Abstract

Langerhans cell histiocytosis (LCH) is a group of rare and enigmatic disorders of the reticuloendothelial system characterised by abnormal, possibly neoplastic, proliferation of Langerhans cells. Oral lesions, in particular osteolytic lesions of the jaws, may be the primary or the sole manifestation of the disease. A 44 year old woman with a history of eosinophilic granuloma on the lower left canine region excised 25 years ago presented with an asymptomatic, ulcerated gingival lesion, extending lingual and distal to the right mandibular second premolar tooth, which was noticed approximately 6 months ago. The underlying bone was not involved. Histopathologic and immunohistochemical examination showed an LCH, consistent with eosinophilic granuloma. Radiotherapy was given, and 10 months later she developed three small painful ulcers located on the palatal gingivae around the right canine, between the second premolar and first molar, and around the right third molar, also diagnosed as eosinophilic granuloma. Eosinophilic granuloma may present in the gingival mucosa, in the absence of bone involvement, and may run a protracted course with remissions, reactivation and progression from single system to multi-system involvement. Therefore, long-term periodical follow-up and restaging is mandatory. The presence of a high proportion of plasma cells expressing lambda-light chains may cause a diagnostic dilemma with plasma cell malignancy would be interesting to be evaluated in additional cases.

Clinical Relevance

This study aims to present a rare case of LCH consistent with eosinophilic granulomas that presented with gingival lesions without bone involvement, to describe the clinical course of the disease over a 27 year period and to report the presence in those lesions of a high proportion of plasma cells predominantly expressing lambda-light chains that caused a diagnostic dilemma with plasma cell malignancy. It is concluded that LCH may present in the gingival mucosa in the absence of bone involvement and a long-term periodical follow-up is mandatory. The high proportion of plasma cells expressing lambda-light chains requires further evaluation.

Introduction

Langerhans cell histiocytosis (LCH) is a group of rare and enigmatic disorders of the reticuloendothelial system characterised by abnormal proliferation of Langerhans cells (LCs). It was first described by Lichtenstein in 1953 as histiocytosis X, and the LC origin was later confirmed by ultrastructural recognition of the characteristic Birbeck granules, as well as immunopositivity for S100 protein, CD1a antigen and human carcinoma-associated antigen. The pathogenesis of LCH remains unknown, with theories suggesting environmental, infectious, immunologic and genetic associations, but more recent evidence indicates a neoplastic aetiology.
LCH shows no sex predilection but is more common in children and young adults, whereas individuals over the age of 50 years are rarely affected\(^5,8\). Clinically, it may manifest as a single-system disease, showing unifocal or multifocal involvement of a single organ or system, that has a good prognosis, or as a multi-system disease, showing involvement of multiple organs or systems, that may be life-threatening\(^5,8,9\). Traditionally, LCH is categorised into a monostic or polyostic form (eosinophilic granuloma), a chronic disseminated form (Hand–Schüller–Christian disease) and an acute disseminated form (Letterer–Siwe disease)\(^1,2\). Single-system LCH usually involves the bones, skin, lymph nodes, lungs, etc, and multi-system LCH involves the haematopoietic system, spleen, liver, etc\(^9\). The bones more commonly involved include the skull, pelvis, ribs, mandible, clavicle, spine and humerus\(^10\). Occasionally, LCH may be associated with Hodgkin’s disease, non-Hodgkin’s lymphoma and leukemia\(^11\), and rarely with lung, thyroid, breast, liver, skin and stomach carcinomas, chondrosarcoma, osteosarcoma, astrocytoma, menigioma, retinoblastoma, apudoma and hepatoma\(^12\).

Oral lesions may be the primary\(^13\) or the sole\(^14\) manifestation of LCH. The jaws are affected twice as frequently as the rest of the oral tissues, and the mandible three times more frequently than the maxilla\(^15,16\). Pain, tenderness and progressive tooth mobility may be the manifesting sign, whereas the teeth ‘floating in air’ is the characteristic radiographic feature\(^14\). LCH of the oral soft tissues is rare and may present with painful gingival swelling or ulceration\(^1,14\), submucosal nodules or white plaques\(^17\).

We describe the unusual case of a patient with eosinophilic granuloma in the gingival mucosa that developed three recurrences over a 27 year period, totalling five lesions. In all lesions, a focal predominance of plasma cells expressing lambda-light chains was recorded.

**Case report**

**Clinical presentation**

A 44 year old woman presented with an asymptomatic enlargement on the right mandibular area, noticed approximately 6 months ago. There was a history of a painful ulcer on the lower left canine region excised 25 years ago, when she was of 19 years old, diagnosed as ‘eosinophilic granuloma’. The patient was managed with external beam radiation, but she did not attend the scheduled follow-up programme. Her medical history was free of any other disease, and she denied use of any medication or alcohol consumption. She was smoking 20 cigarettes per day.

Oral examination showed a 1 × 1 cm ulcerated gingival lesion, extending lingual and distal to the right mandibular second premolar tooth (Fig. 1A,B). It had red color, not well-defined borders and was firm and not painful on palpation. The second premolar showed grade II mobility but no pain on percussion. The remaining of the oral mucosa, as well as a thorough head and neck examination, were within normal limits. A panoramic radiograph showed generalised alveolar bone loss, consistent with periodontitis, but no other bone abnormality in association with the gingival lesion (Fig. 2). With the provisional diagnosis of pyogenic granuloma, the lesion was totally excised under local anaesthesia, and the surgical wound was covered with periodontal dressing. The tissue specimen was fixed in 10% buffered formalin and submitted for histopathologic examination. Post-operative healing was uneventful.

![Figure 1 Ulcerated gingival lesion (A) lingual and (B) distal to the right mandibular second premolar tooth.](image-url)
Histopathology

Grossly, an ovoid solid mass, measuring $1.0 \times 1.0 \times 0.5$ cm, was received. Its external surface was tan-pink with focal haemorrhages, and the cut surface was heterogeneous, with firm white to soft pink areas. Five-micron thick paraffin embedded tissue sections showed a dense infiltration of the connective tissue by large, epithelioid cells with indented vesicular nuclei and ample eosinophilic cytoplasm, intermixed with many eosinophils (Fig. 3A). The diagnosis was LCH, consistent with eosinophilic granuloma, and the focal presence of a high proportion of plasma cells was, also, noticed (Fig. 3B).

Streptavidin-biotin-peroxidase immunohistochemistry was performed with the Ventana BenchMark XT fully automated slide preparation system (Ventana Medical Systems Inc., Tucson, AZ, USA) and the iView DAB detection kit (Ventana). The clone, dilution and manufacturer of the primary antibodies used are summarised in Table 1. Appropriate positive controls were utilised according to the instructions of the antibodies’ manufacturers, whereas for negative controls, primary antibodies were substituted with a non-immune serum of the same specificity. Epithelioid cells showed cytoplasmic positivity for S100 protein (Fig. 4A) and membranous positivity for CD1a antigen (Fig. 4B), confirming the diagnosis of LCH. Due to the focal presence of a high proportion of plasma cells, immunohistochemistry for kappa- and lambda-light chain was performed. A predominance of lambda-light chains (Fig. 4C) was seen, raising the possibility of a plasma cell myeloma. Further investigation showed that the plasma cells showed focal positivity for CD138/syndecan 1, CD20, CD38, CD45/LCA, but no reaction for CD19 and CD27, an immunophenotype not consistent with a plasma cell malignancy.

<table>
<thead>
<tr>
<th>Antibody Clone</th>
<th>Dilution</th>
<th>Manufacturer</th>
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<tbody>
<tr>
<td>S100 Rabbit Polyclonal</td>
<td>1:400</td>
<td>Dako†</td>
</tr>
<tr>
<td>CD1a Mouse Monoclonal</td>
<td>010</td>
<td>1:50 Dako</td>
</tr>
<tr>
<td>CD19 Mouse Monoclonal</td>
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<td>CD20cy Mouse Monoclonal</td>
<td>L26</td>
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<tr>
<td>CD27 Mouse Monoclonal</td>
<td>13B84</td>
<td>1:50 Leica Biosystems‡</td>
</tr>
<tr>
<td>CD38 Mouse Monoclonal</td>
<td>SP3C2</td>
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</tr>
<tr>
<td>CD45 Mouse Monoclonal</td>
<td>2B11+PD7/26</td>
<td>1:60 Dako</td>
</tr>
<tr>
<td>CD138 Mouse Monoclonal</td>
<td>M115</td>
<td>1:30 Dako</td>
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†Dako, Glostrup, Denmark; ‡Leica Biosystems, Newcastle, UK.
Management

The patient was referred to a specialised oncology clinic for further investigation and treatment. In order to further exclude a plasma cell malignancy, complete blood count, blood chemistry and urine; electrophoresis of serum and concentrated urine for paraprotein (M-protein), CT scan of the head and neck, and thorax; and bone marrow biopsy were performed, without pathologic findings. Those findings, as well as gastroscopy, colonoscopy and upper and lower abdominal ultrasonography excluded multi-system LCH. With the diagnosis of eosinophilic granuloma of the gingival mucosa, radiotherapy was given, in a total dose of 50 gy, with complete healing of the lesion.

Follow-up

Ten months later, the patient presented with three small painful ulcers located on the palatal gingivae around the right canine, between the second premolar and first molar (Fig. 5) and around the right third molar. The gingival in the right mandibular second premolar area was clinically normal. A new panoramic radiograph and CT scan of the jaws did not detect osteolytic lesions, other than those associated with the periodontitis. Biopsies were taken from all three lesions, and the microscopic and immunohistochemical findings were diagnostic of eosinophilic granuloma. The focal predominance of plasma cells expressing lambda-light chains was reconfirmed both on the most recent biopsies, as well as on archival tissue material from the first biopsy, performed 27 years ago. The

Figure 4 Epithelioid cells show (A) cytoplasmic positivity for S-100 protein, (B) membranous positivity for CD1a, whereas (C) plasmacytes show a high proportion of lambda-chains (avidin-biotin-peroxidase, original magnification ×400).

Figure 5 Small ulcers on the palatal gingivae around the right canine (two arrows), and between the second premolar and first molar (arrow), 10 months after initial examination.
patient was again referred to the oncology clinic for further evaluation and treatment.

Discussion

In the case of the patient presented herein, a total of five LCH lesions, consistent with eosinophilic granulomas, developed over a 27 year period in the gingival mucosa, in the absence of bone involvement, whereas the histopathologic and immunohistochemical investigation showed a focal predominance of plasma cells expressing lambda-light chains.

Oral lesions appear in 77% of patients with LCH4; however, LCH lesions restricted to soft tissue, in the absence of bone involvement, are rare and to the authors’ knowledge, only eight cases have been reported1,13,17–19. Seven patients were male1,13,17–19 and one female1, aged 24–65 years. The lesions were described as ulcerations1,13,17,18 or leukoplakia and corrugated area17, were single1,13,14 or multiple1,19 in equal numbers and were located on the mandibular gingiva in two cases17 or maxillary gingiva, extending to the mucobuccal fold or hard palate in six cases1,13,17,18. In three cases1,13,14, they were painful, and in two cases further work-up disclosed lung17 or extragnathic bone18 involvement. An additional case17 was not included in our review, as bone involvement was later found in the area where a mucosal lesion had been excised. In our patient, all lesions were located in the gingival soft tissue, were not associated with extragnathic lesions, and recurrences over the 27 year follow-up were not followed by bone involvement.

An unusual microscopic feature of all lesions in our patient was the presence of a dense infiltrate of lambda-light chains expressing plasma cells. This finding caused a diagnostic dilemma as an association of LCH with plasmacytoma was described in three previous reports13,20,21. Our patient had periodontitis with alveolar bone lose, where plasma cells are the most commonly found inflammatory cells22,23, but in periodontitis kappa-light chain positive plasma cell usually predominates24. The association of LCH with plasma cell malignancy is interpreted with the suggestion that the cell of origin of LCH is not the epidermal LC25 but a common bone marrow precursor of LC and plasmacytes26–28. In addition, LCH cells may express cytokines, such as CCl20/MIP-3a, that may influence other cell types, including plasma cells29, or tumor necrosis factor alpha (TNFa) and interleukin-1 (IL-1) that may play a critical role in the pathogenesis of plasmacytoma and multiple myeloma30. In our case, the plasma cell infiltrate was found to be composed of some CD20+ B-cells, CD38+ and CD138+ plasma cells at almost equal ratio but no CD19+ or CD27+ plasma cells. CD38 and CD138 antigens are universal markers of normal and malignant plasma cells, terminally differentiated plasma cells do not express CD19 and lack of CD27 is indicative of naive B cells31–33. Thus, the immunohistochemical findings were not consistent with plasma cell malignancy, and this was confirmed by further laboratory investigation. The high proportion of lambda-light chains expressing plasma cells would be interesting to be evaluated in additional cases.

Pathogenesis of LCH is unknown, and theories suggest environmental, infectious, immunologic and genetic associations4. Immunological abnormalities as a result of suppressor cell deficiency or viral infection of the lymphocytes, especially from human herpesvirus 6, have been recently proposed34. The neoplastic theory is supported by studies showing genetic changes that cause alterations to cell cycle regulation, apoptosis and proliferation5,6, as well as the detection of molecular cytogenetic aberrations, including loss of heterozygosity on chromosomes 1, 4, 6, 7, 9, 16, 17 and 25 and telomere length shortening7,35.

Patients with single-system LCH have a high chance of spontaneous remission and positive outcome3. Spontaneous remission within a few months is seen in approximately 50% of LCH lesions restricted to the skin, but reactivation or progression to a disseminated disease may appear36. Reactivation can occur in up to 25% of patients with multifocal bone lesions and in 50–70% of those with bone lesions as part of multi-system disease37. In a previous case report1, a patient with a unifocal lesion in the palate developed later new lesions on the mandibular gingivae. The risk of reactivation, as well as progression from a single-system to multi-system disease necessitates long-term periodical follow-up with thorough re-evaluation of the patient, in 3–12 months intervals, based on the extent and the activity of the disease38,39. In our patient, reactivation followed a 27 year period of remission, and the interval between the second and third recurrence was just 10 months.

There are no universally accepted international guidelines available for the treatment of adult LCH. Management of oral LCH depends on the size of the lesion, extent of tissue involvement and symptoms9,39. ‘Mild systemic’ therapy with thalidomide, azathioprine or methotrexate6, as well as local radiation and/or surgical excision have been proposed2. Experience considering the management of oral soft tissue eosinophilic granuloma is limited, due to the small number of published cases. Radiotherapy or perilesional triamcinolone acetonide infiltration1, surgical removal with
CO₂ laser, with vaporisation the periosteum and the underlying bone, followed by topical application of triamcinolone acetonide, excisional biopsy alone or followed by radiotherapy have been applied in cases with solitary involvement of the oral mucosa. The disease-free follow-up ranges from 9 months to 3 years. In the case presented herein, surgical excision followed by radiotherapy resulted in complete healing of the lesion.

In conclusion, LCH may rarely develop in the gingival mucosa, in the absence of bone involvement, and may run a protracted course with remissions, reactivation and progression. Therefore, a long-term periodical follow-up with thorough re-evaluation of the patient is mandatory. The high proportion of plasma cells expressing lambda-light chains that in the present case caused a diagnostic dilemma with plasma cell malignancy would be interesting to be evaluated in additional cases.

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References


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Recurrent LCH of the gingival mucosa

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