J Oral Pathol Med (2005) 34: 447–8

www.blackwellmunksgaard.com/jopm

LETTER TO THE EDITOR

Severe oral epithelial dysplasia in a patient receiving adalimumab therapy

The recent report by Sanchez and co-workers (*J Oral Pathol* (2005) **34:** 53–5) indicates that new therapies such as infliximab may not always be effective in the management of relevant oral disease, and may require use of other anti-TNFα therapies such as adalimumab. We have recently observed however that adalimumab might give rise to significant oral mucosal disease.

A 39-year-old female patient was referred to the Oral Medicine Unit of Universidade Federal de Pernambuco, Recife, Brazil with a white patch on the right lateral border of the tongue. The patient neither smoked tobacco nor drank alcohol. She had rheumatoid arthritis affecting the joints of the hands, feet, knee, hip and shoulders for the previous 20 years. Her current treatment included prednisolone (10 mg/day), sodium diclofenac (50 mg, three times a day), chloroquine (150 mg/day) (for 5 years), sodium alendronate (10 mg/day), calcium (1 g/day) and, for 5 months prior to the appearance of the oral lesion, she had received adalimumab (Humira) 40 mg every other week.

Intra-orally, there was a 5 cm adherent white patch on the right lateral border of the tongue with a 3 mm diameter area of superficial ulceration (Fig. 1). There were no other notable oral or extra-oral features. Histopathological examination of lesional tissue revealed oral mucosa covered by partially ulcerated prominently keratinized stratified squamous epithelium with bulbous rete hyperplasia, low-level keratinization and abnormal mitotic activity. Keratinocyte pleomorphism, hyperchromatism and loss of polarity were also present. Fungal stains were negative (Fig. 2). The features were consistent with hyperkeratosis with severe oral epithelial dysplasia, or lichenoid dysplasia. Although the patient had been using alendronate, and chloroquine – both known to give rise to lichenoid reactions (1, 2), the patient did not have any mucocutaneous features of lichen planus and thus a lichenoid drug reaction (LDR) to these agents was unlikely to account for the observed lichenoid infiltration. Likewise, as the patient did not smoke or drink alcohol, oral epithelial dysplasia might have been unlikely to arise.

If TNF-α plays a central role in the pathogenesis of lichen planus, anti-TNF-α therapy such as adalimumab would not be expected to cause an LDR, however, as thalidomide has also been known to give rise to such a reaction (3) the present observations are not entirely unexpected and may suggest that TNF-α at least *in vivo* is not central to LDR nor lichen planus. Epithelial dysplasia is sometimes a feature of oral lichen planus (4) and squamous cell carcinoma occasionally complicates lichen planus (5). However, no role has been described for TNF-α in the pathogenesis of oral epithelial dysplasia, and would indeed seem unlikely. However anti-TNFα therapy is known to give rise to the development of lymphomas, and significantly has now been associated with the development of epithelial tumours, including squamous cell carcinoma of the skin (6). The pathogenic mechanism that underlies these epithelial tumours is not known, however as oral epithelial dysplasia, and oral squamous cell carcinoma have been associated with iatrogenic immunosuppression (7–10) it may be that some aspects of cell mediated immunodeficiency may influence the development of perhaps infection-associated (11, 12) abnormal oral epithelial proliferation and differentiation.

Whatever the exact cause, it would seem that, in view of the reported development of cutaneous malignancy

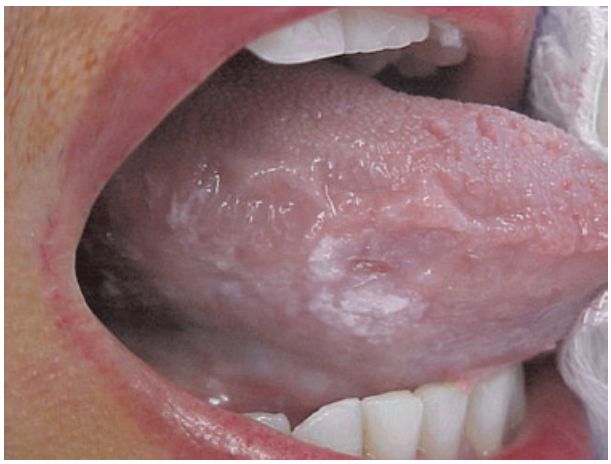

Figure 1 Ulcerated white patch on the lateral border of the tongue.

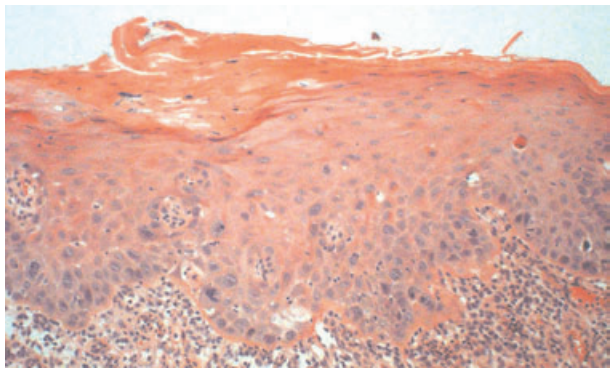

Figure 2 Histopathological findings showing loss of keratinocyte polarity, pleomorphism and dyskeratosis.

with anti-TNF-α therapy, adalimumab may possibly also cause oral epithelial dysplasia, and thus all unusual oral mucosal lesions in patients receiving such therapies warrant histopathological examination.

Jair C. Leão[1,2], Angela Duarte[1], Luiz Alcino M. Gueiros[1], Alessandra A. T. Carvalho[1], A. William Barrett[2], Crispian Scully[2], Stephen Porter[2]

[1]*Universidade Federal de Pernambuco, Departamentos de Clinica e Odontologia Preventiva e de Medicina Clinica, Recife, PE 50670-901, Brazil*

[2]*Division of Maxillofacial Diagnostic, Medical and Surgical Sciences, Eastman Dental Institute for Oral Health Care Sciences, UCL – University of London, 256, Gray's Inn Road, London, WC1X 8LD, UK*

E-mail: s.porter@eastman.ucl.ac.uk

References

1. Lazarov A, Moss K, Plosk N, Cordoba M, Baitelman L. Alendronate-induced lichen planus. *Isr Med Assoc J* 2002; **4**: 389–90.
2. Savage J. Lichenoid dermatitis due to chloroquine. *Br J Dermatol* 1958; **70**: 181.
3. Bez C, Lodi G, Sardella A, Della VA, Carrassi A. Oral lichenoid lesions after thalidomide treatment. *Dermatology* 1999; **199**: 195.
4. Epstein JB, Wan LS, Gorsky M, Zhang L. Oral lichen planus: progress in understanding its malignant potential and the implications for clinical management. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2003; **96**: 32–7.
5. Rodstrom PO, Jontell M, Mattsson U, Holmberg E. Cancer and oral lichen planus in a Swedish population. *Oral Oncol* 2004; **40**: 131–8.
6. Ziakas PD, Giannouli S, Tzioufas AG, Voulgarelis M. Lymphoma development in a patient receiving anti-TNF therapy. *Haematologica* 2003; **88**: ECR25.
7. King GN, Healy CM, Glover MT, et al. Increased prevalence of dysplastic and malignant lip lesions in renal-transplant recipients. *N Engl J Med* 1995; **332**: 1052–7.
8. Regev E, Zeltser R, Lustmann J. Lip carcinoma in renal allograft recipient with long-term immunosuppressive therapy. *Oral Surg Oral Med Oral Pathol* 1992; **73**: 412–4.
9. Thomas DW, Seddon SV, Shepherd JP. Systemic immunosuppression and oral malignancy: a report of a case and review of the literature. *Br J Oral Maxillofac Surg* 1993; **31**: 391–3.
10. Varga E, Tyldesley WR. Carcinoma arising in cyclosporin-induced gingival hyperplasia. *Br Dent J* 1991; **171**: 26–7.
11. Herrero R, Castellsague X, Pawlita M, et al. Human papillomavirus and oral cancer: the international agency for research on cancer multicenter study. *J Natl Cancer Inst* 2003; **95**: 1772–83.
12. Scully C. Oral squamous cell carcinoma; from an hypothesis about a virus, to concern about possible sexual transmission. *Oral Oncol* 2002; **38**: 227–34.