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Narrow-band imaging: a useful tool for early recognition of oral lichen planus malignant transformation?

Background: Oral lichen planus (OLP) lesions have an overall malignant transformation rate of 1.37%. In patients with chronic disease, the diagnosis of malignancy relies on histopathological examination guided by clinical suspicion. Narrow-band imaging (NBI) is a promising endoscopic technique which, using a filtered light with specific wavelengths, can highlight microvascular abnormalities associated with subclinical neoplastic changes of the upper aerodigestive tract epithelium. *Objectives:* This study aimed to analyse the value of NBI in selecting patients for biopsy before the emergence of clinical changes, allowing early detection of oral malignancies arising from OLP. *Materials and methods:* A prospective study was conducted, enrolling 32 consecutive patients with a histological diagnosis of OLP with no previous diagnosis of oral cancer or other oral inflammatory diseases. Patients with suspicious NBI lesions underwent biopsies, while other patients were included in the follow-up. *Results:* Two patients were judged positive at NBI evaluation and squamous cell carcinoma was diagnosed after histological examination. None of the other patients developed clinical features of malignancies during follow-up. *Conclusion:* NBI evaluation may increase the accuracy of detection of subclinical neoplastic transformation in OLP lesions and further encourage clinicians to perform biopsies in selected cases.

Key words: malignant transformation, narrow-band imaging, oral cancer, oral disease, oral lichen planus, oral squamous cell carcinoma

Oral lichen planus (OLP) is one of the most common chronic inflammatory skin diseases occurring in the oral cavity. Its worldwide prevalence has been estimated between 0.5% and 2% [1, 2]. The female/male ratio is 2:1 [1]. The onset age is between the fourth and seventh decade, with very few cases reported in the paediatric population [1, 3, 4].

The prevalent theory regarding the aetiopathogenesis relies on a T-lymphocyte-mediated immuno-pathological reaction, probably induced by a series of various exogenous triggers as the cause of an alteration of endogenous and surface antigens of the oro-mucosal keratinocytes, which ultimately enter into apoptosis [1, 5-12].

Six clinical subtypes of OLP exist individually or in combination: reticular, papular, plaque, erosive/ulcerative, atrophic and bullous [1, 13].

The clinical features of the lesions, particularly when they occur bilaterally and with Wickham's classic lattices, are strongly indicative of OLP, allowing a diagnosis based on the clinical appearance alone [13]. However, such a characteristic appearance is found in a low percentage of cases, therefore a histological examination is recommended as the gold standard, since lichen planus usually shows typical features [1, 13, 14].

Direct immunofluorescence (DIF) has proven to be a valuable method for diagnosing bullous, erosive, and ulcerative diseases of the oral mucosa, especially if lesions are ulcerated with secondary inflammation [15, 16]. DIF findings in patients with OLP are typical and widely reported in the literature [1, 17].

OLP alternates between periods of remission and exacerbation, thus a scheduled follow-up is strongly recommended [10]. Treatment is normally reserved only for symptomatic patients. Topical steroid therapy is generally administered, and systemic folic acid and variants of vitamin B may have therapeutic effects [18-27].

A crucial point for OLP is the potential of malignant transformation. A recent review identified an overall malignant transformation rate of 1.37%, with an annual transformation rate of 0.2% [2].

An important clinical characteristic of carcinomas arising in OLP lesions is their tendency to be multifocal, according to the concept of field cancerization [28].

Regarding their histopathological aspect, most malignant neoplasms that have developed from OLP lesions are well-differentiated squamous cells carcinomas (SCC); together with atypical cells, aberrant microvascular patterns are considered as early histological signs of malignancy [1, 29].

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Malignant transformation has a higher incidence in immunosuppressed patients, smokers, alcohol abusers, and HCV-positive patients [2, 30]. Tongue lesions and erosive OLP lesions are more likely to progress towards malignant transformation [2, 31-33]. Supported by the current biological knowledge, recent studies reported the possible role of *Candida spp.*, which may over-infect OLP lesions both at initial diagnosis and during immunosuppressive therapy, during carcinogenesis [2, 34, 35]. Chronic inflammation of the oral cavity (Koebner phenomenon or poor oral hygiene) may determine molecular alterations, favouring OLP malignant transformation [36].

Nowadays, there is still a lack of clear guidelines for clinicians; in patients with chronic disease, the diagnosis of malignancy relies on histopathological examination guided by clinical suspicion. Less invasive diagnostic tests for oral cancer have been recently reviewed showing conflicting results [37].

Narrow-band imaging (NBI) is a new promising endoscopic technique serving the concept of "biologic endoscopy" [38]. It consists of the use of a blue filtered light with specific (narrow) wavelengths that highlight haemoglobin, to enhance, inside and around a target lesion, submucosal microvascular abnormalities associated with subclinical pre-neoplastic and neoplastic changes of the upper aerodigestive tract epithelium [38-40]. Regarding head and neck (H&N) tumours, its diagnostic value has already been applied to various tasks, such as defining the superficial extension of malignancies or detecting persistent/recurrent disease after (chemo-) radiotherapy and surgery, synchronous and metachronous tumours, and unknown primary squamous cell carcinoma [41].

The validity of NBI in detecting oral malignant lesions has already been reviewed [42] and to the best of our knowledge, no study has been published with the specific aim of investigating the impact of NBI on the identification of subclinical signs of malignant transformation of OLP lesions.

Our study aimed to analyse the value of NBI in selecting patients to undergo a biopsy before the emergence of clinical changes, allowing early detection of oral malignancies arising from OLP.

Materials and Methods

A retrospective study was conducted at the Department of Dermatology and at the Department of Otorhinolaryngology- H&N Surgery of San Martino Polyclinic Hospital, University of Genoa, Italy. Thirty-two consecutive patients affected by OLP were enrolled between May 2015 and December 2016, and follow-up visits were conducted until May 2018. Patients were 14 men and 18 women and age ranged from 49 to 81 years (median: 67 years). Inclusion criteria were: (1) diagnosis of OLP confirmed by histological examination; (2) no previous diagnosis of oral cancer; and (3) no other oral inflammatory diseases.

All patients underwent, at time T0, a dermatological and otorhinolaryngological examination.

The study was approved by the San Martino Human Ethics Review Committee. All patients enrolled in this protocol received information and signed a specific informed consent.

Dermatological examination at T0

A clinical examination of the oral mucosa was performed, which included determination of OLP subtype (reticular, papular, plaque, erosive/ulcerative, atrophic and bullous) and the presence or absence of active lesions. Patients' skin and genital mucosa were also evaluated to look for lichen planus lesions. An assessment of oral cancer risk factors (cigarette smoking, alcohol abuse, and HCV infection) was performed with documentation of treatments used (corticosteroids, immunosuppressants, antimycotics or other products).

Otorhinolaryngological examination at T0

The oral cavity was evaluated first by conventional oral examination with the use of a tongue depressor and frontal light. The entire oral cavity, with particular attention to the macroscopic lesion and surrounding mucosa, was then investigated using a rigid 0° endoscope, coupled to an Evis Exera II HDTV camera with high-definition television (HDTV), connected to Evis Exera II CL V -180B light source (Olympus Medical Systems Corporation, Tokyo, Japan) emitting white light (WL) and NBI light. Lastly, palpation of suspicious lesions and of the whole oral cavity was performed to investigate abnormal consistency and soreness if present [43].

Many authors have described NBI as a useful tool with high sensitivity for the diagnosis of SCC in the H&N area. Due to this tool, in H&N daily practice, excisional biopsy driven by bio-endoscopic examination has progressively been accepted for excision of small and easy-to-access lesions. This method of managing suspicious lesions allows for excision under direct control by NBI light, reaching optimal disease control [39, 44-46].

Aberrant changes in microvascular pattern, visualized during HDTV-NBI evaluation, are considered an early sign of malignant transformation; Takano modified the classification presented by Inoue [47] (*figure 1*) describing four typical vascular patterns due to capillary loops in the intraepithelial papillae (intrapapillary capillary loops [IPCLs]) of the oral cavity. We considered type II, III and IV patterns as suspicious for neoplastic lesions [47].

Follow-up

Dermatological and otorhinolaryngological consultations were carried out, combining conventional oral examination, with rigid 0° endoscope HDTV-WL and NBI.

The entire cohort of patients was divided into two groups. The first group (Group A) included patients with no suspicious lesions on NBI endoscopy at the first examination. For such events, a subsequent NBI examination was rescheduled after three months (T1), then every six months (T2). The second group (Group B) encompassed patients with suspicious lesions on NBI. In order to exclude false positive results due to inflammatory changes, which can be confounding, all patients made any necessary changes to eliminate pro-inflammatory factors, such as poor oral hygiene, dysfunctional dentures, and smoking. Moreover, all patients received anti-inflammatory topical therapy (clobetasol propionate 0.05% mixed with 4% hydroxyethyl

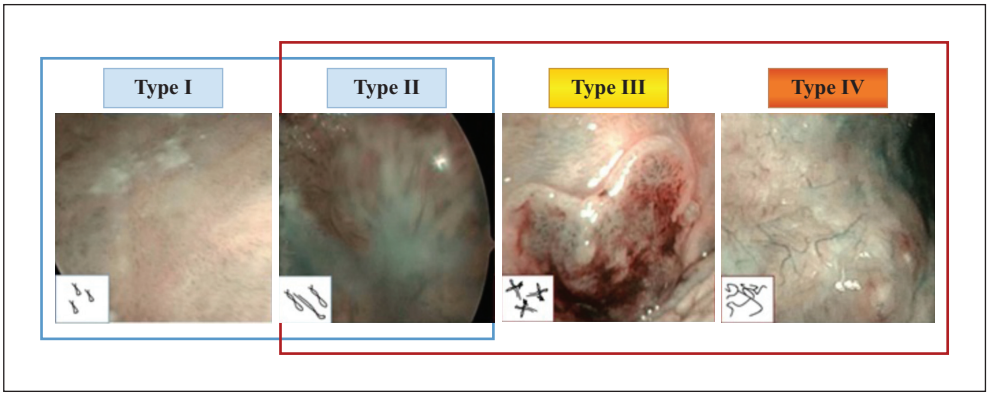

Figure 1. Takano's classification for oral cavity lesions. In type I, point and small intrapapillary capillary loops (IPCLs) appear widespread on the mucosa. Elongated IPCLs with dilated calibre belong to type II. Extremely tangled IPCLs with larger calibre, creating a dotted pattern, are a typical feature of type III. Type IV is characterized by irregular vessels, extremely variable calibre, and no loops. Vascular patterns of type II, III, IV were considered as an indicator of neoplastic progression, and therefore judged as "positive" [47].

cellulose gel) and were re-evaluated 30 days later. Patients with suspicious endoscopic findings (Group B) were stratified into two subgroups. Group B1: patients considered negative at the NBI re-evaluation after one month, who were followed for three months (T1), then every six months, similar to those of Group A. Group B2: patients with endoscopic findings that were still suspicious, in whom an excisional biopsy was consequently performed. Group B2 patients were again divided into two subgroups: Group B2a (patients whose histology was negative for SCC, who were re-evaluated after three months) and Group B2b (patients whose histology was positive for SCC, which was treated by a wider re-resection, and who were subsequently endoscopically re-evaluated after three months) (*figure 2*).

Results

Epidemiological data, types and phase of OLP, risk factors, previous drug therapies, and duration of disease for Groups A, B, B1, and B2 are summarized in *table 1*. A total of 32 patients were enrolled in the study. One patient was excluded from the population as the protocol was not respected; the patient had a positive lesion at the first NBI evaluation but presented with a worrying clinical appearance together with strong risk factors. He was a 67-year-old man with a clinically active erosive OLP, despite therapy with corticosteroids. Therefore, the patient did not join Group B and immediately underwent a histological examination. Despite a positive NBI evaluation as well as the worrisome clinical appearance and history, the histological examination was negative for cancer. The patient was consequently included in the follow-up and currently shows no evidence of malignant transformation.

In our series (*table 1*), erosive (48%) and reticular (32%) types were the most represented, and 21 patients (68%) presented with active lesions. The duration of disease ranged from two months to 34 years. At least two drugs were administered in 29% of patients. Five patients had concurrent cutaneous or genital involvement.

All patients from Group A underwent further WL and NBI examinations at each follow-up visit. No positive lesions were found in any of the patients (*figure 3*). To date, there is no evidence of malignancy in any of them.

In Group B, one month after T0, four patients were judged negative at the second examination under NBI (Group B1) (*figure 4*), while two patients still had positive lesions (Group B2), thus both of them underwent histological examination. Due to the small size of the lesions in both patients, excisional biopsy was performed. In one of them, carcinoma *in situ* (Cis) was diagnosed, and was completely excised with free margins (*figure 5*). To date, there is no evidence of relapse. The other patient was diagnosed with invasive squamous cell carcinoma and was treated by a transoral excision of the cheek mucosa, extending to the retromolar area without any need for tissue reconstruction; the final histological report revealed a SCC staged pT1 with free margins. During the follow-up, three months after surgical treatment, a suspicious novel lesion appeared on a pre-existing reticular OLP lesion involving the gingival mucosa, beside the inferior incisor teeth. The novel lesion was judged positive upon NBI examination, therefore, an excisional biopsy from the gingival mucosa was performed. The histological examination showed an *in situ* squamous cell carcinoma. The patient presented no evidence of disease at the last follow-up visit, two years after last excision; a single erosion in the soft palate, non-suspicious on NBI, was detected. Therefore, both patients were placed in Group B2b. None of the patients were classified in Group B2a.

In summary, both patients with lesions judged to be positive at the second NBI evaluation were histologically diagnosed with neoplastic lesions one month after the first visit.

Discussion

Oral lichen planus is a chronic inflammatory disease, treated by topical therapy only when symptoms are present [18, 20, 25, 26, 48, 49], and this was confirmed by our results on disease duration and treatments used.

In our experience, evaluation with HDTV-NBI turned out to be useful to precociously identify pre-neoplastic and neoplastic changes in patients affected by OLP.

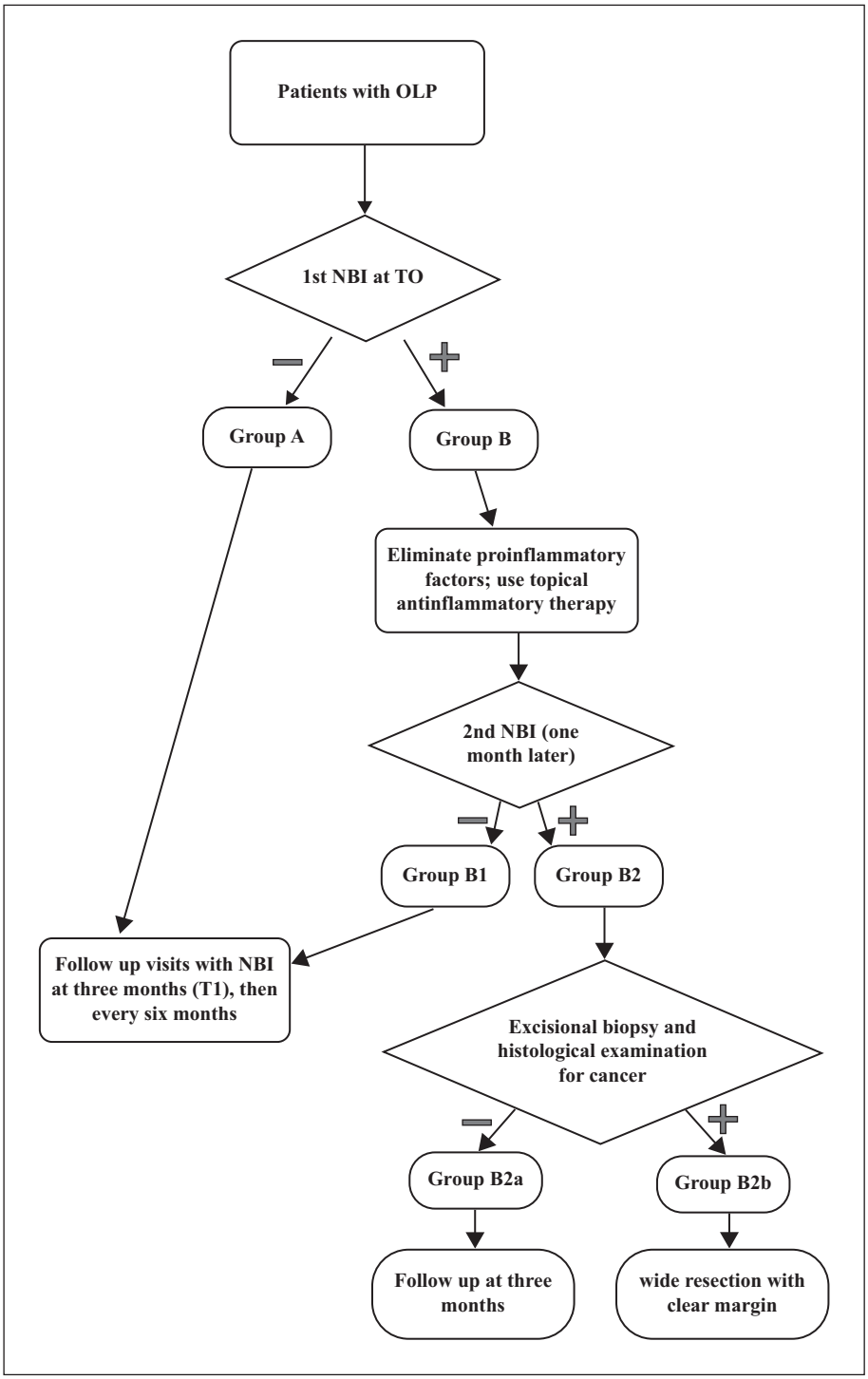

Figure 2. Flow-chart of patient management.

In fact, in our series, two cases raised a suspicion of oral cancer after we repeated HDTV-NBI following topical anti-inflammatory therapy (Group B2b). Those two cases (6.5%) were histologically confirmed as malignant; such a percentage is higher than that described in the literature [2], probably due to the small sample size of patients.

None of the patients with NBI-suspicious lesions underwent biopsy for non-neoplastic lesions (Group B2a). Presumably, histological examination was performed only for neoplastic lesions due to the small sample of patients.

In our limited experience, NBI guided our choice of patients who needed a histological evaluation of their lesion. Notably, through NBI, we were able to find a case of *in situ* squamous cell carcinoma in a patient with clinically classic OLP, with a reticular pattern and without any suspicious feature calling for biopsy after conventional examination under white light.

Table 1. Epidemiology, types and phase of OLP, risk factors, and previous drug therapies of patients in Groups A, B, B1 and B2b (none of the patients were placed in Group B2a).

	Group A (*n*=25)	**Group B (*n*=6)**	**Group B1 (*n*=4)**	**Group B2b (*n*=2)**
Age, median (range; years)	66 (49-81)	71 (50-81)	71 (60-81)	65 (50-80)
Sex, *n* (%)				
Male	8 (32)	3 (50)	2 (50)	1 (50)
Female	17 (68)	3 (50)	2 (50)	1 (50)
Type of OLP, *n* (%)				
Reticular	9 (36)	1 (16.5)	0	1
Papular	1 (4)	0 (0)	0	0
Plaque	5 (20)	1 (16.5)	1	0
Atrophic	1 (4)	0 (0)	3	0
Erosive	9 (36)	4 (67)	0	1
Mixed	0 (0)	0 (0)	0	0
OLP phase, *n* (%)				
Remitting	9 (36)	2 (33)	2	0
Active	16 (64)	4 (67)	2	2
Risk factors, *n* (%)				
Smoking	7 (28)	1 (16.5)	0	1
Alcohol	2 (8)	1 (16.5)	0	1
HCV	3 (12)	0 (0)	0	0
Previous therapies, *n* (%)				
Steroid	3 (12)	2 (33)	2	0
None	8 (32)	1 (16.5)	1	0
Antimycotics	1 (4)	0 (0)	0	0
Immunosuppressant	0 (0)	1 (16.5)	0	1
Other	6 (24)	0 (0)	0	0
Association	7 (28)	2 (33)	1	1
Duration of disease, median (range; months)	48 (2-408)	120 (6-360)	99 (6-192)	270 (180-360)

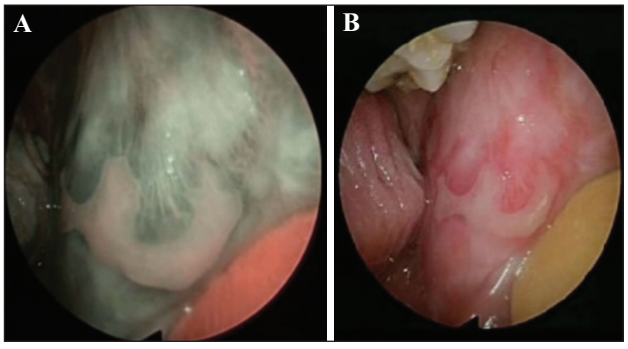

Figure 3. Oral lichen planus (Group A): NBI (**A**) and WL (**B**). On NBI, peri-lesional small dark spots and augmented vascularization without recognizable vessels indicate an inflammatory but benign lesion of the cheek mucosa.

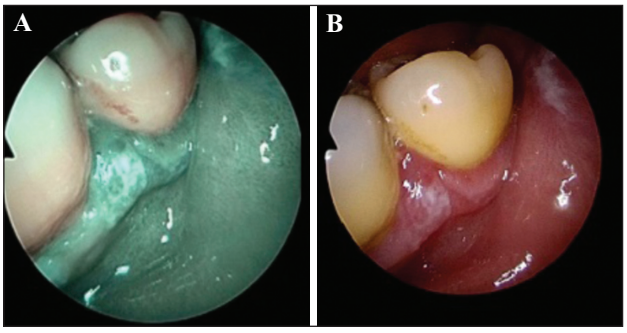

Figure 4. A Group B1 patient: NBI (**A**) and WL (**B**). Small dark intra-papillary capillary loops surround a keratotic gingival lesion with intra-lesional thicker spots.

One month after T0, four patients (Group B1) were judged to be negative at second examination based on NBI; we believe that this result was caused by the removal of any inflammatory factors affecting the oral mucosa during the period between the first and second evaluation, including any effects resulting from topical therapy. No evidence of malignancy was detected in any of those patients during subsequent follow-up visits over the next two years.

The patient excluded from the study, whose NBI was positive at T0 and who was immediately subjected to a biopsy, was found to be negative for cancer upon histological examination. We suppose that a high degree of inflammation, due to an erosive form of OLP, may have altered the microvascular component of the lesion, simulating the NBI patterns of a neoplastic lesion - as already highlighted in the literature [39-41, 47-50]. This patient would likely have been in Group B1, showing no suspicious features one month after T0, once any pro-inflammatory factors were eliminated.

During the follow-up period, each patient from Group A (negative NBI at T0) was evaluated by clinical assessment and HDTV-NBI, without further biopsies; to date, no patient has presented with macroscopic malignant transformations.

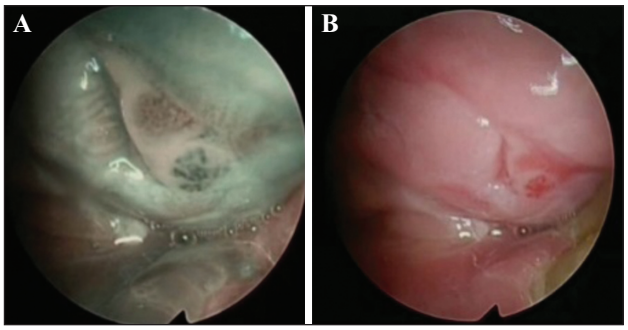

Figure 5. Carcinoma *in situ* of the retro-molar area/cheek mucosa (Group B2b): NBI (**A**) and WL (**B**). Intra-lesional thick dark intra-papillary capillary loops with variable calibre, suspicious for malignant mucosal transformation of the lingual border, are clearly recognizable.

Undoubtedly, our study has some limitations. One limitation is not having performed biopsies on patients with negative NBI lesions. We are therefore unable to conclude whether biopsies that would clearly be negative may be avoided based on NBI, since we were unable to confirm whether such patients were cancer-free based on histological examination. In any case, since patients were all included in a two-year follow-up programme and none of them showed clinical changes for two years, we are confident that no cases of cancer have been misdiagnosed based on our protocol. Of course, malignant changes may require more than two years, therefore speculation about the sensitivity of this diagnostic tool cannot be made on the basis of the present study. Furthermore, the presence of dysplasia in a negative case cannot be excluded without histological examination. On the other hand, we wish to emphasize the absence of false positive results in our study, which lays the foundation for larger studies including histological examination of negative cases.

Finally, the small size of the sample is certainly a significant limitation of the study. Larger, randomized studies are needed to confirm the sensitivity and specificity of the technique. If results are positive, the association between clinical evaluation and HDTV-NBI in routine practice could both increase the accuracy of detection of neoplastic transformation in OLP lesions and drive clinicians to perform biopsies in selected cases. Of course, it is necessary to schedule a protocol for the use of NBI, since a single examination could lead to false positive results, due to concomitant inflammatory factors - as was the case for the patient excluded from this study. Patients with NBI-positive lesions should be re-evaluated one month later with the same technique after eliminating every possible confounding factor, such as inflammatory insults; in our experience, to date, NBI has not generated any false positives.

Based on this study, NBI evaluation has proven to be a cutting-edge tool as part of the follow-up protocol for patients affected by OLP, allowing identification of malignancies otherwise not indicative of neoplastic transformation under conventional examination. Furthermore, biopsy (an invasive technique) may be avoided by NBI in a large number of patients, thus reserving biopsies for only high-risk individuals. Patients with stable or non-suspicious OLP lesions would significantly benefit from this conservative approach. In conclusion, we opine that, in centres where NBI evaluation is accessible, it is worth referring patients with OLP to otorhynolaryngologists in order to perform this non-invasive technique. ■

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