

## GUEST EDITORIAL

# Studies of drug-induced lichenoid reactions: criteria for case selection

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This issue of *Oral Diseases* contains a thought-provoking study by Kragelund and co-workers in Copenhagen into the associations between oral lichen planus (OLP) and the intake of drugs metabolized by polymorphic cytochrome P450 enzymes. This study throws new light on the mechanisms that may explain why an otherwise disparate groups of drugs cause oral lichenoid drug eruptions (LDE) and is, perhaps, indicative of the directions in which research into LDE should be turning.

We have previously reviewed the drugs reported as causing oral LDE (McCartan and McCreary, 1997). At that time we expressed concern at the variability of previous reports and we noted the lack of any internationally agreed management protocol that could produce standardized data for analysis. Stimulated by this current paper we are now proposing certain fundamental preconditions that we believe should be in place if future studies on LDE are to have credibility. These criteria are based on a careful examination of the factors that have created difficulties both in the analysis of previous papers and in the comparison of their findings with those of related papers. It is our conviction that cases must be categorized as far as possible, using the best current knowledge, into idiopathic OLP, oral LDE and oral contact lichenoid lesions. Furthermore, each case not only must be given the fullest clinical description but must also be biopsied. This will allow full histological and immunological reporting to enable a proper analysis to be made of the differences between the three categories and to refine the current clinical, histological and immunological discriminators.

It is our contention that the following criteria should apply to all cases of OLP, oral LDE and contact lesions, where the intention is to publish comparative analyses or the results of clinical or laboratory research investigations.

- (1) Each case selected for investigation should be identified by an accepted sampling method. This might involve the identification of all new cases attending an oral medicine clinic with mucosal disease suggestive of OLP or might occur as a result of a properly designed population study.
- (2) The clinical disease should be accurately described in terms of the sites involved, the degree of bilateral symmetry, the clinical variants present at each site and the symptoms associated with each site. In many previous papers on OLP and LDE, the distribution of clinical variants (Andreasen, 1968) often sums to 100%. This is unlikely as most cases of erosive OLP also have striae and the sum should exceed 100%.
- (3) The spatial relationship must be recorded between lesions and restorations with substances believed to induce contact lichenoid lesions. Such substances include amalgam, gold and composite (diacrylate) restorative materials. This record could involve the use of a standardized diagrammatic representation or clinical photographs.
- (4) Each patient's drug exposure over a substantial preceding period must be known. This would involve much more than the standard drug history frequently taken when patients are clerked by relatively junior staff in specialist clinics. For each patient it would be necessary to take a drug history, we suggest, going back at least 12 months before the first onset of symptoms. Although onset of symptoms does not necessarily correlate with onset of disease, caution should be exercised in interpreting the duration of the condition when the patient has been symptom-free, i.e. if the condition was noted by a clinician rather than by the patient, the start date can be ascertained with even less confidence and such cases should possibly be excluded. The drug history must be exhaustive not only for prescribed drugs but also for self-medication, with both conventional and alternative remedies, and must include mouthwashes, toothpastes and other topical preparations with pharmacologically active agents. The history should carefully detail the start and finish dates of all of these drugs.
- (5) Any data based on withdrawal and subsequent re-challenge must take into account the long withdrawal periods suggested by several authors (Pennys *et al*, 1974).

- (6) Any case where the lesions are in contact with amalgam, gold or composite restorative materials should have appropriate patch testing. Special care must have been taken with mercury testing to ensure that appropriate polymer test chambers have been used rather than aluminium chambers, as mercury is known to react with such chambers to produce irritant by-products capable of eliciting a false positive patch test (Rietschel and Fowler, 1995).
- (7) All cases must have histological verification. While there is no consistent histological differentiation between idiopathic OLP and oral LDE (McCartan and McCreary, 1997), it is essential that cases should be excluded if they do not show any of the patterns falling within the spectrum of histological features accepted as representing OLP or LDE.
- (8) There should be direct and indirect immunological testing to exclude conditions such as discoid lupus erythematosus. Consideration should also be given to testing for substances such as basal cell cytoplasmic autoantibodies (Lamey *et al*, 1995) and OLP specific antigen (Camisa *et al*, 1986).

We are aware that these are stringent requirements that have never been implemented in any previous study of OLP. However, it is our contention that the bulk of the literature on oral lichen and lichenoid lesions should no longer consist of case reports, reports of small series and analytical reports that are unsuitable for meta-analysis. If our standards were to be accepted then much more useful information could be obtained, both from individual papers and from the meta-analysis of multiple papers. Given that most units do not have enough cases of OLP, oral LDE or oral contact lichenoid lesions to provide statistical power for the analysis of results, it is especially important that there is consistency of method and full reporting of relevant factors. If this approach were to be adopted then a number of valuable analyses would become possible. For example, the investigation of oral LDE is hampered by the fact that the commonest LDE inducing drugs in Western societies (anti-hypertensives, diuretics, oral hypoglycaemics and non-steroidal anti-inflammatory agents) are taken by the same older cohort of patients in whom OLP is most prevalent. A well-constructed study of drug ingestion in several

thousand OLP cases vs an age- and sex-matched cohort could well determine which of these drug associations are causal and which are coincidental. Similarly, analysis of features reported in a number of studies could test the previously reported relationships between LDE and unilaterality (Lamey *et al*, 1995) and a preponderance of the erosive variant (Potts, Hamburger and Scully, 1987). Such large data sets might also make it possible to explore the differences in the malignant potential of LP subtypes. We have previously commented on the regional differences in the reported precursor lesions for malignant change in OLP (McCartan and McCreary, 1999). The North American studies have generally reported malignant change in erosive lesions while the European studies have tended to implicate plaque lesions.

Some of our suggestions could be interpreted as a criticism of the methodology employed by Kragelund and co-workers in the present study. However, our intention is not to criticize existing studies but, rather, to attempt to place research into oral LDE and contact lichenoid lesions on to a new plane.

## References

- Andreasen JO (1968). Oral lichen planus: 1. A clinical evaluation of 115 cases. *Oral Surg Oral Med Oral Pathol* **25**: 31–42.
- Camisa C, Allen CM, Bowen B, Olsen RG (1986). Indirect immunofluorescence of oral lichen planus. *J Oral Pathol* **15**: 218–220.
- Lamey P-J, McCartan BE, Macdonald DG, MacKie M (1995). Basal cell cytoplasmic autoantibodies in oral lichenoid reactions. *Oral Surg Oral Med Oral Pathol* **79**: 44–49.
- McCartan BE, McCreary CE (1997). Oral lichenoid drug eruptions. *Oral Dis* **3**: 58–63.
- McCartan BE, McCreary CE (1999). What is the rationale for treating oral lichen planus? *Oral Dis* **5**: 181–182.
- Pennys NS, Ackerman AB, Gotlieb NL (1974). Gold dermatitis, a clinical and histopathological study. *Arch Dermatol* **109**: 372–376.
- Potts AJC, Hamburger J, Scully C (1987). The medication of patients with oral lichen planus and the association of nonsteroidal anti-inflammatory drugs with erosive lesions. *Oral Surg Oral Med Oral Pathol* **64**: 541–543.
- Rietschel RL, Fowler JF (1995). *Fisher's contact dermatitis*, 4th edn. Williams and Wilkins: Baltimore, p. 141.