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PLENARY ABSTRACT

The malignant potential of oral lichen planus

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In the past three decades the issue of a malignant potential of OLP has been a matter of serious controversy (Holmstrup 1992, Eisenberg 2000), while in the same period a large number of studies have linked oral lichen planus (OLP) with the development of squamous cell carcinoma (SCC) (for review, see: Mattsson *et al*, 2002).

What is OLP?

An essential part of the debate is the matter of the diagnosis of OLP, and it has been postulated that many of the reported cases were in fact not OLP, but rather premalignant lesions with dysplastic features. It is obvious that the consequence of this premise is that patients with epithelial dysplasia in lesions with characteristics of OLP represent a particular, identifiable risk group different from patients with "true" OLP with no increased risk of developing SCC. Also, there is a widespread confusion about the term lichenoid lesion as a lesion which is only in part consistent with OLP.

There is no doubt that we do face a diagnostic problem. What is "true OLP" (Eisenberg, 2000, Silverman, 2000). As previously stated (Holmstrup1992) we are dealing with the question "what is understood by a disease entity?" The answer to this question has been given by Wulff (1979), who stated that the nominalistic, in contrast to the essentialistic disease concept, is based on the maxim that there are no diseases living by themselves but there are sick people, and a disease classification is really a classification of patients. Obviously, it is impossible to imagine a clinical science unless the knowledge and experience gained from the study of millions of patients is organized in some way. Further Wulff (1979) states, "The framework of this organization is the disease knowledge, which enables us to pigeonhole patients who resemble one another. In other words, the disease names or diagnoses denote classes of patients which serve as vehicles of clinical knowledge and experience".

In fact, the question is whether there is any type of disease entity that is "true", since a disease entity is not a living organism acting by itself "true" or "false", qualifying for this demotic concept. While disease processes are always modified by factors dependent on the single individual affected, it therefore does not add value to existing knowledge to debate "true" or "false" diseases. If, on the other hand, specified diagnostic criteria are regarded as important tools for the handling of groups of patients, then it is, of course, extremely important to note which diagnostic criteria have been used in studies of the premalignant nature of OLP.

Clinical and histopathological criteria

The identification of OLP patients in several studies has been based on both clinical and histopathological criteria. The clinical criteria are often based on the identification of a number of characteristic changes of the oral mucosa, including papular, reticular, atrophic, ulcerative, bullous and plaque-like lesions (Thorn *et al*., 1988). Most characteristic of the disease are the papular and the reticular lesions.

The histopathological criteria for OLP are a number of epithelial changes, the amount and extension of which vary. They include epithelial hyperkeratosis, atrophy or hyperplasia, acantosis, saw-toothed rete ridges, liquefaction degeneration and single cell necrosis/Civatte bodies in the basal cell layer. In the basement membrane area, a narrow eosinophilic, PAS-positive zone is frequently present. The subepithelial connective tissue shows a band-like inflammatory infiltrate composed of lymphocytes and macrophages.

As mentioned above, the criteria applied in the literature may vary and the main question remains, have the studies performed included patients with other diagnosis which render a higher risk of malignant transformation? The question is complicated by the fact that the clinical appearance of OLP changes with time. The typical reticular type lesion may change to a plaque type lesion without classical OLP features (Thorn et al., 1988).

Moreover, similar developments may apply to the histopathological features over the years. The characteristic bandshaped subepithelial infiltrate composed mainly of lymphocytes and macrophages may become "watered-down" to a less OLP-characteristic appearance. This means that when following typical OLP lesions they may change the appearance and become indistinguishable from leukoplakia. In fact, several lesions identified as leukoplakias may have an OLP origin. If so, part of the patients followed with the diagnoses of leukoplakia may belong to the group of OLP patients, and as a consequence the reported rate of malignant development of OLP and leukoplakia is blurred by this phenomenon. Such developments clearly attempt to deplete the group of patients identified for follow-up studies of OLP rather than to include patients with a diagnosis rendering a higher risk of malignant development. The conclusion of this discussion is that not only do the diagnostic characteristics of OLP patients at admission of a study have a significant impact on the results obtained, but when dealing with OLP, information on the historical clinical background of the lesions is also important. This aspect is complicated by the fact that such information is seldom available. Most likely, the group of patients to be included in follow-up studies of OLP patients is depleted of some patients with a long history of OLP because the lesions have changed to a less characteristic clinical and histological appearance. This implies a serious flaw, since malignant transformation does not occur over night (Holmstrup *et al*., 1988) and these patients presumably possess the largest malignant potential.

A special problem applies to the feature of epithelial dysplasia in lesions with characteristics of OLP, the so-called lichenoid dysplasia. Basically, such dysplastic features may be present in the initial lesion, or they may develop in the course of OLP-lesions without such features being present at inclusion in a follow-up study. Whenever the nature of these two characteristics imply a different susceptibility for malignant transformation, which is unknown at present, inclusion of patients with the primary finding of epithelial dysplasia in lesions that are otherwise compatible with OLP should be avoided, as previously proposed (Holmstrup *et al*., 1988). Patients with lesions, which develop such dysplastic features at a later time point, are not to be excluded from the follow-up study, because such a development is a reflection of the potential of the patients primary lesion, which fulfilled the diagnostic criteria of inclusion.

Moreover, these statements are further complicated by the fact that some of the histopathological findings in OLP lesions may be interpreted as signs of epithelial dysplasia, and the histopathological diagnosis of epithelial dysplasia is subjective with a well-known inter- and intraobserver variation in reading the degree of dysplasia. Moreover, the paradigm of the presence and grade of epithelial dysplasia playing a significant role for future malignant development, has been questioned recently (Holmstrup *et al*., 2007).

Major variations have also been shown in the histopathological interpretation of lichenoid reactions (van der Meij *et al*., 1999). Some diagnoses, as for example lichenoid contact reactions caused by components released from dental restorations, are difficult to distinguish from OLP. As these lesions are not known to be associated with malignant transformation, their inclusion results in a false-positive contribution, which decrease the rate of malignant potential of OLP. However, such lesions can probably be distinguished on the basis of clinical criteria (Bolewska *et al*., 1990).

Several histological markers have been investigated to determine their relevance as diagnostic or prognostic tools in the evaluation of OLP. These include altered expression of alpha9 integrin (Häkkinen *et al*, 1999), laminin-5 staining (Kainulainen *et al*, 1997), and expression of mutated p53. (Girod *et al*, 1993). A method to distinguish between lichen planus and lichenoid dysplasia has also been suggested using involucrin immunoreactivity (Eisenberg and Krutchkoff, 1987). Microsatellite analysis has been used to reinforce the current opinion of lichenoid dysplasia as having a higher tendency to develop into malignancy than OLP (Zhang *et al*., 2000). Thus, several histological markers have been examined or even proposed as prognostic factors, but there is currently no specific marker which has been widely adopted to determine the diagnosis of OLP and to predict a possible future malignant transformation. At present it is quite obvious that more studies are required to conclude on the significance of these features in patients with OLP or OLP-like lesions.

In conclusion, detailed clinical and histopathological diagnostic inclusion criteria are mandatory for studies attempting to identify the malignant potential of OLP. Such criteria imply what is understood by the applied diagnosis of OLP, and widely approved, uniform, standardized criteria are not existing at present, although a revised set of diagnostic criteria has been proposed (van der Meij and van der Waal, 2003). However, conclusive studies on the premalignant potential of OLP should be designed as prospective follow-up studies of patient samples defined on the basis of typical clinical and histopathologic criteria, i.e. reticular and/or papular lesions, demonstrating histopathologic features including hyperkeratosis, liquefaction degeneration of basal cells and a subepithelial band-shaped inflammatory reaction composed of lymphocytes and macrophages. Lichenoid reactions should be excluded on the basis of their clinical characteristics and lesions with dysplastic features should be excluded on the basis of their histopathology.

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Table 1 Studies on malignant transformation of oral lichen planus (OLP) comprising more than 100 patients diagnosed on clinical and histopathological characteristics (Adapted from: Mattsson et al, 2002. References in table not included in list of references due to editorial limitations)

Authors	*Year*	*Type of study*	*Number of OLP Patients*	*Gender*	*No of SCC cases*	*%*	*Follow-up period mean and/or range (yrs)*
Silverman et al.	1985	Retrospective	570	382F, 188M	7	1.2	5.6
Holmstrup et al.	1988	Prospective	611	409 F, 202 M	9	1.5	7.5/1–26
Silverman et al.	1991	Prospective	214	152 F, 62 M	5	2.3	9
Barnard et al.	1993	Retrospective	241	Unknown	9[a]	3.7	0,5 -17
Duffey et al.	1996	Retrospective	955	Unknown	5	0.5	4.25
Lo Muzio et al.	1998	Retrospective	263	156F, 107 M	14	5.3	2–10
Rajentheran et al.	1999	Retrospective	832	Unknown	7	0.8	1–9
Bermejo-Fenoll et al.	2009	Retrospective	550	422F, 128M	5	0.9	2.0

SCC: Squamous cell carcinoma
[a] Eight patients developed invasive carcinoma and one patient carcinoma in situ.

The malignant potential of OLP

In the past decades, many reports have addressed the question of malignant potential of OLP. The literature includes case reports, retrospective studies and prospective follow-up studies. Case reports are of limited value and obviously can only serve as hypothesis generators. Retrospective studies often entail errors, as the patient materials are selected after termination of the observation period and the information available is not defined prior to examining and following the patients. The inclusion criteria in some of the studies are defined clinical and histopathological features of all cases and the present review is restricted to comprise only such studies. To be considered, these studies also have to state the time between the primary diagnoses of OLP and SCC. Eight studies seem to be fulfill these criteria, 6 of which are retrospective and 2 are prospective follow-up studies.

Most of the reported transformation rates are strikingly uniform, the ranges being limited, i.e. between 0.4 and 5%. This is so despite variations in inclusion criteria. In this perspective it is interesting that a study by Sigurgeirsson & Lindelöf (1991) of lichen planus of the skin discovered an increased ratio of oral squamous cell carcinoma in the patient material but not for skin cancer.

All studies have investigated patients referred for consultation. Thus, it is not possible to conclude from these studies that there is an association between OLP and squamous cell carcinoma valid for the total population. Most likely, patients with symptomatic OLP are overrepresented in referred patient materials. In this perspective it is interesting to note that Murti *et al*. (1986) in a study of the background population found an incidence of squamous cell carcinoma among OLP patients that was not very different from studies of referrals.

In conclusion, the existing studies, although varying in their diagnostic criteria, provide accumulated information on which the question about the premalignant potential of OLP, defined by clinical and histopathological criteria, can be settled. Most studies have shown that patients with OLP develop squamous cell carcinoma at an increased rate than does the normal population. Despite differences in experimental designs, it is striking that the majority of papers report a transformation rate of OLP to approximately 0.5-2% in a five-year period. The increased risk for OLP patients has been estimated to be in the range of 10 to 50 times (Macdonald and Rennie, 1975, Holmstrup *et al*., 1988, Drangsholt *et al*., 2001).

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