J Oral Pathol Med (2006) 35: 262–7

www.blackwellmunksgaard.com/jopm

Lichenoid and granulomatous stomatitis: an entity or a non-specific inflammatory process?

C. Max Robinson[1], Jon D. Oxley[2], Justin Weir[3], John W. Eveson[1]

[1]*Department of Oral and Dental Science, University of Bristol;* [2]*Department of Pathology, Southmead Hospital, Bristol;* [3]*Department of Pathology, Charing Cross Hospital, London, UK*

BACKGROUND: The presence of lichenoid or granulomatous inflammation in an oral mucosal biopsy usually suggests a distinct range of diagnostic possibilities. However, the presence of both patterns of inflammation in the same biopsy is uncommon.
METHODS: A clinico-pathological study of six patients.
RESULTS: All the patients in this study presented with similar mucosal lesions of the upper lip. Microscopically the lesions were characterized by the presence of lichenoid inflammation with concomitant granulomatous inflammation. The lesions were persistent and refractory to treatment with steroid medications, but remained localized and did not appear to herald the onset of systemic inflammatory or neoplastic disease.
CONCLUSION: We propose the designation 'lichenoid and granulomatous stomatitis' for the cases described in this study. The clinico-pathological features of a subset of these cases suggest an unusual drug eruption.
J Oral Pathol Med (2006) **35**: 262–7

Keywords: lichenoid; granulomatous; stomatitis; drug eruption

Introduction

The clinical presentation of an inflamed red patch on the labial mucosa of the upper lip prompts a wide differential diagnosis. The separation of such a diverse range of diseases is usually facilitated by incisional biopsy in combination with haematological investigations. The histopathological appearances of oral mucosal diseases that have an inflammatory component can broadly be separated by the composition of cells within the inflammatory infiltrate. For example, the presence of acute and chronic inflammation, in the absence of other distinguishing pathological features, is usually non-specific. However, by contrast, the presence of granulomatous inflammation typically leads to a restricted list of diagnostic possibilities that may be distinguished by additional clinical information or further investigations. Granulomatous disorders affecting the oral cavity can be divided into three groups: those caused by micro-organisms (tuberculosis, syphilis, deep mycoses), those associated with foreign body implantation (toothpaste abrasives, dental materials, pulse granuloma), and idiopathic diseases (oro-facial granulomatosis, Melkersson–Rosenthal syndrome, Crohn's disease, sarcoidosis, Wegener's granulomatosis, giant cell arteritis) (1, 2). Similarly, the presence of lichenoid inflammation at the epithelio-mesenchymal interface suggests a limited range of disorders including lichen planus, lichenoid reactions, oral contact hypersensitivity stomatitis, lupus erythematosus, graft versus host disease and lichen sclerosis et atrophicus (3).

To our knowledge the presence of lichenoid inflammation with concomitant granulomatous inflammation is an uncommon observation within the oral tissues. Lichenoid and granulomatous inflammation have been reported in cases of foreign body gingivitis, which was first described by Daley and Wysocki (4). In a series of patients with foreign body gingivitis, the investigators reported the presence of both patterns of inflammation in 16 of 61 (26%) biopsies studied (5). Foreign body gingivitis is defined by the presence of opaque, refractile foreign material within the gingival connective tissues and studies using energy-dispersive X-ray microanalysis have demonstrated that, in the majority of cases, the material is derived from constituents of toothpastes and dental materials (4, 6).

In the dermatological literature, the concurrent presence of lichenoid and granulomatous inflammation is also uncommon. Magro and Crowson (7) reported a series of 40 patients with skin lesions showing a novel constellation of lichenoid dermatitis with a granulomatous component. In the majority of cases, there were confounding medical problems associated with the disease, however, one-fifth of cases represented idiopathic lichenoid disorders. Similar features have recently been described in a patient with myeloma being treated with erythropoietin (8). Furthermore, other skin lesions,

Correspondence: Dr Max Robinson, Department of Oral and Dental Science, University of Bristol Dental School, Lower Maudlin Street, Bristol BS1 2LY, UK. Tel: +44 117 928 4304. Fax: +44 117 928 4428. E-mail: max.robinson@bristol.ac.uk
Accepted for publication December 15, 2005

Table 1 Clinical features of 'lichenoid and granulomatous stomatitis'

Subject	*Gender*	*Age (years) at onset*	*Presentation*	*Medical history*	*Investigations*	*Treatment*	*Outcome*
1	Female	58	Symptoms: swelling of the upper lip Site: upper labial mucosa Appearance: diffuse swelling with erythematous patch Size: 8 mm Clinical diagnosis: mucocele	Multiple sclerosis Asthma	Incisional biopsy Chest radiograph	30 mg prednisolone for 14 days then 5 mg on alternate days for 3 months	Review period: 64 months No resolution Periods of exacerbation and quiescence
2	Female	55	Symptoms: painful, tender upper lip Site: upper labial mucosa and adjacent gingiva Appearance: diffuse swelling with erythematous patch Size: 20 mm Clinical diagnosis: lichenoid drug eruption, DLE[a]	Osteoarthritis Naproxen Atenolol	Incisional biopsy FBC: normal Haematinics: normal Autoimmune profile: ds DNA 8 iu/ml (normal range <25)	Naproxen discontinued Adcortyl in orobase[b] Betnesol mouthwash[c] Becotide 100[d]	Review period: 59 months No resolution Periods of exacerbation and quiescence
3	Male	63	Symptoms: sore gum above upper incisor teeth Site: upper labial mucosa and adjacent gingiva Appearance: erythematosus patch, no swelling Size: 15 mm Clinical diagnosis: lichen planus, DLE[a]	Prostate hyperplasia	Incisional biopsy	Difflam[e] Betnesol mouthwash[c] Becotide 100[d]	Review period: 40 months No resolution Periods of exacerbation and quiescence
4	Female	54	Symptoms: tender swelling on upper lip Site: upper labial mucosa and adjacent gingiva Appearance: red granular patch with petechiae Size: 15 mm Clinical diagnosis: DLE[a], granulomatous lesion	Hypertension Ramipril Bendrofluazide Allergic to elastoplast	Incisional biopsy	Becotide 100[d]	Review period: 11 months No resolution Periods of exacerbation and quiescence
5	Male	65	Symptoms: no details available Site: upper labial mucosa Appearance: red patch Size: 5 mm Clinical diagnosis: no details available	No details available	Incisional biopsy	No details available	No details available
6	Female	60	Symptoms: no details available Site: upper labial mucosa Appearance: red patch with swelling Size: no details available Clinical diagnosis: no details available	No details available	Incisional biopsy	No details available	No details available

[a]Discoid lupus erythematosus.
[b]Triamcinolone acetonide 0.1% in adhesive basis. Paste applied to lesion four times daily.
[c]Betamethasone sodium phosphate tablets, 500 μg. One tablet dissolved in 10 ml of water used as a mouthwash for 4 min, four times daily.
[d]Beclometasone dipropionate, 100 μg/metered inhalation. One puff directed at the lesion four times daily.
[e]Benzydamine hydrochloride 0.15% oral rinse. Rinse with 15 ml as required.

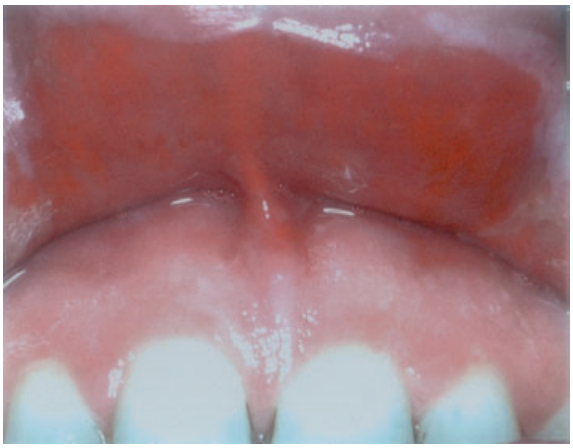

Figure 1 Typical clinical appearance of 'lichenoid and granulomatous stomatitis'.

with comparable histopathological features, but characterized by the presence of giant cells, have been designated giant cell lichenoid dermatitis (9–11). In addition, lichenoid and granulomatous inflammation may coexist in the exceptionally rare skin condition, lupus erythematosus profundus (12).

Materials and Methods

Six patients formed the basis of this clinico-pathological study. Four of the patients were examined and treated by one of the authors (JWE) at the Bristol Dental Hospital. The medical records of these patients were examined along with the biopsy material. Biopsy material from the other two cases were referred to one of the authors (JWE) for a second opinion. The referral letters from these cases were scrutinized along with the biopsy material.

Results

Clinical features

The clinical details of the subjects are documented in Table 1. There were four females and two males, with a mean age of 59 years (range 54–65) and they were all Caucasians. All subjects presented with a localized erythematous patch on the labial mucosa of the upper lip, with or without attendant swelling (Fig. 1). Three patients had similar changes on the labial aspect of the gingiva, in close proximity to the labial lesion. All patients underwent incisional biopsy and two had additional clinical investigations. One patient had a chest radiograph, which did not show any significant abnormality, and the other had haematological investigations, which were essentially normal; the autoimmune profile demonstrated a low titre (8 iu/ml) of double-stranded DNA autoantibodies, which was within the normal range for the test. Four of the subjects had detailed clinical information regarding their medical histories and treatment regimens and were followed up for a mean period of 44 months (range 11–64 months). Two of these individuals were taking medications known to be associated with lichenoid eruptions. Subject 2 was taking naproxen and atenolol and subject 4 was taking ramipril. All four patients received steroid-based therapies and subsequent consultations revealed that the lesions typically failed to resolve and showed phases of active disease followed by periods of quiescence.

Histopathological features

The histopathological features are documented in Table 2 and illustrated in Fig. 2. All the lesions had three distinctive components. First, there was lichenoid inflammation, characterized by hyperkeratosis, basal cell damage, apoptotic bodies and a band-like lymphohistiocytic infiltrate at the epithelio-mesenchymal interface. Secondly, there were variable degrees of granulomatous inflammation throughout the corium. All the granulomas were composed of epithelioid macrophages, giant cells were absent and there was no necrosis. Thirdly, there were lymphoid nodules in the corium with many showing a striking perineural distribution. The nodules were composed of rather monotonous, medium-sized lymphocytes; immunohistochemical analysis of four biopsies demonstrated a mixed population of B and T lymphocytes. Additional studies to demonstrate foreign material and acid-alcohol-fast bacilli were negative. In one case (Subject 1), scanty fungal hyphae were demonstrated in the upper epithelial layers; however, other pathological features suggestive of candidosis, such as acute inflammation with spongiform pustules and psoriasiform hyperplasia, were absent.

Discussion

We have reported a series of six patients who presented with similar mucosal lesions of the upper lip showing concurrent lichenoid and granulomatous inflammation. Although the range of diseases typified by either lichenoid inflammation or granulomatous inflammation is rather distinctive, when the two patterns are present simultaneously, there are problems determining which represents the primary disease process, or indeed, if the coexistence of the two patterns of inflammation represents a distinct disease entity. For example, it is possible that lichenoid inflammation renders the oral mucosa more susceptible to the ingress of foreign material, with subsequent granuloma formation. The biopsy material in the current study was examined systematically using close inspection and polarized light, but no foreign material was observed. Nevertheless, detection of foreign particles in biopsies can be difficult and not all extrinsic materials are refractile using polarized light (4, 6).

Interestingly, two patients were known to be taking medications that have an association with lichenoid eruptions, namely naproxen (non-steroidal anti-inflammatory drug), atenolol (ß-adrenoceptor blocker) and ramipril (angiotensin-converting enzyme inhibitor) (13). Furthermore, these groups of drugs have also been implicated in lichenoid and granulomatous dermatitis (7). This supports the contention that these particular lesions may represent unusual drug eruptions.

Table 2 Histopathological features of 'lichenoid and granulomatous stomatitis'

Subject	*Lichenoid inflammation*[a]	*Granulomatous inflammation*[b]	*Deep lymphocytic infiltrate*	*Foreign material*[c]	*Diastase PAS*[d]	*ZN stain*[e]	*Immunohistochemistry*
1	Present T-cell infiltrate composed of CD4 and CD8 lymphocytes	Numerous, small, well-formed granulomas	Nodules of medium-sized lymphocytes Perineural distribution Mixture of B and T cells	Negative	Positive for fungal hyphae	Negative	CD20 CD3, CD4, CD8 CD68
2	Present T-cell infiltrate composed of CD4 and CD8 lymphocytes	Numerous, small, well-formed granulomas	Nodules of medium-sized lymphocytes Perineural distribution Mixture of B and T cells	Negative	Negative	Negative	CD20 CD3, CD4, CD8 CD68
3	Present T-cell infiltrate composed of CD4 and CD8 lymphocytes	Numerous, small, well-formed granulomas	Nodules of medium-sized lymphocytes Perineural distribution Mixture of B and T cells	Negative	Negative	Not done	CD20 CD3, CD4, CD8 CD68
4	Present T-cell infiltrate	Few, small, poorly formed granulomas	Nodules of medium-sized lymphocytes Perineural distribution Mixture of B and T cells	Negative	Negative	Not done	CD20 CD3
5	Present	Few, small, well-formed granulomas	Nodules of medium-sized lymphocytes Perineural distribution	Negative	Negative	Not done	Not done
6	Present	Numerous, small, well-formed granulomas	Nodules of medium-sized lymphocytes Perineural distribution	Negative	Not done	Not done	Not done

[a]Lichenoid inflammation was characterized by hyperkeratosis, basal cell damage, apoptotic bodies and a band-like lympho-histiocytic infiltrate at the epithelio-mesenchymal interface.
[b]Granulomas were composed of epithelioid macrophages. Giant cells were absent and there was no necrosis. Granulomas were found at all levels of the corium.
[c]The presence of foreign material was assessed by close inspection and polarized light.
[d]Diastase-treated sections were stained using the periodic acid-Schiff technique.
[e]Ziehl–Neelson stain was used for the detection of acid-alcohol-fast bacilli.

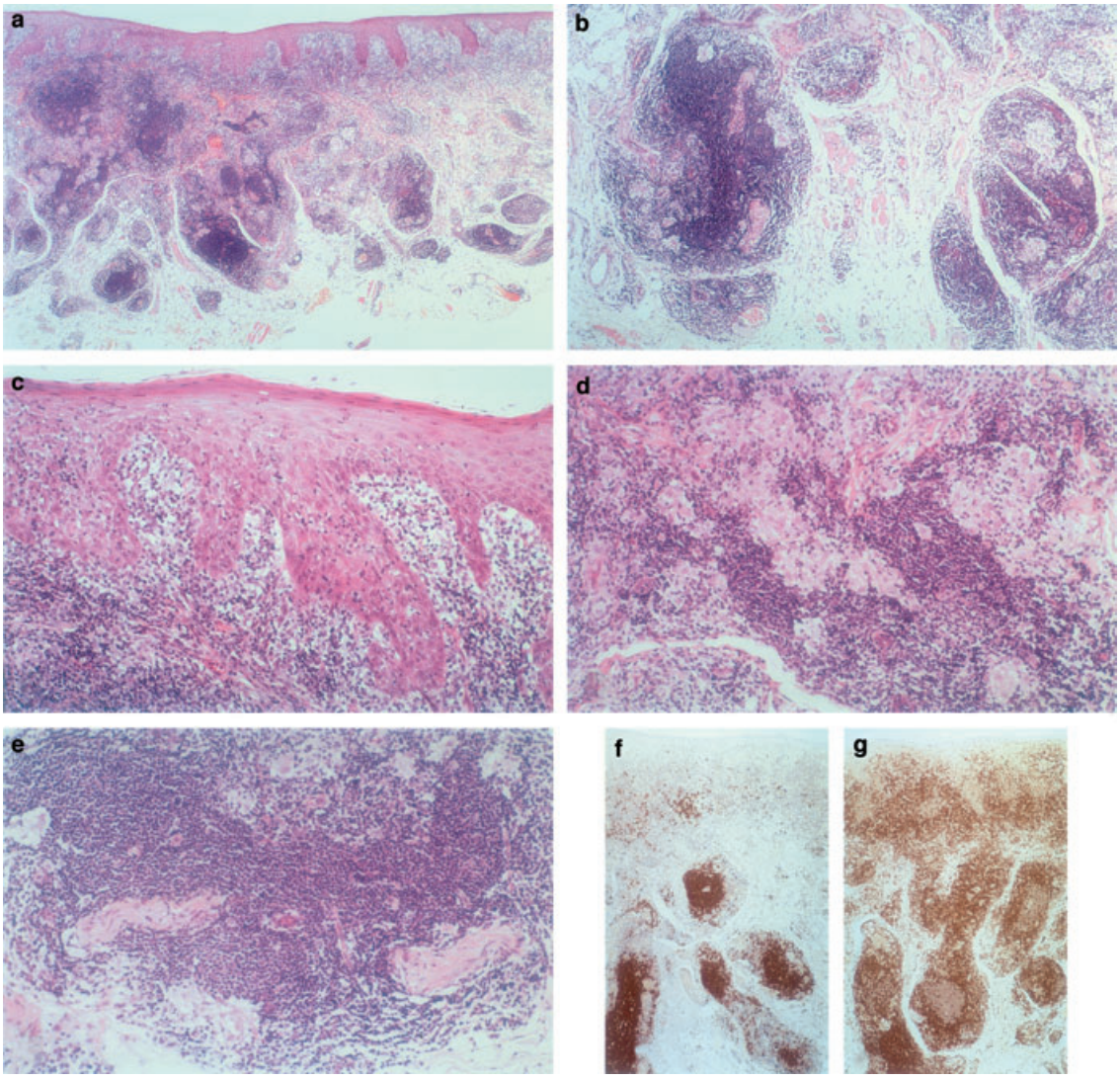

Figure 2 Photomicrographs of 'lichenoid and granulomatous stomatitis'. Photomicrographs are of haematoxylin and eosin preparations, magnification ×300, unless stated. (a) Scanning magnification (×30) showing the distribution of the inflammatory infiltrate. (b) Higher magnification (×60) of the inflammatory infiltrate in the corium. (c) Lichenoid inflammation at the epithelio-mesenchymal interface. (d) Granulomatous inflammation in the corium. (e) Lymphoid nodule surrounding a peripheral nerve and several small granulomas. (f, g) Immunohistochemistry showing the distribution of B (CD20; f) and T lymphocytes (CD3; g) in the inflammatory infiltrate (magnification ×30).

Lupus erythematosus is an autoimmune disease with variable clinical and histopathological features. Lupus erythematosus profundus is an exceptionally rare variant of the disease and is characterized by lichenoid and granulomatous inflammation. Typically, skin lesions have a deep granulomatous component centred on the panniculus and there are also accompanying necrobiotic changes (12). Although the present series of mucosal biopsies demonstrated some of the histopathological features of lupus erythematosus, namely lichenoid inflammation and a deep lymphocytic infiltrate, the granulomas were situated in the corium and not observed within the submucosal tissues.

In one of the cases, fungal hyphae were detected in the superficial epithelial layers, in the absence of other histopathological features of candidosis. It is not possible accurately to determine the significance of this finding in the context of the inflammatory picture observed. However, in one study that examined the frequency of fungal infection in oral mucosal biopsies, there was a significant negative association between fungal hyphae and lichenoid inflammation (14). Furthermore, granulomatous inflammation is not typical of superficial candidosis but is a feature of deep mycoses (15). In addition, it is interesting to note that in 12 of 40 cases of lichenoid and granulomatous dermatitis reported by Magro and Crowson (7), an infective cause was implicated. However, the diseases were either bacterial or viral infections, but not fungal. It is possible, therefore, that the fungal hyphae detected in this case represents an incidental finding.

The documentation of granulomas within an oral biopsy usually prompts the clinician to evaluate the patient for signs of systemic granulomatous disease. All

the patients in this series had isolated oral mucosal lesions and of the four cases that were followed the lesions remained localized.

The prominent lymphoid nodules within the corium demonstrating a perineural distribution prompted the reporting pathologist to immunohistochemically characterize the lymphoid infiltrate in four of the cases. In all these cases, the infiltrate was considered to be reactive; however, it is interesting to note that within the series presented as lichenoid and granulomatous dermatitis, there were three cases of cutaneous T-cell lymphomas (7). Granulomatous reactions may be seen as part of the clinico-pathological spectrum of mycosis fungoides and the closely related disease granulomatous slack skin syndrome (16). However, mycosis fungoides rarely affects the mouth and has never been reported in the absence of skin lesions (17). Incidentally, perineural lymphocytic aggregates with granulomatous inflammation are also a typical feature of leprosy, which should be considered in the appropriate clinical setting (18).

Essentially, all the oral lesions described here were persistent, but remained localized and typically showed phases of active disease followed by periods of quiescence. Furthermore, the lesions failed to resolve using steroid treatments. This type of clinical course is similar to other chronic idiopathic inflammatory diseases, such as lichen planus and oro-facial granulomatosis.

In summary, we have described a series of six patients with similar and unusual oral mucosal lesions showing identical histopathological features and demonstrating a predictable clinical course. We propose that these lesions are designated 'lichenoid and granulomatous stomatitis' to reflect their similarity with lichenoid and granulomatous dermatitis (7). In two cases, the lesions occurred in patients taking medications known to cause lichenoid eruptions and these may represent unusual drug reactions.

References

1. Eveson JW. Granulomatous disorders of the oral mucosa. *Semin Diagn Pathol* 1996; **13**: 118–27.
2. Odell EW, Morgan PR. Biopsy pathology of the oral tissues. London: Chapman & Hall Medical, 1998; 9–33.
3. Odell EW, Morgan PR. Biopsy pathology of the oral tissues. London: Chapman & Hall Medical, 1998; 37–67.
4. Daley TD, Wysocki GP. Foreign body gingivitis: an iatrogenic disease? *Oral Surg Oral Med Oral Pathol* 1990; **69**: 708–12.
5. Gordon SC, Daley TD. Foreign body gingivitis. Clinical and microscopic features of 61 cases. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1997; **83**: 562–70.
6. Gordon SC, Daley TD. Foreign body gingivitis. Identification of foreign material by energy-dispersive x-ray microanalysis. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1997; **83**: 570–6.
7. Magro CM, Crowson AN. Lichenoid and granulomatous dermatitis. *Int J Dermatol* 2000; **39**: 126–33.
8. Wolf IH, Smolle J, Cerroni L, Kerl H. Erythroderma with lichenoid granulomatous features induced by erythropoietin. *J Cutan Pathol* 2005; **32**: 371–4.
9. Gonzalez JG, Marcus MD, Cruz DJ. Giant cell lichenoid dermatitis. *J Am Acad Dermatol* 1986; **15**: 87–92.
10. Goldberg LJ, Goldberg N, Abrahams I, Silvers DN, Szaniawski W, Halperin AJ. Giant cell lichenoid dermatitis: possible manifestation of sarcoidosis. *J Cutan Pathol* 1994; **21**: 47–51.
11. Cordoba S, Fraga J, Bartolome B, Garcia_Diez A, Fernandez-Herrera J. Giant cell lichenoid dermatitis with herpes zoster scars in a bone marrow recipient. *J Cutan Pathol* 2000; **27**: 255–7.
12. Crowson AN, Magro C. The cutaneous pathology of lupus erythematosus: a review. *J Cutan Pathol* 2001; **28**: 1–23.
13. Scully C, Bagan JV. Adverse drug reactions in the orofacial region. *Crit Rev Oral Biol Med* 2004; **15**: 221–39.
14. Barrett AW, Kingsmill VJ, Speight PM. The frequency of fungal infection in biopsies of oral mucosal lesions. *Oral Dis* 1998; **4**: 26–31.
15. Scully C, de Almeida OP. Orofacial manifestations of the systemic mycoses. *J Oral Pathol Med* 1992; **21**: 289–94.
16. Kazakov DV, Burg G, Kempf W. Clinicopathological spectrum of mycosis fungoides. *J Eur Acad Dermatol Venereol* 2004; **18**: 397–415.
17. Wain EM, Setterfield J, Judge MR, Harper JI, Pemberton MN, Russell-Jones R. Mycosis fungoides involving the oral mucosa in a child. *Clin Exp Dermatol* 2003; **28**: 499–501.
18. Cook MG, McKee PH. Infectious diseases. In: McKee PH, ed. *Pathology of the skin with clinical correlations*. London: Gower Medical Publishing, 1989; 4.1–73.