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ORIGINAL ARTICLE

Clinical, histopathological and immunohistochemical study of oral squamous papillomas

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Abstract

Objective. The aim of this study was to analyze the clinicopathological and immunohistochemical features of oral papillomas. ***Materials and methods.*** Biopsies of oral papillomas analyzed in the laboratory between 1996–2012 were extracted from the database and used to conduct this retrospective review. The following clinical data were extracted: sex, age, location, clinical appearance, time of evolution, recurrence and first clinical diagnosis. Immunohistochemical analysis for Human Papillomavirus (HPV)and histological evaluation of the lesions were performed. ***Results.*** A total of 205 papillomas were identified in 197 patients (♂=110, ♀ = 87; mean age = 48.4 ± 17.9 years).The majority of the lesions (n = 47) occurred on the soft palate (23%). The border of the tongue was the second most common site (n = 20, 9.8%). Lesions were more common in males than in females (ratio = 1.26:1). Statistical analysis did not show any correlation between the assessed variables. Clinically, papillomas were predominantly described by the practitioners as small nodules, with a papillary surface (98.1%) and pedunculated attachment(83.1%). Data supported a low recurrence (2.0%) and multiplicity (2.0%). Evolution time varied from a few weeks to several years. Most frequent misdiagnosis was condyloma. Immunohistochemistry rarely showed HPV presence (9.3%). Microscopically, lesions were very often keratinized (93.2%) and showed chronic inflammatory cells (68.8%). ***Conclusions.*** In this series papillomas showed a slight male predilection and occurred mostly in the sixth decade of life. Histologically, they were usually keratotic and exhibited variable inflammation. HPV virus was rarely detected by immunohistochemistry. No statistical correlation could be established between clinicopathological features.

Key Words: *HPV, immunohistochemistry, oral squamous cell papilloma*

Introduction

Squamous cell papilloma (SCP) is the most common benign epithelial tumor of the oral mucosa [1]. It can be recognized by the typical exophytic proliferation, which results in small papillary, finger-like projections (Figure 1). Depending on the degree of keratinization, the surface color of the lesion varies and can, thus, present as red, pink or white. Lesions are common to both sexes and the reported sex predilection varies from one study to the other. SCP may present anywhere on the oral mucosa; however, they most commonly occur on the palate and tongue. Papillomas can be diagnosed at any age, but the average reported age of the patients diagnosed with papillomas is between 20–50 years. Lesions are more often unique and recurrence is rare [2–8].

Papilloma is reported as the most frequent viral lesion of the oral cavity [1]. The etiology of SCP is controversial, but is predominantly considered a lesion of viral origin. The presence of human papillomavirus (HPV) DNA has been demonstrated in several reports; however, the frequency of HPV finding is not confirmatory and varies from one study to another [9–21]. More than 180 genotypes of papillomavirus have been described in the past years, of which 120 types of HPV viruses have been isolated from humans [22]. They appear to have a particular tropism for specific tissues and are associated with specific clinical lesions. Different HPV genotypes are, thus, associated with distinct oral diseases [23]. HPV numbers 6 and 11 are the most frequently found genotypes in oral squamous cell papillomas [10]. HPV is transmitted either sexually or non-sexually. The virus can cross the placental barrier and infect the fetus *in utero*, but also during delivery. Autoinoculation is yet another mode of transmission for this virus [24].

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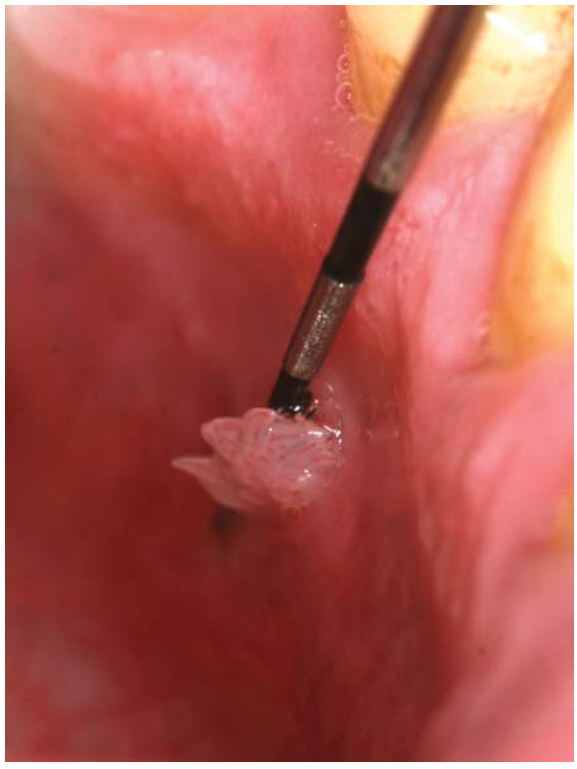

Figure 1. Clinical appearance of an oral squamous cell papilloma: pedunculated lesion displaying finger-like projections, located on the lingual side of the mandibular gingiva.

Clinically, the differential diagnosis of solitary oral SCP includes verruca vulgaris, condyloma acuminatum, verruciform xanthoma, verrucous carcinoma, physiologic papillae and papillary inflammatory hyperplasia [25–27]. The microscopic examination reveals a central fibrovascular connective tissue core from which finger-like projections emerge. These are lined by squamous epithelium with a pseudo or pluri-stratified basal layer. Koilocytes-HPV altered cells are rarely found in papillomas or are absent [26,27].

This study evaluated the epidemiologic variables concerning oral SCP diagnosed at the Laboratory of Oral and Maxillofacial Pathology of the University of Geneva, Switzerland. Our primary aim was to provide an analysis of these lesions and to compare the results with other studies in an attempt to point out similarities or discrepancies. Our secondary aim was to identify a correlation between the clinical and pathological features.

Materials and methods

The ethics committee of the Geneva University Hospital (HUG) approved this study protocol (Protocole no: 12-242). The cases included in this study were selected from our pre-existing laboratory records. The search was conducted over a 17-year period (between 1996–2012). All samples diagnosed with a papilloma were accepted for this study after a histopathological confirmation. Samples displaying proliferation of the keratinized stratified squamous epithelium arranged in finger-like projections with fibrovascular connective tissue cores were included. Human immunodeficiency virus (HIV) seropositive patients were excluded.

All clinical data were extracted from biopsy submission forms, which included sex, age, location of lesion, clinical appearance, duration, recurrence and first clinical diagnosis. Hematoxylin-eosin sections of the lesions were reviewed and histologic patterns of keratosis and inflammation were evaluated. All the samples were immunostained with an antibody against HPV.

Immunohistochemistry

Three-micrometer (μm) thick sections were deparaffinized in xylene, rehydrated in graded alcohol and rinsed with distilled water. For antigen retrieval, slides were immersed in 10 mM sodium citrate buffer (pH6) and boiled three times for 3 min in a micro wave (400W). Then, tris-buffered saline solution (TBS–0.05M,Tris-HCl, 0.05 M, Tris-HCl, 0.15 M NaCl, pH7.6, Dako, Baar, Switzerland) was used as a rinse. Sections were exposed to a peroxidase-blocking solution (Kit K4065, Dako) for 5 min at room temperature to block endogenous peroxidase activity. IgG1 monoclonal mouse anti-HPV antibody (K1H8 clone, code MS 1826-S, Thermo Scientific, Fremont, CA) was applied to the sections at a 1:50 dilution and incubated for 30 min at room temperature. The negative control was obtained by omitting the primary antibody from the assay and by replacing it with non-immune mouse IgG1 serum (code X0931, Dako, 1:50). The sections were then incubated with a secondary antibody HRP (KitDako) for 30 min at room temperature. Visualization of the immunoreaction was completed using 3, 3'-diaminobenzidine for 10 min as the peroxidase chromogenic substrate. The slides were then counterstained with hematoxylin for 30 s, dehydrated in xylene and mounted with Neo-mount (MERCK, Darmstadt, Germany). The immunostained slides were reviewed using a light microscope in order to analyze the cell expression for HPV. Staining was considered positive when there was a distinct nuclear staining.

Statistical analysis

Data analysis was performed using a software package (S-PLUS® version 8.0 for Windows, Insightful Corp., Seattle, WA). Variables such as sex, age, location, inflammation, keratosis and HPV expression were summarized using frequency and percentage. Fisher's exact test was applied to analyze a possible relationship between HPV expression and location; and also to analyze the hypothetical influence of sex on location. Chi-squared test was done to detect whether a

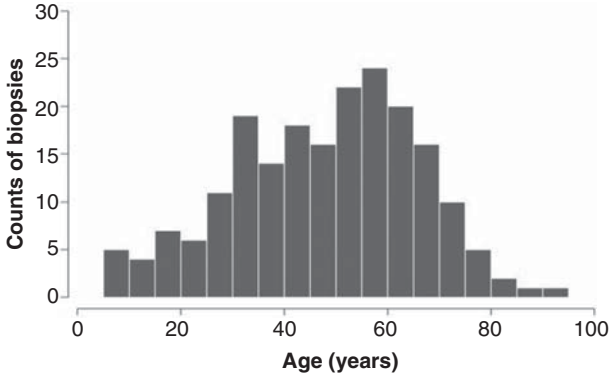

Figure 2. Age distribution of studied subjects at the time of oral papilloma biopsy.

relationship could be found between HPV expression and sex. Mann-Whitney and Student's *t*-test was performed to determine the link between HPV expression and age. Finally, a Fisher's test to analyze an eventual association of keratosis with inflammation, of keratosis with HPV expression and of inflammation with HPV expression was done. The statistical significance was set at 5% ($p \leq 0.05$) to be considered statistically significant.

Results

A total of 205 cases in 197 patients (n = 197; males = 110; females = 87, 55.8% and 44.2%, respectively) were identified and included in the study. Four patients presented with a recurrence, while another four patients presented with two lesions each. This result revealed a slight male predominance with a ratio of 1.26:1.The age of the 197 patients ranged from 5–92 years. The mean age was 48.5. The age distribution is presented in Figure 2.

Site

Twenty-five different localizations were listed, the most frequent being the soft palate with 47 cases (23.0%) followed by the border of the tongue (20 cases, 9.8%), the mucous membrane of the lips (16 cases, 7.8%) and the interdental papilla (15 cases, 7.4%). Table I shows the different frequencies for all 25 localizations. These sites were grouped in larger complexes to late facilitate comparison with other studies. We classified 71 cases (34.8%) under the palatal complex and specified the palatal complex locations into: hard palate, soft palate, uvula, hard/soft palate junction and NOS (not otherwise specified) 'palate'. In the same manner we distinguished 54 cases (26.5%) into the lingual complex consisting of: the lingual frenum, border of the tongue, anterior part of the tongue, ventral tongue, dorsum of the tongue, NOS 'tongue'. The labial complex composed of the mucous membrane of the lips, vermillion of the lips and NOS 'lips', consisting of a further 27 cases (13.2%). Finally the gingival complex consisting of: the gingival papilla, retromolar pad, edentulous ridge, tuberosity and attached tissue (buccal or lingual) included 32 cases (15.7%). The palate and tongue alone comprised over 60% of all the papillomas (n = 125/205). The hypothetical association between localization and sex and between localization and HPV expression were tested with Fisher's exact test. Results did not show any statistically significant correlation (Tables II and III).

Table I. Number and frequencies of the lesions in all 25 localizations.

Localization	Number of occurrences	Frequency
Uvula	1	0.5%
Tonsil	1	0.5%
Glossopalatine arch	4	2.0%
Soft palate	47	23.0%
Hard palate	10	4.9%
Hard/soft palate junction	7	3.4%
Palate (not specified)	6	2.9%
Mucous membrane of the lips	16	7.8%
Lip (not specified)	8	3.9%
Attached tissue (buccal or lingual)	5	2.5%
Vermillion of the lips	3	1.5%
Lingual frenum	4	2.0%
Border of the tongue	20	9.8%
Anterior part of the tongue	7	3.4%
Ventral tongue	11	5.4%
Dorsum of the tongue	9	4.4%
Tongue (not specified)	3	1.5%
Cheek mucosa	6	2.9%
Retro-commissural mucosa	3	1.5%
Commissure	4	2.0%
Floor of the mouth	2	1.0%
Interdental papilla	15	7.4%
Retromolar pad	6	2.9%
Edentoulous ridge	4	2.0%
Tuberosity	2	1.0%
NA (not available)	1	

Surface characteristics

The surface characteristics were reported for only 107 lesions (52.2%).The vast majority of the lesions (n = 105; 98.1%)were described as 'papillary', 'finger-like' or 'warty' and sometimes also as 'strawberry-like', 'cauliflower' or 'blackberry-like'. Only two lesions (n = 2; 1.9%) were described as 'smooth' or 'uniform'. Seventy-seven reports confirmed the

Table II. Correlation between HPV expression and age, gender, inflammation, keratosis and localization.

		HPV negative (n = 186)	HPV positive (n = 19)	p-value
Age	Mean (years)	48.0	54.1	0.27[a]/0.17[b]
Gender	Female	86	4	
	Male	100	15	0.06[c]
Inflammation	No	61	3	
	Yes	125	16	0.19[d]
Keratosis	No	12	2	
	Yes	174	17	0.62[d]
Localization	Uvula	1	0	
	Tonsil	1	0	
	Glossopalatine arch	3	1	
	Soft palate	45	2	
	Hard palate	9	1	
	Hard/soft palate junction	7	0	
	Palate (not specified)	5	1	
	Mucous membrane of the lips	14	2	
	Lip (not specified)	6	2	
	Attached tissue (buccal or lingual)	4	1	
	Vermillion of the lips	3	0	
	Lingual frenum	3	1	
	Border of the tongue	19	1	
	Anterior part of the tongue	7	0	
	Ventral tongue	10	1	
	Dorsum of the tongue	6	3	
	Tongue (not specified)	3	0	
	Cheek mucosa	5	1	
	Retro-commissural mucosa	2	1	
	Commissure	4	0	
	Floor of the mouth	2	0	
	Interdental papilla	14	1	
	Retromolar pad	6	0	
	Edentoulous ridge	4	0	
	Tuberosity	2	0	
	NA (not available)	1	0	0.39[e]

[a]Mann-Whitney test, [b]Student test, [c]Chi-squared test, [d]Fisher test, [e]Fisher exact test; $p \leq 0.05$ was considered as significant.

attachment of the lesion to the mucosa. Sixty-four of these lesions (83.1%) were reported as pedunculated (or pseudo-pedunculated), while 13 lesions (16.9%) were sessile. One hundred and twenty-eight lesions did not contain the information about the presence or absence of a stalk.

Size

Ninety-five out of 205 specimens had information about the size of the lesion. The smallest and the largest lesions measured 1mm in diameter and 23mm × 15mm, respectively. Only 12 lesions (12.6%) were larger than 5 mm and of these only five (5.3%) exceeded 10mm.

Color

The referring practitioners poorly described the color of the lesion. Eleven lesions were described as white, nine as pink and only two as red. Thirty-four practitioners mentioned that the lesion was keratotic (we assume that they probably intended that the lesion was white or whitish).

Table III. Correlation between gender and localization of the lesion.

Localization	Female (n = 90)	Male (n = 115)	p-value
Uvula	0	1	
Tonsil	0	1	
Glossopalatine arch	3	1	
Soft palate	23	24	
Hard palate	4	6	
Hard/soft palate junction	4	3	
Palate (not specified)	5	1	
Mucous membrane of the lips	7	9	
Lip (not specified)	3	5	
Attached tissue (buccal or lingual)	2	3	
Vermillion of the lips	0	3	
Lingual frenum	0	4	
Border of the tongue	14	6	
Anterior part of the tongue	4	3	
Ventral tongue	2	9	
Dorsum of the tongue	2	7	
Tongue (not specified)	3	0	
Cheek mucosa	2	4	
Retro-commissural mucosa	2	1	
Commissure	1	3	
Floor of the mouth	1	1	
Interdental papilla	4	11	
Retromolar pad	2	4	
Edentoulous ridge	1	3	
Tuberosity	1	1	
NA (not available)	0	1	0.10[a]

[a]Fisher exact test; $p \leq 0.05$ was considered as significant.

Presentation

The lesions were usually isolated. Two hundred and one cases presented as solitary lesions (98.0%) and only four patients (2%) had simultaneous multiple lesions (two lesions).

Duration

The duration of the lesions was not often noted in the submission report. Only 51 practitioners gave an appreciation of the evolution time. We, thus, decided to sub-divide this data into three categories: lesions that were present for less than or equal to 1 month (n = 9; 17.6%), between 1 month and 1 year (n = 26; 51.0%) and more than 1 year (n = 16; 31.4%).

Recurrence

Our data revealed that only six cases recurred. However, we possessed the data for only four of these patients (2%), since two cases were not submitted for histological examination. Three of these recurrences appeared in the same location, the information concerning the fourth was absent. Two of them recurred in the same year, one after 2 years and the last after 11 years.

Clinical/differential diagnosis

In 170 out of 205 cases (82.9%) the clinician suggested a diagnosis. The two major clinical diagnoses given were papilloma and condyloma. Some practitioners suggested both possibilities in the differential diagnosis. One hundred and twenty-three clinicians out of 170 (72.4%) provided a correct diagnosis and identified their submitted specimen as a papilloma. Twenty-seven of them also proposed the differential diagnosis of condyloma (15.9%) and 13 (7.6%) considered the lesion as a wart. Five practitioners (2.9%) did not specify the type of lesion but came up with the general term 'viral lesion'.The diagnosis of a hyperplasia was made 18 (10.6%) times. Other proposed diagnoses included: giant cells granuloma (n = 1), epulis (n = 1), keratosis (n = 2), physiologic papillae (n = 2), pyogenic granuloma (n = 1), hamartoma (n = 1), fibroma (n = 4) and verrucous carcinoma (n = 2).

Histopathological analysis

Two hundred and five papillomas were reviewed for histologic features. They consisted of papillary projections covered by hyperplastic stratified squamous epithelium with a fibrovascular core (Figure 3). One hundred and forty-one (68.8%) showed inflammation. One hundred and ninety-one lesions presented

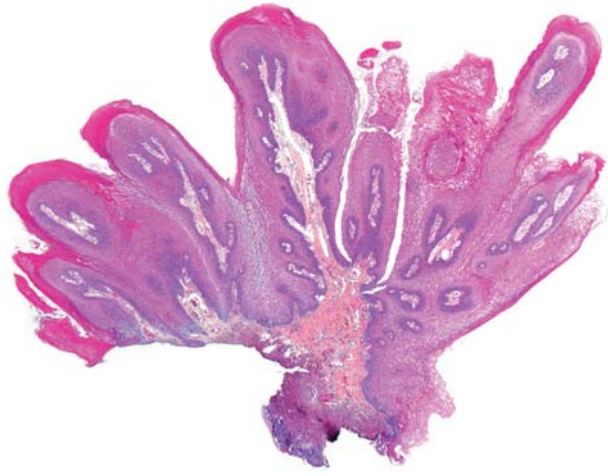

Figure 3. Microscopic aspect of an oral squamous cell papilloma showing multiple finger-like projections with a fibrovascular core, composed of hyperplastic squamous epithelium covered by a keratinized layer (HES, ×3.2).

Table IV. Correlation between keratosis and inflammation.

		No keratosis (n = 14)	Keratosis (n = 191)	p-value
Inflammation	No	6	58	
	Yes	8	133	0.37[a]

[a]Fisher test; $p \leq 0.05$ was considered as significant.

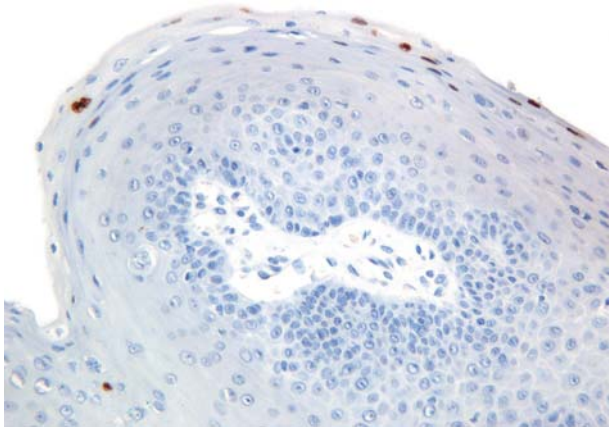

Figure 4. Positive nuclear staining for HPV in some of the upper epithelial cells of a squamous cell papilloma (immunoperoxidase, ×25).

with keratosis (93.2%). No correlation was found between these two variables (Table IV).

Immunohistochemical analysis for HPV

HPV staining was considered positive when there was distinct nuclear staining. Only 19 out of 205 specimens (9.3%) were positive at the immunohistochemical staining. These 19 cases usually presented a few positive stained cells in the upper epithelial layers (Figure 4). Statistical analysis between HPV expression and variables such as the localization of the lesion, the sex and age of the patient or histologic keratosis and inflammation revealed no significance (Table II).

Discussion

This type of retrospective longitudinal study presents the advantage of disposing of a quite considerable sample of specimens. On the other hand, it also has the disadvantage of depending partially on data submitted by different clinicians. This introduces elements of doubt into reported diagnoses and furnishes incomplete data in some categories. In this study, we managed to obtain data between 99–100%, concerning age, sex, location, histologic characteristics such as keratosis and inflammation and presence of HPV at the immunohistochemical analysis. The main missing data concern the clinical appearance of the lesions like color, size, attachment, surface aspect and time of evolution.

The first category, the gender of the patients, showed a male-to-female ratio of 1.26:1. Earlier published studies in the literature also found a male sex predilection similar to the findings in this study. Abbey et al. [2] reported a predilection of 1.16:1 favoring men, as similarly published by Bao et al. [3] and Kakarantza et al. [4], reporting 1.82:1 and 1.6:1, respectively. Lopez Amado et al. [5] reported only a slight difference in the sex predilection (1.1:1; male:female ratio). On the contrary three other studies showed an opposite result. Anselmi and Premoli de Percoco [6] reported a female predilection with a male: female ratio of 1:1.72 in their study, while Greer and Goldman [7] and Carneiro et al. [8] also reported female predilections with ratios of 1:1.25 and 1:3, respectively.

Age exhibited a large variability. The youngest patient in our study was 5 years and the oldest was 92 years old. The mean age was 48.5 years old. Almost all studies display a very wide range of ages, going from little children to old and very old patients. Abbey et al. [2] and Anselmi and Premoli de Percoco [6] obtained a mean age around 35 years old. Lopez Amado et al. [5] claimed 52 as being the median age and so did the Bao et al. [3] study, with 51 years.

In our series of papillomas the most frequent location was the soft palate with 47 cases (23%). When we consider the palate as a complex including also hard palate, uvula and hard/soft palate junction this percentage raised to 34.8%. The second site of predilection was the border of the tongue (9.8%) or the lingual complex (26.5%). In the third position was the mucous membrane of the lips (7.8%) and slightly after the interdental papilla with 7.4% cases. These results are shared by different studies [2–4]. Bouquot and Gundlach [1], Greer and Goldman [7], Anselmi and Premoli de Percoco [6] and Carneiro et al. [8], however, stated that the tongue was the favorite site of presentation of papillomas. These two last authors had the palate as a second location, but for Bouquot and Gundlach [1] the hard and soft palate only came in fourth and fifth position after the tongue, the lips and the buccal mucosa.

Papillomas in our study were mainly described as papillary, pedunculated and of small size by the clinicians. This observation is common to all authors for whom the lesions had a cauliflower surface, a narrow stalk and were rarely bigger than 1cm. Carneiro et al. [8] were the only group who encountered a prevalent round shape (seven cases) of their 12 reported cases.

All authors who recorded the color of the lesions obtained a majority of white lesions [2,4,8], except for Anselmi and Premoli de Percoco [6] who had 67.9% of lesions that were of pink color. In our series, few lesions had a statement about the color, but since most of them were hyperkeratotic this strongly suggests a whitish lesion.

A very low recurrence (2.0%) and multiplicity (2.0%) was found in our 197 patients. Other reports confirm this finding [2,6,8].

The most common differential diagnosis suggested was that of a condyloma. This lesion can effectively be wrongly considered a papilloma because the macroscopic aspect may also display a cauliflower-like surface. These entities can be made differentiated macroscopically, microscopically and immunologically. The numbers of elements, lesion size, stalk, localization and color can help distinguish them [26,27].

In this study, oral SCPs displayed hyperkeratosis in 93.2% of the cases and chronic inflammatory cells in 68.8%. Only Abbey et al. [2] gave a comprehensive description of histologic inflammation and keratosis. The majority of their papillomas (82.4%) exhibited surface hyperkeratosis and 80% inflammatory changes.

Many studies focus on the presence of HPV in oral SCP. Since the etiology of this lesion is still unresolved, many authors leaned over this subject. Different methods have been used to attempt to detect viral antigens or viral DNA in oral papillary lesions with very irregular issues [11]. Different authors with contrasting results have used an *in situ* hybridization technique. Syrjänen et al. [9] had 57.1% of their specimen positive for HPV DNA. For Eversole et al. [12] this was 35%. Some years later Young et al. [13], Zeuss et al. [14] and Bu et al. [15] obtained 62%, 13.3% and 53.3%, respectively, of positive papillomas with their DNA probes. More recently, other studies were conducted using the more sensitive polymerase chain reaction technique. Ward et al. [16] identified virus DNA in 68.4% of SCP, while Barzal-Nowosielska et al. [17] obtained 14 positive cases (36.8%) out of 38. Jimenez et al. [18] reported 11 positive cases (40.7%) out of 27. The method we used to examine samples for HPV presence was immunohistochemistry. This method also gave variable results in the past. Welch et al. [19] had only 4% positive samples, but Padayachee et al. [20] obtained more positive results in their larger study with 41% positive cases displaying intranuclear staining and 9% cases displaying both intranuclear and cytoplasmic staining. More recently Carneiro et al. [8] had a weak or negative immunostaining in 91.6% of their samples. Our analysis for HPV presence also gave us a quite low result, only 9.3% of the lesions were positive for the antibody. These inconsistencies are most likely due to different sensitivity of the methods employed; immunohistochemistry is known to have limited sensitivity [10] and permits to demonstrate viral antigens only where epithelial keratin differentiation is at an appropriate stage [28]. It is indeed possible that 90.7% of our samples not displaying any labeled cell did contain HPV, but at a level too low for detection. Some authors designate 'papilloma' any papillary oral lesions and do not make the difference between SCP, condylomas or warts [21], rendering difficult to assess the causative role of HPV in the development of oral SCP. The failure to demonstrate viral antigens does not exclude the possibility of HPV involvement, but it is very likely that some papillomas are of unknown etiology [29].

In conclusion, the results of this study are in agreement with some previous reports. In our series of oral SCP a slight male predilection was found. The great majority of the lesions were unique, pedunculated, whitish and occurred mostly in adults and palatal mucosa was the most common affected site. The papillomas were frequently hyperkeratotic and exhibited variable inflammatory changes. No statistical correlation could be established between clinical and pathological features. HPV-positive cells were rarely identified by immunohistochemistry.

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Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper

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