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LANGERHANS CELL HISTIOCYTOSIS: ORAL/PERIODONTAL INVOLVEMENT IN ADULT PATIENTS

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ORAL DISEASES

LANGERHANS CELL HISTIOCYTOSIS: ORAL/PERIODONTAL INVOLVEMENT IN ADULT PATIENTS

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Title page

**LANGERHANS CELL HISTIOCYTOSIS: ORAL/PERIODONTAL INVOLVEMENT IN
ADULT PATIENTS****Running title: adult oral histiocytosis**

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3 **LANGERHANS CELL HISTIOCYTOSIS: ORAL/PERIODONTAL INVOLVEMENT IN**
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5 **ADULT PATIENTS**
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11 **ABSTRACT**
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15 **Objective:** Langerhans cell histiocytosis (LCH) is a clonal proliferative multisystem disease.
16 Although bone and mucosae have been classified as non-risk organs, their involvement may
17 increase the risk of disease progression. Oral and periodontal lesions are burdened with a significant
18 impairment of quality of life for associated signs, symptoms and loss of function. Most of
19 information regards pediatric disease; the disease in adults has received limited attention.
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23 **Subjects and Methods:** 31 adult patients affected by immuno-histopathology confirmed LCH have
24 been prospectively examined; attention was paid to the occurrence and characterisation of oral
25 lesions.
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29 **Results:** 12 patients developed oral lesions. Posterior regions of jawbones were always affected; the
30 involvement of anterior regions was not constant. Unifocal oral involvement was significantly
31 associated with multisystemic disease while multifocal lesions were associated with unisystemic
32 disease. Oral disease presented with soft tissues ulcers (50 % of cases), gingival bleeding (66.7%),
33 pain (83.4%), periodontal damage (50%), tooth mobility (16.7%), non-healing extraction socket
34 (8.3%); 41.6% of patients complained of negative outcomes on quality of life. Oral lesions were
35 easily handled with local measures.
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39 **Conclusions:** Posterior regions require attention; single oral lesions may be part of multisystemic
40 disease; oral and periodontal lesions may be early signs of disease reactivation.
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51 **Keywords:** langerhans cell histiocytosis; jaw lesions; oral lesions; adult; treatment;
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LANGERHANS CELL HISTIOCYTOSIS: ORAL/PERIODONTAL INVOLVEMENT IN ADULT PATIENTS

INTRODUCTION

Eosinophilic granuloma, Hand-Schüller-Christian disease and Abt-Letterer-Siwe disease are three different clinical disorders characterised by an abnormal proliferation of histiocytes; they were grouped in 1953 by Lichtenstein under the name of histiocytosis X basing on a common histopathologic feature: the presence of cytoplasmic bodies known as X bodies(Hicks & Flaitz, 2005, Arico et al., 2003). The disorder was renamed to Langerhans cell histiocytosis (LCH) in 1973 when Nezelof proved these histiocytes to be Langerhans cells (Bartnick et al., 2002). The disorder is characterized by a diffuse infiltration of large mononuclear cells, resembling histiocytes, with indistinct cytoplasmic border and rounded or indented vesicular nuclei, and a variable number of eosinophils; plasma cells, as well as lymphocytes and multinucleated giant cells may also be present. According to The Working Group of the Histiocyte Society a definitive LCH diagnosis can be set when, in addition to these light microscopy features, Birbeck granules can be detected in lesional cells by electron microscopy, and/or a positive staining for CD1a antigen can be obtained(Arico et al., 2003, Favara & Jaffe, 1994). The definition of the extent of the disease by adequate work-up(McClain, 1999-2005) is fundamental; in fact, treatment planning and prognosis mostly rely on it (Giona et al., 1997), together with the age of patient at the disease onset. The disease occurring in adults (estimated incidence: from one to two cases per million(Baumgartner et al., 1997)) has received limited attention(Arico, 2004, Baumgartner et al., 1997, Malpas & Norton, 1996, Howarth et al., 1999) especially for treatment protocols standardization and outcomes evaluation. Great emphasis has been placed on the characterization of “risk organs” (liver, spleen, lung, bone marrow) involvement; among “non-risk organs” (skin, mucosae, lymph nodes), oral manifestations received very little attention (Devaney et al., 1997, Milian et al., 2001). The latter encompass a variety of lesions involving jawbones, oral soft tissues and periodontium; due to the high frequency and the wide range of implications, they may significantly impair patient’s quality of life, have the potential for early diagnosis improvement and contribute to predict disease progression (Hicks & Flaitz, 2005).

In this study we have prospectively examined a group of LCH adult patients in order to define the occurrence of oral and periodontal lesions; characterisation of local disease, response to treatment and relation with systemic involvement and therapy have been also addressed.

PATIENTS AND METHODS

A group of 31 patients affected by LCH were studied. Patients were consecutively referred to us between 1989 and 2007 by the Haematology Department of the University "La Sapienza", where they had the LCH diagnosis confirmed by immuno-histopathology, and the disease extent staged by complete work up including skeletal survey, skull series, bone scan, complete blood count, sedimentation rate, liver function tests, electrolytes, and urinalysis. Particular attention was paid to ascertain "risk" organs involvement. According to the number of involved organs, systemic involvement was classified as unisystemic (involvement of a single organ) or multisystemic (two or more organs involved); within each organ the disease was categorized as unifocal or multifocal according to the number of lesions (one or more than one lesion, respectively).

Patients were already receiving the appropriate systemic therapy when evaluation for oral lesions started. At the first oral evaluation patients underwent thorough clinical oral examination, full mouth periodontal probing, intra-oral and panoramic radiograph, and computed tomography (CT) of jawbones with Dentascan imaging reformatting. Patients were then included in a follow up program and recalled every six months; at each recall visit patients' oral status, and especially the presence of oral lesions, was assessed by means of clinical examination of oral mucosa, periodontal examination (probing pocket depth, clinical attachment loss, full mouth plaque and bleeding scores), panoramic and intra-oral radiographs. In particular, periodontal damage by LCH was defined by the presence of increased probing pocket depth, attachment loss and/or bone resorption, and confirmed by histopathology. The clinical evaluation was performed every time by more than a clinician, but not always the same, with different expertise (oral mucosa, bone, periodontal lesions). Whenever oral lesions and/or radiographic abnormalities were found adequate additional investigations, including histopathologic and laboratory examination, were performed and the diagnosis confirmed as LCH; convenient therapeutic measures were undertaken and the frequency of follow up recalls accordingly modified. All data were collected and stored using standardized forms.

RESULTS

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3 The study group (Tab.1) included 16 (51.6%) females and 15 (48.4%) males. Patients' age at the
4 first diagnosis of LCH ranged between 18 and 73, with a mean age of 37.3 years and a median of 36
5 years. According to organs involvement (Tab.1), patients were stratified in different categories of
6 disease extent: 20/31 and 11/31 had unisystemic and multisystemic disease, respectively.
7 Unisystemic disease involved bone in 45% of cases and internal organs in 55% of patients:
8 multifocal lesions were prevalent and accounted for 55% and 90% of bone and internal organ
9 disease, respectively. In multisystemic involvement, bone and internal organs were affected in 82%
10 of cases (Fig.1). Skull involvement was present in 35.5% of cases. Patients were treated according
11 to approaches detailed in Table 1 and in 64.5% of cases remission was obtained. Six patients
12 (19.3%) dropped out from the study (three moved elsewhere, three came from distant regions and
13 decided to continue the follow up for the systemic disease in a nearer haematological disease
14 centre), but they were responsive to treatment while followed up. Only one patient (3.2%) showed
15 relapsing disease, while two (6.4%) experienced progression of the disease, but they had a very
16 small follow up period (0.6 years). Two patients died during the study; death was related to causes
17 other than LCH in one case, while in the other patient it occurred because of pulmonary
18 complications due to lung multifocal LCH involvement. 12 patients of the study group (38.7%)
19 developed oral LCH lesions during the follow up (Tab.2). The observation period ranged between
20 0.6 and 18 years, with a mean of 5.73 years (Tab.1); in particular, patients in whom oral lesions
21 occurred had a mean follow up of 8.45 years. In 7 out of the 12 patients (58.3%) both mandible and
22 maxilla were affected and all of them, except one, had multifocal jawbone involvement; 3 (25%)
23 patients showed posterior mandible unifocal involvement, whereas two (16.7%) had posterior
24 maxilla location of LCH (both as single and multiple lesions). Lesions appeared as punched out or
25 ill-defined radiolucencies without a corticated rim (Fig.2). Posterior regions of the jawbones were
26 always affected. The involvement of anterior regions was not constant; however, whenever present,
27 it was always observed in association with the involvement of posterior regions. It is worth noting
28 that anterior and posterior lesions were not contiguous but separated by unaffected tissues.
29 Oral/periodontal lesions were present in 5 patients with multisystemic disease (4 with unifocal
30 involvement), and in 7 cases with unisystemic disease (6 had multifocal lesions in the affected
31 organ: internal organs in 3 cases, bones in 2 cases, skin in one case) (Tab.1, Tab.2).
32 Oral disease was associated with pain in 83.4% of cases without predilection for bone and/or soft
33 tissues involvement. Clinical signs included oral soft tissues ulcers affecting the gingiva (Fig.3)
34 and/or the alveolar mucosa (50%; half of which overlying bone lesions); ulcers were sometimes
35 associated with proliferative exuberant tissue, producing variable clinical pictures in which tissue
36 destruction and tissue exuberance coexisted (Fig.4). Other signs were gingival bleeding (66.7%),
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3 periodontal damage (50%) in affected teeth of affected areas, tooth mobility (16.7%), non-healing
4 extraction sockets (8.3%).

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7 In a completely asymptomatic case (8.3%) the lesion was discovered by means of an oral x-ray
8 examination made for other reasons. Only one patient (8.3%) was treated with systemic
9 chemotherapy, two (16.7%) with soft tissues excision, two (16.7%) by means of surgical curettage
10 and the others (58.3%) with a combination of teeth extraction, surgical curettage and in one case
11 with intralesional administration of α -interferon. If we consider oral lesions (both bone and soft
12 tissues lesions) we had complete healing in all cases. However, in two patients that have been
13 successfully treated for their systemic disease (16.7%), after treatment and healing of initial oral
14 lesions, we had secondary new oral lesions; these, confirmed as LCH by immunohistopathology,
15 occurred in a different location (same side but more anterior sites), with the same appearance
16 (mucosal ulceration in one case and a small mass with focal ulceration in the other) of previous
17 lesions.
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30 DISCUSSION

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33 The main role in treating LCH patients is taken by oncologist/haematologist because of the current
34 view of its clonal proliferative etiopathogenesis (Willman et al., 1994, Willman & McClain, 1998);
35 however, due to the possible widespread involvement of multiple organ systems, a team approach
36 may be appropriate and advisable in disease diagnosis, staging, treatment and follow up. Thus,
37 addressing oral and periodontal manifestations should be included in patients' evaluation and
38 management. In fact, even if bone and mucosae have been classified as non-risk organs, their
39 involvement may carry a 40.7 relative risk of disease progression (Howarth et al., 1999). In addition,
40 in the particular case of oral location, lesions are associated with a variety of signs, symptoms and
41 loss of function, which may significantly impair the quality of life.
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49 In our prospective study, 38.7% of patients developed oral LCH, while the remaining 19 patients
50 (61.3%), followed up for a mean of 4.02 years (range 0.6-18), remained free from oral lesions. This
51 rate of occurrence is in accordance with other prospective studies and reports (Sigala et al., 1972,
52 Arico et al., 2003, Arico, 2004); however, the frequency of oral involvement reported in literature
53 ranges between 4.5% (Blevins et al., 1959) and 86% (Bartnick et al., 2002). This wide variation may
54 be explained by the heterogeneity of case series as regards the case definition, the length of follow
55 up and the stratification for patients' age; under the latter point of view, the most of data belong to
56 paediatric literature. In our series only adult patients are considered. In the present study patients
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3 were not assessed by the same clinician at each follow up evaluation, but all the reported lesions
4 were diagnosed by means of clinical, radiological, laboratory, and histopathological procedures;
5 thus, within this standardized diagnostic work-up, inter-examiner or intra-examiner variability has
6 little chance to significantly alter results.
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10 Oral manifestations include signs and symptoms involving bone, periodontium and oral soft tissues,
11 with pain and gingival bleeding/ulceration being the most frequent as reported in other
12 series(Hartman, 1980, Schepman et al., 1998). These can cause a significant loss of oral function
13 and detrimental effects in patients' quality of life, as well as aesthetics impairment when anterior
14 regions are involved. In the majority of patients (58.3%), oral lesions involved, both the mandible
15 and the maxilla in a multifocal pattern; in addition, a preference for posterior regions was observed.
16 In particular, the absence of isolated anterior lesions let us speculate that posterior regions may be
17 interested in earlier phases of the disease. From a clinical point of view, this could mean that
18 whenever involvement of anterior regions of jawbones is discovered, a careful evaluation should be
19 always carried on in order to exclude the presence of posterior lesions. The analysis of data shows
20 that unifocal oral involvement is significantly associated with multisystemic disease while
21 multifocal oral lesions are associated with unisystemic involvement (chi-square test, $p < 0.05$). This
22 may seem a bit contradictory but we have no explanation for it. The only implication that we can
23 draw from this finding is that attention should be deserved for oral unifocal involvement; in fact, the
24 control of local lesions may be easier, but patient prognosis might be worse due to the
25 multisystemic disease. Oral and periodontal lesions were easily handled with local measures
26 (Tab.2). In particular, bone disease was treated by surgical curettage; this was associated with teeth
27 extraction when periodontal damage caused by histiocytosis infiltration was present, and excision of
28 involved soft tissues. Only one case received intralesional injection of α -interferon in order to treat
29 a localized oral mucosa lesion. In fact, α -interferon promotes the terminal differentiation of
30 histiocytes and dendritic cells; it has proved to be most efficacious in small tumour masses(Simko
31 & Nagy, 1996), and its efficacy in the therapy of LCH has been suggested to coincide with the
32 expression and activation of the protein kinase C- α signalling pathway in LCH-histiocytes(Brown,
33 2003). As regards the patient receiving systemic chemotherapy, it is important to note that this was
34 intended not to treat oral lesions but systemic disease. In fact, the patient was diagnosed with LCH
35 few months before and was still under active treatment for systemic disease control. Systemic
36 medications were useful also in healing oral lesions, but soon a new different oral site was involved.
37 We can speculate that this occurred because systemic disease, and oral lesions included in its
38 spectrum, was not completely controlled yet. On the other hand, the second patient who
39 experienced a new oral lesion after treatment had a stable systemic disease since many years. The
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3 oral lesion was again controlled by local measures and the adjusted follow up showed no systemic
4 relapses without any other systemic treatment; nonetheless, it is not possible to completely rule out
5 that the new oral lesion might be considered the first sign of disease reactivation.
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10 **Authors' statements**

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12 The authors disclose that they have no conflict of interest related to this study.

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9 **FIGURE LEGENDS**

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11 **Figure 1:** Organ involvement in adult LCH patients.

12 **Figure 2:** Radiographic appearance of mandibular bone LCH lesions.

13 **Figure 3:** Clinical appearance of gingival LCH lesions (same case in fig.2).

14 **Figure 4:** LCH lesion extending to alveolar mucosa; note ulcerations associated with proliferative
15 exuberant tissue.

16 **Figure 5:** A) dense infiltration by clusters of eosinophils and mononuclear cells. The surface
17 epithelium is ulcerated with exocytose and granulocytic microabscesses (Haematoxylin-
18 Eosin, 10X).

19 **B)** Immunophenotyping: positivity for CD1a antigen. (LSAB-HRP, nuclear
20 counterstaining with haematoxylin, 10X).

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60**Table 1:** Clinical features of adult LCH patients.

Systemic involvement	Case	Age at first diagnosis	Sex	Involved Organs	Therapy	Disease status	Follow up (years)
UNISYSTEM							
Unifocal	1	28	F	skull	PDN	Drop out	1
	2	33	F	skull	PDN	Drop out	5.7
Multifocal	3	36	M	skull	PDN	Progression	0.6
	4	42	F	lymphnodes	PDN	Remission	0.6
	5	40	M	clavicle	RAD	Remission	0.6
	6	18	M	skull, hip, scapula	VBL + PDN	Drop out	18
	7	19	M	lung	PDN	Remission	13
	8	22	F	lung	PDN	Drop out	6
	9	22	F	abdominal lymphnodes	PDN	Remission	4.1
	10	26	M	lung	IFN	Remission	13
	11	34	M	lung	PDN	Remission	5.5
	12	38	M	lung	VBL + HDMP	Remission	11
	13	39	F	ilium	VBL	Remission	13
	14	43	M	femur, ilium	VBL + HDMP	Remission	18
	15	45	M	lung	VBL + HDMP	Remission	5
	16	51	M	lung	VBL + HDMP	Died	8
	17	71	F	skin	VBL	Died	4.6
	18	40	F	skull	PDN	Remission	0.6
	19	29	F	hypophysis, lung	VBL + HDMP	Remission	0.6
	20	22	M	skull, ribs, scapula	VBL + PDN	Remission	0.6
MULTISYSTEM							
Unifocal	21	18	M	skull, hypophysis	VBL + HDMP	Remission	14
	22	18	F	skull, lung, vulva	VP-16 + HDMP	Relapse	14
	23	36	F	lung, ribs	PDN	Remission	4.2
	24	39	M	skin, tibia, omerus	IFN	Drop out	1
	25	46	M	bone, lung	VBL + HDMP	Drop out	4.2
Multifocal	26	57	F	lung, vulva	VBL + HDMP	Remission	8
	27	72	F	skull, hypophysis	PDN	Progression	0.6
	28	37	F	lung, skull	PDN	Remission	0.6
	29	73	F	lung, skull	PDN	Remission	0.6
	30	34	F	neck lymphnodes, hypophysis	PDN	Remission	0.6
	31	29	M	hypophysis, skull, lung, femur, tibia	VBL + PDN	Remission	0.6

VBN: vinblastina; PDN: prednisone; IFN: α -interferone; HDMP: methylprednisolone; VP-16: etoposide; RAD: radiotherapy.

Table 2: Clinical features of oral LCH involvement in adult patients.

Case	Oral involvement				Oral lesions	Therapy for oral disease	Oral lesions Outcome*
	Maxilla		Mandible				
	anterior	posterior	anterior	posterior			
1	-	-	-	+	single	SC	Complete Response
7	-	-	-	+	single	SC	Complete Response
10	-	+	-	+	multiple	TE + SC + IFN	Complete Response
13	-	+	+	+	multiple	TE + SC + STE	New oral lesion
14	-	+	-	+	multiple	TE + SC	Complete Response
15	-	+	-	-	multiple	STE	Complete Response
17	+	+	+	+	single	TE + SC	Complete Response
21	-	-	-	+	single	TE + SC	Complete Response
22	-	+	-	+	multiple	TE + SC	Complete Response
24	+	+	+	+	multiple	TE + SC	Complete Response
25	-	+	-	-	single	STE	Complete Response
27	-	+	+	+	multiple	Systemic Chemotherapy	New oral lesion

TE: teeth extraction

SC: surgical curettage

IFN: local α -interferon

STE: soft tissues excision

*: to the last follow up visit

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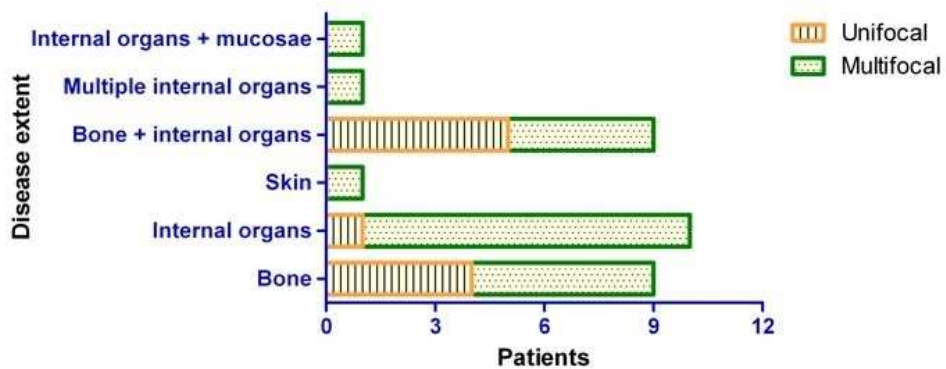


Figure 1: Organ involvement in adult LCH patients.
190x142mm (96 x 96 DPI)

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Figure 2: Radiographic appearance of mandibular bone LCH lesions.
292x247mm (72 x 72 DPI)

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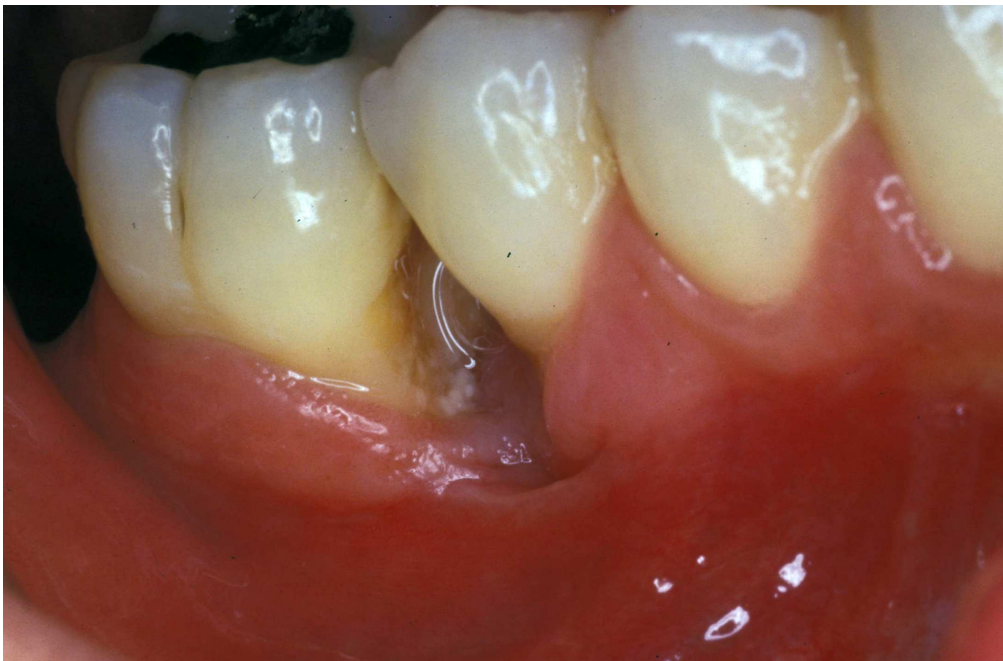


Figure 3: Clinical appearance of gingival LCH lesions (same case in fig.2).
137x90mm (400 x 400 DPI)

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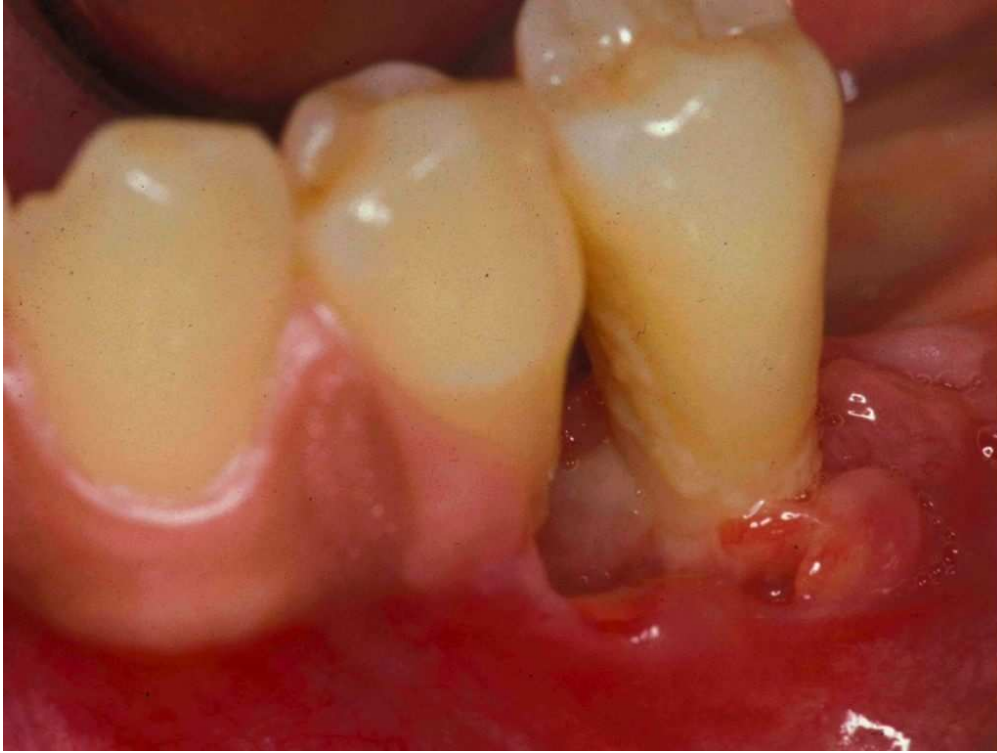


Figure 4: LCH lesion extending to alveolar mucosa; note ulcerations associated with proliferative exuberant tissue.

361x270mm (72 x 72 DPI)

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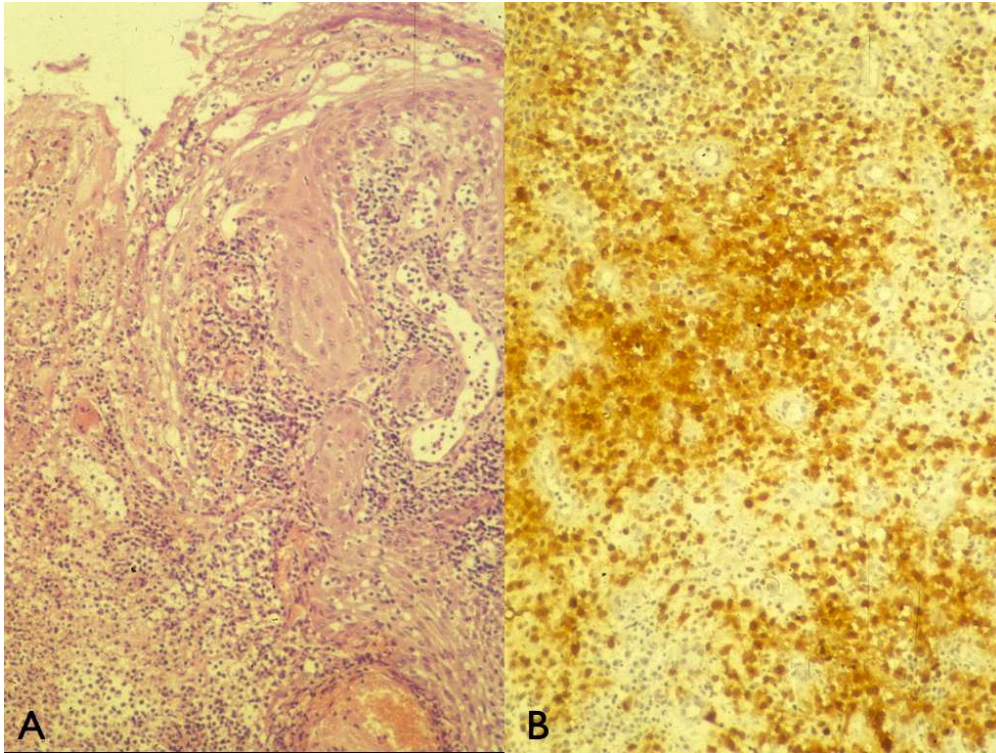


Figure 5: A) dense infiltration by clusters of eosinophils and mononuclear cells. The surface epithelium is ulcerated with exocytose and granulocytic microabscesses (Haematoxylin-Eosin, 10X). B) Immunophenotyping: positivity for CD1a antigen. (LSAB-HRP, nuclear counterstaining with haematoxylin, 10X).
361x270mm (72 x 72 DPI)