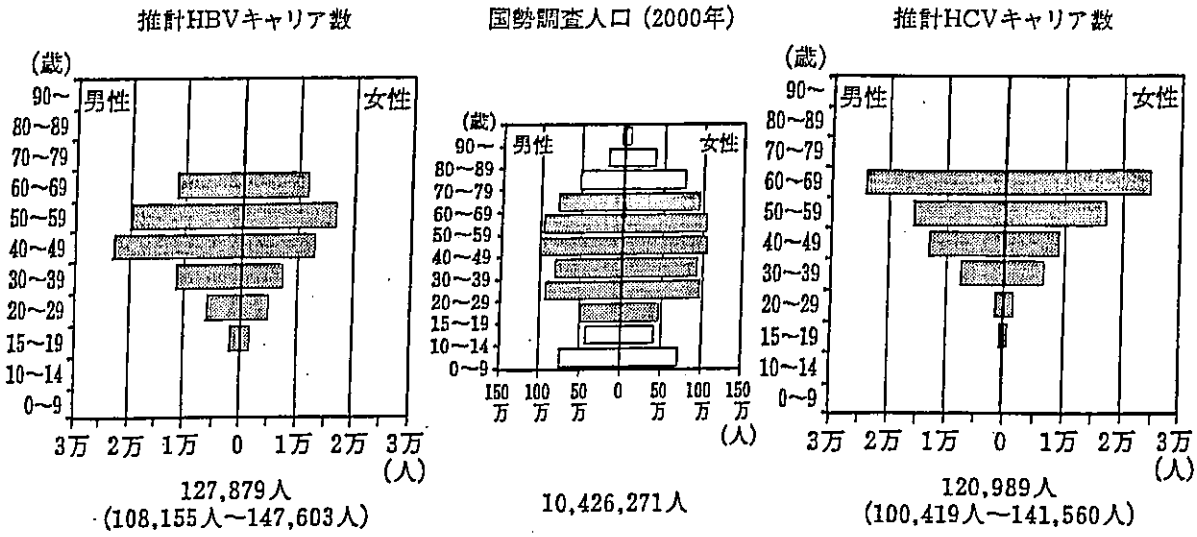

図14 九州 area における人口ピラミッドと年齢階級別にみた推計 HBV キャリア数，HCV キャリア数―15～69 歳の年齢層における推計値―

が認められた．

今後は，地域ごとに潜在・偏在するキャリアの分布を念頭において，さらなる肝炎ウイルス検診[12)～14)]の受診率の向上を図ることが求められる．また，同時に，検診により見い出されたキャリアの組織的な健康管理，治療体制[15)]の整備を急ぐことも求められていると言える．

文　献

1) 厚生労働省大臣官房統計情報部：平成13年　人口動態統計，2001.
2) 日本肝癌研究会：第5回―第16回全国原発性肝癌追跡調査報告．日本肝癌研究会事務局，2004.
3) Koyama T, Matsuda I, Sato S, et al：Prevention of perinatal hepatitis B virus transmission by combined passive-active immunoprophylaxis in Iwate, Japan (1981-1922) and epidemiological evidence for its efficacy. Hepatology Research 26：287-292, 2003.
4) Noto H, Terao T, Ryou S, et al：Combined passive and active immunoprophylaxis for preventing perinatal transmission of the hepatitis B virus carrier state in Shizuoka, Japan during 1980-1997. Jornal of Gastroenterology and Hepatology 18：943-949, 2003.
5) 田辺泰登，佐々木富美子，守屋　尚，ほか：覚醒剤常用者におけるB型肝炎ウイルスおよびC型肝炎ウイルスの感染状況についての検討．肝臓　34(4)：349，1993.
6) Sasaki F, Tanaka J, Moriya T, et al：Very low incidence rates of community- acquired hepatitis C virus infection in company employees, long-term inpatients, and blood donors in Japan. Journal of Epidemiology 6：198-203, 1996.
7) Moriya T, Sasaki F, Mizui M, et al：Transmission of hepatitis C virus from mothers to infants：its frequency and risk factors revisited.
8) 三浦宣彦：肝がん死亡の地理的分布―平成14年度　厚生労働科学研究費補助金　肝炎等克服緊急対策研究事業（肝炎分野）C型肝炎の自然経過および介入による影響等の評価を含む疫学的研究報告書，24-30，2003.
9) Tanaka J, Kumagai J, Katayama K, et al：Sex-and age-specific carriers of hepatitis B and C viruses in Japan estimated by the prevalence in the 3,485,648 first-time blood donors during 1995-2000. Intervirology 47：1, 32-40, 2004.
10) 田中純子，山中烈次，片山恵子，ほか：わが国の健常者集団におけるHCVキャリア，HBVキャリアの推計数　平成14年度　厚生労働科学研究費補助金　肝炎等克服緊急対策研究事業（肝炎分野）C型肝炎の自然経過および介入による影響等の評価を含む疫学的研究　報告書，11-23，2003.
11) Watanabe J, Matsumoto C, Fujimura K, et al：Predictive Value of Screening Tests for Persistent Hepatitis C Virus Infection Evidenced by Viraemia. Vox Sang 65：199-203, 1993.
12) 田中純子，片山恵子，熊谷純子，ほか：簡便，安価，かつ高い精度でHCVキャリアを見出すための検査手順確立のための基礎的検討　平成13年度　厚生科学研究費補助金　新興・再興感染症

研究事業　C型肝炎の自然経過および介入による影響等の評価を含む疫学的研究　報告書，31-36，2003.
13) 阿部弘一：HCV キャリアを見出すための効率的な検診システム　平成14年度　厚生労働科学研究費補助金　肝炎等克服緊急対策研究事業(肝炎分野)　肝がんの発生予防に資するC型肝炎検診の効率的な実施に関する研究　報告書，15-19，2003.
14) 吉澤浩司：肝がんの発生予防に資するC型肝炎検診の効果的な実施に関する研究　平成13年度厚生科学研究費補助金(21世紀型医療開拓推進研究事業)中間報告書，2000.
15) 熊田博光：C型肝炎ウイルスの感染者に対する治療の標準化に関する臨床的研究　平成14年度厚生労働科学研究費補助金　肝炎等克服緊急対策研究事業(肝炎分野)　C型肝炎ウイルスの感染者に対する治療の標準化に関する臨床的研究　報告書，2003.

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REVIEW

Hepatitis C virus and lichen planus

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Abstract

Hepatitis C virus (HCV) is an important factor in the development of chronic liver disease and hepatocellular carcinoma. In recent years it has become known that HCV induces various extrahepatic manifestations including mixed cryoglobulinemia, membranoproliferative glomerulonephritis, Sjögren's syndrome, autoimmune thyroiditis, malignant lymphoma, porphyria cutanea tarda and lichen planus. Although the mechanisms of extrahepatic manifestations remain unclear, it is known that interferon (IFN) therapy and coadministration of IFN with ribavirin are effective in promoting the disappearance or alleviation of such extrahepatic lesions, which have tended to be overlooked. The present review focuses on lichen planus, one of the major extrahepatic manifestations.

Key words: extrahepatic manifestation, hepatitis C virus, hepatitis C virus RNA, interferon, lichen planus, oral cancer, oral lichen planus, ribavirin.

INTRODUCTION

Hepatitis C virus (HCV) was found to be the principal virus causing non-A, non-B hepatitis in 1989 (when Choo *et al.* cloned part of the cDNA[1]), and to be a major cause of hepatocellular carcinoma.[2,3] The rate of post-transfusion hepatitis C in Japan decreased drastically since 1989, when blood for transfusion began to be screened using HCV antibody.[4] However, HCV infection persists in more than 60% of cases, and the incidence of hepatocellular carcinoma is found to be increasing yearly both in Japan and in the USA.[5]

Currently, approximately 2 million people in Japan are HCV carriers,[6] and more than 70% of chronic hepatitis and liver cirrhosis cases and 80% of hepatocellular carcinoma cases are known to be caused by the virus.[7] The majority of HCV carriers are infected through blood and blood preparations or traumas caused by instruments contaminated with blood containing HCV, for example, in medical treatment with syringes and knives, various invasive folk medicine, tattoos,[8,9] and through perinatal and sexual transmission of HCV infection.[10]

The hepatitis virus, while being an important factor in the development of chronic liver disease and hepatocellular carcinoma, induces damage to organs and tissues other than the liver.[11–13] Such damage is generally called extrahepatic manifestation (Table 1). Particularly, HCV is known to induce various extrahepatic manifestations including mixed cryoglobulinemia, membranoproliferative glomerulonephritis, Sjögren's syndrome, autoimmune thyroiditis, malignant lymphoma, porphyria cutanea tarda and lichen planus. Our research also suggested that it is highly possible that HCV plays a role in the development of oral cancer.[14,15]

It is thought that following the viral infection, the virus itself or the host immune response plays a role in HCV extrahepatic manifestations. However, the mechanism of most manifestations remains unclear.[11] It has been confirmed that HCV infects and replicates in various cells and organs other than the liver;[16] HCV increases the expression of autoantibody;[17,18] and interferon (IFN) and ribavirin are effective in the treatment of extrahepatic lesions.[19,20] These findings suggest a close relationship between HCV and extrahepatic manifestation. Epidemiological studies have found that the occurrence of extrahepatic manifestations is high in HCV carriers.[21–24]

Hepatitis C virus RNA is detected in the saliva of HCV carriers.[25–29] Persistent HCV infection in the oral mucous membranes may trigger HCV-related oral

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Table 1 Extrahepatic manifestations

Hepatitis A virus	Hepatitis B virus	Hepatitis C virus
Acute renal failure	Nephropathy	Cryoglobulinemia
Disorders in hematopoietic organs	Arteritis nodosa	Membranoproliferative glomerulonephritis
Pure red cell aplasia	Skin disease	Porphyria cutanea tarda
Aplastic anemia	Gianotti disease	Lichen planus
Hemolytic anemia	Chronic rheumatoid arthritis	Sjögren's syndrome
Idiopathic thrombocytopenic purpura	Schölein-Henoch purpura	Myositis
Myocardiopathy	Polymyositis	Myocardiopathy
Myositis	Disorders of hematopoietic organs	Malignant lymphoma
Angiitis	Pure red cell aplasia	Chronic rheumatoid arthritis
Meningoencephalitis	Thrombocytopenic purpura	Chronic thyroiditis
Meningitis	Aplastic anemia	Diabetes mellitus
Guillain-Barré syndrome		Interstitial pneumonia
Pancreatitis		Mooren corneal ulcer
Induction of autoimmune hepatitis		Oral cancer
Impaired glucose tolerance		

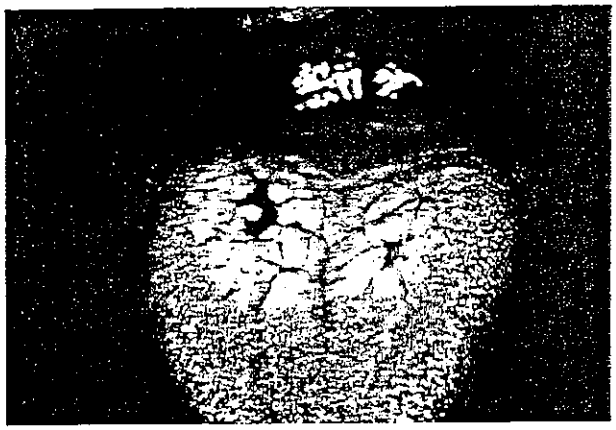

Figure 1 Lichen planus of the tongue; patient with chronic hepatitis C.

lesions. The detailed mechanisms of extrahepatic manifestations remain unclear.

LICHEN PLANUS

Lichen planus (LP) is an inflammatory disease in which chronic keratonosis occurs in the skin or mucous membranes or both (Figs 1,2). Skin lesions are found in the extremities (high prevalence), genitalia, nails, face and scalp. Lesions in the mucous membranes are found in the oral cavity (high prevalence), nasal mucous membranes, throat, esophagus, stomach, bladder, vulva, vagina and glans penis.[30–47]

Oral lichen planus (OLP) occurs often in women in their 50s to 60s. Buccal mucous membrane is the favorite site and OLP mostly occurs on both sides. The chief subjective symptom is contact pain. Most lesions consist of mixtures of opaline, lacey white lesions, flare and erosions. These lesions are chronic and intractable.

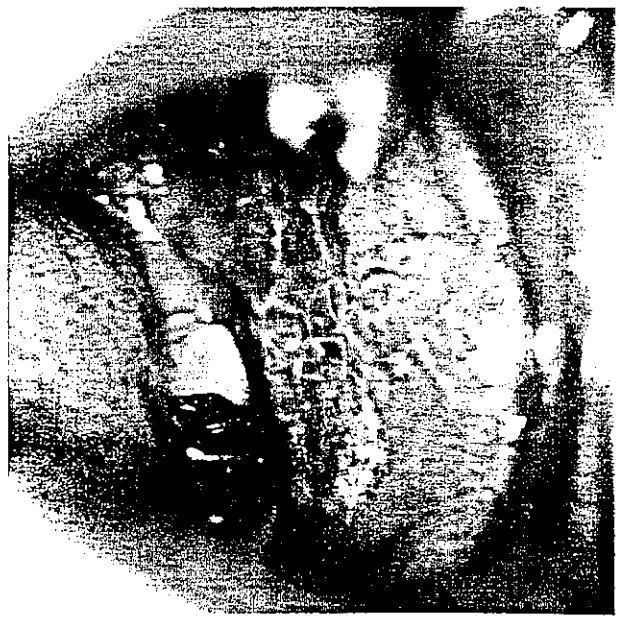

Figure 2 Lichen planus of the left buccal mucosa; patient with hepatitis C virus-related liver cirrhosis.

VULVO-VAGINAL–GINGIVAL SYNDROME

Pelisse *et al.* (1982) reported the 'vulvo-vaginal gingival syndrome', a new form of erosive lichen planus.[32] The vulvo-vaginal–gingival syndrome is a variant of mucosal lichen planus, which is characterized by erosions and desquamation of the vulva, vagina, and gingiva. The clinical features of this condition were reviewed and summarized based on the personal examination of 19 affected patients by Pelisse *et al.*,[35] five affected patients by Bermejo *et al.*[36] and 22 affected patients by Eisen.[40] Mann and Kaufman reported that nine of 17 patients with vulvo-vaginal lichen planus had OLP consisting

primarily of gingival erosions with lacy-white plaque in the buccal mucosa.[38] Eisen evaluated extraoral involvement in a large series of patients with OLP.[45] It was reported that extraoral manifestations included cutaneous LP in 16% (93/584 patients), and genital LP in 19% of 399 women and 4.6% of 174 men. In Japan approximately 40% of HCV-related OLP patients suffered from genital LP.[48] Clinicians should follow OLP patients with sufficient attention to the presence of extraoral manifestations. These data suggest the occurrence of intraspousal transmission of HCV through erosive vulvar LP.

PREVALENCE OF HEPATITIS C VIRUS INFECTION IN PATIENTS AFFECTED WITH LICHEN PLANUS

The first report indicating the association between chronic liver diseases and LP was made by Rebora *et al.* in 1978.[49] Since then, several studies reported that OLP patients had a high prevalence of HCV infection.[50–81] The HCV infection rates vary greatly by country (Table 2).[50–54,56–81] The HCV infection rates in LP patients are high in Japan and Italy and low in the UK and Germany. The difference is due to geographic differences in HCV infection and selection of study subjects (sex and average age) in the respective countries. Moreover, not all reported studies included screening of hepatic damage and measurement of serum HCV-RNA to determine the presence or absence of hepatic diseases. In the case of Japan, most of the subjects in reports are the inhabitants of the northern Kyushu region, where the HCV infection rate and the mortality rate from hepatocellular carcinoma are the highest in Japan.

It is estimated that approximately 170 million people worldwide are infected with HCV. The global prevalence of HCV carriers is estimated to average 3%, ranging from 0.1% to 10% or more in different countries.[82] In Europe, the overall prevalence is 1% with a north–south gradient, ranging from 0.5% in northern countries to 2% in Mediterranean countries. Recent studies have shown a high prevalence in Eastern Europe, ranging from 0.7% to 5%. Asia, Mongolia, Vietnam, Myanmar, and China all have a high prevalence. In Africa, a high prevalence is seen in countries of the central region and in Egypt.[83] In North America the prevalence is low. In South America, a high prevalence is seen in Brazil.[84] In Japan, the average prevalence of HCV carriers is approximately 2%, with the number estimated at 2 million.[6] The recent increase in the incidence of hepatocellular carcinoma is ascribed to poor socioeconomic conditions instrinsic to Japan in the recent past.[6,85,86] These differences in HCV infection may influence the prevalence of HCV infection among OLP patients.

PREVALENCE OF ORAL LICHEN PLANUS IN SUBJECTS AFFECTED WITH HEPATITIS C VIRUS-RELATED LIVER DISEASES

Although there are many studies of the HCV infection rate in LP patients, few concern the incidence of LP in HCV carriers (Tables 3,4).[21,24,61,79,87–90] The first reason for the difference in the incidence may be explained by geographic differences in the respective countries. However, the prevalence of OLP is high in the UK (20%; Tables 3,4),[88] where the prevalence of HCV infection in the general population is low. The inconsistency may be due to the fact that the diagnosis of OLP was carried out only clinically. The second reason for the discrepancy may be the diagnostic criteria of OLP, such as clinical or histopathological OLP. In addition, Mignogna *et al.* reported that the presence of drug- or dental restoration-related lichenoid reactions may have been included in the previous reports.[89] The third reason may be due to the difference in age or ratio of female subjects. The average age of the inhabitants in the Japanese studies was higher than that in the studies of Italy, UK, Spain, and Brazil.[61,79,88,89] Mignogna *et al.* investigated the incidence of OLP among 300 individuals with HCV infection in southern Italy.[89] However, the incidence of OLP in subjects positive for serum HCV antibodies was reported to be not significantly higher than that of the general population. Mignogna *et al.* suggested that the hypothesis that OLP can be categorized among the extrahepatic manifestations of HCV infection should be revised on the basis of the age-specific prevalence of HCV infection and stricter diagnostic criteria.[81,89] Also as a fourth reason for the discrepancy, racial differences, such as differences in human leukocyte antigen (HLA) typing, may influence the incidence of OLP found in different countries. Carrozzo *et al.* reported a significant association of exclusive OLP and HCV infection with the HLA class II allele HLA-DR6 in Italy.[91] This could partially explain the peculiar geographic heterogeneity of the association between HCV and OLP.

Since 1993 we have investigated every year the large-scale epidemiological studies of OLP in an HCV hyperendemic area (H town) in Japan; the positive rate of HCV antibody in the inhabitants is very high at 23.6% (in random sampling).[21,92] In this area, approximately half of the HCV carriers died of hepatocellular carcinoma or liver cirrhosis.[93] We reported that the incidence of OLP was significantly higher in persons with positive HCV antibody and HCV-RNA than in persons with negative findings, and that the occurrence of any extrahepatic manifestations other than OLP was higher in HCV carriers than in non-carriers.[24] We consider that it is important to search for clinical and biological extrahepatic manifestations as well as liver diseases among patients with HCV infection,[24,90] although the rate of OLP in HCV-related liver disease differs in the respective countries.

PATHOGENESIS: VIRAL FACTORS AND HOST FACTORS

The association of viral factors such as the HCV level (HCV-RNA level) and HCV genotypes (or HCV serotype)[94–96] in the development of OLP has been studied. However, the direct association of viral factors has been denied in all reports.[97–100] Although it is unclear how HCV affects the immune system of hosts who will contract LP, it is thought that the host immune system plays

Table 2 Prevalence of hepatitis C virus (HCV) infection in patients affected with lichen planus

Country	Ref. no.	Year	Population *n*	Population Only OLP/only CLP/both	LP patients Positive for anti-HCV (%)	LP patients Positive for HCV-RNA (%)	Controls Positive for anti-HCV (%)
Japan	57	1995	45	(45/0/0)	62	60	No controls
	58	1995	45	(28/8/9)	37.8	Not done	6.7 (3 of 45)
Italy	50	1992	46	(0/46/0)	32.6	Not done	No controls
	51	1992	50	(50/0/0) (group 1: without CLD)	4	Not done	No controls
			29	(29/0/0) (group 2: with CLD)	65	Not done	No controls
			46	(46/0/0) (group 3: with or without CLD)	24	Not done	No controls
	54	1994	105	(105/0/0)	9.5	Not done	No controls
	59	1996	70	(70/0/0)	27.1	21.4	4.3 (3 of 70)
	68	1998	263	(263/0/0)	28.8	Not done	3 (3 of 100)
	81	2002	600	(600/0/0)	27.5	Not done	No controls
Spain	52	1994	187	(187/0/0)	15	Not done	No controls
	60	1996	78	(22/22/34)	20	16.7	2.4 (2 of 82)
	61	1998	100	(100/0/0)	23	Not done	5 (5 of 100)
France	53	1994	52	(4/48/0)	3.8	Not done	2.6 (3 of 112)
	62	1997	102	(102/0/0)	4.9	Not done	4.5 (14 of 306)
	64	1998	28	(28/0/0)	28.6	17.9	No controls
UK	67	1998	55	(55/0/0)	0	Not done	0 (0 of 110)
	70	1999	45	(13/32/0)	0	0	3.1 (1 of 32)
Scotland	71	2000	6	(6/0/0)	0	0	No controls
USA	56	1995	30	(0/30/0)	23	16.7	4.8 (2 of 41)
	69	1999	22	(0/22/0)	55	Not done	25 (10 of 40)(control 1) 0.17 (255 of 149 756) (control 2)
	74	2001	24	(0/24/0)	17	Not done	5 (1 of 20)
	75	2001	31	(31/0/0)	45	Not done	No controls
	77	2002	195	(195/0/0)	0	Not done	No controls
Germany	63	1997	84	(22/62/0)	16	14	1.1 (1 of 87)
	65	1998	24	(24/0/0)	4.2	Not done	No controls
Netherlands	72	2000	55	(55/0/0)	0	Not done	No controls
Turkey	66	1998	75	(0/75/0)	0	Not done	0 (0 of 75)
	73	2000	73	(27/46/0)	6.8	Not done	1.36 (1 of 73)
	76	2001	54	(0/54/0)	12.9	9.3	3.7 (2 of 54)
Nepal	80	2002	64	(14/35/15)	0	Not done	0 (unknown)
Nigeria	78	2002	57	(0/55/2)†	15.8	Not done	25 (6 of 24)(control A) 0 (0 of 24)(control B)
Brazil	79	2002	68	(63/0/5)	8.8	Not done	0.6 (6 of 898)

†Data communicated directly from author. OLP, oral lichen planus; CLP, cutaneous lichen planus; both, oral and cutaneous lichen planus; CLD, chronic liver disease; control 1, psoriasis; control 2, volunteer blood donors; control A, dermatoses without lichen planus; control B, normal individuals.

Table 3 Prevalence of oral lichen planus in subjects affected with hepatitis C virus-related liver diseases: subject details

Ref. no. Year	21 1997	24 2000	90 2002	89 2001	87 2000	88 2001	61 1998	79 2002
Country	Japan	Japan	Japan	Italy	Australia	UK	Spain	Brazil
Region	Fukuoka prefecture, northern Kyushu	Fukuoka prefecture, northern Kyushu	Hiroshima prefecture, Honshu	Naples, southern Italy	Adelaide	Glasgow	Valencia	São Paulo
Subjects	Inhabitants of H town for screening test	Inhabitants of H town for screening test	Inhabitants of O town for screening test	Patients referred to the Department for dental diseases	Patients referred to the Adelaide Dental Hospital	Patients referred to the Glasgow Dental School	Patients referred to the Stomatology Service and Hepatology Unit of the Valencia University General Hospital	Patients referred to to the Clinical Hepatology Branch at the University of São Paulo
Country of birth or race	Japanese 100%	Japanese 100%	Japanese 100%	Italian 100%	Australia 81% Europe 13.1% Oceania 2.4% SE Asia 2.4% Other 1.2%	British 95% Italian 2.5% Pakistan 2.5%	Unknown	Unknown
Diagnostic criteria of OLP	Clinical and histopathological findings	Clinical and histopathological findings	Clinical and histopathological findings	Clinical and histopathological findings	Unknown	Clinical findings	Clinical and histopathological findings	Clinical and histopathological findings

OLP, oral lichen planus.

Table 4 Prevalence of oral lichen planus in subjects affected with hepatitis C virus (HCV)-related liver diseases

Ref. no.	21		24		90	
Year	1997		2000		2002	
	Total	OLP	Total	OLP	Total	OLP
No. patients	685†	10 (1.5)†	190†	12 (6.3)†	59	5 (8.5)
Age (years) (mean ± SD)	56.1 ± 16.1	60.8 ± 11.6	59.3 ± 13.9	60.5 ± 9.1	70.7 ± 7.2	74.8 ± 5.2
Sex (M/F)	295/390	8/2	74/116	9/3	21/38	1/4
Anti-HCV(+)	84	4/84	40	5/40	59	5/59
(%)	(12.3)	(4.8)**	(21.1)	(12.5)	(100)	(8.5)
HCV-RNA(+)	61	4/61	31	5/31	57	5/57
(%)	(8.9)	(6.6)***	(16.3)	(16.1)*	(96.6)	(8.8)
Anti-HCV(–) and HCV-RNA(–)	591	6/591	150	7/150	0	0
(%)	(86.3)	(1.0)**‡‡‡‡	(78.9)	(4.7)*	(0)	(0)

*$P < 0.05$; **$P < 0.01$; ***$P = 0.001$. †The subjects included HCV-positive and -negative adult inhabitants in a mass health screening in a hyperendemic area of HCV infection. ‡One of six exhibited cutaneous lichen planus. §Data communicated directly from author. OLP, oral lichen planus.

an important role in the development of OLP in HCV carriers.[101]

EFFECTS OF HEPATITIS C VIRUS INFECTION ON CLINICOPATHOLOGIC CHARACTERISTICS OF ORAL LICHEN PLANUS

Rebora, and Rebora and Rongioletti reported that patients with erosive LP had chronic active hepatitis.[102,103] Carrozzo *et al.* reported that HCV infection was more frequently found in patients with erosive OLP (58.8%) than in patients with non-erosive OLP (13.2%; $P = 0.004$).[59] Lo Muzio *et al.* analyzed the presence of signs of malignant transformation.[104] These considerations are particularly important in the case of atrophic or erosive OLP, and plaque OLP, especially when involving the dorsum of the tongue. And HCV-related OLP was observed not only in patients with severe liver dysfunction but in patients without it.[57]

Although there are not many reports on detailed histologic features of OLP in which HCV is thought to play a role,[58,105–107] commonly held views are that HCV infection has no effect on histopathologic characteristics specific to OLP or the ratios of T cells and B cells in infiltrating lymphocytes. In addition, there is no fixed correlation between stage of fibrosis and grade of inflammation of the liver and severity of OLP inflammation.[58,87] Mega *et al.* reported that the different distributions of CD8+ cells may be involved in the pathogenetic mechanisms of OLP.[108]

OLP AND INTERFERON THERAPY

Chronic hepatitis C is often treated with IFN. As regards the effects of IFN therapy on LP lesions, there is a report of improvement in LP lesions,[109] reports of LP manifestation triggered by IFN,[110–114] and a report of aggravation of LP.[115] Doutre *et al.* reported two cases of disappearance of LP under IFN.[109] Lichen planus with chronic hepatitis C was reported to have disappeared in treatment with IFN-α, without the combination of any other local or general therapies, the recovery lasting for several months after the end of the IFN treatment. Protzer *et al.* reported the case of exacerbation of cutaneous and oral LP during IFN-α-2a therapy for chronic hepatitis C.[115] The IFN therapy was stopped in the middle of a treatment because local measures did not improve skin lesions. Interferon-α can induce the appearance of LP lesions with cytokine cascade. Interferon may induce the expression of previously hidden surface antigens on keratinocytes.[115] In general, it is reported that caution should be exercised when IFN therapy is applied to chronic hepatitis C patients with preceding OLP manifestation.[11] Dalekos *et al.* studied a prospective evaluation of dermatological side-effects during IFN therapy for chronic viral hepatitis.[114] That study demonstrated that IFN-α may rarely (3.3%) induce immune-mediated dermatological disorders, especially LP. The authors reported that the development of these disorders may reflect a subclinical or covert autoimmune background of patients.

However, there is no report on oral mucosal lesions that were subsequently observed in detail. In Japan, we observed oral lesions in chronic hepatitis C patients who were treated with IFN, and studied the long-term histologic prognosis.[112,116] In observations of oral lesions made before, during and after IFN treatment, OLP occurred in 16.7% of subjects. Some OLP lesions that appeared during IFN treatment and were aggravated temporarily were improved by symptomatic therapy, so that IFN treatment was continued. Other mucous-membrane lesions included leukoplakia found in four subjects before IFN treatment and oral cancer in one patient 6 months after IFN treatment.[117]

89 2001		87 2000		88 2001		61 1998		79 2002	
Total	OLP	Total	OLP	Total	OLP	Total	OLP	Total	OLP
300	5 (1.6)	87	7(8.0)	40	8 (20)	505	17 (3.36)	126	6‡ (4.7)
56.4	56§	Unknown	Unknown	35	Unknown	46.09	Unknown	48.5	Unknown
130/170	2/3§	42/45	Unknown	29/11	8/0	286/219	Unknown	56/70	2/4
300	5/300	87	7/87	40	8/40	505	17	126	6
(100)	(1.6)	(100)	(8.0)	(100)	(20)	(100)	(3.36)	(100)	(4.7)
Unknown	Unknown	Unknown	Unknown	38 (95)	7/38 (18.4)	Unknown	Unknown	Unknown	Unknown
0	0	0	0	0	0	0	0	0	0
(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)

The clinical course and the loci of positive-strand and negative-strand HCV-RNA in lesions were studied in four cases of OLP that were followed up for 3 years or longer after IFN treatment.[116] Although no macroscopic change was observed in OLP in all cases within 1 year after IFN treatment, some OLP lesions were observed to be improved not only macroscopically but also in histopathologic examination in the long-term (≥3 years). That is, a disappearance or a decrease in lymphocytic infiltration below the mucosal epithelial cells was observed. This finding resembles the phenomenon of histologic cure confirmed in cases of chronic hepatitis C for which IFN treatment is markedly effective. In such cases, grades of inflammation and stage of fibrosis improve over 4–5 years.

There is no report that describes the effect of IFN and ribavirin treatment in detail for the patients with HCV-related LP. Therapeutic effects of IFN and ribavirin have also been confirmed in extrahepatic lesions other than OLP. In 1994, Johnson *et al.* reported the therapeutic effects of IFN on membranoproliferative glomerulonephritis with HCV infection.[118] However, it is problematic that serum HCV-RNA returns to positive and renal dysfunction recurs after the completion of the treatment. Recently, high-dose IFN,[119] ribavirin[120] and IFN + ribavirin combination therapy[19] have attracted attention as effective treatments. Interferon therapy[121] or IFN + ribavirin combination therapy[20] has also been reported for cryoglobulinemia with HCV infection. However, there is one report of renal dysfunction that was induced by IFN therapy.[122] No treatment has been established for membranoproliferative glomerulonephritis in association with HCV. For intractable HCV-associated membranoproliferative glomerulonephritis and cryoglobulinemia, IFN as well as IFN + ribavirin combination therapy are thought and expected to be effective. An accumulation of cases and long-term follow up are needed for elucidation of the therapeutic effects of IFN therapy on extrahepatic lesions. The therapeutic effects of IFN on porphyria cutanea tarda have also been reported in several reports in rapid succession.[123–126]

Zuckerman *et al.* analyzed the translocation of t(14:18) and the rearrangement of *immunoglobulin heavy-chain gene* (*IgH*) in 29 HCV carriers before and after IFN therapy or IFN + ribavirin combination therapy.[127] Of 15 HCV carriers who received the aforementioned treatment, nine had IgH rearrangement, seven of whom lost it. The t(14:18) translocation occurred in seven HCV carriers, six of whom lost it. Of 14 HCV carriers who did not receive the treatment, eight had IgH rearrangement, only one of whom lost it. The t(14:18) translocation occurred in six HCV carriers, one of whom lost it during the follow-up period. B-cell non-Hodgkin's lymphoma (NHL) developed in two of 14 HCV carriers who did not receive said treatment. Because IFN is thought to be effective for eliminating clonal proliferation of B cells, IFN may prevent B-cell NHL from occurring. Hermine *et al.* reported interesting cases of splenic lymphoma with villous lymphocytes in nine HCV carriers.[128] Interferon therapy or IFN + ribavirin combination therapy resulted in alleviation of said lymphoma.

MALIGNANT TRANSFORMATION OF ORAL LICHEN PLANUS

Malignant transformation of OLP lesions has been widely reported, although the malignant potential of disease is still controversial.[129–132] Barnard *et al.* found evidence to support the important premalignant potential of OLP, although the incidence of malignant change in OLP is not high.[130]

We reported for the first time the association between HCV and oral cancer.[14,15] We also reported that HCV infection rates were the highest in oral cancer among the gastrointestinal cancers.[14] Multicenter joint studies in Japan found that the presence of HCV antibody and HCV-RNA was significantly higher in patients with squamous cell carcinoma of the head and neck than in controls.[15] A recent report described the association between HCV-related OLP and the development of cancer.[133] While it has not been agreed whether or not OLP is a precancerous manifestation, there are many reports of aggravation of OLP. Lo Muzio *et al.* studied canceration of OLP and HCV infection in 263 patients and reported that malignant transformation of OLP

occurred in 5.32% of said patients, and that HCV antibody was positive in three of 14 patients who had squamous cell carcinoma.[104] The authors suggested that close attention be paid particularly to malignant transformation of atrophic or erosive OLP. Conversely, cutaneous LP does not tend toward malignant transformation.[134] Hepatitis C virus secreted in saliva may be a factor in malignant transformation. Therefore we feel that it is necessary for HCV carriers to have regular oral examinations, and for OLP patients to be monitored for canceration once a year.

Hepatitis C virus is not only a hepatotropic virus but also a lymphotropic virus. The particular association with non-Hodgkin's lymphoma has been suggested.[135,136] Sikuler *et al.* found that the incidence of extrahepatic malignant tumors was significantly higher in individuals with positive HCV antibody and reported that HCV carriers had high probabilities of having extrahepatic malignant tumors.[137]

It is also known that oral cancer patients often have carcinoma of the stomach (18%) and hepatic cancer (16%) as double cancers, and double-cancer patients have significantly higher HCV infection rates than controls.[138] These findings suggest that HCV plays a role in the development of oral cancer and that HCV carriers need to be aware of the high occurrence of cancers.

ORAL MUCOSAL MANIFESTATION AND LOCALIZATION OF HEPATITIS C VIRUS

The HCV genome consists of a single chain of positive-strand RNA. In HCV duplication in infected cells, the negative strand is synthesized based on its own positive-strand RNA, and positive-strand RNA is made using the negative strand as the template. Thus, negative-strand HCV-RNA is produced as the virus replicates. The detection of negative-strand RNA establishes the existence and replication of HCV. The recent development of strand-specific RT-PCR makes it possible to detect the specific RNA strand.

Detection of the HCV-RNA negative strand has been reported not only in hepatocytes but also in many other cells, suggesting extrahepatic replication of HCV.[16] We studied the existence of positive-strand and negative-strand HCV-RNA in tissues of OLP and oral cancers.[139,140] Of 14 specimens of OLP obtained from anti-HCV(+) individuals, 13 were detected to have HCV-RNA. The detection rate of the HCV-RNA positive strand was 92.9% and that of the negative strand was 21.4%. Hepatitis C virus RNA was detected in all seven specimens of oral cancer tissues obtained from anti-HCV(+) individuals; the detection rate of the HCV-RNA positive strand was 100% and that of the negative strand was 71.4%. It was also confirmed that the amino acid sequence from HCV-RNA in serum differed from that in tissues, demonstrating that the detection of HCV-RNA in tissues was not due to blood contamination. The aforementioned findings suggest that HCV is present and replicates in lesions of OLP and oral cancers.[140]

Arrieta *et al.* detected the HCV-RNA negative strand in OLP tissues using *in situ* hybridization (ISH).[141] The authors detected negative-strand RNA in tissues whether OLP was present or absent, demonstrating HCV replication in epithelial cells and reached a conclusion similar to ours.

Moreover, Carrozzo *et al.* also have shown that HCV replicates in tissue, based on the detection of negative-strand HCV-RNA, as determined by strand-specific RT-PCR.[142] Genomic and negative-strand HCV-RNA were detected in, respectively, 12 of 17 specimens (70.6%) and four of 17 specimens (23.5%) from chronic hepatitis C patients.

Roy *et al.* in Scotland reported that HCV-RNA was not detected in the tissues of any of the six patients with OLP.[71] However, all six patients were not serologically infected with HCV and six patients may not be sufficient for the study. Their conclusion that 'hepatitis C virus is not commonly associated with OLP in Scotland' seems questionable. Mangia *et al.* reported that HCV-RNA was not detected in the tissues of HCV-infected patients with cutaneous LP.[143] Erkek *et al.* reported that HCV-RNA was detected in the tissues of five patients with LP, all of whom were serologically positive for HCV-RNA.[76] In one of those five patients, HCV-RNA was detected not only in the tissues of LP lesions but also in normal cutaneous tissues. Their findings were the same as those of our study[140] and that of Arrieta *et al.*,[141] that is, HCV-RNA was detected in normal mucous membranes in HCV carriers. It is possible that extrahepatic lesions will develop in HCV carriers, for whom clinical follow up is important.

Recently, Pilli *et al.* reported a role for HCV-specific T-cell responses in the pathogenesis of epithelial cell damage in OLP associated with HCV infection.[144] The authors demonstrated that recruitment of HCV-specific $CD4^+$ and/or $CD8^+$ T cells was detected in the LP tissue of five out of seven patients with chronic HCV infection.

Ferri *et al.* reported that HCV-RNA was detected in peripheral blood lymphocytes of all cases of HCV-infected malignant lymphoma (diffuse B-cell NHL).[136] De Vita *et al.* detected positive (+) and negative (–) strand HCV-RNA in the parotid gland of HCV-infected patients with parotid B-cell NHL and the presence of HCV in the parotid gland using immunohistologic staining and ISH.[145] Reported also are the high prevalence of hepatic cancer as the secondary double cancer of NHL,[146] and significantly high rates of extraglandular lesions in the liver and major salivary glands in HCV-infected NHL.[147] It is unclear whether the proliferation of HCV and the ensuing degeneration of glandular tissues induce sialadenitis or an immune response reacting to the infection, or whether the proliferation of the virus induces sialadenitis or formation of mucosal lesions.

It is unclear what role HCV plays in tumorigenesis of lymphocytes. Hepatitis C virus detected in saliva is both hepatotropic and lymphotropic. The virus may be sialotropic at the same time. The possibility is understandable that HCV plays a role in inducing hepatic cancer as well as B-cell NHL. Some cases of cryoglobulinemia progress to NHL and several percent of Sjögren's syndrome cases do the same. It is

unclear whether HCV has a direct role or promotes other tumor factors. Hepatitis C virus infects lymphocytes and replicates in them. However, HCV has no reverse transcriptase, is not taken up in the genome of the host cell and has not been demonstrated to contain cancer genes. Lymphocytes have CD 81, which is an HCV receptor and is thought to play an important role in the host immune response.[148] Hepatitis C virus-infected dendritic cells are known to have decreased immunological functions.[149] Monoclonal production of B cells has been confirmed in the peripheral blood of HCV patients.[150] It is inferred that persistent chronic inflammation caused by HCV stimulates lymphocytes, inducing polyclonal production of B cells.[151]

CONCLUSION

Hepatitis C virus has been noted to play an important role in extrahepatic manifestations other than LP. However, the mechanisms of extrahepatic manifestations remain unclear and further progress in research is anticipated.

Clinicians must always keep in mind that OLP may be associated with systemic disease. We have encountered a case of malignant lymphoma that occurred during treatment of OLP in a chronic hepatitis C patient, lingual cancer and articular rheumatism in a patient with type C liver cirrhosis, and lingual cancer in a hepatocellular carcinoma patient with hypothyroidism.[152]. These diseases tend to be regarded as being independent of each other, but they may be a series of extrahepatic manifestations of HCV. We would like to emphasize that it is necessary to examine and follow up HCV carriers, keeping in mind the presence of extrahepatic manifestations. We must know the many extrahepatic manifestations, and attempt early detection and treatment of extrahepatic lesions. Education of patients also is important.

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REFERENCES

1 Choo QL, Kuo G, Weiner AJ, Overby LR, Bradley DW, Houghton M. Isolation of a cDNA clone derived from a blood-borne non-A, non-B viral hepatitis genome. *Science* 1989; 244: 359–62.
2 Bruix J, Barrera JM, Calvet X *et al.* Prevalence of antibodies to hepatitis C virus in Spanish patients with hepatocellular carcinoma and hepatic cirrhosis. *Lancet* 1989; 2: 1004–6.
3 Colombo M, Kuo G, Choo QL *et al.* Prevalence of antibodies to hepatitis C virus in Italian patients with hepatocellular carcinoma. *Lancet* 1989; 2: 1006–8.
4 Sasaki F, Tanaka J, Moriya T *et al.* Very low incidence rates of community-acquired hepatitis C virus infection in company employees, long-term inpatients, and blood donors in Japan. *J. Epidemiol.* 1996; 6: 198–203.
5 El-Serag HB, Mason AC. Rising incidence of hepatocellular carcinoma in the United States. *N. Engl. J. Med.* 1999; 340: 745–50.
6 Yoshizawa H. Hepatocellular carcinoma associated with hepatitis C virus infection in Japan: projection to other countries in the foreseeable future. *Oncology* 2002; 62: 8–17.
7 Nishioka K, Watanabe J, Furuta S *et al.* A high prevalence of antibody to the hepatitis C virus in patients with hepatocellular carcinoma in Japan. *Cancer* 1991; 67: 429–33.
8 Ko YC, Ho MS, Chiang TA, Chang SJ, Chang PY. Tattooing as a risk of hepatitis C virus infection. *J. Med. Virol.* 1992; 38: 288–91.
9 Sodeyama T, Kiyosawa K, Urushihara A *et al.* Detection of hepatitis C virus markers and hepatitis C virus genomic-RNA after needlestick accidents. *Arch. Intern. Med.* 1993; 153: 1565–72.
10 Akahane Y, Aikawa T, Sugai Y, Tsuda F, Okamoto H, Mishiro S. Transmission of HCV between spouses. *Lancet* 1992; 339: 1059–60.
11 Pawlotsky JM, Ben Yahia M, Andre C *et al.* Immunological disorders in C virus chronic active hepatitis: a prospective case-control study. *Hepatology* 1994; 19: 841–8.
12 Gumber SC, Chopra SC, Hepatitis C. A multifaceted disease. Review of extrahepatic manifestations. *Ann. Intern. Med.* 1995; 123: 615–20.
13 Sata M, Nagao Y. Hepatitis virus and extrahepatic manifestations: skin, mucosa, muscle, and hematopoietic organs. *Intern. Med.* 2001; 40: 185–9.
14 Nagao Y, Sata M, Tanikawa K, Itoh K, Kameyama T. High prevalence of hepatitis C virus antibody and RNA in patients with oral cancer. *J. Oral Pathol. Med.* 1995; 24: 354–60.
15 Nagao Y, Sata M, Itoh K *et al.* High prevalence of hepatitis C virus antibody and RNA in patients with head and neck squamous cell carcinoma. *Hepatol. Res.* 1997; 7: 206–12.
16 Laskus T, Radkowski M, Wang LF, Vargas H, Rakela J. Search for hepatitis C virus extrahepatic replication sites in patients with acquired immunodefeciency syndrome: specific detection of negative-strand viral RNA in various tissues. *Hepatology* 1998; 28: 1398–401.
17 Fried MW, Draguesku JO, Shindo M *et al.* Clinical and serological differentiation of autoimmune and hepatitis C virus-related chronic hepatitis. *Dig. Dis. Sci.* 1993; 38: 631–6.
18 Prieto J, Yuste JR, Beloqui O *et al.* Anticardiolipin antibodies in chronic hepatitis C: implication of hepatitis C virus as the cause of the antiphospholipid syndrome. *Hepatology* 1996; 23: 199–204.
19 Misiani R, Bellavita R, Baio P *et al.* Successful treatment of HCV-associated cryoglobulinaemic glomerulonephritis with a combination of interferon-alpha and ribavirin. *Nephrol. Dial. Transplant.* 1999; 14: 1558–60.
20 Zuckerman E, Keren D, Slobodin G *et al.* Treatment of refractory, symptomatic, hepatitis C virus related mixed

cryoglobulinemia with ribavirin and interferon-alpha. *J. Rheumatol.* 2000; 27: 2172–8.
21 Nagao Y, Sata M, Fukuizumi K, Tanikawa K, Kameyama T. High incidence of oral precancerous lesions in a hyperendemic area of hepatitis C virus infection. *Hepatol. Res.* 1997; 8: 173–7.
22 Cacoub P, Poynard T, Ghillani P *et al.* Extrahepatic manifestations of chronic hepatitis C. MULTIVIRC Group. Multidepartment Virus C. *Arthritis Rheum.* 1999; 42: 2204–12.
23 Cacoub P, Renou C, Rosenthal E *et al.* Extrahepatic manifestations associated with hepatitis C virus infection. A prospective multicenter study of 321 patients. *Medicine Baltimore* 2000; 79: 47–56.
24 Nagao Y, Sata M, Fukuizumi K, Ryu F, Ueno T. High incidence of oral lichen planus in HCV hyperendemic area. *Gastroenterology* 2000; 119: 882–3.
25 Takamatsu K, Koyanagi Y, Okita K, Yamamoto N. Hepatitis C virus RNA in saliva. *Lancet* 1990; 336: 1515.
26 Komiyama K, Moro I, Mastuda Y *et al.* HCV in saliva of chronic hepatitis patients having dental treatment. *Lancet* 1991; 338: 572–3.
27 Abe K, Inchauspe G. Transmission of hepatitis C by saliva. *Lancet* 1991; 337: 248.
28 Wang JT, Wang TH, Lin JT, Sheu JC, Lin SM, Chen DS. Hepatitis C virus RNA in saliva of patients with post-transfusion hepatitis C infection. *Lancet* 1991; 337: 48.
29 Chen M, Yun ZB, Sallberg M *et al.* Detection of hepatitis C virus RNA in the cell fraction of saliva before and after oral surgery. *J. Med. Virol.* 1995; 45: 223–36.
30 Ronchese F. Nail in lichen planus. *Arch. Dermatol.* 1965; 91: 347–50.
31 Kunel'skaia VI, Arievich AM. Lesion of the laryngeal mucosa in lichen ruber planus. *Vestn. Otorinolaringol.* 1978; 5: 32–5.
32 Pelisse M, Leibowitch M, Sedel D, Hewitt J. A new vulvovaginogingival syndrome. Plurimucous erosive lichen planus. *Ann. Dermatol. Venereol.* 1982; 109: 797–8.
33 Alinovi A, Barella PA, Benoldi D. Erosive lichen planus involving the glans penis alone. *Int. J. Dermatol.* 1983; 22: 37–8.
34 Pecoraro V, Romano Boix E. Anal manifestations of lichen planus. *Med. Cutan. Ibero. Lat. Am.* 1984; 12: 339–44.
35 Pelisse M. The vulvo-vaginal–gingival syndrome. A new form of erosive lichen planus. *Int. J. Dermatol.* 1989; 28: 381–4.
36 Bermejo A, Bermejo MD, Roman P, Botella R, Bagan JV. Lichen planus with simultaneous involvement of the oral cavity and genitalia. *Oral Surg. Oral Med. Oral Pathol.* 1990; 69: 209–16.
37 McKay M. Vulvar dermatoses. *Clin. Obstet. Gynecol.* 1991; 34: 614–29.
38 Mann MS, Kaufman RH. Erosive lichen planus of the vulva. *Clin. Obstet. Gynecol.* 1991; 34: 605–13.
39 Neumann R, Dutt CJ, Foster CS. Immunohistopathologic features and therapy of conjunctival lichen planus. *Am. J. Ophthalmol.* 1993; 115: 494–500.
40 Eisen D. The vulvovaginal–gingival syndrome of lichen planus. The clinical characteristics of 22 patients. *Arch. Dermatol.* 1994; 130: 1379–82.
41 Scully G, El-Kom M. Lichen planus: review and update on pathogenesis. *J. Oral Pathol.* 1985; 14: 431–58.
42 Kutting B, Bohm M, Luger TA, Bonsmann G. Oropharyngeal lichen planus associated with interferon-alpha treatment for mycosis fungoides: a rare side-effect in the therapy of cutaneous lymphomas. *Br. J. Dermatol.* 1997; 137: 836–7.
43 Lewis FM. Vulval lichen planus. *Br. J. Dermatol.* 1998; 138: 569–75.
44 Bobadilla J, van der Hulst RW, ten Kate FJ, Tytgat GN. Esophageal lichen planus. *Gastrointest. Endosc.* 1999; 50: 268–71.
45 Eisen D. The evaluation of cutaneous, genital, scalp, nail, esophageal, and ocular involvement in patients with oral lichen planus. *Oral Surg. Oral Med. Oral Pathol. Oral Radiol. Endod.* 1999; 88: 431–6.
46 Sharma R, Singhal N. Lichen planus of the eyelids. A report of 5 cases. *Dermatol. Online J.* 2001; 7: 5.
47 Abraham SC, Ravich WJ, Anhalt GJ, Yardley JH, Wu TT. Esophageal lichen planus: case report and review of the literature. *Am. J. Surg. Pathol.* 2000; 24: 1678–82.
48 Nagao Y, Tomonari R, Kage M *et al.* The possible intraspousal transmission of HCV in terms of lichen planus. *Int. J. Mol. Med.* 2002; 10: 569–73.
49 Rebora A, Patri P, Rampini E. Erosive lichen planus and cirrhotic hepatitis. *Ital. Gen. Rev. Dermatol.* 1978; 15: 23–31.
50 Divano MC, Parodi A, Rebora A. Lichen planus, liver kidney microsomal (LKM1) antibodies and hepatitis C virus antibodies. *Dermatology* 1992; 185: 132–3.
51 Rebora A, Robert E, Rongioletti F. Clinical and laboratory presentation of lichen planus patients with chronic liver disease. *J. Dermatol. Sci.* 1992; 4: 38–41.
52 Bagan JV, Aguirre J, del Olmo JA *et al.* Oral lichen planus and chronic hepatitis disease: a clinical and morphometric study of the oral lesions in relation to transaminase elevation. *Oral Surg. Oral Med. Oral Pathol.* 1994; 78: 337–42.
53 Cribier B, Garnier C, Laustriat D, Heid E. Lichen planus and hepatitis C virus infection: an epidemiology study. *J. Am. Acad. Dermatol.* 1994; 31: 1070–2.
54 Gandolfo S, Carbone M, Carrozzo M, Gallo V. Oral lichen planus and hepatitis C virus (HCV) infection: is there a relationship? A report of 10 cases. *J. Oral Pathol. Med.* 1994; 23: 119–22.
55 Jubert C, Pawlotsky JM, Pouget F *et al.* Lichen planus and hepatitis C virus-related chronic active hepatitis. *Arch. Dermatol.* 1994; 130: 73–6.
56 Bellman B, Reddy RK, Falanga V. Lichen planus associated with hepatitis C. *Lancet* 1995; 346: 1234.
57 Nagao Y, Sata M, Tanikawa K, Itoh K, Kameyama T. Lichen planus and hepatitis C virus in the Northern Kyushu region of Japan. *Eur. J. Clin. Invest.* 1995; 25: 910–14.
58 Tanei R, Watanabe K, Nishiyama S. Clinical and histopathologic analysis of the relationship between lichen planus and chronic hepatitis C. *J. Dermatol.* 1995; 22: 316–23.
59 Carrozzo M, Gandolfo S, Carbone M *et al.* Hepatitis C virus infection in Italian patients with oral lichen planus: a prospective case-control study. *J. Oral Pathol. Med.* 1996; 25: 527–33.
60 Sanchez-Perez J, Castro De M, Buezo GF *et al.* Lichen planus and hepatitis C virus: prevalence and clinical presentation of patients with lichen planus and hepati-

tis C virus infection. *Br. J. Dermatol.* 1996; 134: 715–19.
61 Bagan JV, Ramon C, Gonzales L *et al.* Preliminary investigation of the association of oral lichen planus and hepatitis. *Oral Surg. Oral Med. Oral Pathol. Oral Radiol. Endod.* 1998; 85: 532–6.
62 Dupin N, Chosidow O, Lunel F, Fretz C, Szpirglas H, Frances C. Oral lichen planus and hepatitis C virus infection: a fortuitous association? *Arch. Dermatol.* 1997; 133: 1052–3.
63 Imhof M, Popal H, Lee JH, Zeuzem S, Millbradt R. Prevalence of hepatitis C virus antibodies and evaluation of hepatitis C virus genotypes in patients with lichen planus. *Dermatology* 1997; 195: 1–5.
64 Dupond AS, Lacour JP, Lafont C, Ortonne JP. Prevalence of hepatitis C virus in oral erosive lichen. *Ann. Dermatol. Venereol.* 1998; 125: 676–8.
65 Grote M, Reichart PA, Berg T, Hopf U. Hepatitis C virus (HCV)-infection and oral lichen planus. *J. Hepatol.* 1998; 29: 1034–5.
66 Ilter N, Senol E, Gurer MA, Altay O. Lichen planus and hepatitis C-virus infection in Turkish patients. *J. Eur. Acad. Dermatol. Venereol.* 1998; 10: 192–3.
67 Ingafou M, Porter SR, Scully C, Teo C. No evidence of HCV infection or liver disease in British patients with oral lichen planus. *Int. J. Oral Maxillofac. Surg.* 1998; 27: 65–6.
68 Mignogna MD, Lo Muzio L, Favia G, Mignogna RE, Carbone R, Bucci E. Oral lichen planus and HCV infection: a clinical evaluation of 263 cases. *Int. J. Dermatol.* 1998; 37: 575–8.
69 Chuang TY, Stitle L, Brashear R, Lewis C. Hepatitis C virus and lichen planus. A case-control study of 340 patients. *J. Am. Acad. Dermatol.* 1999; 41: 787–9.
70 Tucker SC, Coulson IH. Lichen planus is not associated with hepatitis C virus infection in patients from north west England. *Acta Derm. Venereol.* 1999; 79: 378–9.
71 Roy KM, Dickson EM, Staines KS, Bagg J. Hepatitis C virus and oral lichen planus/lichenoid reactions: lack of evidence for an association. *Clin. Lab.* 2000; 46: 251–4.
72 van der Meij EH, van der Waal I. Hepatitis C virus infection and oral lichen planus: a report from the Netherlands. *J. Oral Pathol. Med.* 2000; 29: 255–8.
73 Kirtak N, Inalöz HS, Özgöztasi O, Erbagci Z. The prevalence of hepatitis C virus infection in patients with lichen planus in Gaziantep region of Turkey. *Eur. J. Epidemiol.* 2000; 16: 1159–61.
74 Beaird LM, Kahloon N, Franco J, Fairley JA. Incidence of hepatitis C in lichen planus. *J. Am. Acad. Dermatol.* 2001; 44: 311–12.
75 Chainani-Wu N, Silverman S Jr, Lozada-Nur F, Mayer P, Watson JJ. Oral lichen planus: patient profile, disease progression and treatment responses. *J. Am. Dent. Assoc.* 2001; 132: 901–9.
76 Erkek E, Bozdogan Ö, Olut AI. Hepatitis C virus infection prevalence in lichen planus: examination of lesional and normal skin of hepatitis C virus-infected patients with lichen planus for the presence of hepatitis C virus RNA. *Clin. Exp. Dermatol.* 2001; 26: 540–4.
77 Eisen D. The clinical features, malignant potential, and systemic associations of oral lichen planus: a study of 723 patients. *J. Am. Acad. Dermatol.* 2002; 46: 207–14.
78 Daramola OO, George AO, Ogunbiyi AO. Hepatitis C virus and lichen planus in Nigerians: any relationship? *Int. J. Dermatol.* 2002; 41: 217–19.
79 Figueiredo LC, Carrilho FJ, de Andrage HF, Migliari DA. Oral lichen planus and hepatitis C virus infection. *Oral Dis.* 2002; 8: 42–6.
80 Garg VK, Karki BM, Agrawal S, Agarwalla A, Gupta R. A study from Nepal showing no correlation between lichen planus and hepatitis B and C viruses. *J. Dermatol.* 2002; 29: 411–13.
81 Mignogna MD, Fedele S, Lo Russo L, Ruoppo E, Adamo D, Lo Muzio L. Extrahepatic manifestations of hepatitis C virus infection: the slowly unraveling picture of oral lichen planus. *J. Hepatol.* 2002; 3: 412–13.
82 Cohen J. The scientific challenge of hepatitis C. *Science* 1999; 285: 26–30.
83 Frank C, Mohamed MK, Strickland GT *et al.* The role of parenteral antischistosomal therapy in the spread of hepatitis C virus in Egypt. *Lancet* 2000; 355: 887–91.
84 Schmunis GA, Zicker F, Pinheiro F, Brandling-Bennett D. Risk for transfusion-transmitted infectious diseases in Central and South America. *Emerg. Infect. Dis.* 1998; 4: 5–11.
85 Kiyosawa K, Tanaka E. Characteristics of hepatocellular carcinoma in Japan. *Oncology* 2002; 62: 5–7.
86 Higuchi M, Tanaka E, Kiyosawa K. Epidemiology and clinical aspects on hepatitis C. *Jpn. J. Infect. Dis.* 2002; 55: 69–77.
87 Coates EA, Walsh L, Logan R. The increasing problem of hepatitis C virus infection. *Aust. Dent. J.* 2000; 46: 13–17.
88 Henderson L, Muir M, Mills PR *et al.* Oral health of patients with hepatitis C virus infection: a pilot study. *Oral Dis.* 2001; 7: 271–5.
89 Mignogna MD, Fedele S, Lo Russo L, Ruoppo E, Lo Muzio L. Unexpected low incidence of oral lichen planus in an HCV hyperendemic area of southern Italy. *Gastroenterology* 2001; 121: 1528–9.
90 Nagao Y, Tanaka J, Nakanishi T *et al.* High incidence of extrahepatic manifestations in an HCV hyperendemic area. *Hepatol. Res.* 2002; 22: 27–36.
91 Carrozzo M, Francia Di Celle P, Gandolfo S *et al.* Increased frequency of HLA-DR6 allele in Italian patients with hepatitis C virus-associated oral lichen planus. *Br. J. Dermatol.* 2001; 144: 803–8.
92 Sata M, Nakano H, Suzuki H *et al.* Sero-epidemiologic study of hepatitis C virus infection in Fukuoka, Japan. *J. Gastroenterol.* 1998; 33: 218–22.
93 Nagao Y, Fukuizumi K, Kumashiro R, Tanaka K, Sata M. The prognosis for life in an HCV hyperendemic area. *Gastroenterology* 2003; 125: 628–9.
94 Simmonds P, Alberti A, Alter HJ *et al.* A proposed system for the nomenclature of hepatitis C viral genotypes. *Hepatology* 1994; 19: 1321–4.
95 Okamoto H, Sugiyama Y, Okada S *et al.* Typing hepatitis C virus by polymerase chain reaction with type-specific primers; application to clinical surveys and tracing infectious sources. *J. Gen. Virol.* 1992; 73: 673–9.
96 Tanaka T, Tsukiyama-Kohara K, Yamaguchi K *et al.* Significance of specific antibody assay for genotyping of hepatitis C virus. *Hepatology* 1994; 19: 1347–53.
97 Pawlotsky JM, Benchiki H, Pellet C *et al.* Lichen planus and hepatitis C virus (HCV)-related chronic hepatitis:

evaluation of HCV genotype. *Br. J. Dermatol.* 1995; 133: 666–7.
98 Nagao Y, Sata M, Itoh K, Tanikawa K, Kameyama T. Quantitative analysis of HCV RNA and genotype in patients with chronic hepatitis C accompanied by oral lichen planus. *Eur. J. Clin. Invest.* 1996; 26: 495–8.
99 Lodi G, Carrozzo M, Hallett R *et al.* HCV genotypes in Italian patients with HCV-related oral lichen planus. *J. Oral Pathol. Med.* 1997; 26: 381–4.
100 Sanchez-Perez J, Moreno-Otero R, Borque MJ, Rios-Buceta L, Garcia-Diez A. Lichen planus and hepatitis C virus infection: a clinical and virologic study. *Acta Derm. Venereol.* 1998; 78: 305–6.
101 Nagao Y, Sata M, Abe K, Tanikawa K, Kameyama T. Immunological evaluation in oral lichen planus with chronic hepatitis C. *J. Gastroenterol.* 1997; 32: 324–9.
102 Rebora A. Lichen planus and the liver. *Lancet* 1981; 1: 805–6.
103 Rebora A, Rongioletti F. Lichen planus and chronic active hepatitis. *J. Am. Acad. Dermatol.* 1984; 10: 840–1.
104 Lo Muzio L, Mignogna MD, Favia G, Procaccini M, Testa NF, Bucci E. The possible association between oral lichen planus and oral squamous cell carcinoma: a clinical evaluation on 14 cases and a review of the literature. *Oral Oncol.* 1998; 34: 239–46.
105 Kirby AC, Lodi GL, Olsen I, Porter SR. Immunohistochemical and serological comparison of idiopathic and hepatitis C virus-associated forms of oral lichen planus. *Eur. J. Oral Sci.* 1998; 106: 853–62.
106 Romero MA, Seoane J, Varela-Centelles P, Diz-Dios P, Otero XL. Clinical and pathological characteristics of oral lichen planus in hepatitis C-positive and -negative patients. *Clin. Otolaryngol.* 2002; 37: 22–6.
107 Nagao Y, Sata M, Kage M, Kameyama T, Ueno T. Histopathological and immunohistochemical study of oral lichen planus-associated HCV infection. *Eur. J. Int. Med.* 2000; 11: 277–82.
108 Mega H, Jiang WW, Takagi M. Immunohistochemical study of oral lichen planus associated with hepatitis C virus infection, oral lichenoid contact sensitivity reaction and idiopathic oral lichen planus. *Oral Dis.* 2001; 7: 296–305.
109 Doutre MS, Beylot C, Couzigou P, Long P, Royer P, Beylot J. Lichen planus and virus C hepatitis: disappearance of the lichen under interferon alfa therapy. *Dermatology* 1992; 184: 229.
110 Boccia S, Gamberini S, Dalla Libera M, Strumia R, Venturini D. Lichen planus and interferon therapy for hepatitis C. *Gastroenterology* 1993; 105: 1921–2.
111 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.
112 Nagao Y, Sata M, Ide T *et al.* Development and exacerbation of oral lichen planus during and after interferon therapy for hepatitis C. *Eur. J. Clin. Invest.* 1996; 26: 1171–4.
113 Schlesinger TE, Camisa C, Gay JD, Bergfeld WF. Oral erosive lichen planus with epidermolytic hyperkeratosis during interferon alfa-2b therapy for chronic hepatitis C virus infection. *J. Am. Acad. Dermatol.* 1997; 36: 1023–5.
114 Dalekos GN, Christodoulou D, Kistis KG, Zervou EK, Hatzis J, Tsianos EV. A prospective evaluation of dermatological side-effects during alpha-interferon therapy for chronic viral hepatitis. *Eur. J. Gastroenterol. Hepatol.* 1998; 10: 933–9.
115 Protzer U, Ochsendorf FR, Leopolder-Ochsendorf A, Holtermuller KH. Exacerbation of lichen planus during interferon alfa-2a therapy for chronic active hepatitis C. *Gastroenterology* 1993; 104: 903–5.
116 Nagao Y, Sata M, Suzuki H, Kameyama T, Ueno T. Histological improvement of oral lichen planus in patients with chronic hepatitis C treated with interferon. *Gastroenterology* 1999; 117: 283–4.
117 Nagao Y, Sata M, Fukuizumi K, Harada H, Kameyama T. Oral cancer and hepatitis C virus (HCV): can HCV alone cause oral cancer? A case report. *Kurume Med. J.* 1996; 43: 97–100.
118 Johnson RJ, Gretch DR, Couser WG *et al.* Hepatitis C virus-associated glomerulonephritis. Effect of alpha-interferon therapy. *Kidney Int.* 1994; 46: 1700–4.
119 Yamabe H, Johnson RJ, Gretch DR *et al.* Membranoproliferative glomerulonephritis associated with hepatitis C virus infection responsive to interferon alpha. *Am. J. Kidney Dis.* 1995; 25: 67–9.
120 Lopes E, Lopes LV, Silva AE. Mixed cryoglobulinemia and membranoproliferative glomerulonephritis associated with hepatitis C virus infection. *Ann. Intern. Med.* 1996; 125: 781–2.
121 Misiani R, Bellavita R, Fenili D *et al.* Interferon alpha-2a therapy in cryogloblinemia associated with hepatitis C virus. *N. Engl. J. Med.* 1994; 330: 751–6.
122 Ohta S, Yokoyama H, Wada T *et al.* Exacerbation of glomerulonephritis in subjects with chronic hepatitis C virus infection after interferon therapy. *Am. J. Kidney Dis.* 1999; 33: 1040–8.
123 Takikawa H, Yamazaki R, Shoji S, Miyake K, Yamanaka M. Normalization of urinary porphyrin level and disappearance of skin lesions after successful interferon therapy in a case of chronic hepatitis C complicated with porphyria cutanea tarda. *J. Hepatol.* 1995; 22: 249–50.
124 Okano J, Horie Y, Kawasaki H, Kondo M. Interferon treatment of porphyria cutanea tarda associated with chronic hepatitis type C. *Hepatogastroenterology* 1997; 44: 525–8.
125 Sheikh MY, Wright RA, Burruss JB. Dramatic resolution of skin lesions associated with porphyria cutanea tarda after interferon-alpha therapy in a case of chronic hepatitis C. *Dig. Dis. Sci.* 1998; 43: 529–33.
126 Furuta M, Kaito M, Gabazza E *et al.* Ineffective interferon treatment of chronic hepatitis C-associated porphyria cutanea tarda, but with a transient decrease in HCV RNA levels. *J. Gastroenterol.* 2000; 35: 60–2.
127 Zuckerman E, Zuckerman T, Sahar D *et al.* The effect of antiviral therapy on t(14;18) translocation and immunoglobulin gene rearrangement in patients with chronic hepatitis C virus infection. *Blood* 2001; 97: 1555–9.
128 Hermine O, Lefrere F, Bronowicki JP *et al.* Regression of splenic lymphoma with villous lymphocytes after treatment of hepatitis C virus infection. *N. Engl. J. Med.* 2002; 347: 89–94.
129 Silverman S Jr, Gorsky M, Lozada-Nur F, Giannotti K. A prospective study of findings and management in 214 patients with oral lichen planus. *Oral Surg. Oral Med. Oral Pathol.* 1991; 72: 665–70.

130 Barnard NA, Scully C, Eveson JW, Cunningham S, Porter SR. Oral cancer development in patients with oral lichen planus. *J. Oral Pathol. Med.* 1993; 22: 421–4.
131 Markopoulos AK, Antoniades D, Papanayotou P, Trigonidis G. Malignant potential of oral lichen planus: a follow-up study of 326 patients. *Oral Oncol.* 1997; 33: 263–9.
132 Mignogna MD, Lo Muzio L, Lo Russo L, Fedele S, Ruoppo E, Bucci E. Clinical guidelines in early detection of oral squamous cell carcinoma arising in oral lichen planus: a 5-year experience. *Oral Oncol.* 2001; 37: 262–7.
133 Porter SR, Lodi G, Chandler K, Kumar N. Development of squamous cell carcinoma in hepatitis C virus-associated lichen planus. *Oral Oncol.* 1997; 33: 58–89.
134 Sigurgeirsson B, Lindelöf B. Lichen planus and malignancy: an epidemiologic study of 2071 patients and a review of the literature. *Arch. Dermatol.* 1991; 127: 1684–8.
135 Ferri C, Caracciolo F, Zignego AL *et al.* Hepatitis C virus infection in patients with non-Hodgkin's lymphoma. *Br. J. Haematol.* 1994; 88: 392–4.
136 Ferri C, La Civita L, Monti M *et al.* Can type C hepatitis infection be complicated by malignant lymphoma? *Lancet* 1995; 346: 1426–7.
137 Sikuler E, Shnaider A, Zilberman D *et al.* Hepatitis C virus infection and extrahepatic malignancies. *J. Clin. Gastroenterol.* 1997; 24: 87–9.
138 Yoshida M, Nagao Y, Sata M, Kusukawa J, Kameyama T. Multiple primary neoplasms and HCV infection in oral cancer patients. *Hepatol. Res.*, 1997; 9: 75–81.
139 Nagao Y, Sata M, Kameyama T. Hepatitis C virus RNA detection in oral lichen planus tissue. *Am. J. Gastroenterol.*, 1998; 93: 850.
140 Nagao Y, Sata M, Noguchi S *et al.* Detection of hepatitis C virus RNA in oral lichen planus and oral cancer tissues. *J. Oral Pathol. Med.*, 2000; 29: 259–66.
141 Arrieta JJ, Rodriguez-Inigo E, Casqueiro M *et al.* Detection of hepatitis C virus replication by in situ hybridization in epithelial cells of anti-hepatitis C virus-positive patients with and without oral lichen planus. *Hepatology 2000*, 2000; 32: 97–103.
142 Carrozzo M, Quadri R, Latorre P *et al.* Molecular evidence that the hepatitis C virus replicates in the oral mucosa. *J. Hepatol.* 2002; 37: 364–9.
143 Mangia A, Andriulli A, Zenarola P *et al.* Lack of hepatitis C virus replication intermediate RNA in diseased skin tissue of chronic hepatitis C patients. *J. Med. Virol.* 1999; 59: 277–80.
144 Pilli M, Penna A, Zerbini A *et al.* Oral lichen planus pathogenesis: a role for the HCV-specific cellular immune response. *Hepatology* 2002; 36: 1446–52.
145 De Vita S, Sansonno D, Dolcetti R *et al.* Hepatitis C virus within a malignant lymphoma lesion in the course of type II mixed cryoglobulinemia. *Blood* 1995; 86: 1887–92.
146 Tanaka H, Tsukuma H, Teshima H *et al.* Second primary cancers following non-Hodgkin's lymphoma in Japan: increased risk of hepatocellular carcinoma. *Jpn. J. Cancer Res.* 1997; 88: 537–42.
147 De Vita S, Sacco C, Sansonno D *et al.* Characterization of overt B-cell lymphomas in patients with hepatitis C virus infection. *Blood* 1997; 90: 776–82.
148 Pileri P, Uematsu Y, Campagnoli S *et al.* Binding of hepatitis C virus to CD81. *Science* 1998; 282: 938–41.
149 Kanto T, Hayashi N, Takehara T *et al.* Impaired allostimulatory capacity of peripheral blood dendritic cells recovered from hepatitis C virus-infected individuals. *J. Immunol.* 1999; 162: 5584–91.
150 Franzin F, Efremov DG, Pozzato G, Tulissi P, Batista F, Burrone OR. Clonal B-cell expansions in peripheral blood of HCV-infected patients. *Br. J. Haematol.* 1995; 90: 548–52.
151 Silvestri F, Pipan C, Barillari G *et al.* Prevalence of hepatitis C virus infection in patients with lymphoproliferative disorders. *Blood* 1996; 87: 4296–301.
152 Nagao Y, Sata M, Noguchi S *et al.* Various extrahepatic manifestations caused by hepatitis C virus infection. *Int. J. Mol. Med.* 1999; 4: 621–5.

A cohort study of chronic liver disease in an HCV hyperendemic area of Japan: a prospective analysis for 12 years

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Abstract. A mass screening in 1990 of H town in Japan demonstrated a high prevalence of hepatitis C virus (HCV) infection in our previous studies. The purpose of the present study was to evaluate the prognosis and natural history of liver disease among the same residents after 12 years. Of 509 residents, 69 people had died, and 55 people had moved to other regions. In all, 139 persons of the remaining 385 residing in H town were examined for liver function tests, antibodies to HCV (anti-HCV), serum HCV RNA, and hepatitis B virus surface antigen (HBsAg). The data of 14 of these 385 people were collected from medical records. The cause of death of the 69 individuals was investigated. The prognosis of liver disease could be clarified after 12 years in 222 of the 509 residents. Most of the residents with liver disease had an advanced stage of disease. Of the 69 persons who died, the mortality rate caused by liver cirrhosis or hepatocellular carcinoma (HCC) was 44 and 53%, respectively, among 25 persons with positive anti-HCV, and 19 with positive HCV RNA. One person with positive HBsAg died of HCC. Persons with chronic HCV or HBV infection had significantly higher mortality rates from liver cirrhosis and HCC than those without infection ($P<0.00001$). The present study suggests that early detection and treatment for HCC should be carried out as HCV carriers age. Furthermore, persistent HCV carriers should receive therapy for suppression of the development of HCC. The eradication of HCC should be considered a national goal.

Introduction

Hepatitis C virus (HCV) is recognized as a major threat to global public health. Although representative prevalence data are not available from many countries, the available data indicate that ~3% of the world's population is infected with HCV. It is estimated that ~170 million people worldwide are infected with HCV (1), of whom some 2 million (1%) reside in Japan (2,3). HCV leads to serious consequences such as liver cirrhosis and hepatocellular carcinoma (HCC) (4,5). Of the HCC cases in Japan, ~16% is caused by hepatitis B virus (HBV) infection and ~80% by HCV infection. The growing incidence of HCC is expected to reach a plateau around the year 2015, and then to start to decrease according to the study of Yoshizawa (2).

Up to now we have continued carrying out health screenings of the residents of H town (adult population: 7,389) (Fig. 1), Fukuoka prefecture in northern Kyushu, Japan where the prevalence of HCV infection is the highest in the country (6). We previously reported that the town had a high prevalence of HCV carriers, and that HCV infection was the principal cause of liver disorders (7-13). In 1990, 10% (739 people) of the 7,389 inhabitants were randomly selected, and as a result, 509 subjects participated in the study for examination of liver diseases accompanying HCV or HBV infections. In the study, the positive findings of antibodies to HCV (anti-HCV), HCV RNA, and hepatitis B surface antigen (HBsAg) were 23.6 (120/509), 17.9 (91/509), and 2.6% (13/509), respectively (7).

In the present study, we conducted cohort studies from August 1990 to May 2002 on the long-term prognosis of HCV carriers with the same subjects in the town and investigated risk factors for deaths due to HCC and liver cirrhosis.

Materials and methods

Subjects. Of the 509 subjects, 69 people had died, and 55 people had moved to other regions. Thus, just 385 people of the original subjects resided in H town in May 2002. Of these 139 persons (51 men/88 women; mean age ± SD, 66.6±13.1) agreed to participate in the follow-up survey (Fig. 2). These 139 subjects were interviewed in person by 2 trained interviewers. The following items were questioned: present health condition, regular hospital visits, medical treatment received in the past 12 years in the hospital, the name of the family doctor, and the kind of medicine taken. The data of 14 of the 385 people were collected from their medical records. Informed consent was obtained from all residents after the purpose and methods of the study were explained.

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Abbreviations: HCV, hepatitis C virus; HBV, hepatitis B virus; anti-HCV, antibodies to HCV; HBsAg, hepatitis B virus surface antigen; HCC, hepatocellular carcinoma; IFN, interferon

Key words: hepatitis C virus (HCV), hepatocellular carcinoma (HCC), hyperendemic area, epidemiology, cohort prospective study

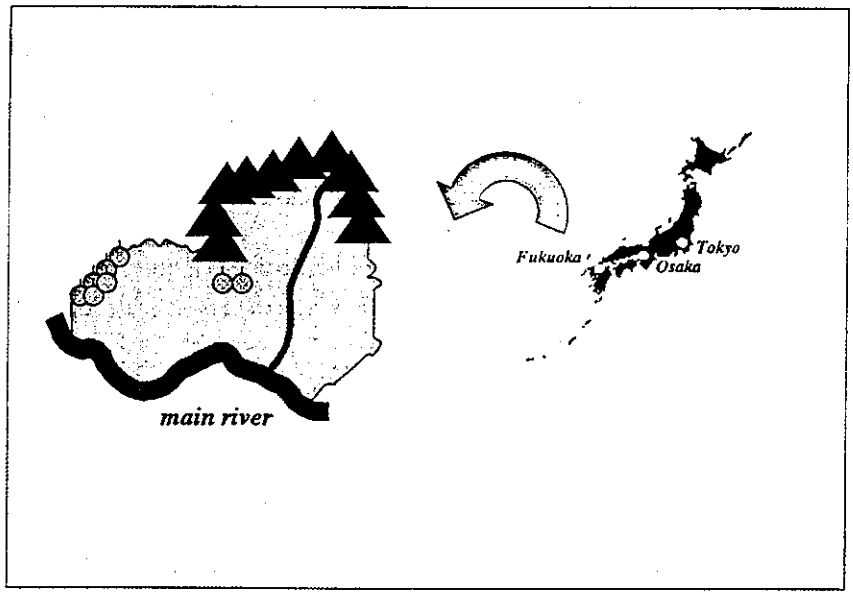

Figure 1. Location of H town of Fukuoka prefecture in northern Kyushu, Japan. The total area of the town is 44.98 km^2, and there are 7,389 adults in the population. Centering on the hot springs of the Chikugo River, production of fruit trees is a prosperous endeavor.

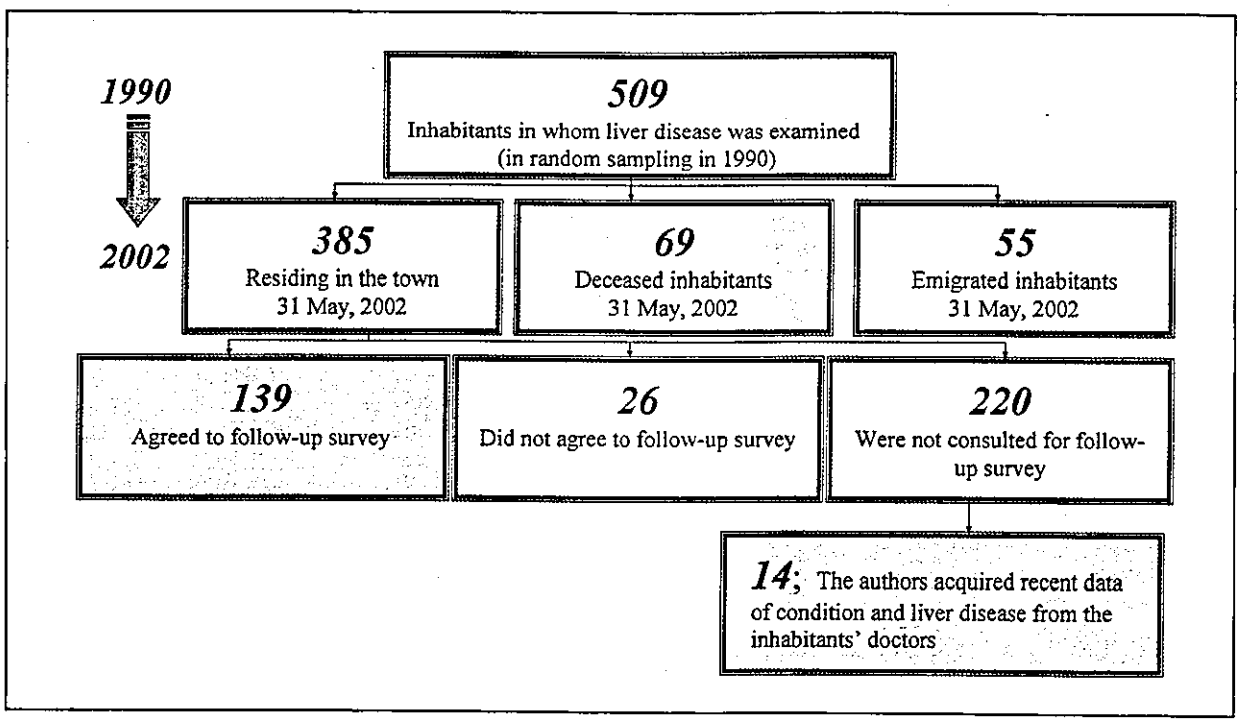

Figure 2. Diagram for pursuing the prognostic investigation of 509 inhabitants. Of the 509 subjects, 69 people had died, and 55 had moved to other regions by May 31, 2002. Thus, just 385 people of the original inhabitants investigated in 1990 resided in H town in May 2002. Of these 139 persons agreed to participate in the medical follow-up survey, but 26 did not agree. The remaining 220 inhabitants did not declare their intention either way. Among these 220 persons, data of 14 people were collected from their medical records. The cause of death of the 69 persons was investigated. Consequently, we were able to follow-up the outcome of liver diseases in 222 of the 509 original residents with or without liver diseases.

Examination for liver diseases. Sera from 139 residents were provided for the following liver function tests: serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ-glutamyl transpeptidase (γ-GTP), lactate dehydrogenase (LDH), total bilirubin (T.Bil), total protein (TP), albumin (Alb) and γ-globulin (γ-glob). Sera were also examined for the presence or absence of HCV or HBV infection. Anti-HCV was measured by a chemiluminescent enzyme immunoassay (CLEIA) kit (Lumipulse II HCV, Fujirebio Inc., Tokyo, Japan). HCV RNA in the sera was detected using the Amplicore HCV

Table I. Progression in 35 inhabitants with positive anti-HCV in 2002.

1990	1995	1999	2002	No.
+	ND	+	+	1
+	+	ND	+	11
+	+	+	+	22
-	+	+	+	1

+, positive; -, negative; ND, not done.

test (Nippon Roche, Tokyo, Japan). Hepatitis B virus surface antigen (HBsAg) was assayed by a chemiluminescent immunoassay (CLIA) kit (Architect™, HBsAg QT, Dainabot Co. Ltd., Tokyo, Japan). Ultrasonographic examination in subjects with abnormalities in the liver function tests and positive for anti-HCV or HBsAg was performed in order to investigate the shape of the liver and lesions occupying the hepatic space.

Data of 14 of the 385 persons who resided in H town were collected from their medical records.

Documentary notices to the residents. The detailed results of the liver disease tests and a letter of introduction to the medial office were mailed in written form to all the subjects who received the medical check-up.

Statistical analysis. The χ^2 test and the unpaired Student's t-test were used for statistical analyses. Differences were judged significant when $p<0.05$ (two-tailed).

Results

The prevalence of anti-HCV in 2002. Of the 139 subjects examined, those positive for anti-HCV, HCV RNA, and HBsAg were 25.2 (35/139), 15.1 (21/139), and 2.9% (4/139), respectively. When the data over time of 35 subjects with positive anti-HCV were compared, it was found that 34 persons continued being positive from 1990 (Table I). One person who was negative in 1990 was newly infected by 1995. Of the 35 subjects with positive anti-HCV (Table II), 26 persons (26/35, 74.3%) continued being positive or negative for HCV RNA, but 9 persons (9/35, 25.7%) showed changes in these indicators.

When HCV RNA changes between 1990 and 2002 were examined, it was found that of the 139 subjects (Table III), 3 of 24 persons with positive HCV RNA had received interferon (IFN) treatment. HCV RNA had become negative in only 1 of these 3 subjects due to IFN treatment.

The prevalence of the HCV infection classified by age. Fig. 3 shows the prevalence of HCV infection according to age, which compares the findings for 1990 and 2002. The highest rate of positive anti-HCV in both 1990 and 2002 was found in subjects aged 70-79 years. However, the highest rate of positive HCV RNA in 1990 was found in the group aged 70-79 years, while it was found in subjects >80 years, in 2002. Therefore, it appeared that the HCV carrier was aging.

Table II. Progression of HCV RNA in 35 inhabitants with positive anti-HCV.

	1990	1995	1999	2002	n	Total
+→+	+	ND	+	+	1	
	+	+	ND	+	6	19
	+	+	+	+	12	
+→-	+	ND	+	-	1	
	+	-	ND	-	1	
	+	-	-	-	2	5
	+	+	-	-	1	
-→+→-	-	+	-	-	2	2
-→+	-	+	ND	+	1	
	-	+	+	+	1	2
-→-	-	-	ND	-	2	
	-	-	-	-	5	7

+, positive; -, negative; ND, not done.

Table III. Comparison of HCV RNA in 1990 and 2002 for 139 inhabitants examined in 2002 in the town.

1990		2002
+/24[a]	→	+/19 (79.2%)
	→	-/5 (20.8%)
-/115	→	+/2 (1.7%)
	→	-/113 (98.3%)

+, positive; -, negative. [a]Three inhabitants of 24 HCV RNA positive inhabitants were treated by interferon (IFN) for chronic liver disease. The therapeutic response of one of them was judged as CR after IFN therapy. However, the others were judged as NR after therapy. The therapeutic response after IFN therapy was judged as: complete responder (CR), normal AST and ALT levels and HCV RNA-negative × ≥24 weeks; partial responder (PR), normal AST and ALT levels but HCV RNA-positive × ≥24 weeks; non-responder (NR), neither normal nor negative results × ≥24 weeks.

Moreover, there were no HCV carriers in subjects aged 30-39 years and 40-49 years of the subjects who participated in the study in 2002.

Analysis of cause of death of the 69 persons who died by May 31, 2002. Of the 509 inhabitants in whom liver diseases were examined in 1990, 69 (34 men/35 women; mean age at death, 76.6 years) had died by May 31, 2002 during the follow-up period (Fig. 2, Table IV). Of these 69, 36.2% (25/69) were positive for anti-HCV, 27.5% (19/69) for HCV RNA, and 1.4 % (1/69) for HBsAg. Anti-HCV, HCV RNA,

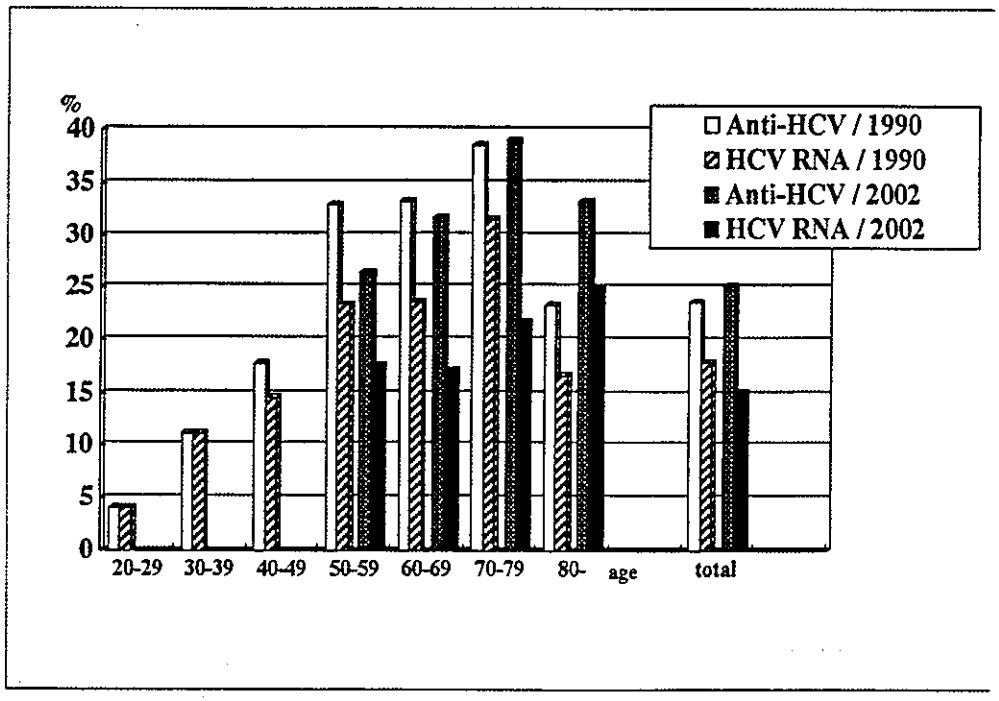

Figure 3. The rate of HCV infection according to age in the inhabitants in H town in 1990 and 2002. The highest rate of positive HCV RNA in 1990 was found in the group aged 70-79 years, while in 2002, it was in persons >80 years. Thus, the HCV carrier was aging. There were no 20-29-year-old among the residents who were consulted in the medical follow-up in 2002, because residents who were 20 years old in 1990 were 32 years old in 2002. Although 8 residents in the 30-39-year-old group and 21 residents in the 40-49-year-old group participated in the medical follow-up in 2002, all of these persons were negative for anti-HCV and HCV RNA.

Table IV. Characteristics of persons who died due to HCC or HCV-related liver cirrhosis of 69[a] inhabitants who died from 1990 to 2002.

	Total	HCC	LC	HCC or LC
n (%)	69	9 (13)	4 (5.8)	13 (18.9)
Average age	76.6	74	69.8	72.7
Sex (male/female)	34/35	6/3	3/1	9/4
Anti-HCV (+) (%)	25 (36.2)	8 (32.0)	3 (12.0)	11 (44.0)
HCV RNA (+) (%)	19 (27.5)	8 (42.1)	2 (10.5)	10 (52.6)
HBsAg (+) (%)	1 (1.4)	1 (100)	0 (0)	1 (100)
Anti-HCV(-) + HCV RNA(-) + HBsAg(-)(%)	43 (62.3)	0 (0)	1 (2.3)	1 (2.3)

[a]As shown in Fig. 3, of the 509 inhabitants examined for liver diseases in 1990, 69 had died by May 31, 2002 as found during the follow-up. [b]$p<0.05$, [c]$p<0.0001$, [d]$p<0.00001$.

and HBsAg were negative in 62.3% (43/69). Nine of these 69 people had died of HCC (6 men/3 women, mean age at death: 74 years) and 4 had died of liver cirrhosis (3 men/1 woman, mean age at death: 69.8 years).

Of the 25 people with positive anti-HCV, 11 (44.0%) had died of HCC or liver cirrhosis. Of the 19 people with positive HCV RNA, 10 (52.6%) had died of HCC or liver cirrhosis during the 12-year observation period. One person with positive HBsAg had died of HCC. Of the people with negative findings for anti-HCV, HCV RNA, and HBsAg, 1 had died of alcoholic liver cirrhosis (1/43, 2.3%). Persons with chronic HCV or HBV infection had significantly higher mortality rates from HCC and liver cirrhosis than persons who were not infected with HCV or HBV ($P<0.00001$).

Change of individuals with liver disease for 12 years. Of the 509 persons examined in 1990, the outcome of liver disease could be shown clearly in 222 residents in 2002 (Figs. 2 and 4).

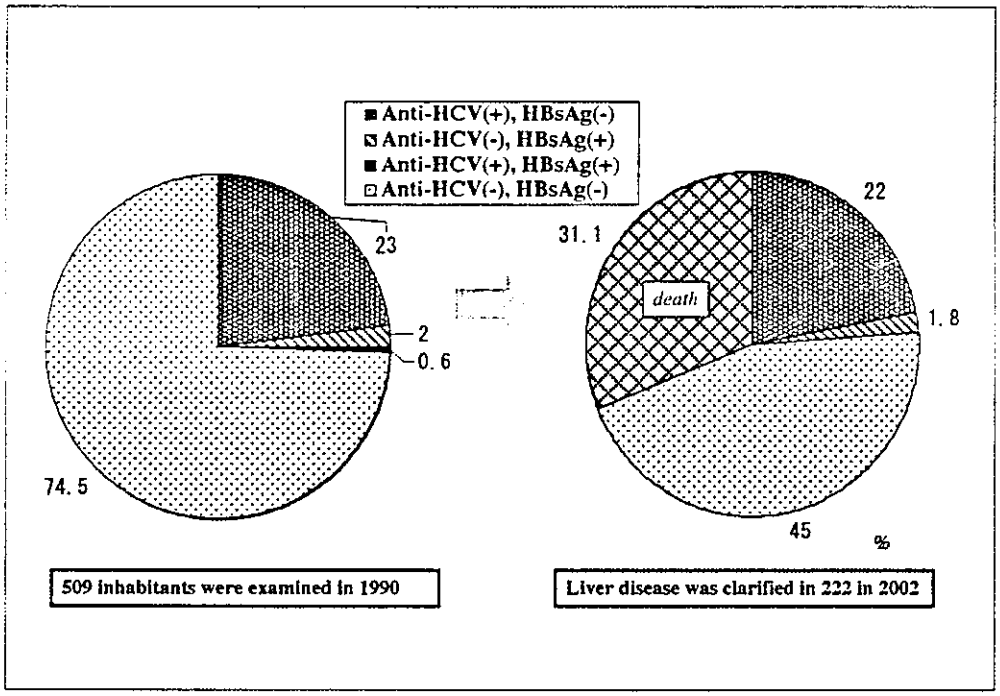

Figure 4. Patterns of liver disease in residents who received medical checkups in 1990. Of 509 persons examined in 1990, there were 222 residents in whom the outcome of liver disease could be clearly shown in 2002.

Table V. Twelve years after residents were diagnosed with past history of HCV infection in 1990.

1990	n		2002	n
Past history of HCV infection	31	→	Past history of HCV infection	11
		→	HCV-related ASC	1
		→	Normal	1
		→	Deceased	7
Anti-HCV (+), HCV RNA (-), HBsAg (-)			Cause of death Alcoholic LC (1) Other than liver disease (6)	
		→	Unknown liver disease due to non-participation in the follow-up survey	11

ASC, asymptomatic healthy carrier; LC-C, HCV-related liver cirrhosis; HCC, hepatocellular carcinoma.

These include the 139 persons who agreed to the follow-up survey, the 69 persons in whom the cause of death was clear, and 14 persons for whom we were able to collect their medical records from the family doctors. Of the 222 people, the rate of positive anti-HCV and negative HBsAg was 22%. On the other hand, the rate of positive HBsAg and negative anti-HCV was 1.8% (Fig. 4).

Meanwhile, how did the liver disease progress in the 12 years? Table V shows the distribution of the diagnosis of liver disease in 2002 among the persons diagnosed with past history of HCV infection (positive anti-HCV, negative HCV RNA, negative HBsAg, and normal liver function data) in 1990. Of 31 people diagnosed with a past history of HCV infection in 1990, the diagnosis of liver disease in 2002 was: those just with past history of HCV infection (n=11), asymptomatic healthy carrier (n=1), normal (n=1), deceased (n=7), and unknown liver disease due to non-participation in the follow-up survey (n=11). Among the 7 deceased, 1 died from alcoholic liver cirrhosis, and 6 persons died from causes other than liver disease. Of 18 persons diagnosed as HCV-related asymptomatic healthy carriers (positive anti-HCV, positive HCV RNA, negative HBsAg, and normal liver function data) in 1990, the diagnosis of liver diseases in 2002 was: past history of HCV infection only (n=4), chronic hepatitis C (n=3), death by causes other than liver disease (n=1), and unknown liver disease due to non-participation in the follow-up survey (n=10). Table VI shows the distribution of the diagnosis of liver disease in 2002 among the persons