CASE REPORT

Neoplastic transformation of oral lichen: case report and review of the literature

Trasformazione neoplastica di lichen orale: caso clinico e revisione della letteratura

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Key words

Oral lichen planus • Oral cancer • Squamous cell carcinoma

Parole chiave

Lichen planus orale • Cancro del cavo orale • Carcinoma squamocellulare

Summary

Aim of the present investigation was to analyse the possible malignant transformation of oral lichen planus to carcinoma, especially in the atrophic erosive forms and those displaying plaques involving the top of the tongue. A review has been made of the literature, from 1986 to the present day. This search outlines the relationship between oral lichen planus, hepatitis C virus infection, Epstein-Barr virus infection and the importance of periodic follow-up in all patients with oral lichen planus. The case is described of malignant transformation of oral lichen planus to oral cancer in a female presenting asymptomatic hepatitis C virus infection. The clinical history confirms the most important aspects of the relationship between oral lichen planus and oral cancer. Oral lichen planus should be considered as a precancerous lesion, particularly in patients presenting hepatitis C virus infection, requiring follow-up, at close intervals, starting from 3 months after diagnosis.

Riassunto

Lo scopo di questa ricerca è descrivere la possibile trasformazione maligna del lichen planus orale (OLP) in carcinoma, particolarmente nel caso di forme atrofiche erosive e a placche interessanti il dorso della lingua. Gli Autori riferiscono una revisione della letteratura dal 1986 a tutt'oggi. Questa ricerca descrive il rapporto tra il lichen planus orale, l'infezione da HCV, l'infezione da EBV e l'importanza di un periodico follow-up di tutti i pazienti affetti da OLP. Gli Autori riportano un caso di trasformazione maligna di OLP in cancro orale in una donna affetta da epatite C asintomatica. La storia clinica conferma i più importanti aspetti del rapporto tra OLP e cancro orale. In conclusione il lichen planus orale deve essere considerato una lesione precancerosa soprattutto in pazienti affetti da epatite C e necessita di un follow-up ravvicinato nel tempo a partire da 3 mesi dopo la prima diagnosi.

Case report

A 60-year-old female, in apparently good health, came to our Outpatient Department in November 2001 complaining of a sharp and widespread pain in the oral cavity which had been present for approximately one year and which worsened when in contact with food.

The most significant anamnestic findings were:

- cholecystectomy, 20 years previously, for gallstones;
- chronic gastritis with hiatus hernia, under treatment with omeprazole and levosulpiride;
- hypothyroidism oral treatment with levothyroxine sodium with hormonal levels of FT3 and FT4 within normal limits and thyroid stimulating hormone (TSH) < 0.005 mIU/l (nv 0.27-4.2 mIU/l);
- asymptomatic hepatitis C virus (HCV) positive;
- non drinker, non smoker.

Serum levels of mean corpuscular haemoglobin (MCH) were 33.3 pg; erythrocyte sedimentation rate (ESR) 27 mm/h, fibrinogen 403 mg/dl, glutamic-pyruvic transaminase (GPT) 52 IU/l, none of which were within normal limits.

Electrocardiogram (ECG) and chest X-ray were both negative.

ENT examination revealed an exophytic neoformation with a smooth whitish surface a well-defined

sessile lesion, approximately 5 mm in diameter, in correspondence to the mucosa of the right cheek.
Results of the histological examination of the neoformation, removed under local anaesthesia on 28.11.2001, referred to a diagnosis of an inflammatory polyp with inflammation of the lichen planus type (Fig. 1).

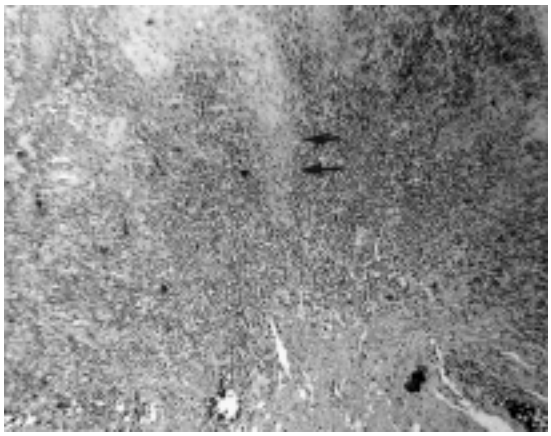

Fig. 1. Inflammation of lichen planus type. Lymphocyte infiltration occupies connective stroma even covering basal layer of epithelium (arrow) (Biopsy 06464-I-01, H&E, 40X).

At follow-up 4 months later, a whitish plaque adhering to the oral mucosa was found in correspondence to the previous lesion, the surface of the lesion was irregular but was not painful.
A biopsy specimen was collected on 13.3.2002. The histological diagnosis was keratosic epithelial hyperplasia, resulting from focally ulcerated leucoplakia (Fig. 2) associated with lichenoid dysplasia (Fig. 3).

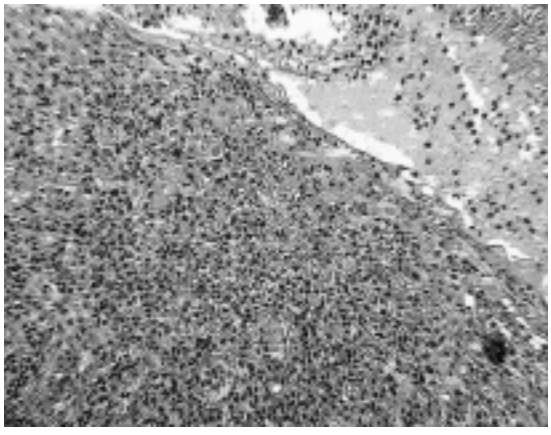

Fig. 2. Ulcerated area. No evidence of important cytological abnormalities (Biopsy 00467-I-03, H&E,100X).

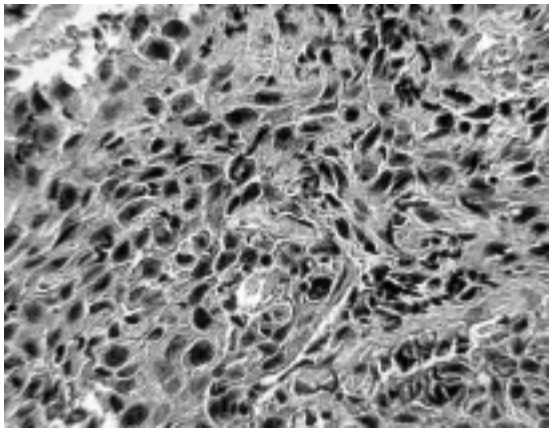

Fig. 3. Lichenoid dysplasia. Epithelial thecae display structural disorders and cytological abnormalities e.g. increased nucleo-plasmic ratio anisokaryosis, nuclear hyperchromatism, irregular nuclear margin (Biopsy 01484-I-02, H&E, 250X).

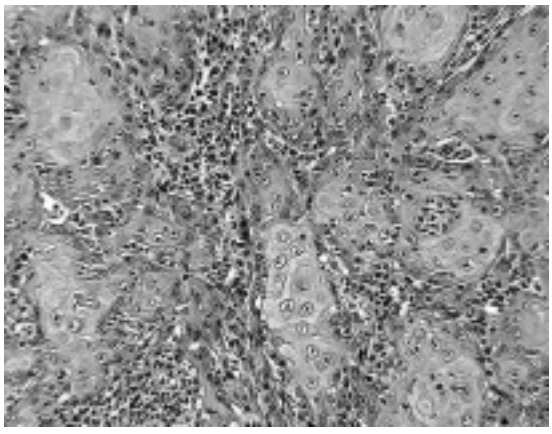

Fig. 4. Squamous cell carcinoma. Area showing marked degree of differentiation (Biopsy 03166-I-02, H&E, 100X).

The patient was programmed for follow-up after 3 months: at the beginning of June the lesion was ulcerated, slightly raised with granulating surfaces and well-defined, hard, margins. The histological diagnosis on 5.6.2002 was: fragments of well-differentiated G1 squamous cell carcinoma (Fig. 4) with moderately differentiated areas G2 ulcerated and infiltrating; lichen was also present.

Review of the literature

Lichen planus is a chronic inflammatory disease occurring in adult age [1,2]. It is relatively common [3-8], of-

ten recurrent, itchy [9 10] not contagious [11] and involves the skin and mucosa [7 11-14].
The mouth is involved in only ~1/3rd cases whilst in another 1/3rd lesions are both oral and cutaneous [7 12].
The incidence, in the general population, is approximately 1%, affecting all races and both sexes, a greater frequency being observed in females, 70% of whom between 30 and 60 years of age [6 11 14 15].
Familial cases Are rare. An association has been observed with HLA-A3, A11, A26, A28, B3, B5, B7, B8, DR1, DRW9 [6 11 14].
The aetiopathogenesis remains unknown [6 7 11 16], even if recent data have shown that immunological mechanisms may play a role [6]: it would appear to be an anomalous immune response in which the epithelial cells are not recognized, secondary to mutations in the superficial antigens [4].
It would thus be a graft versus host reaction in which the cell-mediated reaction involves cytotoxic lymphocytes versus the impaired basal keratinocytes [2 11 14].
In keeping with the hypothesis of an autoimmune aetiopathogenesis is the frequent association of lichen planus with autoimmune diseases, such as primary biliary cirrhosis, chronic active hepatitis, ulcerative colitis, myasthenia gravis, thymoma [8 11].
As demonstrated in the literature, and the focal point of numerous studies, are also the associations of lichen planus with several viruses, such as, for example, human papilloma virus (HPV 16 and HPV 18) [17 18], Epstein Barr virus (EBV) [19], human Herpes virus 6 (HHV-6) [20] and hepatitis C virus (HCV) [9 21-25].
The syndrome of Grinspan has been described with a symptomatological triade – arterial hypertension, diabete mellitus, erosive oral lichen planus with malignant transformation [26].
Cases of lichen planus have been reported after the use of certain pharmaceutical agents such as antimalaria drugs, gold salts, penicillamine, diuretics, thiazide, β-blocking agents, non-steroidal anti-inflammatory drugs (NSAIDs), quinidine, angiotensin converting enzyme inhibitors [9], streptomycin, methyldopa, phenothiazine [27].
Clinically, oral lichen planus (OLP) may manifest in various forms:

- reticular (the most frequent, with small isolated or confluent small white papules or, network of white lines, the so-called Wickham's striae).
- Erosive and ulcerated (painful lesions of various sizes).
- Atrophic (less common, often resulting from the erosive-ulcerative form with reddish lesions with a rough surface and irregular, poorly defined. margins).
- Hypertrophic (rare whitish well-circumscribed raised plaque similar to leucoplakia).
- Bullous (very rare, pemphgoid, para-neoplastic).

Very rare pigmentous, due to local overproduction of melanine during the acute phase of the disease [6 8 10-12 27 28].
Mucosal lesions, which are multiple, generally have a symmetrical distribution [6 8 12 28], particularly on the mucosa of the cheeks, in correspondence to the molars, and on the mucosa of the tongue, less frequently on the mucosa of the lips (lichenous cheilitis [11 15 27]) and on the gums (the atrophic and erosive forms localized on the gums manifest as a desquamative gengivitis [8]), more rarely on the palate and floor of the mouth [8].
The lichenous papula can be recognized by the semeiological Bizzozzero sign: rubbing the lesion induces transformation into a bleeding papula on account of micro-haemorrhage at the dermo-epidermic junction due to fragility of the capillaries [11]. Furthermore, the initial lichen lesion may develop after rubbing (reactive isomorphism the so-called Köbner phenomenon [8 11]).
Oral lichen planus is often asymptomatic [6 28] or may give rise to a burning or painful feeling [8 11], irritation following contact with certain foods, an unpleasant sensation of a dry mouth [8].
The erosive and boil-like forms tend to be painful [8].
The clinical history includes phases of remission and exacerbations [8].
From a histological point of view, OLP is characterised by oedema and dense lymphohistiocyte infiltration, localized in the papillary derma, which penetrates and detatches the basal layer which becomes unrecognizable.
Within the papillary derma, hyaline Pas positive bodies (Civette bodies) can be found containing immunoglobulins, primarily IgM, evident at direct immunofluorescence, and cytoids bodies which are degenerated keratinocytes. Furthermore, it is possible to find orthokeratosic hyperkeratosis, focal hypergranulosis, irregular acanthosis, vacuolar degeneration of the basal layer, acantholysis of the basal cells, loss of the hemidesmosomes responsible for the basal cells becoming adhered [6 10 11 27-30].
Treatment consists in short-term topical fluorurated and systemic corticosteroids [11 28 31].
In some cases, lichen planus responds to griseofulvin *per os*, which is administered until complete disappearance of the lesion [28].
Photochemotherapy PUVA, retinoids per os, and anxiolytics are also used [11].
Much controversy still exists and studies are being focused on the possible transformation of OLP to epidermoid carcinoma [5 6 12 16 21 29 31-39].
OLP is considered a precancerous lesion [32 34 35], an unrecognised leucoplakia [12]; a greater malignant potential has been recognized for lichen ruber planus [12], the erosive or erythematous [5] form, the ulcerative form [31 35], atrophic, erosive form and the plaques on the back of the tongue [21 27], when a smoker is involved [36]. In the latter case, the doubt remains as to whether the OLP is intrinsecally precancerous or pre-

disposes to malignant transformation mediated by external factors [16].
Furthermore, it should not be forgotten that the erosive and atrophic forms may resemble the appearance of a carcinoma [6].
In most cases, malignant transformation to carcinoma in situ (28.5%) and in microinvasive carcinoma (30-38%) is observed, less frequently stage I and II carcinoma [38 39].
Oral cancer-correlated OLP predisposes to the development of multiple primary metachronous tumours of the oral cavity and of lymph node metastases.
Therefore, ORL examinations are recommended every month, for the first 6-9 months after diagnosis, and, thereafter, 3 times a year [39].

Results

This clinical case presenting the typical aspects found in the literature was, in our opinion, worthwhile describing, namely:
- lesions of the oral mucosa which can be classified as lichen planus – slightly symptomatic, bilateral symetrical, on the mucosa of the cheeks;
- ulcerated form of OLP transformed, in approximately seven months, to squamous carcinoma;
- asymptomatic HCV positivity.

A review of the literature led us to the following considerations:
- follow-up of OLP should be programmed for 6 months to 15 years [5 8 14 32 39-46] with cases of malignant transformation 40 years after the initial diagnosis of OLP [12];
- the percentage of OLP cases that transform to epidermoid carcinoma varies from 0.4% to 3.7% [5 8 14 31 32 40-44];
- the site most frequently involved in the malignant transformation is the back of the tongue [3 15 21 24 36 40-44];
- the malignant transformation does not always occur in the presence of the well-known risk factors of oral cancer, i.e., smoking and alcohol [49];
- the OLP form that most frequently transforms into carcinoma is the erosive symptomatic form [15,17,23,27,29,30,31,38,48] while the atrophic form is probably a predisposing factor [44];
- there is no general agreement as to whether females are more likely to present malignant transformation of an OLP, than males;
- patients with oral and cutaneous lichen planus are at greater risk of developing oral cancer from OLP [13 36];

OLP may be considered an extrahepatic manifestation of HCV infection [23-25] and, in these cases, more frequently undergoes malignant transformation [24].

Discussion and conclusions

It is mandatory, in patients with oral lesions of the lichen planus type, even if asymptomatic or barely symptomatic, to programme scrupulous long-term follow-up.
Considering the rapid malignant transformation observed in the case described (3 months after lichen planus with lichenoid dysplasia and 3 months after lichenoid dysplasia and ulcerated infiltrating cancer G1-G2) suggests the need for histopathological observations at more frequent intervals (at least every 3 months) from the time of the first diagnosis.
Even more scrupulous attention is necessary in those cases presenting concomitant skin invasion of lichen, HCV infection, HBV infection, autoimmune diseases.

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