Proliferative Verrucous Gingival Leukoplakia: A Sinister Condition

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Proliferative verrucous leuoplakia (PVL) is widely accepted as an aggressive variant of oral leukoplakia, which tends to manifest itself as a longstanding, persistent leukoplakia that is typically resistant to treatment. Although the aetiology of PVL is unknown, the potential for recurrence and malignant transformation is such that treatment of this lesion requires an aggressive approach. Even with this approach, reports suggest that affected patients are at risk of developing verrucous or oral squamous cell carcinoma during episodes of recalcitrant disease. This report describes the clinical presentation of a patient with PVL. It outlines the difficulties in treatment planning for patients with the condition and discusses the long-term implications of such a diagnosis.

Key words: aggressive, gingivae, management, proliferative verrucous leukoplakia (PVL)

INTRODUCTION

Proliferative verrucous leukoplakia (PVL) is regarded as an aggressive form of oral leukoplakia. It often presents as a multifocal, persistent lesion (Ghazali et al, 2003) and classically exhibits a high morbidity and mortality rate (Silverman and Gorsky, 1997; Campisi et al, 2004). PVL is more commonly seen to affect the female population, with some authors quoting a male to female ratio of 1:4 (Silverman and Gorsky, 1997). The mean age at presentation is 62 years (Silverman and Gorsky, 1997; Campisi et al, 2004).

The aetiology of PVL is unknown. It is a clinicopathological entity that tends to develop slowly and, as such, a wide phenotypic spectrum of disease is described. Some authors outline specific disease categories (Greer et al, 1999) including verrucous hyperplasia, with degrees of epithelial dysplasia and varying types of carcinoma, such as verrucous and oral squamous cell carcinoma. It is felt that the progressive nature of the lesion is inevitable and often irreversible (Greer et al, 1999) and multiple site presentation has been reported. The potential for malignant transformation does not appear to be related to smoking habits, although results have been somewhat ambiguous in the past (Silverman and Gorsky, 1997; Bagan et al, 2003; Bagan et al, 2004).

What remains undisputed is that PVL is aggressive in nature and has a high recurrence rate and potential for malignant change. The condition is often refractory to treatment and with PVL being acknowledged as the forerunner of verrucous carcinoma (Bataski et al, 1999), treatment modalities are frequently radical and not necessarily curative.

With PVL and oral leukoplakia, it has been suggested that human papillomavirus (HPV) infection

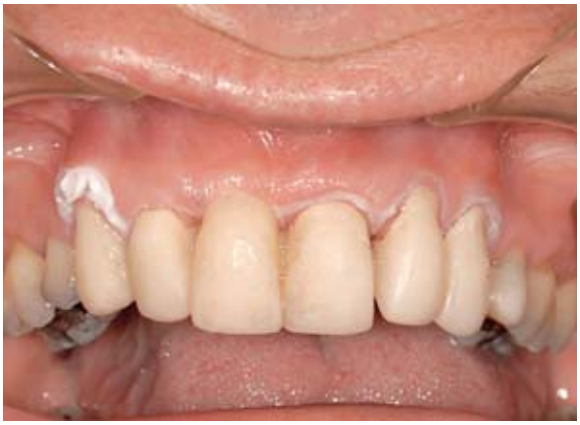

Fig 1 Initial presentation: linear gingival leukoplakia affecting 13 to 23 region.

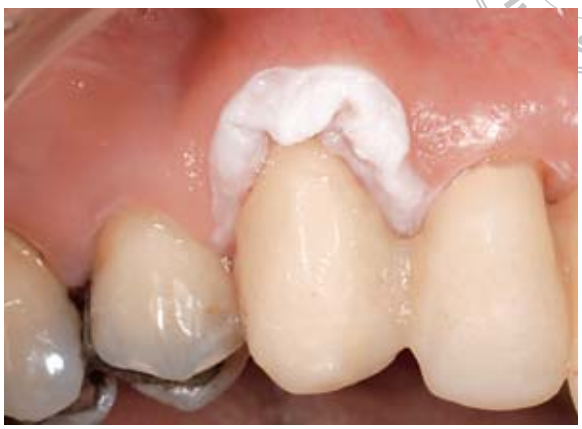

Fig 2 The exophytic appearance affecting the gingiva of the 13 at initial presentation.

may be implicated in the pathogenesis of potentially malignant lesions (Bouda et al, 2000; Gillison et al, 2000). Links between the presence of HPV and PVL have been suggested (Campisi et al, 2004), but reports to date have been somewhat ambiguous. Campisi et al (2004) examined the prevalence of HPV DNA in PVL in comparison with oral leukoplakia. They found that in a study of 58 patients, the detection rate of HPV DNA was 24.1% with PVL, in comparison to 25.5% in oral leukoplakia. The authors concluded that no significant difference in the occurrence of HPV infection existed between the two conditions.

This report is of a 59-year-old female who presented to the periodontal department with linear gingival leukoplakia. This leukoplakia was broad in its distribution and of unknown duration or aetiology. This patient had previously been seen at a maxillofacial unit where a clinical diagnosis of frictional keratosis had been made.

CASE REPORT

A 59-year-old female was referred by her general dental practitioner to the Periodontal Department. The patient's presenting complaint was the presence of widely distributed white patches on her gums. The 13, 12, 22 and 23 were reported as the worst affected sites. The exact duration of the leukoplakia was unknown. The patient was asymptomatic. No obvious skin lesions were identified and no family history of similar problems was identified.

At the time of referral, the patient suffered with hypertension and her medication included Enalapril, Bendrofluazide and HRT. She had never smoked and consumed minimal alcohol.

At initial presentation, extra-oral examination revealed no abnormality with the temporomandibular joints or soft tissues. There were no palpable submandibular or cervical nodes. Intraorally, the patient's oral hygiene was good. There were temporary crowns present from the 13 to the 23, which were aesthetic with good marginal adaptation. The gingival tissues exhibited a linear leukoplakia extending from the 13 to the 23 along the gingival margin (Fig 1). This leukoplakia appeared relatively homogenous although there was a notable exophytic appearance to the buccal gingiva of the 13 (Fig 2). A BPE score of 2 was recorded in all sextants. No significant bleeding on probing was recorded. The 11 had been extracted previously due to periodontal involvement.

The clinical appearance of the leukoplakia suggested a differential diagnosis:

- a lichenoid reaction
- lichen planus
- allergy/contact sensitivity
- an atypical manifestation of white sponge naevus
- keratoacanthoma
- a lesion of viral aetiology, including oral manifestation of Epstein–Barr virus (EBV).

Initial investigations involved routine immunology, including complement C3, C4, IgG, IgA, IgM and total IgE, to identify the potential for an aller-

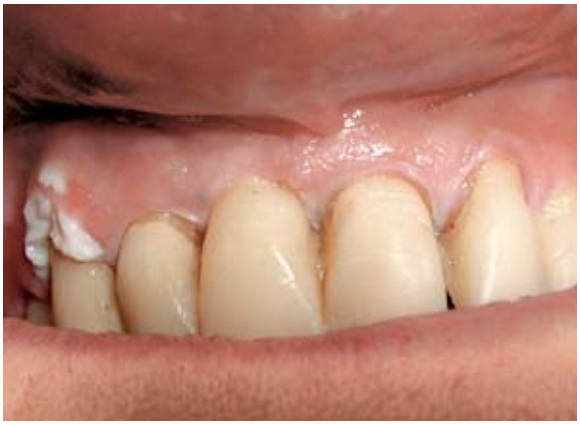

Fig 3 Post-gingivectomy.

gic aetiology. A biopsy was performed and arrangements were made for patch testing to be carried out. The results of all blood tests were normal. The results of the initial biopsy taken from the buccal aspect of the 13-, 14-area provided a diagnosis of keratosis without dysplasia, and patch testing revealed a mild positive reaction to potassium dichromate and lauryl gallate. Potassium dichromate is a substance often used for chrome-plating or in the manufacture of chrome-nickel steel alloys. A frequent source of allergy may be cement, which caused some concern due to the use of dental cements for the anterior crown restorations. Lauryl gallate is a preservative. A mild positive response to both of these substances was thought to be insignificant in the aetiology of the gingival leukoplakia.

At review, the leukoplakia had recurred very rapidly. The patient had developed an abscess associated with the 13. This was subsequently drained and a gingivectomy was carried out on the relatively localised exophytic tissue associated with this tooth. The 13 was not tender to percussion and there was no associated apical pathology. The tooth exhibited up to 45% vertical bone loss. The surgical site was dressed with a kalzinol and coe-pak dressing and the patient was reviewed one-week post-operatively.

At this review, the site of gingival surgery appeared to be healing well although there was a rapid and noticeable return of the leukoplakia buccally (Fig 3). The histological report post-gingivectomy suggested the presence of mild dysplasia. No fungal hyphae were found.

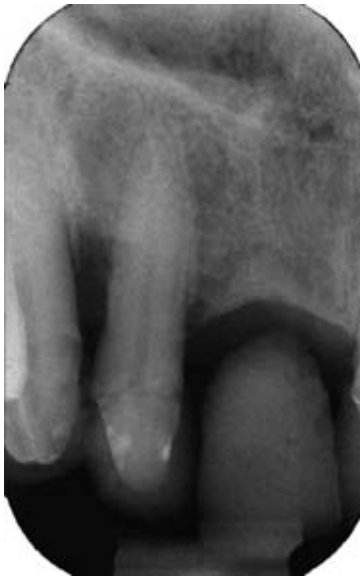

Fig 4 Periapical radiograph of 13.

The rapid recurrence of the gingival leukoplakia, with increased palatal involvement and the histopathological report aroused further clinical suspicion. The 13 underwent an inverse bevel flap procedure and re-excision of the leukoplakia. At the time of surgery, the keratotic tissue was found to be undermining the flap in an infiltrative manner, to the distal of 14. It was therefore dissected out prior to localised root surface debridement and complete excision of the keratosis present in the 13 to the 23 area also. The working diagnosis obtained from this biopsy was keratosis with mild dysplasia and therefore a palatal gingivectomy was subsequently also carried out.

The histological report for the palatal tissue suggested the presence of keratosis without dysplasia. This lesion was reviewed with a high index of suspicion and eventually the palatal papilla of the 13 was completely excised as this area looked especially atypical at one review appointment. A periapical radiograph was taken of the 13 with the bony appearance being suggestive of early intraosseous change (Fig 4).

As a result of a case conference between the lead clinician (ILC), the original pathologist and a further pathologist, the sequential histology was reviewed and a definitive diagnosis of PVL was made. This diagnosis was significant in that PVL is recognised as being aggressive in nature and exhibits marked potential for malignant transformation.

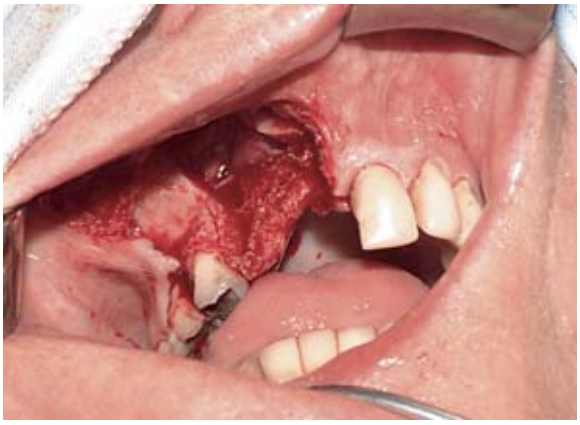

Fig 5 Intra-operative view of surgical site 12, 13 area.

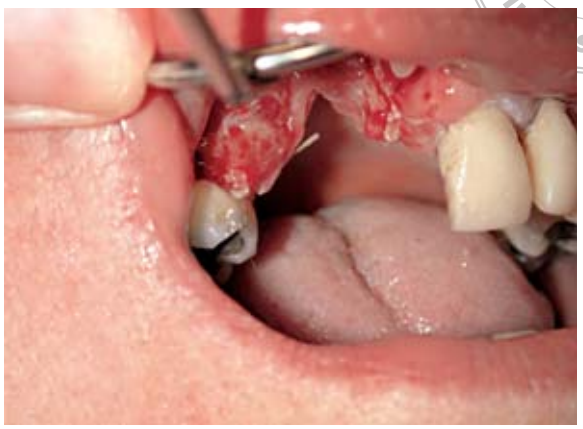

Fig 6 Post-surgical view, buccal.

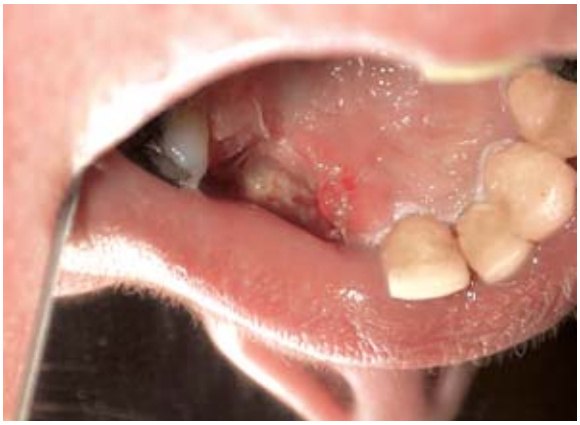

Fig 7 Post-surgical view, palatal.

After further discussions between the periodontist, the pathologist and a maxillofacial surgeon, it was concluded that a maxillary rim resection, to include a suitable sample for bone biopsy, with extraction of the 13 and 12 should be carried out (Figs 5–7). Following the outlined treatment, a removable maxillary prosthesis was fitted with a view to providing a fixed prosthesis in the long-term, should the operative site remain stable.

DISCUSSION

PVL is a clinico-pathological diagnosis, encompassing a spectrum of disease. It is a lesion that is classically described as being multifocal, persistent and refractory to treatment (Bataski et al, 1999; Greer et al, 1999; Ghazali et al, 2003). These characteristics and its recognised potential for dysplastic and malignant change (Reichart and Philipsen, 2003) mean that PVL is regarded by some as a precancerous lesion with a high subsequent mortality rate (Silverman and Gorsky, 1997; Greer et al, 1999). Owing to the likelihood of progression and the high recurrence rate, it is generally accepted that treatment should be aggressive in nature and follow-up should be frequent and meticulous (Silverman and Gorsky, 1997).

In a report of two cases of PVL, Greer et al (1999) suggest that PVL may sometimes present as a simple benign keratosis in the first instance. However, its pattern of development is such that this keratosis tends to spread and become more diffuse. Although this progression may take time, it is thought to represent an irreversible condition (Greer et al, 1999). These authors have described a continuum of oral epithelial disease with hyperkeratosis being found at one end of the spectrum and verrucous and squamous cell carcinoma at the other.

Evidence of PVL to date suggests that although it may initially present as a flat keratosis, verrucous lesions may subsequently develop (Reichart and Philipsen, 2003). It is also felt that microscopic findings may be dependent on the stage of disease and the adequacy of the biopsy sample taken (Greer et al, 1999). Therefore this should not be looked at in isolation when reviewing the patient. The fact that PVL represents a spectrum of disease is important (Reichart and Philipsen, 2003). In a report of five cases, Reichart and Philipsen delin-

eated the spectrum to include homogenous, flat leukoplakia, but suggested that acanthosis, hyperkeratosis and often parakeratosis may be present. They emphasised that dysplasia may or may not be present.

Sites affected by PVL can vary although those reported include the buccal mucosa, gingivae and the edentulous ridge (Reichart and Philipsen, 2003). Others have reported the involvement of the tongue, especially in males (Silverman and Gorsky, 1997).

The fact that PVL represents a continuum of disease means that lesions can be advanced in their natural history before a definitive diagnosis is made (Bataski et al, 1999). PVL tends to be refractory to treatment and radiotherapy is not thought to improve the surgical management, suggesting that an aggressive approach is merited (Silverman and Gorsky, 1997). In the reported case, the leukoplakia present was longstanding, with repeated biopsies giving equivocal histopathology results. However, the clinical appearance of this persistent lesion, and its rapid recurrence and aggressive behaviour in general, was such that it prompted less conservative management. A rim resection, which facilitated the provision of a bone biopsy, was felt to be the most appropriate option to provide the best long-term prognosis in view of the inclusion of this leukoplakia as part of the continuum that constitutes PVL. The rim resection and provision of a removable maxillary prosthesis has led to some acclimatisation problems in the short-term. However, the long-term treatment plan is to provide a fixed prosthesis with indefinite follow-up of the affected site.

Reports of malignant change with PVL have been widespread. Silverman and Gorsky (1997) followed 34 patients with PVL prospectively and found that in 7.7 years, 70.3% of patients developed squamous cell carcinoma at the site of PVL. Overall, the affected sites can vary and include the gingivae, tongue, palate and floor of mouth (Silverman and Gorsky, 1997; Bagan et al, 2004), with the gingivae and palate in particular being susceptible to malignant change (Bagan et al, 2003; Bagan et al, 2004). It has also been suggested that patients can develop cancers at sites remote from the initial PVL (Bagan et al, 2004). Lesions seem to recur regardless of employing different treatment approaches. In the past these have included conservative excision by scalpel or indeed laser (Fettig et al, 2000), with the provision of radiotherapy not seen as being helpful (Silverman and Gorsky, 1997).

Photodynamic therapy is a treatment modality that has been used with PVL on occasion. It involves the activation of a previously administered sensitiser by a non-thermal light source of an appropriate wavelength. It has been found that successful outcomes are less likely with lesions showing evidence of field change (Fan et al, 1997). This form of treatment can predispose to tissue tethering and necrosis of normal mucosa due to the scattering of light in the mouth (Fan et al, 1997).

Due to the refractory nature of PVL and the high instance of recurrence, it is advised that an aggressive treatment approach is adopted. This may be the only means of treating a phenomenon that exhibits indisputable malignant potential in a progressive and unpredictable manner.

ACKNOWLEDGEMENTS

The authors are grateful to Dr H.K. Williams and Professor P. Speight for their histopathological expertise and for their invaluable advice.

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