Leukoplakia-like lesions developing in patients with oral discoid lupus erythematosus

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In a long-term follow-up of 52 patients with oral lesions of discoid lupus erythematosus (DLE) 8 patients showed a gradual transition of the typical DLE lesions to lesions which closely resemble leukoplakia. Histopathologically and immunopathologically the leukoplakia-like lesions generally showed features similar to those in leukoplakias not preceded by DLE. Ultrastructurally, the leukoplakia-like lesions showed the presence of cytoplasmic tubular structures in vascular endothelium in two out of three patients examined. The leukoplakia-like stage is considered to be an inactive or scar-like stage, which may be the mucous membrane counterpart of the atrophic scars following DLE lesions of the skin.
A primary examination of a DLE patient presenting oral lesions at the leukoplakia-like stage may result in an incorrect diagnosis. Therefore, when investigating patients with leukoplakias, they should be questioned on previous or present skin lesions as well as symptoms of systemic lupus erythematosus.

Key-words: Leukoplakia; oral pathology; mouth mucosa; oral manifestations

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Oral lesions in discoid lupus erythematosus (DLE) are characterized clinically by a central erythema with white spots and a border zone of irradiating white striae (1). Such lesions may also occur in systemic lupus erythematosus (SLE) (5).

It is well known that oral lesions of DLE may resemble lichen planus or leukoplakia clinically as well as histopathologically (4, 5). In a clinical follow-up of 52 patients with oral lesions of DLE it was observed that in a number of these, the typical DLE lesion had undergone a transition to a lesion which closely resembled leukoplakia. The present paper reports clinical, histological, immunhistochemical and ultrastructural findings in 8 patients showing this transition.

The term leukoplakia is defined as a white patch or plaque that cannot be

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characterized clinically or pathologically as any other disease (8). The term leukoplakia-like lesion is used in this paper, as all the patients included in the study were known to have DLE and some also SLE.

MATERIAL AND METHODS

A series of 52 patients (10 males, 42 females) with oral discoid lesions are being followed systematically at half-year intervals at the Department of Oral Medicine & Oral Surgery, University Hospital (Rigshospitalet), Copenhagen. The diagnosis was based initially on clinical and histopathological features as follows: Clinically, the lesions showed a central atrophic area with small white spots surrounded by a border with irradiating white striae. Histologically, the epithelium showed hyperortho- and/or hyperparakeratosis and acanthosis alternating with atrophy. Liquefactive degeneration was seen in basal layers. In the connective tissue an infiltration by lymphocytes was seen. The infiltrate was often arranged in foci and extended into the deeper parts of the connective tissue. Periodic acid-Schiff (PAS) positive deposits were seen as a subepithelial cell-free band (5). Biopsies were taken in all patients but one (see below). Eight of the 52 patients, who showed a gradual change from typical oral discoid lesions into leukoplakia-like lesions, form the basis of the present study. Clinical data, tobacco consumption, and local and systematic treatment were recorded for each patient. Seven of these patients had a biopsy taken at the first examination. One patient (Case 8) had a haemorrhagic diathesis in association with SLE, and for this reason no biopsy was taken at the first examination. Seven patients had a second biopsy taken at a later stage when they had developed leukoplakia-like lesions. The second biopsy was in all cases taken from the same lesion as the first biopsy, but not in the same area in order to avoid tissue changes due to post-surgical scarring from the first biopsy. A second biopsy from the leukoplakia-like lesions could not be obtained from one patient (Case 1). Histopathological studies of the 14 biopsies were done on three representative sections stained with haematoxylin and eosin (H & E) and PAS. Material for histopathological study was numbered randomly from 1 to 14 and evaluated in this sequence without knowledge of the clinical features corresponding to each microscopic specimen. The following histological features were recorded as present or absent: Hyperparakeratosis, hyperorthokeratosis, keratin plugs, epithelial atrophy, epithelial acanthosis/hyperplasia, migration of leukocytes into epithelium and liquefactive degeneration of the basal cell layer. The morphology of the inflammatory infiltrates were recorded as band-shaped and/or diffuse and/or focal/perivascular, and the intensity of the infiltrate as absent (–), slight (+), moderate (+ +) or severe (+ + +). Predominant cell types were recorded. The PAS positive cell-free band in the basement membrane zone was recorded as absent, continuous or patchy. PAS-stained sections were evaluated for the presence of Candidal hyphae. For each specimen a general histological diagnosis was given: If all histologic criteria were met a diagnosis of DLE was given. If one or two criteria were missing a diagnosis of «suggestive of DLE» was given.

Direct immunofluorescence (IF) staining for demonstration of deposits of immunoglobulins (Ig) and complement C3 according to methods described elsewhere (7) was performed at the first examination in five cases and at the leukoplakia-like stage in seven

Table 1. *Clinical data of patients with oral lesions of discoid lupus erythematosus (DLE) developing into leukoplakia-like lesions*

Age at the time of diagnosis of leukoplakia like lesions			Localization of leukoplakia-like lesions	Period between diagnosed oral discoid lesions and diagnosed leukoplakia-like lesions	DLE skin lesions present at first examination or developed during observation period	SLE present at first examination or developed during observation period	Total follow-up period
Patient No.	Sex	Years		years			years
1	F	43	left and right buccal mucosa	3.3	developed	–	5.9
2	F	42	left buccal mucosa	2.6	present	present	6.8
3	F	45	left and right buccal mucosa	7.4	developed	–	13.1
4	F	21	right buccal mucosa	4.5	–	–	14.3
5	F	60	left and right buccal mucosa	5.3	present	–	9.3
6	F	29	left commissure and lower labial mucosa	2.0	present	–	5.3
7	F	56	left and right buccal mucosa	2.1	–	developed	4.0
8	F	36	left buccal mucosa	1.2	present	present	2.5

cases. IF-staining was not possible in our laboratory at the time of the first biopsy for two patients (Cases 4 & 5). All biopsies were recut, restained and examined in the fluorescence microscope without knowledge of the clinical features for each specimen.

Three biopsies (Cases 6–8) were examined ultrastructurally at the leukoplakia-like stage for the presence of cytoplasmic tubular structures (CTS) in capillary endothelium. Five vessels were examined in each of two randomly selected sections from each

biopsy. The sections were mixed with sections from 18 other biopsies from active oral DLE, lichen planus and leukoplakia and evaluated without knowledge of the diagnosis corresponding to each section. Details of the method and the results of the evaluation of the 18 other biopsies are reported elsewhere (6).

RESULTS

Clinical features

The change from the typical oral discoid lesions (Figs. 1 & 5) into white homogeneous lesions was gradual and often associated with a decrease in size (Figs. 2 & 6). Clinical data appear in Table 1. The transition period between diagnosed oral DLE and diagnosed leukoplakia-like lesions ranged from 1.2 – 7.4 years with a mean of 3.4 years.

The leukoplakia-like lesions were stable in six cases, but in two cases (7 & 8) the leukoplakia-like lesions showed episodes of recurrence with focal areas of clinically typical DLE lesions (Fig. 7). These areas were treated with local steroid and developed again into leukoplakia-like lesions over some weeks. Further recurrences were prevented in case 7 during a period of 14 months by chloroquine treatment (200 mg per day). Seven patients were daily smokers, whereas one patient had never smoked (Table 2). The tobacco consumption had been unchanged from the time of the first examination to the time of the latest follow-up.

The development of leukoplakia-like lesions was associated with disappearance of oral symptoms as seen in Table 2. The recurrent episodes of DLE-like lesions in cases 7 & 8 were always associated with symptoms.

During the transition period, topical treatment with 0.1 % triamcinolone in Orabase® had been performed in six patients for periods of 1–5 months. Two patients (Cases 1 & 5) received no treatment during the transition period. No patients received systemic treatment during the same period.

Fig. 1. Case 6. Oral lesion of DLE involving left commissure and lower labial mucosa in active stage at first examination.

Fig. 2. Case 6. Same area as shown in Fig. 1 in leukoplakia-like stage two years later.

The activity of the skin lesions during the transition period was unchanged in four cases, whereas two cases (2 & 8) showed increased activity.

Histopathology

The histopathological diagnoses are

Table 2. *Tobacco consumption, symptoms, histopathology and immunofluorescence findings in oral discoid lesions in active stage compared to later developed leukoplakia-like stage of the same lesions in patients with DLE*

		Symptoms from oral lesions		Histopathology		Direct immunofluorescence staining	
Patient No.	Tobacco consumption per day	DLE-like stage (active)	Leukoplakia-like stage (inactive)	DLE-like stage (active)	Leukoplakia-like stage (inactive)	DLE-like stage (active)	Leukoplakia-like stage (inactive)
1	10 cigarettes	+	–	DLE	not biopsied	IgM, C3	not biopsied
2	8 cigarettes	+	+	DLE	Keratosis	IgM, C3	negative
3	10 cigarettes	+	–	DLE	Suggestive of DLE	negative	negative
4	none	–	–	Suggestive of DLE	Keratosis	not examined	negative
5	5 cigarettes 1 cheroot	–	–	Suggestive of DLE	Keratosis	not examined	negative
6	20 cigarettes	+	–	DLE	Keratosis	IgM, C3	negative
7	20 cigarettes	+	–	DLE	Keratosis	IgM, C3	small amounts of IgM, C3
8	15 cigarettes	+	–	not biopsied	Keratosis	not biopsied	negative

Fig. 3. Case 6. Histology of lesion in active stage seen in Fig. 1 showing slight hyperparakeratosis and acanthosis alternating with atrophy of the epithelium. X 75.

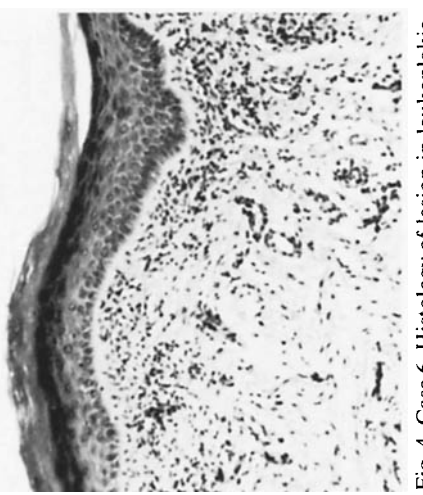

Fig. 4. Case 6. Histology of lesion in leukoplakia-like stage seen in Fig. 2. showing hyperorthokeratosis and an epithelium of uniform thickness. X 75.

shown in Table 2. None of the leukoplakia-like lesions which were biopsied showed histological features diagnostic of DLE, although isolated features usually associated with DLE were present.

Histopathological parameters which changed from the first to the second biopsy are shown in Table 3. It appears that keratin plugs disappeared and ac-

anthosis/hyperplasia of the epithelium was found more rarely in the leukoplakia-like stage. The inflammatory components of the lesions disappeared or decreased in intensity in the leukoplakia-like lesions. Inflammatory cell migration into the epithelium was not observed. The subepithelial PAS-positive band showed a change from patchy deposits towards either continuous band-like deposits or disappearance of the deposits.

Immunohistochemistry

The IF examination (Table 2) showed a disappearance or marked decrease of deposits of Ig and C3 from the first to the second biopsy in the three cases who had IF examination in both stages. In case 7 Ig and C3 were also present in clinically normal oral mucosa at both examinations.

Ultrastructure

The ultrastructural examination of leukoplakia-like lesions showed the presence of cytoplasmic tubular structures (CTS) in endothelial cells in two of the three biopsies examined. The positive biopsies (Cases 6 & 8) showed CTS in 7 and 1 vessel, respectively, out of 10 examined. CTS appeared as branched structures which were tubular in cross section and with a diameter of approximately 20 nm. The morphology was similar to that of CTS found in active stages of oral DLE lesions (6).

Table 3. *Histopathological parameters present in biopsies of oral discoid lesions at active stage compared to later leukoplakia-like stage in patients with DLE*

		DLE-like stage (active) N = 7	Leukoplakia-like stage (inactive) N = 7
Hyperparakeratosis		4	2
Hyperorthokeratosis		6	7
Keratin plugs		3	0
Acanthosis/hyperplasia		6	2
Atrophy		7	7
Migration of leukocytes into epithelium		6	0
Liquefactive degeneration		7	0
Intensity of inflammatory infiltrate	− or +	0	5
	+ + or + + +	7	2
Morphology of inflammatory infiltrate	bandshaped	0	0
	diffuse	7	6
	focal/perivascular	5	5
PAS-positive deposits at basement membrane zone	absent	0	3
	continuous	2	4
	patchy	5	0
Candidal hyphae		0	0

DISCUSSION

The present study has shown that in about 15 % of patients with oral lesions of DLE, the oral lesions may partly or totally lose their clinical, histological and immunopathological characteristics and become leukoplakia-like. A proportion of cases which are usually regarded as leukoplakia is caused by tobacco smoking (3). The patients in the present test had a considerable tobacco consumption. However, in this respect they did not differ from the 44 DLE patients who did not develop leukoplakia-like lesions. 40 of these were daily smokers and 12 had a consumption of 20 cigarettes or more a day. Therefore, it appears that factors other than tobacco may also determine whether oral DLE lesions become leukoplakia-like. This assumption is further supported by the recurrences of active lesions in two patients in spite of unchanged tobacco habits.

We consider the leukoplakia-like stage of oral DLE to be an inactive or scar-like stage, which may be the mucous membrane counterpart of the atrophic scar which characterize a burnt-out skin lesion. The increased activity of the skin lesions in two patients

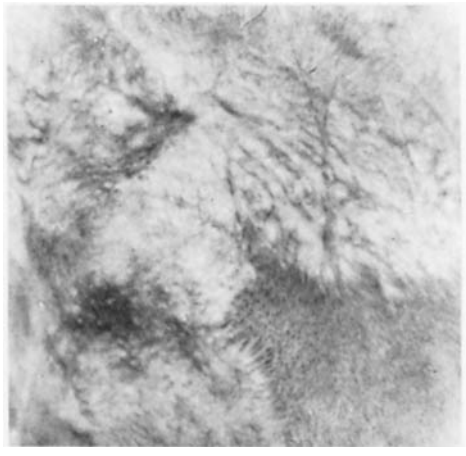

Fig. 5. Case 7. Lesion of DLE involving left buccal mucosa in active stage at first examination.

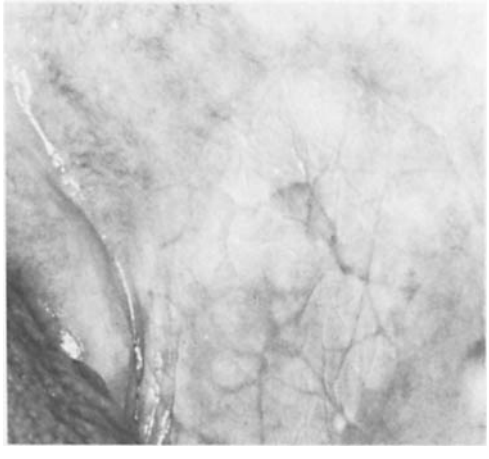

Fig. 6. Case 7. Same area as shown in Fig. 5 in leukoplakia-like stage 2.1 years later.

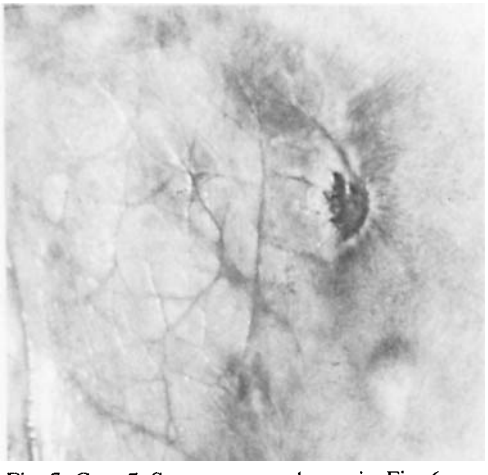

Fig. 7. Case 7. Same area as shown in Fig. 6 one year later showing focal activity at edge of leukoplakia-like lesion.

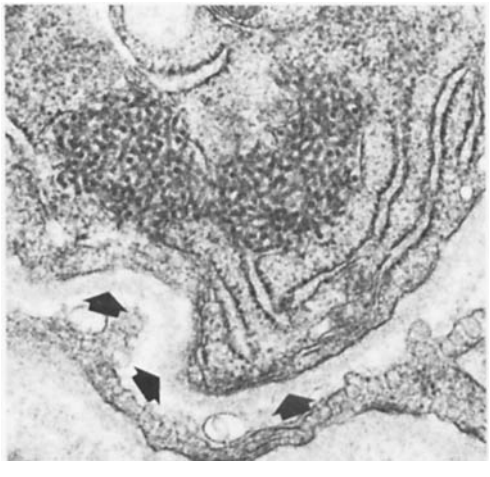

Fig. 8. Case 6. Cytoplasmic tubular structures in vascular endothelial cell of leukoplakia-like lesion seen in Fig. 2. The diameter of the tubules is 20 nm. Note relation to endoplasmic reticulum. Arrows indicate basal lamina surrounding the capillary. X 17,500

during the transition period indicates that the transition of oral DLE lesions into leukoplakia-like lesions does not reflect the level of activity of the skin lesions.

As leukoplakia is an exclusion diagnosis, care should be taken in making it. If a DLE patient is seen for the first time when the oral lesion is leukoplakia-like, this may possibly result in an incorrect diagnosis of the oral lesion. Therefore, questioning on previous or present skin lesions as well as symptoms of SLE should be done before making a diagnosis of leukoplakia. When diagnosing atypical oral lesion of DLE, direct IF-examination is usually of value as a supplement to clinical and histological examination (7). However, IF-examination appears to be of only minor value in diagnosing leukoplakia-like oral DLE lesions. The presence of CTS in vascular endothe-

lium of active oral DLE lesions has been shown to be a consistent finding, and CTS appears to be absent in true oral leukoplakia (6). The presence of CTS in two out of three biopsies of the present leukoplakia-like DLE lesions suggests that ultrastructural examination may be of diagnostic value for inactive oral DLE.

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