

Epidemiological survey of oral lichen planus among HCV-infected inhabitants in a town in Hiroshima Prefecture in Japan from 2000 to 2003

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Abstract. The objective of our study was to evaluate the natural history of oral lichen planus (OLP) and other extrahepatic manifestations in the inhabitants of an area in Japan that is hyperendemic for hepatitis C virus (HCV) infection. Over 4 years, 224 adult inhabitants with HCV infection were examined for OLP by a single oral surgeon. All subjects were interviewed regarding the natural history of other extrahepatic manifestations they had developed. The antibodies to HCV (anti-HCV) and serum HCV RNA were determined. Anti-HCV were detected in sera from 224 subjects (100%); HCV RNA in 210 (93.8%). Of the 224, 88 had at least 1 oral examination for OLP during the 4-year period. In 2000, 2001, 2002 and 2003, OLP was observed in 8.5 (5/59), 14.8 (8/54), 20 (11/55) and 21.4% (12/56) of subjects, respectively. OLP prevalence increased as the subjects grew older. The incidence of OLP over the 4 years among all subjects with HCV infection was 17.0% (15/88, 2 men and 13 women). None experienced natural healing or the development of malignant transformations. Between 2000 and 2003, there was an increase in the prevalence of type 2 diabetes mellitus (DM), thyroid dysfunction, skin disease, renal disease and hypertension. Screening for extrahepatic manifestations should be conducted in patients with risk factors for HCV infection.

Introduction

Hepatitis C virus (HCV) infection is a major health problem in Japan. It is highly prevalent in subjects with chronic liver disease and is strongly associated with hepatocellular carcinoma (HCC). HCV-related HCC accounts in large part for the recent increase in HCC and now constitutes about 80% of all HCC cases in Japan. HCV also incites many extrahepatic manifestations (1,2) of which lichen planus is the most common (3,4). Other associated diseases include cryoglobulinaemic nephropathy and glomerulonephritis (5), thyroid dysfunction (6), porphyria cutanea tarda (7) and type 2 diabetes mellitus (DM) (8).

We previously reported that the incidence of oral lichen planus (OLP) in subjects with HCV infection was significantly higher than in those without HCV. We reached this conclusion by mass screening 685 inhabitants of a hyperendemic area, H town, located in the Fukuoka prefecture of Northern Kyushu, Japan (Fig. 1) for HCV infection (9). The prevalence of other extrahepatic manifestations in subjects with antibodies to HCV (anti-HCV) was higher than in those without HCV (10).

We also conducted an epidemiological study of another HCV hyperendemic area, O town, in the northwest of the Hiroshima prefecture in Honshu, Japan (Fig. 1). The presence of HCV-associated extrahepatic manifestations was found in 66.1% (39/59) of those screened (11). These findings suggest that the high prevalence of various extrahepatic manifestations among HCV-infected subjects is not unique to specific areas.

In the present investigation, we annually examined extrahepatic manifestations in the inhabitants of O town from 2000 to 2003. The aim of this study was to evaluate the natural history of OLP and other extrahepatic manifestations in individuals with HCV infections.

Patients and methods

Patients. From 2000 to 2003, we studied a total of 224 adult inhabitants of O town, a hyperendemic area of HCV infection. All were HCV carriers, though the causes of viral transmission were unknown. In 2000, 2001, 2002 and 2003,

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Abbreviations: HCV, hepatitis C virus; OLP, oral lichen planus; HCC, hepatocellular carcinoma; anti-HCV, antibodies to HCV; DM, diabetes mellitus

Key words: lichen planus, hepatitis C virus, extrahepatic manifestations

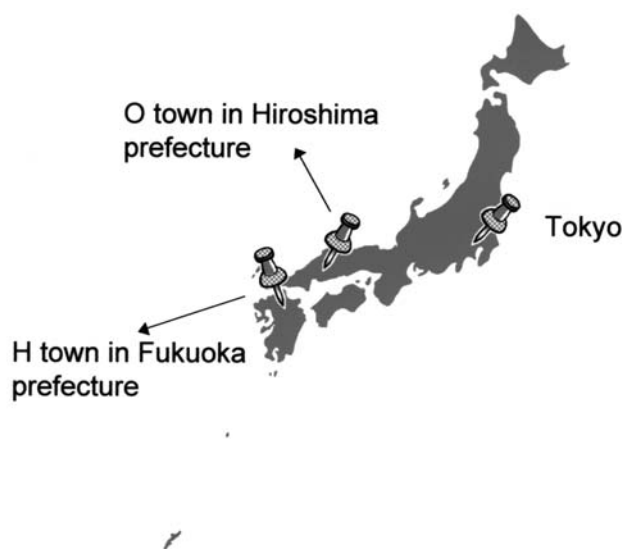


Figure 1. The research area. The location of O town in the northwest region of the Hiroshima prefecture in Honshu, Japan.

we examined 59, 54, 55 and 56 inhabitants, respectively (Table I). A single oral surgeon examined subjects for oral membrane diseases. A topographic classification of the oral mucosa, with location codes indicated, is shown in Fig. 2 (12). The diagnosis of OLP was made based on clinical and histopathological features.

All subjects were interviewed in person by 2 trained interviewers. We inquired about the following: cigarette smoking habits, present health condition and the presence of extrahepatic manifestations of HCV infection such as type 2 DM, rheumatoid arthritis, thyroid dysfunction, skin disease, renal disease, hypertension and extrahepatic malignant tumors.

Informed consent was obtained from all subjects once the purpose and methods of the study were explained.

Examination for anti-HCV and HCV RNA in serum. Sera were examined for the presence or absence of HCV. Anti-HCV were measured by a second-generation, enzyme-linked immunosorbent assay (Abbott HCV PHA 2nd Generation, Dainabot Co., Ltd., Tokyo, Japan). HCV RNA in the sera was detected using the Ampcore HCV test (Nippon Roche, Tokyo, Japan).

Examination of the prevalence of extrahepatic manifestations from 2000 to 2003. We have previously reported on the prevalence of extrahepatic manifestations in HCV infection, including OLP, for inhabitants of the same town (11). We now examined the prevalence of these extrahepatic manifestations from 2000 to 2003.

Results

Anti-HCV were detected in the sera of 224 subjects (100%) and HCV RNA in 210 subjects (93.8%), as shown in Table I. Of the 224, 88 had at least 1 oral examination over the course of the 4 years of the study (34 men and 54 women).

Table I shows the prevalence of OLP in all subjects. In 2000, 2001, 2002 and 2003 it was 8.5 (5/59), 14.8 (8/54), 20 (11/55) and 21.4% (12/56), respectively. The prevalence

of OLP in HCV RNA positive subjects in 2000, 2001, 2002 and 2003 was 8.8 (5/57), 16 (8/50), 21.6 (11/51) and 23.1% (12/52), respectively. The prevalence of OLP increased with age. The incidence of OLP among all subjects with HCV infection over the 4-year period was 17.0% (15/88, 2 men and 13 women). A history of smoking was found in 1/15 OLP cases (6.7%) among inhabitants. Of the 15 cases, 2 had medical checkups once a year, 3 had them 3 times a year, 9 had them twice a year and 1 had a checkup just once in the 4-year period from 2000 to 2003 (Table II). No one had visited a clinic for the treatment of their OLP prior to our discovery of their OLP lesions. By far the most common site for OLP was the buccal mucosa. The predominant type in 53.3% of the 15 cases (8/15) was the reticular form of the disease. In 46.7% (7/15) it was the erosive form. Fig. 3 shows the erosive form (inhabitant No. 6 in Table II). Reticular lesions were generally asymptomatic. Two of the 15 cases had aggravated oral symptoms during the 4-year period. None experienced natural healing or developed malignant transformation.

From 2000 to 2003, there was an increase in the prevalence of type 2 DM, thyroid dysfunction, skin disease, renal disease and hypertension (Table I).

Discussion

HCV carriers in Japan are presumed to number 2 million (13). The growing incidence of HCC is expected to reach a plateau by around the year 2015. However, there are many people who are not aware that they are infected, some of whom will advance to liver cirrhosis or HCC (14). The incidence of HCC varies greatly among different regions. Epidemiological studies conducted by the Japanese Ministry of Health, Labour and Welfare showed that the mortality rate associated with HCC was high in several prefectures in Western Japan. Areas with high rates of anti-HCV, such as the Saga prefecture (3.9%), Hiroshima (1.8%), Fukuoka (1.7%) and Kagawa (1.7%), had high death rates for primary liver cancer of 43.1, 39.6, 39.8 and 31.9 per 100,000 people, respectively. These rates were higher than the national average (15).

HCV is associated with a wide range of extrahepatic manifestations. Zignego *et al* classified the extrahepatic manifestations of HCV into 4 main categories (16). The first category (A) includes extrahepatic manifestations characterised by a very strong association to HCV and supported by both epidemiological and pathogenetic evidence. Category A comprises mixed cryoglobulinaemia. The second category (B) includes disorders which are significantly associated with HCV infection, supported by adequate data. Category B comprises B-cell non-Hodgkin's lymphoma, monoclonal gammopathies, porphyria cutanea tarda and lichen planus. The third category (C) includes manifestations whose association with HCV still requires confirmation and/or a more detailed characterisation of similar pathologies of different aetiology or idiopathic nature. Finally, the fourth category (D) includes only anecdotal observations.

Lichen planus is a chronic inflammatory disease of the skin and mucous membranes that frequently involves the oral mucosa. In Japan, the age-adjusted incidence rate of OLP is 59.7 per 100,000 males and 188.0 per 100,000 females (17).



	2000	2001	2002	2003
Subjects	59	54	55	56
Age (mean years \pm SD)	70.7 \pm 7.2	71.2 \pm 7.2	72.0 \pm 6.5	73.4 \pm 6.8
Sex (M/F)	21/38	22/32	23/32	24/32
% with history of smoking	18.6 (11/59)	11.1 (6/54)	12.7 (7/55)	14.3 (8/56)
% positive for anti-HCV	100 (59/59)	100 (54/54)	100 (55/55)	100 (56/56)
% positive for HCV RNA	96.6 (57/59)	92.6 (50/54)	92.7 (51/55)	92.9 (52/56)
Extrahepatic manifestations				
% positive for oral lichen planus	8.5 (5/59)	14.8 (8/54)	20.0 (11/55)	21.4 (12/56)
Age (mean years \pm SD)	74.8 \pm 5.2	74.3 \pm 5.7	73.1 \pm 5.1	74.7 \pm 5.8
Sex (M/F)	1/4	2/6	2/9	2/10
% positive for anti-HCV	8.5 (5/59)	14.8 (8/54)	20.0 (11/55)	21.4 (12/56)
% positive for HCV RNA	8.8 (5/57)	16.0 (8/50)	21.6 (11/51)	23.1 (12/52)
% positive for DM	15.3 (9/59)	24.1 (13/54)	20.0 (11/55)	19.6 (11/56)
Age (mean years \pm SD)	67.9 \pm 7.2	68.8 \pm 7.9	69.5 \pm 7.9	68.6 \pm 7.4
Sex (M/F)	5/4	10/3	8/3	7/4
% positive for anti-HCV	15.3 (9/59)	24.1 (13/54)	20.0 (11/55)	19.6 (11/56)
% positive for HCV RNA	14 (8/57)	20.0 (10/50)	15.7 (8/51)	15.4 (8/52)
% positive for rheumatoid arthritis	1.7 (1/59)	1.9 (1/54)	5.5 (3/55)	5.4 (3/56)
Age (mean years \pm SD)	67.9 \pm 7.2	70.0 \pm 0	70.0 \pm 0.8	73.0 \pm 2.9
Sex (M/F)	5/4	0/1	1/2	1/2
% positive for Anti-HCV	15.3 (9/59)	1.9 (1/54)	5.5 (3/55)	5.4 (3/56)
% positive for HCV RNA	14 (8/57)	2.0 (1/50)	5.9 (3/51)	5.8 (3/52)
% positive for thyroid dysfunction	0	3.7 (2/54)	3.6 (2/55)	8.9 (5/56)
Age (mean years \pm SD)	-	67.0 \pm 1.0	68.0 \pm 1.0	72.0 \pm 3.3
Sex (M/F)	-	1/1	1/1	1/4
% positive for anti-HCV	-	3.7 (2/54)	3.6 (2/55)	8.9 (5/56)
% positive for HCV RNA	-	4.0 (2/50)	3.9 (2/51)	9.6 (5/52)
% positive for skin disease	5.1 (3/59)	11.1 (6/54)	7.3 (4/55)	16.1 (9/56)
Age (mean years \pm SD)	70.3 \pm 7.3	71.3 \pm 5.8	70.8 \pm 5.2	74.1 \pm 5.9
Sex (M/F)	0/3	1/5	1/3	4/5
% positive for anti-HCV	5.1 (3/59)	11.1 (6/54)	7.3 (4/55)	16.1 (9/56)
% positive for HCV RNA	5.3 (3/57)	12.0 (6/50)	7.8 (4/51)	15.4 (8/52)
% positive for renal disease	1.7 (1/59)	5.6 (3/54)	0	1.8 (1/56)
Age (mean years \pm SD)	76.0 \pm 0	76.0 \pm 2.2	-	86.0 \pm 0
Sex (M/F)	1/0	1/2	-	1/0
% positive for anti-HCV	1.7 (1/59)	5.6 (3/54)	-	1.8 (1/56)
% positive for HCV RNA	1.8 (1/57)	6.0 (3/50)	-	1.9 (1/52)
% positive for hypertension	28.8 (17/59)	40.7 (22/54)	43.7 (24/55)	55.4 (31/56)
Age (mean years \pm SD)	71.0 \pm 6.9	70.9 \pm 6.3	72.6 \pm 6.0	74.4 \pm 6.7
Sex (M/F)	6/11	7/15	10/14	13/18
% positive for anti-HCV	28.8 (17/59)	40.7 (22/54)	43.6 (24/55)	55.4 (31/56)
% positive for HCV RNA	26.3 (15/57)	42.0 (21/50)	41.8 (13/51)	57.7 (30/52)
% positive for extrahepatic malignant tumor	11.9 (7/59)	13 (7/54)	9.1 (5/55)	7.1 (4/56)
Age (mean years \pm SD)	74.4 \pm 3.5	76.3 \pm 3.7	77.2 \pm 4.2	79.3 \pm 2.2
Sex (M/F)	2/5	3/4	3/2	3/1
% positive for anti-HCV	11.9 (7/59)	13 (7/54)	9.1 (5/55)	7.1 (4/56)
% positive for HCV RNA	12.3 (7/57)	14 (7/50)	9.8 (5/51)	7.7 (4/52)

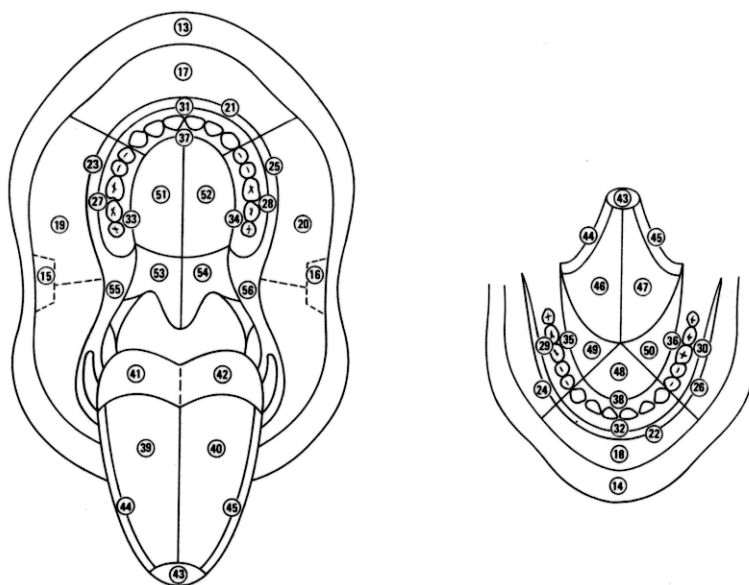


Figure 2. Topography of the oral mucosa modified from Roed-Petersen *et al* (12). The numbered locations are referred to in Table II.

Table II. Site involvement and clinical form of oral lichen planus (OLP) in subjects with HCV infection.

No.	Sex	Type	Smoking history	2000	2001	2002	2003	Course of OLP
1	F	Reticular	Negative	30	30	24, 30	24, 30	No change
2	M	Reticular	Negative	20	20	20	20	No change
3	F	Erosive	Negative	15, 16, 19-21, 23, 25, 27, 28, 31, 33, 34, 37, 39, 40, 46, 47	15, 16, 19-21, 23, 25, 27, 28, 31, 33, 34, 37, 39, 40, 46, 47	Not screened	Liver cirrhosis death	Unknown
4	F	Erosive	Negative	14, 19, 20	Not screened	Not screened	14, 19, 20	Exacerbation
5	F	Erosive	Negative	20, 45	Not screened	20, 45	Not screened	Unknown
6	F	Erosive	Negative	Not screened	19, 20, 47	Not screened	14, 19, 20, 46, 47, 51	Exacerbation
7	F	Reticular	Negative	ND	19, 55	Not screened	19, 55	No change
8	F	Reticular	Negative	Not screened	20, 26, 30	20, 26, 30	20, 26, 30	No change
9	M	Reticular	Negative	ND	46	29, 30, 35, 36, 46	29, 30, 35, 36, 46	No change
10	F	Reticular	Negative	Not screened	26, 30	26, 30	26, 30	No change
11	F	Erosive	Negative	ND	ND	14	14	No change
12	F	Erosive	Negative	Not screened	Not screened	17	17	Alleviation
13	F	Reticular	Negative	ND	Not screened	30	30	No change
14	F	Reticular	Negative	ND	ND	29	29	No change
15	F	Erosive	Positive	Not screened	Not screened	14-16, 19, 20, 24, 26, 32, 44, 45, 51, 52	Not screened	Unknown

ND, not detected. The numbers below the dates refer to locations in the oral mucosa as seen in Fig. 2.



Figure 3. A representative oral erosive lichen planus on the right buccal mucosa.

We conducted an epidemiological investigation to ascertain the possible correlation between OLP and HCV infection in patients living in Western Japan (9-11,18), where the prevalence of HCV infection is the highest in the country (15,19). We found the incidence of OLP in our patients to be higher than in the general population. OLP aside, the prevalence of other extrahepatic manifestations in subjects with anti-HCV was also higher than in those without HCV (10).

We previously reported a study on an HCV hyperendemic area, O town, with a population of approximately 3,900 in the northwest region of the Hiroshima prefecture in Honshu, Japan (11). The incidence there of subjects with 1 or more extrahepatic manifestations of HCV was 66.1%. In the present investigation, we examined extrahepatic manifestations in the same place over a 4-year period. Inhabitants with HCV infection had various extrahepatic manifestations, including OLP. The prevalence of OLP increased with the age of the subjects. This is consistent with an earlier study of inhabitants of the Fukuoka prefecture (20).

Patients with HCV-associated HCC in Japan are aging. People with chronic HCV infection should be monitored and followed carefully for extrahepatic manifestations. It is necessary for physicians and dentists to have an increased awareness of OLP in order for it to be detected at an early stage and treated promptly.

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