



## Case Report

# Langerhans's cell histiocytosis in old subjects: two rare case reports and review of the literature

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## Langerhans's cell histiocytosis in old subjects: two rare case reports and review of the literature

**Background:** Langerhans cell histiocytosis (LCH) is a proliferative disease of histiocyte-like cells that generally affects children; LCH onset is rare in adults; immunohistochemistry is essential to obtain the correct diagnosis, and treatment protocols are controversial.

**Objective:** To describe two new cases of adult onset oral LCH.

**Case reports:** Case 1: a 71-year-old woman, complaining of diffuse oral pain, presented with erythematous mucosal lesions; the panoramic radiograph and CT scan showed multiple mandible radiolucent areas. Immunohistochemical assay for S-100, CD1a and langerin test was essential in reaching the correct diagnosis. Case 2: a 77-year-old female patient presented with a non-painful, non-bleeding, slightly elevated erythematous palatal lesion of 6 months duration, together with a genital vulvar lesion of uncertain nature. The pathology confirmed the diagnosis of LCH. Many therapies (etoposid, radiotherapy) could induce only a clinical partial remission; Cladribine induced a complete recovery.

**Conclusion:** The first case was difficult to diagnose: the clinical presentation and course of the disease (LCH) in the elderly are multiple and unpredictable. An immunohistochemistry study is often essential to obtain the correct diagnosis. The second case required several therapeutic interventions: even though some cases regress spontaneously, others require systemic chemotherapy.

**Keywords:** langerhans's cell histiocytosis, old subjects, langerin, oral, immunohistochemistry.

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## Introduction

Among histiocytic disorders<sup>1-3</sup>, which include a group of several diseases characterised by a pathological proliferation and accumulation of histiocytes (i.e. monocytes/macrophages, dermal/interstitial dendritic cells, Langerhans cells) and other immune effectors cells within multiple tissues, Langerhans cell histiocytosis (LCH) is a proliferative disease of histiocyte-like cells that have been identified as Langerhans cells histiocytes (LCHC), an immature dendritic cell that lacks the ability to be a functional antigen-presenting cell<sup>3-5</sup>.

Even though the aetiology of the disease still remains unclear, classically, this condition has been described as a neoplastic process because of the monoclonal proliferation of LCs, as LCHCs

expresses many LC antigens like S-100, CD1a and langerin<sup>6-8</sup>; more recent studies highlight the possibility that LCH is the result of an immune dysregulation<sup>9-12</sup>.

Histologically, LCH is generally characterised by immature LC proliferation accompanied by an infiltrate of lympho-monocytes together with eosinophilic and neutrophilic cells, which results in the destruction of the affected tissues. As the atypical cellular proliferation of LCHCs occur in various organs and tissues (i.e. bone, liver, lungs, lymph nodes, spleen, hematopoietic and mucocutaneous tissues), clinical manifestations might be particularly different and complex<sup>6,10,11</sup>. For this reason, the classical classification of the Histiocyte Society into five different clinical types (eosinophilic granuloma – localised disease, Letterer-Siwe

syndrome – systemic acute disease, Hand–Schüller–Christian syndrome – systemic chronic disease, congenital self-healing LCH and pulmonary LCH) should be replaced by the clinical classification of the LCH study group, which divides LCH into single-system LCH and multi-system LCH: the single system is further subdivided into single site and multiple site; the multi-system in low risk and high risk according to the involvement of some organs (liver, lungs, spleen, haematopoietic system)<sup>5</sup>, high-risk patients presenting an higher mortality rate.

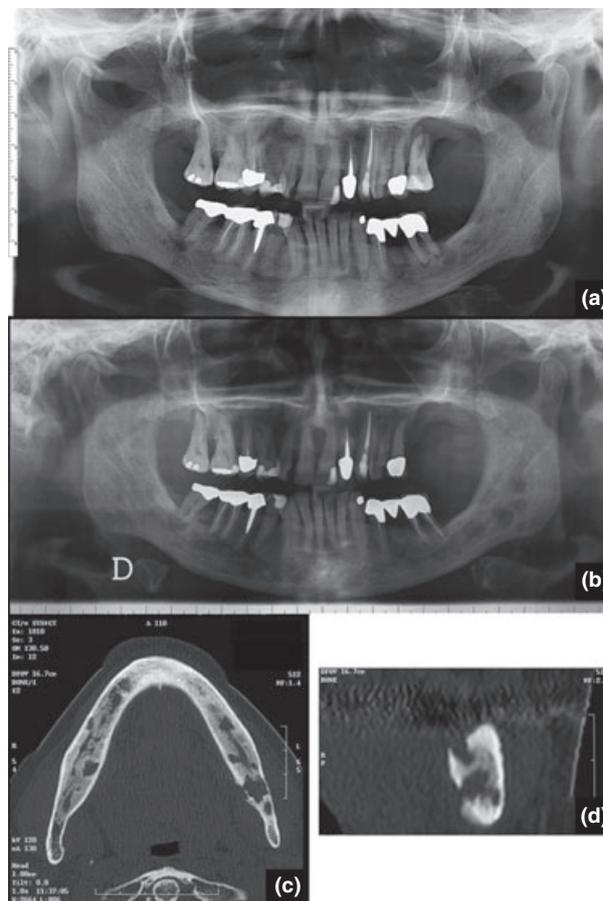
A presumptive diagnosis of LCH may be made based upon light microscopic findings, but a definitive diagnosis requires that lesional cells reveal positive staining with S-100, langerin and CD1a or the identification of Birbeck granules upon electron microscopy<sup>3</sup>. LCH generally affects childhood (peak incidence from 1 to 3 years), but a report of the Histiocyte Society on late-onset LCH was published stating that in these cases, the diagnosis can be very difficult, and immunohistochemistry techniques (S-100, CD1a and langerin) can help in the differential diagnosis. The clinical course of the adult onset LCH seems to be unpredictable, but in many cases, it regresses spontaneously or after adequate therapy<sup>12–14</sup>.

This report describes two cases of LCH with oral involvement detected in two elderly female patients (71 and 77 year olds, respectively).

## Case reports

### Case 1

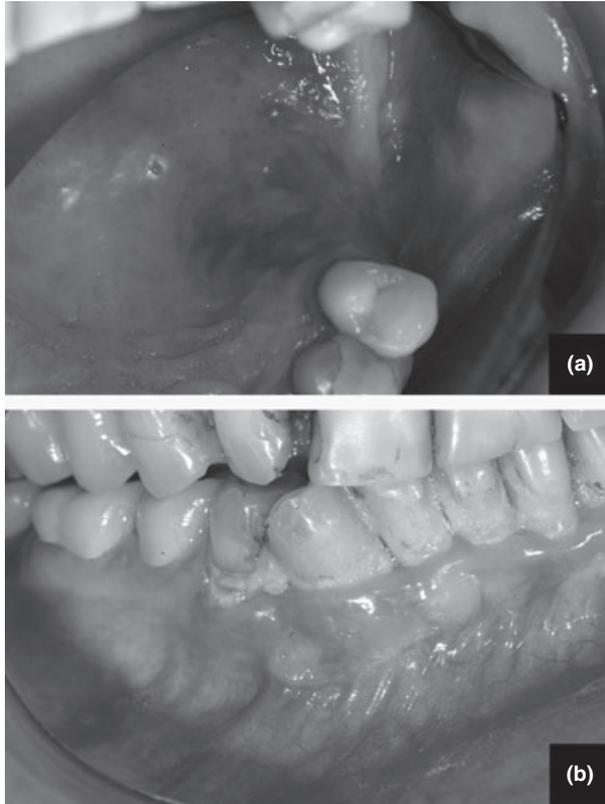
A 71-year-old Caucasian woman, complaining of diffuse oral pain, was referred by her dentist to our Clinic (October 2003). She reported mouth and gingival discomfort since the beginning of 2001, when she went to her dentist to be treated. Her dentist considered the pain as a pulpitis and decided to perform a root canal of the left superior canine and the first lower right molar (teeth number 2.3 and 4.6). As the symptoms did not disappear (November 2002), a panoramic radiograph was requested (Fig. 1a): a periapical radiolucency of the lower left first molar and of the lower right second molar (teeth number 3.6 and 4.7) and a diffuse periodontal disease (mostly related to maxilla) were noticed. The dentist extracted the first upper left molar (tooth number 2.6) affected by severe periodontal disease and did a root canal of first left lower molar (tooth number 3.6). Few months later, as the symptoms were still present, the dentist asked for a new radiograph from which some new



**Figure 1** Case 1 – Radiological findings. (a) First panoramic radiograph (November 2002) showing a periapical radiolucency of the lower left first molar and of the lower right second molar (teeth number 3.6 and 4.7) and a diffuse periodontal disease (mostly related to maxilla). (b) Second panorex, performed few months later, showing some new radiolucent areas, mainly located in the left mandible: the lesions were multiple, but uniloculate with well-defined margins, but without any sclerotic reactive halo. (c) CT scan section shows many diffuse osteolytic lesions in the cancellous bone of the mandibular body. (d) Cross-section showing a detail of the left mandible: the lingual cortical plate is perforated.

radiolucent areas, mainly located in the left mandible, could be noticed (Fig. 1b).

At this point (October 2003), the patient was referred to our Clinic. During the first interview, the patient reported to be suffering from a Wolf–Parkinson–White syndrome and from mild hypertension and was treated with ACE inhibitors. No other relevant information was collected on the medical history. The oral examination revealed chronic periodontal disease (vertical and horizontal bone loss), furcation involvement on teeth number 3.6 and 4.6 and endo-perio pathologies, but all

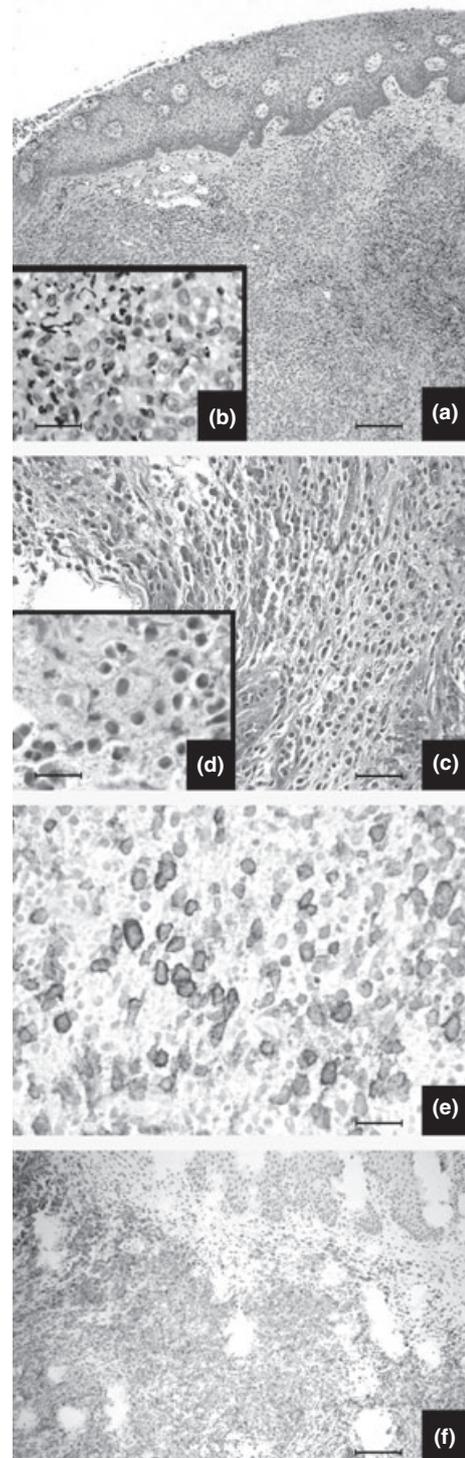


**Figure 2** Case 1 – Clinical presentation. (a) Intraoral examination revealed an erythematous mucosal lesion on the upper left palate and on the upper left edentulous ridge: the lesions had undefined margins and were not elevated, presenting areas of ulceration, non-bleeding and slightly sore. (b) Some well-defined smaller ulcers, surrounded by an erythematous halo, were present on the gingival mucosa (from tooth – 4.2 – to lower right second premolar – 4.5).

teeth were stable and non-mobile. On the upper left palate and on the upper left edentulous ridge, an erythematous mucosal lesion was present, with undefined margins and areas of ulceration

**Figure 3** Case 1 – Pathological features and immunohistochemical assay. (a) Low-power magnification of the palatal biopsy revealed a subepithelial inflammatory infiltrate (EE 25 $\times$ ). (b) In higher magnification, a blastic inflammatory cell infiltration can be noted: blastic cells with nuclear atypias, mitoses and eosinophilic cytoplasm can be seen (EE 200 $\times$ ). (c) Pathology revealed a complete change of the bone tissue pattern: a diffuse inflammatory infiltrate can be noted (EE 50 $\times$ ). (d) In higher magnification, plasmacytic-like cells with nuclear atypias, hyperchromic nuclei in eccentric position and eosinophilic cytoplasm replaced the normal bone tissue (EE 200 $\times$ ). (e) Immunohistochemical staining for langerin on bone tissue (200 $\times$ ). (f) Immunohistochemical staining for langerin on palatal mucosa (25 $\times$ ).

(Fig. 2a); other smaller ulcers were present on the gingival mucosa (from lower right lateral incisor – tooth number 4.2 – to lower right second premolar – tooth number 4.5 – Fig. 2b). Routine blood tests were all normal. A biopsy from the edentulous ridge of the palate was performed, and the pathology revealed a subepithelial blastic infiltrate:



immunohistochemistry staining was negative for lymphoid markers (CD34 and keratins) and positive for myeloid markers, thus suggestive of a myeloid proliferative disease (Fig. 3a, b), but the bone marrow biopsy was negative. CT scan of the jaws showed diffuse osteolytic lesions, mainly located in the left mandible; these lesions were well defined, and in some areas, the mandibular cortical bone showed perforations (Fig. 1c, d).

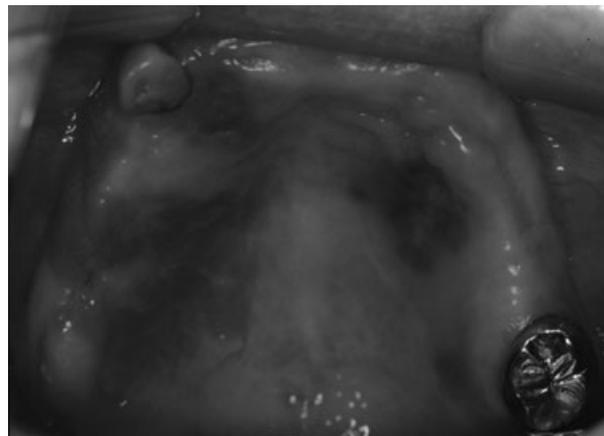
There were many aspects that did not make sense. In particular, the faint and shifty nature of the symptoms, which characterised the history of this patient, did not correlate with the 'severity' of the pathology report. Furthermore, blood exams and the bone marrow biopsy excluded any haematological disease.

In a further appointment (beginning of 2004), we completely re-evaluated the case, and during a thorough medical history interview, the patient reported that she was also suffering from diabetes insipidus for approximately 6 years and she was on desmopressin. Then, a bone biopsy of the mandibular lesions was performed (February 2004), and the pathology report revealed a complete change of the bone tissue pattern; plasmacytic-like cells with nuclear atypias, hyperchromic nuclei in eccentric position and eosinophilic cytoplasm were infiltrating the bone. Mitosis was also present (Fig. 3c, d). Immunohistochemical assay to rule out LCH (S-100, CD1a and langerin) was positive (Fig. 3e); all markers were also positive on the previous biopsy of the palatal mucosa (Fig. 3f); total body CT scan excluded other organs involved. Systemic chemotherapy was performed, consisting of vinblastine (10 mg) and prednisone (60 mg) I.V. in six weekly courses, followed by additional six courses performed every 2 weeks; zoledronic acid (6 monthly doses of 4 mg) was also administered. Following this treatment, the patient had complete resolution of the oral symptoms and lesions; steroids were tapered slowly with a small maintenance dose (10 mg/day) for 6 months. No further relapses were detected thus far.

### Case 2

In April 2004, a 77-year-old Caucasian woman was referred to the Dental Clinic of the University of Palermo with a non-painful and non-bleeding palatal swelling for about 6 months duration. At the same time, the patient complained a genital vulvar lesion of unknown nature.

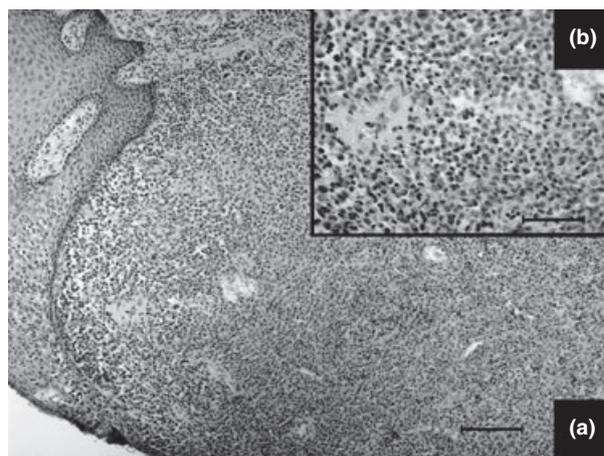
The medical history revealed type II diabetes mellitus diagnosed 5 years earlier and treated with gliclazide 30 mg once daily and high blood pressure



**Figure 4** Case 2. Clinical presentation. Two main lesions can be noted: the right palate and the right maxillary edentulous ridge presented a slightly elevated reddish plaque (1.5 × 4 cm), tender-elastic in consistency with non-defined margins, non-painful and non-bleeding; a dark reddish, two cm in diameter, tender elastic in consistency, non-bleeding lesion can be seen in the left palate.

treatment for the past 15 years, treated with chlortalidone 12.5 mg plus atenolol 50 mg once daily; no smoking or drinking habits.

The intraoral examination revealed two distinct lesions (Fig. 4): a slightly elevated erythematous plaque in the right palate (1.5 × 4 cm), tender-elastic in consistency with irregular margins, non-painful and not bleeding; the second one, in the left palate, was dark reddish, two centimetres in diameter, tender elastic in consistency, non-bleeding. Panoramic radiograph and a CT scan as



**Figure 5** Case 2. Pathological feature. (a) Low-power magnification: subepithelial acute inflammatory infiltrate (EE 25×). (b) In higher magnification, eosinophils together with localised areas of mononuclear hyperplastic cells with cleft nuclei can be noted (EE 100×).

well as serologic tests (routine blood tests and rheumatoid factor, anti-streptococcus titre, HBV and HCV antibodies) were all non-contributory. The incisional biopsy of the right lesion revealed an acute inflammatory infiltrate, mainly consisted of eosinophils clustered together with localised areas of mononuclear hyperplastic cells with cleft nuclei. The pathology was consistent with LCH (Fig. 5).

A bone triphasic scintigraphy and a whole-body single-photon emission tomography revealed the presence of some areas of a tracer uptake in the right maxilla, but no further bone pathological focal lesions were detected. An abdominal ultrasound did not reveal any abdominal abnormalities. After 4 months of follow-up, the clinical appearance did not change, so a steroid therapy (prednisone 25 mg once daily) was started. After 1 month of steroid therapy, the lesions did not show any improvement, so the patient was referred to the haematology department. The haematologist, as no bone lesions were present, proposed six cycles of chemotherapy with etoposide (100 mg once daily) and dexamethasone (0.5 mg once daily) for three consecutive days every 3 weeks. Routine blood tests (blood count test, azotemia, cretinemia, uricemia, glycaemia, transaminases, bilirubin) were carried out before every cycle, and a co-therapy with sulfamethoxazole 800 mg plus trimethoprim 160 mg bid and pantopazole 20 mg once daily was administered for 7 days.

After 2 cycles (September 2004), the clinical presentation improved and the patient decided to undergo only two further cycles (only four cycles instead of 6). Two months after the 4th cycle (January 2005), a new biopsy was performed on the residual lesions showing a necrotizing vasculitis; the patient showed a clinical partial remission for 5 months (May 2005), when a relapse was discovered and confirmed by biopsy. After some months of follow-up, radiotherapy was performed (November 2005), and the clinical presentation improved and remained stable for 1 year, when a further oral and vaginal relapse occurred (April 2006). A vaginal biopsy confirmed the relapse of the disease. At that time, a head and neck Magnetic Resonance Imaging (MRI) revealed bilateral intraparenchymal parotid lesions (max. diameter 2.5 cm), and therefore, a further chemotherapy with cladribine was performed for a total daily dose of 10 mg for five consecutive days (0.14 mg/Kg/day). After two cycles, a regression of the oral salivary glands (MRI documented) and vaginal lesions was seen, but it was necessary to diminish the dose because of a systemic toxicity. The third cycle (8 mg daily) caused severe neutropenia (2730

white blood cells/ $\mu$ l of which 1569 neutrophils) and anaemia (9.3 g/dl), and it was necessary to support the patient with g-CSF (filgrastim) and three transfusions. The 4th cycle (7 mg daily) was well tolerated, but an oral candidosis arose and it was treated with miconazole 2% oral gel. After the 4th cycle, a complete recovery was obtained, and no other relapses showed up so far.

## Discussion

Clinical-pathological correlations and the onset in older adults made the diagnosis of LCH and the clinical management interesting and difficult at the same time. The first case had a difficult time to diagnose, whereas the second one, easier to diagnose, required several therapeutic interventions, showing several relapses.

First of all, considering the epidemiology of LCH, our cases differ from usual distribution of the disease: LCH affects mainly children (5 per million), whereas in our case, it arose in two adult women, 71 and 77-year olds, respectively (1–2 adults affected per million and even fewer on adults older than 60 years of age)<sup>6</sup>. According to the report of the International Registry of the Histiocyte Society on adult LCH (IRHSA), which studied the clinical characteristics of 274 cases from 13 nations, the mean age of the first manifestation in adults was 33 years with a peak between 20 and 30 years and only few records refer to people older than 60 years; considering all cases diagnosed through a biopsy (253 subjects), in the majority of cases, it was performed on bone (38.8%), whereas only in few cases, it was performed on mucosal membranes (3.9%): in our second case, the mucosal biopsy was sufficient to reach a correct diagnosis, but a further jaw bone biopsy was necessary for the correct diagnosis in the first one. Considering clinical manifestation of adult patients suffering from a multiple organ involvement (188 subjects) presented in the IRHSA, bone (66.0%), skin (50.5%) and lung (61.7%) lesions, together with diabetes insipidus (43.1%), were the most frequent symptoms, and, because of the rarity of the disease, the median latency time was 4 months (interquartile ranges – 0 to 22 months); patients presenting with isolated diabetes insipidus had a median latency time in diagnosis of 11 months (interquartile ranges – 0–48)<sup>6,12–14</sup>. In our first case, the patient did not report diabetes insipidus during the first medical interview neither we further investigated the matter which could have addressed the diagnosis towards a wider group of systemic diseases. In any case, the latency time was almost 4 years since she

was diagnosed with diabetes insipidus and 5 months since the patient was referred to our Clinic.

Langerhans cell histiocytosis in general can affect all hard and soft tissues of the oral and maxillofacial region (gingiva, floor of the mouth and palatal mucosa, the sinus cavity), presenting as unifocal single-system disease in about 50% of maxillofacial LCH. The mandibular bone, especially in its posterior region, seems more frequently affected (three times more than maxilla). Clinical appearance can vary from intraoral mass to gingivitis, loose teeth, oral ulcers with impaired healing, whereas tooth displacement and root resorption are seen less frequently<sup>14–16</sup>. The oral clinical presentation of the first case was faint and shifty: the patient reported only an initial diffuse oral discomfort, mainly characterised by diffuse periodontal symptoms that, considering the age of the patient, were first attributed to chronic periodontal disease (diffuse horizontal and vertical bone loss). The presence of bone radiolucencies far from periodontal structures, together with the finding of the diabetes insipidus during the second collection of her medical history, brought up the question of a possible multi-system disease. In this case, radiolucencies were multiple, uniloculate and well defined, not specific of LCH: such radiolucencies can be seen in many other diseases such as metastases, osteomyelitis or malignant haematological tumours as multiple myeloma, but, in our case, blood exams and bone marrow biopsy excluded any other haematological diseases. The clinical presentation of the second patient was easier as she was edentulous in the affected area, a vulvar contemporary lesion was present and the first mucosal biopsy was diagnostic.

Generally speaking, pathology is characterised by LCHCs, T-cell lymphocytes, eosinophils and macrophages: LCHCs are characterised by an abundant eosinophilic to amphophilic cytoplasm, reniform nucleus, deeply indented or grooved; mitosis are rare. The number of eosinophils is quite variable from rare to predominant giant cells, and necrosis can be present in the granulomatous process. The clinical–pathological correlation was essential to reach the correct diagnosis in the second case, but was not sufficient in the first case, where immunohistochemistry played a fundamental role. Among the possible antigens, recently, a highly specific and sensitive monoclonal antibody against CD207 (langerin) is available. This protein seems important in the formation of the Birbeck-Broadbent granules, which are always present in LCH and can be detected through ultrastructural study making the diagnosis certain<sup>6,7,17,18</sup>.

In the last years, many molecular aspects of the disease were better understood, suggesting the possibility that LCH could be the result of an immune dysregulation<sup>9–12</sup>: many pro-inflammatory chemokines (CCL20, CCL2, CCL3, CCL4, CCL5, CXCL8, CXCL10) can be released by LCH, which contribute to the recruitment of other inflammatory cells. Through autocrine and paracrine mechanisms, these molecules contribute to the onset and maintenance of the lesions. The recruited cells (Lymphocyte, macrophages and eosinophils) contribute themselves to this process producing many other cytokines (IL-1, IL-3, IL-4, IL-5, IL-8, IL-10, TNF- $\alpha$ ). This particular immunological setting, called ‘cytokines storm’, can explain many clinical local and systemic symptoms as fever, pain, osteolysis, anaemia, fatigue, lymphadenopathy, etc. On the other hand, many genetic abnormalities (i.e. loss of heterozygosity, damages of chromosomes 1, 7, 9, 17, damages of genes IDE, PAN, PAX7, E2F2, TNFR-2, TCEB, cyclin-dependent kinases, cyclin-dependent kinases inhibitors, p14, p15, p16, p53, NF2, c-myc, h-ras) were detected in LCH during the last decade, supporting the possible clonal-expansive nature of the disease. Both these molecular pathways are now under investigation as possible targets for molecular therapy (i.e. gene therapy, monoclonal antibodies, immunomodulators)<sup>6–11,19–22</sup>.

The treatment protocol, which was really demanding in the second case, must consider the general stadiation of the disease (single-system vs. multi-system; single-site vs. multiple-site) and can vary from local surgery to radiotherapy to chemotherapy<sup>11</sup>. The Histiocyte Society performed three major study protocols for paediatric LCH (LCH-I, LCH-II and LCH-III), and, more recently, a protocol for adult onset was started, considering vinblastine plus prednisone for multisystem disease, but the therapy regimen for adult still remains dubious: it can vary from watchful waiting to local therapy (surgery and radiotherapy) to systemic chemotherapy in the refractory cases (i.e. cladribine, thalidomide, vinblastine, steroids)<sup>6,23–27</sup>. In our second case, many relapses occurred after local or mild systemic therapies: at the end, the administration of cladribine was necessary to control the disease.

In an interesting article, Bartnick reviewed 12 cases of oral LCH and proposed a new classification for oromaxillofacial region (OMF-LCH), which can suggest a prognostic–therapeutic approach for clinicians and should be used for research purpose: stage I with single maxillofacial lesion, Stage II with multiple maxillofacial lesions and Stage III with

oromaxillofacial lesions plus other regions. For each stage three different sublevels are possible: (i) only bone lesions, (ii) only soft tissues and (iii) additional visceral involvement. According to this classification, the first case was oromaxillofacial region (OMF-LCH) stage III, sublevel C, whereas the second case was oromaxillofacial region (OMF-LCH) stage III, sublevel B, both cases requiring an aggressive therapeutic approach<sup>15</sup>. A further classification, which take into consideration both OMF-LCH<sup>15</sup> and LCH study group classification<sup>5</sup>, could help clinicians in addressing the more suitable therapeutic regimen and in forecasting the prognosis.

## Conclusion

Langerhans cell histiocytosis (LCH) is a proliferative disease of histiocyte-like cells and generally affects childhood (peak incidence 1–3 years). Adult onset LCH is rare, especially in the elderly; often immunohistochemistry techniques (S-100, CD1a and langerin), as we showed in our first case, are essential to reach the correct diagnosis, as the clinical presentation and course of the disease are often multiple and unpredictable; there is still no consensus on therapeutic protocols and several relapses could occur, as happened in our second case: the presence of oromaxillofacial lesions could give good prognostic–therapeutic information for clinicians.

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