermobility, bleeding, and sensory disturbances. General malaise, fever, cervical lymphadenopathies and headaches occasionally accompany the oral symptoms (9, 13).

Oro-facial manifestation of LCH

The oral lesions may be the earliest clinical signs of EG and in many cases the jaw and mandible may be the only sites involved. Such lesions are commonly in the gingiva, hard palate and floor of the mouth. According to the published data, the incidence of oral lesions is about 70 % (13), but the jaws are involved twice as frequently as the oral soft tissues (4, 6).

In the head and neck region EG often involves the calvarium, maxilla, mandible and temporal bone. And in the mandible the body and the angle are most commonly affected (3, 8, 10). However, the skull and the facial bones are predominantly affected by EG: about 60 % to 70 % of all bone lessions found in LCH cases (9, 11, 20).

Pereda et al. (13) summarized the observed clinical lesions, according to the localization of the oral manifestations, into:

- **Bone lesions** – alongside the cranium, the maxilla and mandible are the most affected bones, usually infiltrating together. The different types of lesions produced by LCH in the maxilla and mandible are described according to their radiographic characteristics as: 1. solitary intra-bony lesions; 2. multiple alveolar lesions; 3. "scooped-out" alveolar lesions; 4. alveolar lesions with bone sclerosis; and 5. alveolar lesions with bone neoformation (13).
- **Periodontal lesions** – seen in 80 % to 90 % of cases: gingival recession (due to the periodontal changes), periodontal pockets, etc. As a result of bone loss, the teeth resemble "floating teeth" and premature loss of teeth is possible (10, 13).

- **Mucosal lesions:** ulcerative, ovoid or round lesions, with erythematous, inflamed borders, painful on palpation, usually on the buccal mucosa and at the back of the vestibule, and unusual soft tissue lesions.

Management of patients with EG

It is a known fact that the management of patients with EG continues to be a therapeutic dilemma and usually a multidisciplinary approach is recommended. The treatment depends on many factors: visceral involvement (liver, spleen, lungs), age at first presentation, presence of solitary or numerous bones or soft tissue lesions, etc. Treatment options usually include surgical approaches (resection, curettage), antibiotic therapy, adrenocorticotropic hormone, radiotherapy, and chemotherapy, or a combination, systemic corticosteroid therapy, and topical injection of steroid, immunosuppressant agents, immune modulators or cytostatic drugs (9, 13).

Case Details

In March 2010, a 42-year-old male was referred by his dentist for diagnosis and treatment with spontaneous and intense pain of the left maxillar region.

The patient had repeatedly visited his dentist, who had treated an oral lesion with different topical agents without any improvement. The patient complained of pain, soreness, and spontaneous bleeding in the mouth during eating.

At his primary visit in our department the patient did not mention any general health complaints and common diseases.

The intraoral examination revealed poor oral hygiene and halitosis, ulceration and swelling on the left side on the palatinal mucosa and gingiva surrounding the permanent teeth 24 to 27 (left first and second premolars, first and second molars). The oral mucosa in this area was erythematous, ulcerated and necrotic and bled easily (**Fig. 1**). The teeth in this region did not show mobility. The submandibular, submental and cervical lymph nodes were palpable, painless, tender, and mobile.

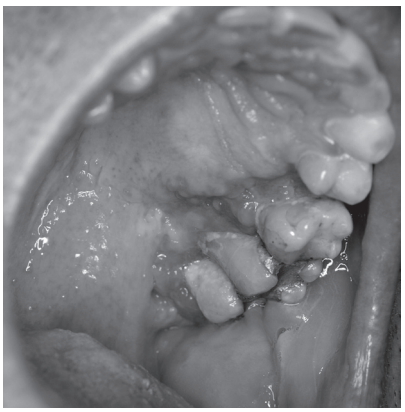

Fig. 1. Massive lesion of the palatinal mucosa and the alveolar left ridge of the maxilla.

At the second visit we found a white lesion resembling lichen planus, on the left side of the mandibular vestibular gingiva (in the region 36 to 37).

On the basis of the clinical examination, in order to establish the diagnosis we recommended:

- radiological examination – X-ray of the jaws, the scalp, the pelvis, and the long bones, ribs and hand bones;
- biopsies of the oral lesions and histopathological study;
- urinalysis and laboratory tests;
- consultation with internist – concerning the general health of the patient.

Results and Discussion

Radiologic findings

The orthopantomography result is given in **Fig. 2**. The panoramic radiograph showed generalized osteolytic changes of the interdental spaces of the mandible and maxilla, resembling lesions seen in aggressive periodontitis.

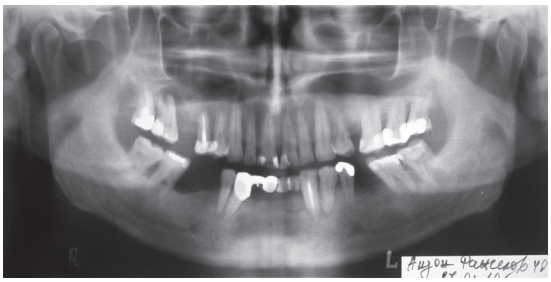

Fig. 2. Panoramic radiograph.

Loss of the normal lamina dura around the roots of teeth 24 and 26, and bone loss around their roots were observed. It was found that osteolysis begins from the alveolar crest of 26 toward the furcal level and around the medial and distal roots of 26 – an image typical of a periodontal lesion (**Fig. 3**).

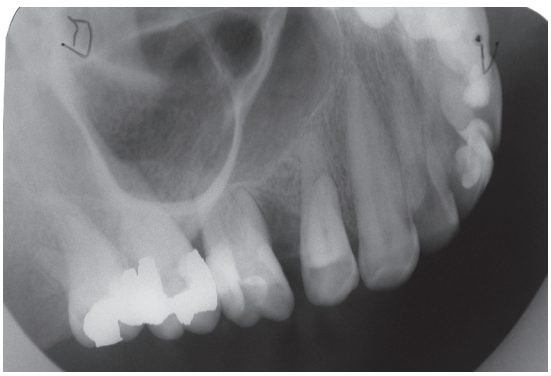

Fig. 3. Intraoral X-ray of the region of upper left premolars and molars:

The radiologic views of flat and long bones did not show any lytic lesions at the scalp, pelvis, ribs and hand bones.

Consultation with internist

The gastroenterologist revealed only an indurative anal lesion (**Fig. 4**). Colonoscopy and echography were made and they did not show any abnormality.

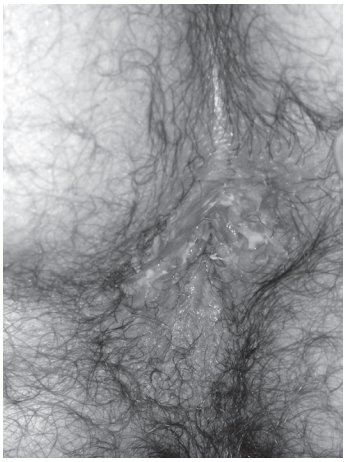

Fig. 4. Anal lesion.

Urinalysis and laboratory tests

The urinalysis and laboratory tests, including complete blood cell count, coagulation factors, liver function tests, C-reactive protein, glycemia, and thyroid hormones (TSH, T3, and T4), were all within the normal limits.

Histopathologic examination

For diagnostic purposes the patient underwent two oral incisional biopsies (from the left maxillary region – the area of the oral lesion, and from the left vestibular mandibular area) and one from the anal lesion under local anesthesia. The samples were sent for histopathological and immunohistochemical examination. A biopsy specimen showed a light microscopic and immunohistochemical pattern consistent to EG.

On the basis of the clinical and radiological findings and biopsy we considered the diagnosis LC/EG.

Our management in this case included:

1. Local oral therapy (only): the therapeutic protocol used for the maxillar lesion included causal periodontal therapy (supragingival and subgingival scaling). Extraction of the teeth (16) and alveolar curettage were performed. An individual oral hygiene program was made – to use a super soft toothbrush, dental flosses, inter-dental brushes, and a solution of $KMnO_4$ as a mouth rinse.
2. Medical treatment with mesalazine suppository (Salofalk 500) – for a period of 3 months, 2 times per day.
3. Systemic and local therapy included:

3.1. Systemic and local corticosteroids:

- Dehydrocortisone – 12 tabl. 0.5 g daily for 1 month, and decreasing the dose gradually over a 1-year period;
- Locoid solution (hydrocortisone butyrate 0.1 %) for local application (in the oral cavity, and on the anal lesion) – 2 times a day.

3.2. Antifungal agents

- Daktacort cream (miconazole), for local application (in the oral cavity, and on the anal lesion) – 2 times a day.

4. Systemic therapy – the dose and duration were prescribed individually according to the clinical improvement:

4.1.Tinidazole 500 mg for a long period of time: 2 tablets daily for 3 months; after that, 1 tablet daily for 2 months; finally, 1 tablet every 3 days, for a period of 2 months.

Follow up was performed at monthly intervals with radiographic evaluation.

The clinical evaluation 4 months after the treatment showed:

- Oral manifestation and anal involvement after treatment

At present after 11 months follow-up a stable healed appearance of the left maxillar lesion and anal involvement with no signs of recurrence is apparent (**Fig. 5** and **Fig. 6**).

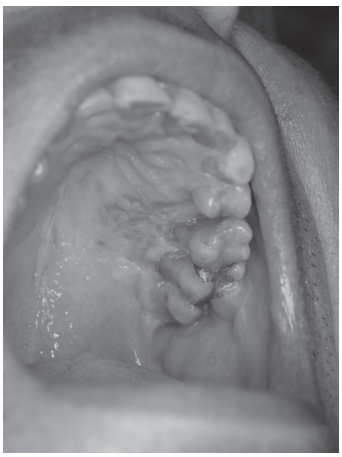

Fig. 5. Oral mucosal lesion 11 months after treatment.

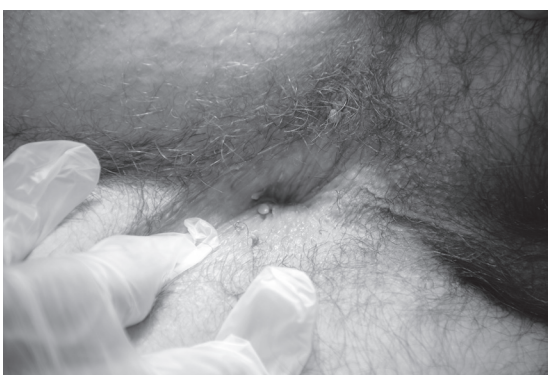

Fig. 6. Anal region 11 months after treatment.

- X-ray findings after treatment

The intraoral X-ray (**Fig. 7**) demonstrated a decrease in size of the bone lesions and loss of lucency with progressively increasing trabeculation.

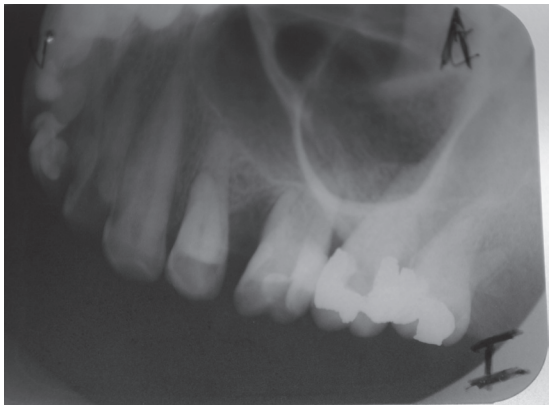

Fig. 7. Intraoral X-ray of the region of the upper left premolars and molars, taken 11 months after the treatment.

Final remarks

The clinical spectrum of EG is very broad: it ranges from a single localization in bone and mucosa to multiskeletal involvement leading to dysfunction of organs (19). Lesions on the mucosa are rare – they can occur not only in the oral cavity, but also in the gastrointestinal, urogenital, and vaginal tracts (17, 18). We did not find previous reports concerning localization of LCH in the perianal region.

According to Esen et al. (9) the most common oral findings of EG are local pain and swelling. If the periodontal tissue is affected, clinical features can resemble and mimic the characteristic signs and symptoms of severe localized periodontitis, characterized by gingival bleeding, gingival recession, deep periodontal pockets, and tooth mobility. Our patient showed a chronic ulceration of the hard palate, followed by development of a similar lesion of the gingival mucosa of the alveolar ridge.

Having in mind the clinical symptoms, the differential diagnosis included: periodontitis, infectious disease (tuberculosis, fungal infection), an inflammatory condition (sarcoidosis), allergic reaction, leukemia, LCH, and soft tissue sarcoma.

As EG can be a multifocal disease, radiologic skeletal survey is needed for a complete evaluation of the disease (1, 7). The radiologic views in our case did not show any lytic lesions at the scalp, pelvis, ribs, and hand bones, but the intraoral X-ray revealed lytic changes in the left upper premolar region, undistinguishable from these of periodontal disease. This may lead to mistakes with periodontal disease or with periapical process of dental or periodontal origin. Because EG lacks pathognomonic clinical or radiographic characteristics, an acute diagnosis can be made only from biopsy and histologic examination. Therefore, a definitive diagnosis should be based on a histological and immunohistochemical study of lesional biopsy specimens, which are characteristically observed to be positive for S-100 protein and CD 1a (15). In our case a biopsy was taken of each lesion: from the oral and anal mucous, and thus the diagnosis EG was proved.

After the diagnosis of gnathic EG is confirmed, the extent (staging) should be assessed, according to thorough physical examination, radiographic skeletal survey, and a biopsy. And finally, a plan for treatment should be made (16).

Treatment modalities for LHC are variable according to the location, extensions, and number of lesions. Treatment options usually include surgical approaches (resection, curettage), antibiotic therapy, adrenocorticotropic hormone, radiotherapy, and chemotherapy, or a combination, radiation, systemic corticosteroid therapy and topical injection of steroid, immunosuppressant agents, immune modulators or cytostatic drugs (9, 13).

In cases of EG with oral manifestations, it is unnecessary to extract all the teeth involved in the process – those with marked mobility, or with periapical osteolytic lesions and those presenting symptomatology.

Correct mucosal and periodontal treatment include: tartar removal, and radicular scaling and planing, as well as rigorous hygiene and maintenance to conserve both the teeth and the periodontal tissue (2, 10, 15, 13). An alternative treatment approach for the localized musocal lesion is intralesional steroid injection (13). It is a fact that long-term use of corticosteroids can cause various adverse effects and as we know, there are no adverse effects reported in treatment of LLCH with the technique of intralesional injection.

The published reports on treatment planning and clinical manifestation in cases similar to that in our patient (only mucosal and periodontal manifestations and the lack of changes in bones and visceral involvement) encouraged us for the favorable course of the disease in our case.

The treatment of our patient included local oral therapy: supragingival and subgingival scaling, extraction of the teeth (16), and maintenance of good oral hygiene program. Using corticosteroid medicine for local and systemic application and antifungal agents correspond to the therapeutic strategies for Langerhans cell histiocytosis.

Recurrence rates depend on the treatment method and localization of the lesion and should be closely followed up for a long period of time. That is why we required a control visit for clinical examination – every two weeks for 4 months, and after that, once monthly; X-ray examination control every 6 months.

Conclusions

Oral lesions may be the first manifestation of EG and the dentist is often the first specialist consulted.

Early diagnosis of EG is considered an important factor which can improve the patient's prognosis and quality of life and also the cost-effectiveness of therapy. The dentists could play a fundamental role in the diagnosis and management of EG, performing routine examinations, periodic follow-up of the oral manifestations and their complications.

The present clinical case demonstrates that the oral and anal findings may be an early manifestation of multiple eosinophilic

granuloma and the definitive diagnosis needs to be determined by correlation of the clinical findings and histological features.

We would like to emphasize the difficulties connected with early detection of oral and systemic findings; the difficult differential diagnosis and difficulties connected with determining the degree of damage on the basis of which the adequate therapy will be appointed. We would like to also point out the role of the dental professional and the role of the multidisciplinary approach for the diagnosis and management of EG.

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