

Oral Mucosal Conditions in Chronic Hepatitis C Brazilian Patients: A Cross-Sectional Study

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Abstract

Objective: Our purpose was to carry out an epidemiological study to assess the prevalence of oral mucosal conditions in Brazilian patients with chronic hepatitis C. **Methods:** A cross-sectional survey was carried out on 215 patients with chronic hepatitis C who were examined for oral mucosal conditions, including oral mucosal lesions and variations of normality. **Results:** The prevalence of patients with chronic hepatitis C presenting oral mucosal conditions was 96.3 percent (207 patients). Oral mucosal lesions were present in 147 patients (68.4 percent), whereas variations of normality were observed in 173 patients (80.5 percent). The most common lesions included cheek biting in 42 cases (19.5 percent), candidiasis in 39 cases (18.1 percent), and leukoplakia in 28 cases (13.0 percent). The association of oral lichen planus with hepatitis C virus (HCV) infection proved to be statistically significant ($P = 0.002$). The most frequent variations of normality included Fordyce's spots in 96 cases (44.7 percent), lingual varicosities in 67 cases (31.2 percent), and fissured tongue in 60 cases (27.9 percent). **Conclusion:** The prevalence of patients with chronic hepatitis C presenting oral mucosal conditions was 96.3 percent. Despite this high prevalence, only the association between oral lichen planus and hepatitis C showed statistical significance. Considering that HCV infection may be associated with extrahepatic disorders, such as oral manifestations, efforts should be made to clarify the possible relation between oral conditions and HCV infection. This may be helpful in the earlier diagnosis of the infection mainly in asymptomatic patients.

Key Words: oral mucosal conditions, oral lesions, hepatitis C, HCV

Introduction

Hepatitis C virus (HCV) infection is a major cause of chronic liver disease as well as liver-related morbidity and mortality worldwide (1). HCV infection is a significant public health problem, which represents the core reason for liver transplants in Europe and the United States (1,2).

Hepatitis C is caused by an RNA virus, identified in 1989 (3), and its transmission occurs primarily through exposure to infected blood (4). The prevalence of HCV infection shows a great geographic variation. In Brazil, the estimated prevalence is 1.23 percent (5). As hepatitis C often

remains mild or completely asymptomatic for many years, it is largely underdiagnosed (4).

Extrahepatic manifestations may result from immunologic trigger mechanisms as well as virus invasion and replication that affect extrahepatic tissues and organs (6). Currently, HCV can be considered a virus with a triple tissue tropism – hepatotropism, lymphotropism, and sialotropism. However, the role of HCV and of its viral proteins in the pathogenesis of extrahepatic manifestations is still not clear.

Some studies of nonhepatic manifestations in patients with HCV

infection have been focused on possible oral alterations (7-10). However, the real prevalence and the relation of these conditions to the HCV-positive status in such patients remained to be better clarified. Xerostomia, Sjögren's syndrome (7,8), sialoadenitis (8,10), and oral lichen planus (OLP) (9-13) have been the main conditions associated with HCV infection in the literature (14-16). Nevertheless, further research from different geographic areas is warranted to better understanding of the real prevalence of oral mucosal conditions in this group of patients (10), looking for the earlier diagnosis of HCV infection mainly in asymptomatic patients.

Therefore, the purpose of this study was to assess the prevalence of oral mucosal conditions in patients with HCV infection who were attended to at Alfa Gastroenterology Institute from the Clinical Hospital of Universidade Federal de Minas Gerais (IAG-HCUFGM), Belo Horizonte, Minas Gerais, Brazil.

Methods

A cross-sectional survey was carried out during a period of 12 months on consecutive 215 patients with chronic hepatitis C infection attended to at IAG-HCUFGM, which is the main referral center in viral hepatitis in the state of Minas Gerais, Brazil.

As OLP is the main oral lesion associated to HCV infection, according to the literature, the size of the

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present sample was calculated with a standard error of 1 percent, 99 percent confidence interval level, and an expected prevalence of 8.8 percent of OLP described by Figueiredo and colleagues (17).

All patients presented a positive third-generation enzyme-linked immunosorbent assay for HCV (anti-HCV test) and a positive serum HCV RNA by means of reverse transcription-polymerase chain reaction. As it has been extensively demonstrated that interferon may induce or worsen immunologic diseases (18-20), the patients who were receiving antiviral treatment, as well as the patients with HIV or hepatitis B virus co-infection, were excluded from the study. Oral examinations were performed on patients with HCV infection on the day of their routine appointment at IAG-HCUFMG. They were examined under artificial light, using disposable retractors, observing all universal biohazard safety procedures (21).

Clinical diagnostic criteria for oral mucosal conditions, as established by the World Health Organization (22) and proposed by Axéll (23), were applied. Oral examination was performed following a sequential procedure modified from the original sequence proposed by the World Health Organization (24). Dental caries and endodontic and inflammatory periodontal lesions were excluded from this study. Oral mucosal conditions identified included pathological processes and variations of normality. Patients who needed incisional biopsies and histopathologic exams for final diagnosis of oral mucosal lesions were directed to the Department of Oral Pathology of the School of Dentistry of UFMG.

Clinical data, information about medical history, and the use of medications were obtained from medical records of the patients. Most patients had still not been submitted to a liver biopsy at the time of the oral examination. Thus, the status of their liver-related disease was not known.

Data were analyzed by using the χ^2 test (EpiInfo) (25). *P* values less

than or equal to 0.05 were defined as statistically significant.

The study was approved by the UFMG Ethic Committee on Surveys, and all patients signed an informed consent form.

Results

A total of 215 patients with chronic hepatitis C were examined: 115 (53.0 percent) men and 100 (47.0 percent) women. The patients were categorized in six age groups, with 171 (79.5 percent) patients in the fifth decade of life, with a median age of 50.15 years (range from 18 to 76 years of age). A total of 111 patients examined were white (51.6 percent), while 104 (48.4 percent) were nonwhite.

Infection sources included blood transfusions in 86 cases (40.0 percent), percutaneous exposure in 28 cases (13.0 percent), intravenous drug use in 22 cases (10.2 percent), sexual intercourse in 3 cases (1.4 percent), and hemodialysis treatment in 3 cases (1.4 percent). The source of HCV infection could not be identified in 73 patients (34.0 percent).

Clinical manifestations of hepatitis C were present only in 72 patients (33.5 percent), presenting nonspecific symptoms, such as malaise, anorexia, and nausea.

Our results showed that, in 207 (96.3 percent) patients with chronic hepatitis C, oral mucosal conditions could be identified. A total of 147 patients (68.4 percent) presented oral mucosal lesions, 98 (45.6 percent) of which presented only one kind of pathological disorder, while 49 (22.8 percent) presented two or more lesions at the same time. A total of 113 patients (52.6 percent) presented simultaneous oral mucosal lesions and variations of normality; 68 patients (31.6 percent) presented no oral mucosal lesions. In 8 patients (3.7 percent), neither oral mucosal lesions nor variations of normality were observed. The prevalence of patients with simultaneous chronic hepatitis C infection and oral mucosal lesions was higher in the group of patients from 41 to 60 years of age (43.6 percent), with no clear differ-

ences between genders. Table 1 summarizes the findings regarding the oral mucosal conditions observed in the patients.

Nineteen different oral mucosal lesions were diagnosed; the most common included cheek biting in 42 cases (19.5 percent), candidiasis in 39 cases (18.1 percent), and leukoplakia in 28 cases (13.0 percent). Oral lesions found in HCV-infected patients, and their respective prevalence, categorized by age and sex groups, are summarized in Table 2.

In this study, cheek biting was diagnosed when erosions, petechias, or ulcerations of 1-3 mm were seen on the buccal mucosa near the occlusal plane, unilaterally or bilaterally, in close relationship with the etiological agent. This could be observed in 42 patients (19.5 percent). *Morsicatio buccarum*, which is a similar lesion, can occur in the same anatomic site as a consequence from the habit of chewing, biting, and sucking of the cheeks. Clinically, this appears as macerated gray-white lesions of the buccal mucosa with small loose tags or fragments of epithelium on the surface. This lesion was observed in 9 patients (4.2 percent).

Candidiasis, including denture stomatitis, angular cheilitis, and pseudomembranous candidiasis, was present in 39 patients (18.1 percent) and was associated with denture wearers in 33 cases (84.6 percent), proving to be statistically significant ($P < 0.0001$). In the remaining 6 cases (15.4 percent), the patients were not denture wearers, and a predisposing factor for the condition could not be established.

In 28 cases (13.0 percent), oral lesions were diagnosed as leukoplakias, based on clinical features described by Axéll (23). Among them, 26 (92.8 percent) were smokers or ex-smokers ($P < 0.0001$), and, for all these patients, incisional biopsies were recommended. However, only 9 patients (31.0 percent) actually underwent the biopsy procedure; others presented medical contraindications, associated mainly with a low platelet level or arterial

Table 1
Prevalence of Patients with Chronic Hepatitis C Presenting Oral Mucosal Conditions, According to Sex and Age Group (IAG-HCUFUMG)

	Sex		Age group										Total (n %)			
	Male (n %)	Female (n %)	11-20 years		21-30 years		31-40 years		41-50 years		51-60 years			60+ years		
			n	%	n	%	n	%	n	%	n	%		n	%	
Oral mucosal lesions																
Present	71 (33.0)	76 (35.3)	1 (0.5)	7 (3.3)	21 (9.8)	45 (20.8)	49 (22.8)	24 (11.2)	147 (68.4)*							
Absent	39 (18.2)	29 (13.5)	2 (0.9)	4 (1.8)	9 (4.2)	14 (6.6)	23 (10.7)	16 (7.4)	68 (31.6)							
Total n %	110 (51.2)	105 (48.8)	3 (1.4)	11 (5.1)	30 (14.0)	59 (27.4)	72 (33.5)	40 (18.6)	215 (100.0)							
Variation of normality																
Present	89 (41.4)	84 (39.1)	3 (1.4)	10 (4.6)	20 (9.4)	46 (21.4)	61 (28.4)	33 (15.3)	173 (80.5)*							
Absent	21 (9.8)	21 (9.7)	0 (0.0)	1 (0.5)	10 (4.6)	13 (6.0)	11 (5.1)	7 (3.3)	42 (19.5)							
Total n %	110 (51.2)	105 (48.8)	3 (1.4)	11 (5.1)	30 (14.0)	59 (27.4)	72 (33.5)	40 (18.6)	215 (100.0)							

* In 113 patients, oral mucosal lesions and oral variations of normality were diagnosed simultaneously.
IAG-HCUFUMG, Alfa Gastroenterology Institute from the Clinical Hospital of Universidade Federal de Minas Gerais; n, absolute prevalence; %, relative prevalence.

Table 2
Prevalence of Oral Mucosal Lesions According to Sex and Age Group (IAG-HCUFUMG)

	Sex		Age group										Total (n %)			
	Male (n %)	Female (n %)	11-20 years		21-30 years		31-40 years		41-50 years		51-60 years			60+ years		
			n	%	n	%	n	%	n	%	n	%		n	%	
Oral mucosal lesions																
Cheek biting	22 (11.6)	18 (8.8)	1 (0.5)	6 (3.3)	7 (3.7)	25 (13.2)	10 (5.2)	11 (5.7)	17 (9.3)	16 (8.5)	7 (3.7)	17 (9.3)	3 (1.6)	42 (22.2)		
Candidiasis	12 (6.3)	25 (13.5)	0 (0.0)	0 (0.0)	1 (0.5)	15 (8.0)	5 (2.6)	17 (9.3)	12 (6.3)	21 (11.2)	6 (3.2)	29 (15.6)	20 (10.7)	39 (20.9)		
Leukoplakia	19 (10.0)	9 (4.8)	1 (0.5)	2 (1.1)	15 (8.0)	15 (8.0)	12 (6.3)	21 (11.2)	21 (11.2)	21 (11.2)	6 (3.2)	27 (14.5)	2 (1.1)	28 (15.2)		
Actinic cheilitis	12 (6.3)	3 (1.6)	0 (0.0)	1 (0.5)	4 (2.1)	7 (3.7)	4 (2.1)	18 (9.5)	4 (2.1)	18 (9.5)	4 (2.1)	18 (9.5)	2 (1.1)	15 (8.0)		
Papillary hyperplasia	4 (2.1)	9 (4.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.1)	3 (1.6)	3 (1.6)	5 (2.6)	5 (2.6)	7 (3.7)	7 (3.7)	14 (7.6)		
Frictional keratosis	5 (2.6)	6 (3.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.1)	7 (3.7)	6 (3.2)	4 (2.1)	4 (2.1)	5 (2.6)	3 (1.6)	12 (6.4)		
Vascular lesion	8 (4.2)	3 (1.6)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.1)	7 (3.7)	6 (3.2)	4 (2.1)	4 (2.1)	5 (2.6)	3 (1.6)	12 (6.4)		
<i>Morsicatio buccarum</i>	7 (3.7)	1 (0.5)	1 (0.5)	1 (0.5)	2 (1.1)	7 (3.7)	2 (1.1)	7 (3.7)	2 (1.1)	7 (3.7)	2 (1.1)	7 (3.7)	2 (1.1)	12 (6.4)		
Traumatic lesions	2 (1.1)	3 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)		
Reactive lesions	1 (0.5)	4 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)		
Melanotic macule	0 (0.0)	5 (2.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)		
Lichen planus*	2 (1.1)	3 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)		
Recurrent herpes	2 (1.1)	1 (0.5)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)		
Amalgam tattoo	2 (1.1)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)		
Recurrent aphthous ulcers	2 (1.1)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)		
Perioral nevus lesions	2 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)		
<i>Lupus erythematosus</i>	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)		
<i>Pemphigus vulgaris</i>	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)		
Mucocoele	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)		
Total n % Prev.	103 (51.2)	107 (48.8)	4 (1.9)	13 (6.2)	28 (13.3)	100 (53.5)	68 (33.2)	56 (27.3)	100 (53.5)	68 (33.2)	41 (20.0)	190 (92.5)	210 (100.0)	477 (227.5)		

* P = 0.002.
IAG-HCUFUMG, Alfa Gastroenterology Institute from the Clinical Hospital of Universidade Federal de Minas Gerais; n, absolute prevalence; %, relative prevalence; Prev., prevalence.

hypertension, while 19 (69.0 percent) did not attend the appointment. In all 9 cases, the histological features were compatible with clinical diagnosis of leukoplakia. Only in one case (3.6 percent) was epithelial mild dysplasia observed. Frictional keratosis was diagnosed in 12 patients (5.6 percent) when a whitish or grayish patch on the mucosa was observed associated with the site as a readily recognizable mechanical trauma and could not be rubbed off or attributed to any other specific lesion.

Twelve (5.6 percent) patients with chronic hepatitis C complained of oral dryness. In eight (3.7 percent) of these patients, three cases of candidiasis, two cases of traumatic lesions, and one case of actinic cheilitis, frictional keratosis, and cheek biting each were observed with no differences related to gender. In four patients, neither pathological processes nor variations of normality were observed.

Although lichen planus lesions were not a common finding in the group studied, when considering clinical and histological features, these lesions could be diagnosed in five patients (2.3 percent). Two patients presented simultaneous oral and cutaneous lichen planus lesions. Statistical analysis revealed significantly higher prevalence ($P=0.002$) of OLP in this group than in the general population (26).

In our study, at least one of the eight different variations of normality identified could be observed in 173 patients (80.5 percent) with no differences related to sex (Table 3). The most prevalent conditions were Fordyce's spots in 96 cases (44.7 percent), lingual varicosities in 67 cases (31.2 percent), and fissured tongue in 60 cases (27.9 percent). Prevalence of the oral variations of normality stratified by age and sex is summarized in Table 3.

Discussion

Hepatitis C is often asymptomatic or shows no specific manifestations in the acute phase. In this stage, HCV infection is rarely recognized and

Table 3
Prevalence of Oral Variations of Normality According to Sex and Age Groups (IAG-HCUFMG)

Oral variations of normality	Sex		Age group												Total												
	Male		Female		11-20 years			21-30 years			31-40 years			41-50 years			51-60 years			60+ years							
	n	%	n	%	n	%	Prev. (%)	n	%	Prev. (%)	n	%	Prev. (%)	n	%	Prev. (%)	n	%	Prev. (%)	n	%	Prev. (%)					
Fordyce's spots	63	43.15	29.30	33	27.97	15.35	1	25.00	0.47	4	26.67	1.86	13	52.00	6.05	29	41.43	13.49	32	32.00	14.88	17	34.00	7.90	96	36.37	44.65
Lingual varicosities	33	22.60	15.34	34	28.81	15.82	0	0.00	0.00	2	13.33	0.93	3	12.00	1.40	12	17.14	5.58	32	32.00	14.88	18	36.00	8.37	67	25.38	31.16
Fissured tongue	30	20.55	13.95	30	25.42	13.95	0	0.00	0.00	4	26.67	1.86	4	16.00	1.86	17	24.28	7.90	22	22.00	10.23	13	26.00	6.05	60	22.72	27.90
Leukoedema	13	8.90	6.05	7	5.93	3.26	0	0.00	0.00	1	6.67	0.47	4	16.00	1.86	8	11.43	3.72	6	6.00	2.79	1	2.00	0.47	20	7.58	9.31
Palatine torus	4	2.74	1.86	10	8.47	4.65	1	25.00	0.47	2	13.33	0.93	0	0.00	0.00	3	4.29	1.40	7	7.00	3.26	1	2.00	0.47	14	5.30	6.51
Mandibularis torus	1	0.69	0.47	3	2.54	1.40	1	25.00	0.47	2	13.33	0.93	1	4.00	0.47	0	0.00	0.00	0	0.00	0.00	0	0.00	0.00	4	1.51	1.86
Geographic tongue	2	1.37	0.93	0	0.00	0.00	1	25.00	0.47	0	0.00	0.00	0	0.00	0.00	0	0.00	0.00	1	1.00	0.47	0	0.00	0.00	2	0.76	0.93
Gingival fibrous nodule	0	0.00	0.00	1	0.86	0.47	0	0.00	0.00	0	0.00	0.00	0	0.00	0.00	1	1.43	0.47	0	0.00	0.00	0	0.00	0.00	1	0.38	0.47
Total n (%) Prev.	146	100.00	55.30	118	100.00	44.70	4	100.00	1.52	15	100.00	6.98	25	100.00	9.47	70	100.00	26.52	100	100.00	37.88	50	100.00	18.94	264	100.00	-

IAG-HCUFMG, Alfa Gastroenterology Institute from the Clinical Hospital of Universidade Federal de Minas Gerais; n, absolute prevalence; % relative prevalence; Prev., prevalence.

largely underdiagnosed, thus leading to chronic hepatitis C (1). The World Health Organization estimates that there are millions of HCV-infected people who go undiagnosed, constituting an important link in the chain of HCV transmission (27).

HCV infection is reported to predispose patients to extrahepatic disorders involving renal, dermatologic, hematologic, and rheumatologic systems (28) as well as autoimmune abnormalities (29). Recognition of the type and magnitude of comorbid extrahepatic disorders in patients with hepatitis C infection is important for early diagnosis and appropriate management of the patients. Moreover, people with extrahepatic disorders reported in the literature may therefore be targeted for HCV testing (30).

The population examined in this study was composed predominantly of men whose average age was 50.2 years and who were, in 86 cases (40.0 percent), HCV infected mainly, as expected, by blood transfusion (4). An important point to be emphasized is that, in 73 patients (34.0 percent) with chronic hepatitis C, the source of infection was unknown. This observation strongly encourages the need for research regarding possible but still greatly unknown sources of infection.

As clinical manifestations of chronic hepatitis C were present in only 72 patients (34.0 percent), our results reinforce the asymptomatic character of this disease (1), justifying its probable underestimated prevalence. Thus, the establishment of the possible extrahepatic disorders associated with HCV infection may allow earlier recognition of this infection.

There are some difficulties in comparing results from epidemiological studies on oral mucosal conditions in a special population mainly because of differences in the methodologies used and geographic characteristics of the sample studied. Moreover, in the majority of studies, pathological processes are considered together with variations of normality. In our study, the prevalence

of patients presenting some of these alterations was 96.3 percent, a higher index than that reported by Vieira and colleagues (31), who found a prevalence of 75.3 percent of patients with at least one oral mucosal condition in a population of the same geographic region and socioeconomic status. It is important to observe that the presence of HCV infection in their patients was not known. However, considering the low expected prevalence of HCV infection in our country and the lower mean age of their sample, the presence of HCV-positive patients is unlikely.

Nineteen different lesions were diagnosed on the oral mucosa in the patients with chronic hepatitis C. The most prevalent lesions were cheek biting in 42 cases (19.5 percent), candidiasis in 39 cases (18.1 percent), and leukoplakia in 28 cases (13.0 percent), respectively.

Cheek biting was the most common oral mucosal lesion and was observed mainly in patients from 41 to 60 years of age. Epidemiological studies of oral mucosal lesions in the general population show prevalence rates ranging from 1.89 to 6.11 percent (31-38). Axéll (23) and Reichart (38), in a study focused on adults, reported a reduction in the prevalence of traumatic lesions upon increase in age. Bessa and colleagues (33), in a study carried out on 1,211 children, observed no correlation between this condition and age. Although it was not the purpose of our study, we could observe a large number of patients with poor dental health. At least one decayed tooth requiring treatment, as well as the presence of cutting surfaces and extensive cavities, was observed in close relation to the site of this lesion on the buccal mucosa, in addition to the lack of occlusal stability related to irregular fillings and to the use of dentures. These oral health problems may explain the highest prevalence of cheek biting in this group of patients. Moreover, these findings show that oral health in patients with hepatitis C infection is still an underestimated problem (10,15) and can contribute to

a reduction in the quality of life during HCV-related liver disease (39).

Candidiasis was the second most prevalent lesion in patients with chronic hepatitis C, at 18.1 percent (39 cases), mostly observed in female patients over 51 years of age, which is in accordance with results from Jaikittivong and colleagues (40). Furthermore, in 33 of the 39 cases (84.6 percent $P < 0.0001$), a clear association with denture wearers could be made, which is strongly emphasized by the literature (35,40,41). Other authors (31,32) reported a lower prevalence of candidiasis in the general adult population than was found in our study. These distinct results could be a result of differences of the sample as the majority of patients included in our study were more elderly than those in other studies.

Leukoplakia, which was the third most prevalent lesion in this study, was observed in 28 cases (13.0 percent). This prevalence was higher than in other studies performed in the general population (25,35) and in adult people (40). Leukoplakia was more prevalent in men (19 cases, 8.8 percent) than in women (9 cases, 4.2 percent), and 26 patients (92.9 percent) reported a history of smoking ($P < 0.0001$). These results are in agreement with previous findings that demonstrated tobacco association with leukoplakia in men (23,32). Thus, the prevalence of leukoplakia in our study seems to reflect the oral habits of tobacco consumption in the studied group and possibly does not represent a real association with hepatitis C infection. This observation is in accordance with research from Bokor-Bratic (42) on Serbian patients.

Two of the most frequently reported oral extrahepatic manifestations of HCV infection are lichen planus (9,13,14) and sialadenitis (10,30,43,44). The search for salivary gland alterations was not the purpose of this study. Thus, prevalence of sialadenitis, xerostomia, and Sjögren syndrome was not assessed. However, 12 patients (5.6 percent) complained of oral dryness, and, in 8

of them (66.7 percent), oral mucosal lesions could be observed. In the study of Henderson and colleagues (15), performed on 40 patients with chronic hepatitis C, significantly reduced salivary flow was observed even though only a few patients (8.0 percent) actually complained of oral dryness. According to the authors, the xerostomia may predispose patients with HCV infection to both dental caries and oral soft tissue disease. Further research to elucidate the possible association among complaint of oral dryness, real reduced salivary flow, oral mucosal conditions, and HCV infection is clearly warranted.

In a previous study, our results showed a statistically significant higher prevalence of OLP in patients with chronic hepatitis C (2.3 percent) than in the general population (0.4 percent) ($P=0.002$) (14). The viral genotype 1b was the most common (4 of 5 cases) in accordance with Nagao and colleagues (13). As there are no studies on the prevalence of OLP in the general Brazilian population, we used the prevalence of 0.4 percent observed by Grossmann and Carmo (26) in a study of OLP cases retrieved from the files of Oral Pathology Laboratory, School of Dentistry, UFMG. As many cases of OLP are not submitted to histological examination, especially the asymptomatic lesions, these data may not reflect the real prevalence of OLP in our population. Nevertheless, the observed prevalence of OLP can be considered higher than that reported in the literature (44). Vieira and colleagues observed a lower prevalence of OLP (1.5 percent) in their study (31). However, only 23 percent (49 cases) of the patients examined were older than 40 years of age, which may explain in part the lower prevalence of OLP found in them. Moreover, we stress the importance of the biopsy to confirm the clinical diagnosis of OLP lesions as they may mimic or be mimicked by several other oral conditions (44). Studies in which the diagnosis of OLP is based merely on clinical features (15,31) can in fact result in an overestimation of its prevalence.

Oral lesions in patients with chronic hepatitis C, such as frictional keratosis, candidiasis, leukoplakia, buccal mucosal pigmentation, epithelial dysplasia, petechial hemorrhages, mucosal ulcers, oral squamous cell carcinoma, sialadenitis, and lichen planus (10,12-15,45,46) have been reported. Most of these oral conditions, except oral squamous cell carcinoma, could be observed in our study as well. Nevertheless, other different oral mucosal lesions were also diagnosed, such as actinic cheilitis (6.9 percent), papillary hyperplasia (6.5 percent), vascular lesions (5.6 percent), *Morsicatio buccarum* (4.2 percent), among others (Table 2). These prevalence rates were, in many cases, higher than those in the general population (23,32-38,40) although the real correlation between the lesions and the HCV infection could not be demonstrated.

In our study, the prevalence of recurrent conditions, such as recurrent aphthous ulcerations and recurrent herpes, was lower than in some studies (23,36). However, as this was a cross-sectional study, the prevalence of recurrent conditions may have been underestimated (47).

One patient presented *pemphigus vulgaris* (0.5 percent), while another presented *lupus erythematosus* (0.5 percent), diagnosed on a clinical and histological basis. Both disorders show poor prognosis and had gone undiagnosed until this study. This finding emphasizes the importance of periodic oral examinations in patients with chronic hepatitis C.

The prevalence of variations of normality in patients with HCV infection was 80.5 percent. Fordyce's spots (44.7 percent), lingual varicosities (29.8 percent), and fissured tongue (28.4 percent) were the three most common variations of normality in patients with chronic hepatitis C. Vieira *et al.* (31) found lower prevalence of Fordyce's spots (8.8 percent) and fissured tongue (6.7 percent) in the general population and did not observe lingual varicosities in their study population. This difference might be attributed to the lower age range of the patients because these

conditions are more frequent in elderly people as emphasized in other studies (32,40). However, an increase in the prevalence of fissured tongue upon an increase in age is reported in the literature in children (33), where a link between this alteration and the presence of extraoral congenital abnormalities was also observed.

Whether some of the oral mucosal conditions observed in this study are or are not associated with chronic hepatitis C should be clarified by further research. Whether or not the HCV is in fact involved in the pathogenesis of oral mucosal lesions in HCV-infected patients, principally *via* an immunologic pathway, still remains to be defined. Moreover, as most of the patient liver biopsies had yet to be performed and the viral genotype was unknown, no specific oral mucosal condition could be related to their HCV liver status nor to the viral genotype.

There are few studies that investigated the prevalence of oral mucosal lesions in adults based on population (23,35). To the best of our knowledge, this is the first report regarding the prevalence of oral mucosal conditions in patients with HCV infection, considering pathological processes and variations of normality although the diagnosis of a wide variety of lesions in the oral cavity is an essential part of dental practice. As many extrahepatic disorders in patients with chronic hepatitis C have been reported, oral examination in patients with HCV infection should be periodically and routinely performed to promote a suitable and full health assistance to these patients.

Considering the high global prevalence and severity of chronic hepatitis C, further epidemiological prospective studies in this group of patients from different geographic areas are warranted (10,48). As cross-sectional studies are not able to establish a definitive causal relationship among diseases, the putative association between oral conditions and hepatitis C infection is still a debatable issue (10,36,39). These

observations suggest that attention should be focused on the possible development of extrahepatic disorders in patients with chronic hepatitis C, especially those with oral mucosal manifestations. It may be of great value to identify people to be targeted for HCV testing. As few studies regarding the prevalence of oral conditions in patients with HCV infection are available, our results can be used as baseline data for future studies.

Acknowledgments

This study was supported by grants from Coordenação de Aperfeiçoamento de Pessoal de Nível Superior and Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) – National Counsel of Technological and Scientific Development. Dr. Aguiar MCF, Dr. Teixeira R, and Dr. Carmo MAV are research fellows of CNPq.

References

- Alberti A, Benvenuto L. Management of hepatitis C. *J Hepatol.* 2003;38:104-18.
- Poynard T, Yuen M, Ratzin V, Lai CL. Viral hepatitis C. *Lancet.* 2003;362:2095-100.
- Choo Q, Kuo G, Weiner A, Overby L, Bradley D, Houghton M. Isolation of a cDNA clone derived from a bloodborne non-A, non-B viral hepatitis genome. *Science.* 1989;244:359-62.
- National Institutes of Health. Consensus development conference statement: management of hepatitis C: 2002 – June 10-12. *Hepatology.* 2002;36:S3-20.
- Relatório do Grupo de Estudos da Sociedade Brasileira de Hepatologia. Epidemiologia da infecção pelo vírus da hepatite crônica pelo vírus C no Brasil [accessed January 20, 2003]. Available from: <http://www.sbhepatologia.org.br>.
- Hadziyannis SJ. Nonhepatic manifestations and combined diseases in HCV infection. *Dig Dis Sci.* 1996;41(S12):S63-74.
- Nagao Y, Hanada S, Shishido S, Ide T, Kumashiro R, Ueno T, Sata M. Incidence of Sjögren's syndrome in Japanese patients with HCV infection. *J Gastroenterol Hepatol.* 2003;18:258-66.
- Roy KM, Bagg J. HCV and oral disease: a critical review. *Oral Dis.* 1999;5:270-7.
- Lodi G, Giuliani M, Majorana A, Sardella A, Bez C, Demarosi F, Carrasi A. Lichen planus and hepatitis C virus: a multicentre study of patients with oral lesions and a systematic review. *Br J Dermatol.* 2004;151(6):1172-81.
- Carrozzo M, Gandolfo S. Oral diseases possibly associated with HCV. *Crit Rev Oral Biol Med.* 2003;14:115-27.
- Cunha KSG, Manso AC, Cardoso AS, Paixão JBA, Coelho HSM, Torres SR. Prevalence of oral lichen planus in Brazilian patients with HCV infection. *Oral Surg Oral Med Oral Pathol.* 2005;100:330-3.
- Grossmann SMC, Aguiar MCF, Teixeira R, Carmo MAV. Oral lichen planus and chronic hepatitis C: a controversial association. *Am J Clin Pathol.* 2007;127:800-4.
- Nagao Y, Tanaka J, Nakanishi T, Moriya T, Katayama K, Kumagai J, Komiya Y, Itoh Y, Myoken Y, Fujihara M, Sata M, Yoshizawa H. High incidence of extrahepatic manifestations in an HCV hyperendemic area. *Hepatol Res.* 2002;22:27-36.
- Gandolfo S, Richiardi L, Carrozzo M, Broccoletti R, Carbone M, Pagano M, Vestita C, Rosso S, Merletti F. Risk of oral squamous cell carcinoma in 402 patients with oral lichen planus: a follow-up study in an Italian population. *Oral Oncol.* 2004;40:77-83.
- Henderson L, Muir M, Mills PR, Spence E, Fox R, McCrudden EA, Bagg J. Oral health of patients with HCV infection: a pilot study. *Oral Dis.* 2001;7:271-5.
- Carrozzo M. Oral health in patients with HCV infection: an underestimated problem? *Oral Dis.* 2001;7:267-70.
- Figueiredo LC, Carrilho FJ, de Andrade HF, Migliari DA. Oral lichen planus and hepatitis C virus infection. *Oral Dis.* 2002;8:42-6.
- Protzer U, Ochsendorf FR, Leopolder-Ochsendorf A, Holtermuller KH. Exacerbation of lichen planus during interferon alpha-2a therapy for chronic active hepatitis C. *Gastroenterology.* 1993;104:903-5.
- Barreca T, Corsini G, Franceschini R, Gambini C, Garibaldi A, Rolandi E. Lichen planus induced by interferon-alpha-2a therapy for chronic active hepatitis C. *Eur J Gastroenterol Hepatol.* 1995;7:367-8.
- Nagao Y, Sata M, Ide T, Suzuki H, Tanikawa K, Itoh K, Kameyama T. Development and exacerbation of oral lichen planus during and after interferon therapy for hepatitis C. *Eur J Clin Invest.* 1996;26:1171-4.
- Brasil. Ministério da Saúde. Controle de infecções e a prática odontológica em tempos de AIDS: manual de condutas. Brasília, Brazil: Ministério da Saúde; 2000.
- World Health Organization. Guide to epidemiology and diagnosis of oral mucosal diseases and conditions. *Community Dent Oral Epidemiol.* 1980;8:1-26.
- Axéll T. A prevalence study of oral mucosa lesions in an adult Swedish population. *Odontol Revy.* 1976;27:1-103.
- World Health Organization. Oral health surveys. Basic methods, 4th ed. Geneva: World Health Organization; 1997.
- EPIINFO. A word-processing, database, and statistics system for epidemiology on microcomputers [software online]. Produced by Centers for Disease Control and Prevention (CDC), Atlanta, in collaboration with World Health Organization (WHO), Geneva; 2003 [accessed August 12, 2004]. Available from <http://www.cdc.gov/EpiInfo>.
- Grossmann SMC, Carmo MAV. Estudo epidemiológico de lesões bucais de LP do laboratório de patologia bucal da Faculdade de Odontologia da Universidade Federal de Minas Gerais. *Arquivos em Odontologia.* 2001;37:163-74.
- Ministério da Saúde. Secretaria Executiva. Programa Nacional de Hepatites Virais. Hepatites Virais: o Brasil está atento / Ministério da Saúde, Secretaria Executiva. Brasília, Brazil: Ministério da Saúde; 2003.
- Gumber SC, Chopra S. Hepatitis C: a multifaceted disease. Review of extrahepatic manifestations. *Ann Intern Med.* 1995;123:615-20.
- Zignego AL, Ferri C, Pileri SA, Caini P, Bianchi FB. For the Italian Association of the Study of Liver Commission on Extrahepatic Manifestations of HCV infection. Extrahepatic manifestations of hepatitis C virus infection: a general overview and guidelines for a clinical approach. *Dig Liver Dis.* 2007;39:2-17.
- El-Serag HB, Hampel H, Yeh C, Rabeneck L. Extrahepatic manifestations of hepatitis C among United States male veterans. *Hepatology.* 2002;36:1439-45.
- Vieira VG, Fernandes AF, Machado APB, Grossmann SMC, Aguiar MCF. Development alterations and lesions of the oral mucosa in patients assisted in the integrated clinics of primary attention (CIAPS) of the School of Dentistry of UFMG. *Arquivos em Odontologia.* 2006;42:257-336.
- Kovac-Kovacic M, Skaleric U. The prevalence of oral mucosal lesions in a population in Ljubljana, Slovenia. *J Oral Pathol Med.* 2000;29:331-5.
- Bessa CFN, Santos PJB, Aguiar MCF, do Carmo MAV. Prevalence of oral mucosal alterations in children from 0 to 12 years old. *J Oral Pathol Med.* 2004;33(1):17-22.
- Santos PJB, Bessa CFN, de Aguiar MCF, do Carmo MAV. Cross-sectional study of oral mucosal conditions among a central Amazonian Indian community, Brazil. *J Oral Pathol Med.* 2004;33:7-12.
- Shulman JD, Beach MM, Rivera-Hidalgo F. The prevalence of oral mucosal lesions in U.S. adults: data from the Third National Health and Nutrition Examination Survey, 1988-1994. *J Am Dent Assoc.* 2004;135:1279-86.
- Shulman JD. Prevalence of oral mucosal lesions in children and youths in the USA. *Int J Paediatr Dent.* 2005;15:89-97.
- Parlak AH, Koybasi S, Yavuz T, Yesildal N, Anul H, Aydogan I, Cetinkaya R, Kavak A. Prevalence of oral lesions in 13- to 16-year-old students in Duzce, Turkey. *Oral Dis.* 2006;12:553-8.
- Reichart PA. Oral mucosal lesions in a representative cross-sectional study of

- aging Germans. *Community Dent Oral Epidemiol.* 2000;28:390-8.
39. Strauss E, Dias Teixeira MC. Quality of life in hepatitis C. *Liver Int.* 2006;26:755-65.
40. Jankittivong A, Aneksuk V, Langlais RP. Oral mucosal conditions in elderly dental patients. *Oral Dis.* 2002;8:218-23.
41. Daniluk T, Tokajuk G, Stokowska W, Fiedoruk K, Sciepek M, Zaremba ML, Rozkiewicz D, Cylwik-Rokicka D, Kedra BA, Anielska I, Gorska M, Kedra BR. Occurrence rate of oral *Candida albicans* in denture wearer patients. *Adv Med Sci.* 2006;51(Suppl 1):77-80.
42. Bokor-Bratic M. No evidence of hepatitis C virus infection in Serbian patients with oral leukoplakia. *J Oral Pathol Med.* 2006;35:626-9.
43. Ramos-Casals M, Garcia-Carrasco M, Cervera R, Font J. Is hepatitis C virus a sialotropic virus? *Am J Pathol.* 2001;159:1593-4.
44. Huber MA. Oral lichen planus. *Quintessence Int.* 2004;35:731-52.
45. Jaber MA, Porter SR, Bain L, Scully C. Lack of association between hepatitis C virus and oral epithelial dysplasia in British patients. *Int J Oral Maxillofac Surg.* 2003;32:181-3.
46. Nobles J, Wold C, Fazekas-May M, Gilbert J, Friedlander PL. Prevalence and epidemiology of hepatitis C virus in patients with squamous cell carcinoma of the head and neck. *Laryngoscope.* 2004;114:2119-22.
47. Kleinman DV, Swango PA, Niessen LC. Epidemiologic studies of oral mucosal conditions – methodologic issues. *Community Dent Oral Epidemiol.* 1991;19:129-40.
48. Carrozzo M, Quadri R, Latorre P, Pentenero P, Paganin S, Bertolusso G, Gandolfo S, Negro F. Molecular evidence that the HCV replicates in the oral mucosa. *J Hepatol.* 2002;37:364-9.

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