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CASE REPORT

Adefovir Dipivoxil as a Treatment for Hepatic Failure Caused by Lamivudine-Resistant HBV Strains

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KEY WORDS: hepatitis B virus; hepatic failure; lamivudine; YMDD motif; adefovir dipivoxil; drug resistance.

Hepatitis B virus (HBV) infection is a serious worldwide problem because it is one of the major causes of cirrhosis and hepatocellular carcinoma in endemic areas. The number of people with chronic HBV infection is 350 million globally (1). Until recently, the therapeutic option for chronic HBV infection has been limited to interferon. Seroconversion from hepatitis B e antigen (HBeAg) to anti-hepatitis B e antibody (anti-HBe) occurs in up to about 40% of patients treated with interferon monotherapy (2–4).

Recently, lamivudine, a nucleoside analogue, has become the main therapeutic option for chronic HBV infection. Some clinical trials showed that lamivudine suppressed HBV replication effectively and induced histological improvement (5–7). However, the prolonged therapy with lamivudine has been associated with the emergence of drug-resistant viruses with the mutations in the polymerase gene coding for the YMDD (tyrosine, methionine, aspartate, aspartate) motif (8, 9). The lamivudine-resistant HBV strains have been observed in 14 to 32% of patients undergoing a 1-year treatment regimen of 100 mg daily (6, 7).

Several new nucleoside analogues are now under development. Adefovir dipivoxil, a prodrug of the acyclic deoxyadenosine monophosphate analogue adefovir, displays potent antiviral activity against HBV (10, 11) and an in vitro study demonstrated the antiviral activity to be against both wild-type and lamivudine-resistant strains of HBV (12). Recently, it was reported that rtN236T mutation conferred reduced susceptibility to adefovir dipivoxil and that the emegence of the mutation was limited to 1.6% during the 96-week observation (13). This mutation did not confer cross-resistance to lamivudine (14).

We report the case of a patient who successfully recovered from hepatic failure caused by lamivudine-resistant HBV strains by the additional treatment with adefovir dipivoxil.

CASE REPORT

A 52-year-old Japanese male patient was diagnosed as having HBV-related decompensated liver cirrhosis in 1996. At that time abdominal ultrasonography revealed ascites and gastrointestinalscopy showed esophageal varices, and he had a history of elevated serum alanine aminotransferase (ALT) and serum aspartate aminotransferase (AST) concentrations in 1998, before we were consulted. At Kurume University Hospital, lamivudine therapy was initiated on April 6, 1999.

Laboratory examinations at the initiation of lamivudine treatment (Table 1) revealed a platelet count of $7.6 \times 10^4/\mu l$, a serum ALT concentration of 41 U/L, a serum AST concentration of 40 U/L, and a HBV-DNA level of more than 8.8 log genome equivalent (LGE)/ml by transcription-mediated amplification (TMA) (14), and HBeAg was positive. Anti-hepatitis C antibody and antinuclear antibody were negative, the prothrombin activity was 57%, and abdominal ultrasonography showed an irregular surface of the liver, ascites, and mild splenomegaly.

The patient started to receive lamivudine at a dose of 150 mg daily. During the first year, the serum ALT and AST concentrations were within twice the upper limit of normal and the serum albumin concentration was improved, from 3.30 to 4.10 g/dl. The serum bilirubin concentration also improved, from 2.01 to 0.61 mg/dl. Although the HBV-DNA level was decreased to 5.5 LGE/ml, HBV-DNA and HBeAg were still positive through the 1-year treatment.

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TABLE 1. LABORATORY DATA

Date	RBC, 430–570 (10^4/mm^3)	WBC, 40–90 (10^2/mm^3)	Platelet, 13–36 (10^4/mm^3)	Prothrombin, 60–130 (%)	ALT, 8–42 (U/L)	Total protein, 6.7–8.3 (g/dl)	Albumin, 4.0–5.00 (g/dl)	Bilirubin, 0–1.50 (mg/dl)	HBV-DNA, <3.7 (LGE/ml)
6 Apr 99	376	76	6.7	55	39	6.3	3	1.41	8.7
9 May 00	469	59	11.6	70	306	6.35	3.75	0.67	8.6
23 Dec 00	270	41	2.1	20	35	7.4	3.43	11.6	7.8
23 Oct 01	253	52	3.1	29	36	6.78	2.23	8.27	8
5 Nov 02	441	44	11.5	72	19	8.3	3.6	1.31	5.2
1 July 03	517	35	15.5	80	25	8.05	4.32	0.68	3.9

Laboratory examinations on May 9, 2000, 13 months after the beginning of treatment, showed an elevation in the serum ALT and AST concentrations of 307 and 227 U/L, respectively. The patient was admitted to our hospital and treated with 100 ml of Strong Neo-Minophagen C (SNMC), an injection of a medicine that contains glycyrrhizin, and 600 mg of ursodesoxycholic acid (UDCA). The HBV-DNA level increased to a maximum of 8.6 LGE/ml. At the same time, the lamivudine-resistant HBV strains, the YIDD and YVDD mutants, were detected in the serum. The serum albumin concentration and prothrombin activity were gradually decreased to 3.05 g/dL and 46% on June 5. The serum ALT concentration decreased from a maximum of 307 to 49 U/L 1 month later. The patient was discharged and followed up as an outpatient every 2 weeks at our hospital. The SMNC dosage was reduced to 60 ml and continued daily together with 600 mg of UDCA.

On October 5, the patient visited another hospital with complaints of abdominal pain, abdominal distension, and jaundice. Laboratory examinations revealed a white blood cell total count of 8500/μl, with the differential count for neutrophils being 65%. The serum bilirubin concentration increased to 4.08 mg/dl. Abdominal ultrasonography showed massive ascites and their appearance was muddy. He was diagnosed as having spontaneous bacterial peritonitis.

Five days later, the patient was transferred to our hospital because of the progression of hepatic failure. Despite the administration of fresh-frozen plasma, human serum albumin, furocemide, and spironolactone, his liver function did not improve. The serum bilirubin concentration increased to 11.6 mg/dl and the prothrombin activity was 15% on December 23. In addition to 150 mg of lamivudine, he received 1500 mg of famciclovir daily and 1000 U of human anti-hepatitis B s immunoglobulin (HBIG) once a week from December 23. Despite additional treatment with antiviral agents, the HBV-DNA level did not decrease remarkably and the minimum HBV-DNA level was 7.0 LGE/ml during the 3 months of treatment with famciclovir and HBIG. Although the coagulation factors were replenished continuously, intestinal bleeding from esophageal varices occurred on February 18 and on April 2, 2001. Although the patient received 2 U of fresh-frozen plasma twice a week continuously up to August 2, 2001 the prothrombin activity did not exceed 30% and the serum albumin concentration was below 2.5 g/dl continuously.

From October 13, he was enrolled in a clinical trial at Queen Mary Hospital in Hong Kong and started to receive adefovir dipivoxil at a dose of 10 mg daily. Three months after the beginning of the additional treatment with adefovir dipivoxil, the HBV-DNA level decreased to a minimum of 5.0 LGE/mL, upon which his liver function improved gradually. The amount of infused fresh-frozen plasma was gradually decreased over a 2-month period and the prothrombin activity did not decline without replenishment of the coagulation factors 3 months after initiation of the administration of adefovir dipivoxil. Laboratory examinations on July 1, 2003, showed a serum ALT concentration of 27 U/L, a serum AST concentration of 25 U/L, a serum bilirubin concentration of 0.68 mg/dl, and a serum albumin concentration of 4.32 g/dl. The prothrombin activity recovered to 80% without replenishment of the coagulation factors. Although HBeAg has remained positive, the replication of HBV-DNA was suppressed to the range of 5.0 to 6.0 LGE/mL and the serum ALT and AST concentrations were controlled to within twice the upper limit of normal (Figure 1). And at the time of this last observation, the HBV-DNA level was decreased to 3.9 log copy/ml by quantification with Cobas Amplicor HBV monitor kits (Roche Molecular Systems, Inc., USA), although YIDD and YVDD mutants were detected in the serum. Now the patient is being checked every 4 weeks and is receiving combination therapy of lamivudine and adefovir dipivoxil as an outpatient. The serum ALT and the serum bilirubin concentrations have not flared up since adefovir dipivoxil was administrated. The side effect of adefovir dipivoxil, renal dysfunction, has not been observed during this treatment.

DISCUSSION

The clinical course after selection of the lamivudine-resistant HBV strains seems to be benign (16). However, in this case, hepatic failure developed after the emergence of lamivudine-resistant HBV strains, and in some reports, it is stated that hepatic failure and mortality developed after the breakthrough infection with lamivudine-resistant HBV strains (17, 18). We suggest that the reason hepatic failure developed in this patient may be that chronic liver disease had already progressed to decompensated liver cirrhosis at the initiation of lamivudine therapy and that his liver function had not recovered sufficiently during the 1-year treatment with lamivudine when the breakthrough hepatitis occurred.

In this case, famciclovir was administered for 3 months after the emergence of lamivudine-resistant HBV strains. However, efficacy was not observed and HBV replication was not sufficiently suppressed. In a recent study concerning combination therapy with lamivudine and famciclovir, the degree of HBV-DNA suppression was below 1.0-$\log_{10}$ in five patients with lamivudine-resistant HBV

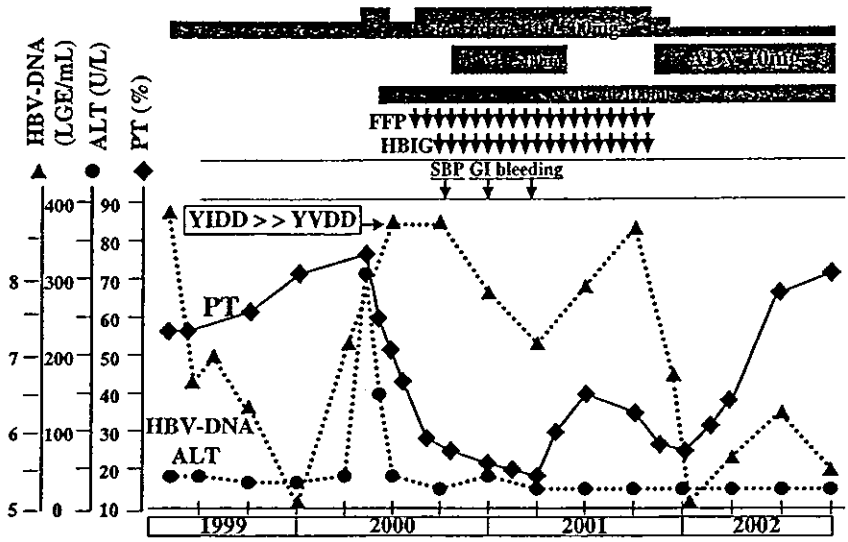

Fig 1. The clinical course of this patient. Circles express the serum alanine aminotransferase concentration and squares express the prothrombin activity. Triangles express the HBV-DNA level by the TMA method. Solid bars and arrows express the principal medications undergone in the clinical course. To the major complications which occurred in this clinical course, spontaneous bacterial peritonitis (SBP) and gastrointestinal bleeding (GI bleeding) were added. The lamivudine-resistant HBV strains, the YIDD and YVDD mutants, were detected in May 2000 and the serum HBV-DNA level increased to 8.6 LGE/ml at that time. Although the ALT concentration was improving after the flare-up of HBV-DNA, prothrombin activity did not exceed 30% until the initiation of adefovir dipivoxil. After the introduction of adefovir dipivoxil, prothrombin activity has been improving, with a decrease in HBV-DNA.

strains (19). Famciclovir seems to be ineffective in the treatment of breakthrough hepatitis caused by lamivudine-resistant HBV strains.

On the other hand, HBV replication was well suppressed with adefovir dipivoxil monotherapy in a clinical trial of adefovir monotherapy. The mean level of the decrease in HBV-DNA was 4.1-log in this recent study (20). Other research showed that adefovir dipivoxil demonstrated an antiviral effect on both wild-type and lamivudine-resistant strains of HBV (12, 21). Recently, it was reported that rtN236T mutation conferred reduced susceptibility to adefovir dipivoxil (13). However, the frequency of the emergence of the mutation was limited to 1.6% during the 96-week observation and the mutation remained susceptible to lamivudine (13, 14, 21). It is reported that in combination therapy with interferon and lamivudine, the emergence of lamivudine-resistant HBV strains was rare or nonexistent (22–24). Because of some side effects, such as thrombocytopenia and leukocytepenia, on occasion it is not suitable to administer interferon to patients with liver cirrhosis. For these reasons, we suggest that, for patients with liver cirrhosis, the emergence of lamivudine-resistant HBV strains in the serum may be a good indication to administer adefovir dipivoxil in addition to lamivudine. We speculate that hepatic regeneration is one of the reasons for this patient's recovery from hepatic failure. It is also known that lamivudine contributed to the histological improvement (25–27). We suppose that prolonged therapy with adefovir dipivoxil, too, may contribute to the improvement of hepatic inflammation and promote hepatic regeneration. When the HBV-DNA level decreased below 6.0 LGE/ml, the activity of hepatitis was sufficiently suppressed. So we suggest that it does not matter much whether or not lamivudine-resistant HBV strains exist in the serum and that the most important thing in the treatment of chronic HBV infection is to control viral replication.

Although our patient considered having a liver transplant on the basis of a relative donor, he gave it up because of the emergence of the lamivudine-resistant HBV strains. Taking the recovery from hepatic failure and the efficacy against HBV into consideration, he has no need for a liver transplant now. Adefovir dipivoxil may be useful for patients who are no longer candidates for liver transplantation because of lamivudine-resistant HBV strains.

In conclusion, the interesting aspects of this case are that prolonged treatment with adefovir dipivoxil made it possible for the patient to recover from his hepatic failure and that the continuation of treatment with lamivudine and adefovir dipivoxil has been sustaining the stable status of his liver function. Since patients with severe decompensated liver cirrhosis have more risk of developing hepatic

failure due to lamivudine-resistant HBV strain, combination therapy with lamivudine and adefovir dipivoxil seems to be more desirable than lamivudine monotherapy for patients with decompensated liver cirrhosis.

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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		

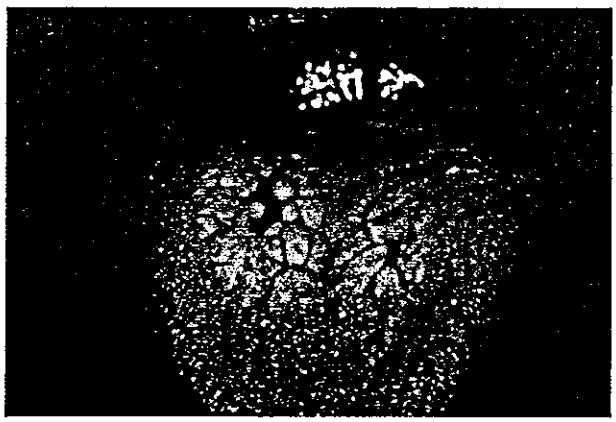

Figure 1 Lichen planus of the tongue; patient with chronic hepatitis C.

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*	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 (12.3)	4/84 (4.8)**	40 (21.1)	5/40 (12.5)	59 (100)	5/59 (8.5)
HCV-RNA(+) (%)	61 (8.9)	4/61 (6.6)***	31 (16.3)	5/31 (16.1)*	57 (96.6)	5/57 (8.8)
Anti-HCV(–) and HCV-RNA(–) (%)	591 (86.3)	6/591 (1.0)**,***	150 (78.9)	7/150 (4.7)*	0 (0)	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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Exacerbation of oral erosive lichen planus by combination of interferon and ribavirin therapy for chronic hepatitis C

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Abstract. Hepatitis C virus (HCV) induces extrahepatic manifestations such as oral lichen planus (OLP) as well as chronic liver diseases. The treatment of HCV-related chronic liver disease has evolved from the use of a single agent, mainly interferon (IFN), to the combination of IFN and ribavirin. We present a case of erosive OLP, cutaneous lichen planus (CLP), and leukoplakia of the vocal cord in a man with chronic hepatitis C infection treated with IFN and ribavirin. A 65-year-old man suffered from OLP before undergoing combination of IFN and ribavirin therapy for chronic hepatitis C. He was initially treated with IFNß (6 million units (MU) /day for 2 weeks), then a combination of IFNα-2b (6 MU/day for 2 weeks and 3 times a week for 14 weeks) and ribavirin (400-600 mg/day). The OLP lesion was not aggravated by application of steroids during the 7 weeks after the treatment, but after 18 weeks, the combination of IFN and ribavirin was stopped because of aggravation of the OLP. Elevated aminotransferase levels returned to normal during the therapy. But 7 weeks after discontinuation, aminotransferase levels rose to 10 times the normal range. Five months after discontinuation, the papules of CLP appeared. Eight months after discontinuation, the OLP erosion had gradually reduced, but some erosion remained. Aminotransferase levels were decreased, but serum HCV RNA had not disappeared. Caution should be exercised when IFN or ribavirin therapy is given to chronic hepatitis C patients with prior erosive OLP.

Introduction

It is thought that about 170 million people are infected with hepatitis C virus (HCV) worldwide, and 2 million people in Japan (1,2). HCV is recognized as a main major threat to global public health. HCV is a major cause of chronic hepatitis, liver cirrhosis, and hepatocellular carcinoma (HCC) (3,4). Moreover, HCV induces extrahepatic manifestations such as oral lichen planus (OLP) as well as chronic liver diseases (5,6). In some patients, treatment with a single agent, mainly interferon (IFN), or with a combination of IFN and ribavirin, leads to sustained eradication of the HCV (7). As regards the effects of IFN therapy on lichen planus (LP) lesions, there are several reports (8-22). We report the course of a patient with chronic hepatitis C who experienced the exacerbation of a severe OLP by combination therapy of IFN and ribavirin.

Materials and methods

On February 18, 2003, a 65-year-old Japanese man consulted the Digestive Disease Center of Kurume University for examination of chronic liver disease. He had chronic hepatitis at age 49, and had periodical blood tests and abdominal ultrasound exams by a family doctor, but did not receive treatment. Concerning his past history, the patient underwent an appendectomy at age 23. At ages 37 and 47, the patient underwent hemorrhoidectomy. Hypertension was noted at age 50, and antihypertensive treatment was started. There was no habitual alcohol drinking or smoking. The patient had discontinued smoking 13 years prior to presentation. There was no history of blood transfusion or tattoo, and his family history was not contributory. In 2002 (at age 64), the patient noted contact pain at in the left buccal mucosa, consulted a local otolaryngologic clinic and was treated under a diagnosis of ulcer, but there was repeated aggravation and resolution of the oral lesion without the patient ever recovering completely.

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Abbreviations: HCV, hepatitis C virus; LP, lichen planus; OLP, oral lichen planus; CLP, cutaneous lichen planus; IFN, interferon; anti-HCV, antibodies to HCV; HBsAg, hepatitis B virus surface antigen; HCC, hepatocellular carcinoma; MU, million units; RBC, red blood red cell; Hb, hemoglobin; WBC, white blood white cell; AST, aspartate aminotransferase; ALT, alanine aminotransferase; γ-GTP, gammaglutamyl transpeptidase; LDH, lactate dehydrogenase; ZTT, zinc sulfate turbidity test

Key words: hepatitis C virus, oral lichen planus, cutaneous lichen planus, interferon, ribavirin

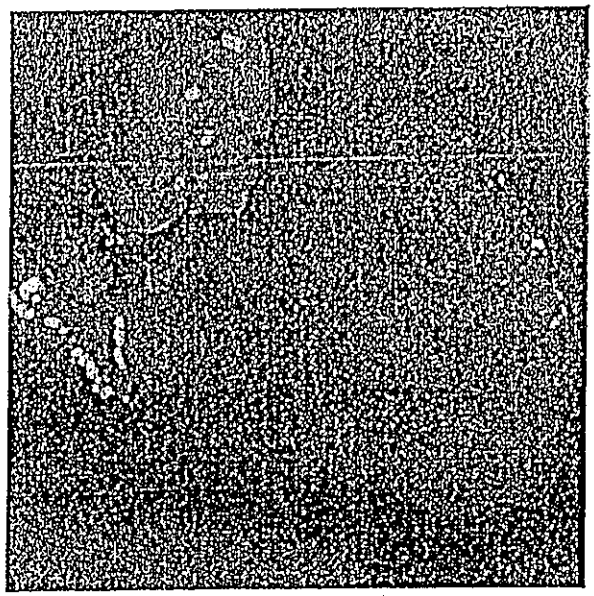

Figure 1. Lichen planus of the left buccal mucosa before administration of interferon and ribavirin as shown in Fig. 5A.

Among his physical findings, characteristic observations were an erosive type with white papules on his bilateral buccal mucosae, lower lip, and gingivae of the upper and lower molars (Fig. 1). Contact with most of the lesions caused mild contact pain. A biopsy specimen of his left buccal mucosa showed LP with parakeratosis and band-like lymphocytic infiltration. A physical examination by a dermatologist indicated that he did not have cutaneous LP (CLP) and genital LP.

Other findings were as follows: blood pressure, 150/100 mm Hg; pulse, 60/min; no anemia in the palpable conjunctiva; no jaundice in the bulbus conjunctiva; no findings such as palmar erythema, vascular spider and pitting edema of either leg or foot; no abnormalities in the heart and breath sounds; and no distention or fluctuation of the abdomen. The liver was palpable by one finger's breadth below the right costal margin, the liver edge was blunt and smooth, and its consistency was soft. The spleen was not palpable and the area of splenic dullness was widened.

Clinical examinations were as follows: the results of peripheral blood examination included red blood cells (RBC), $448 \times 10^4/mm^3$; hemoglobin (Hb), 15.9 g/dl; hematocrit, 44.3%; white blood cells (WBC), $6000/mm^3$ (Seg, 59.7%); and platelets, $14.4 \times 10^4/mm^3$. Blood chemistry tests on serum showed aspartate aminotransferase (AST), 57 IU/l; alanine aminotransferase (ALT), 96 IU/l; γ-glutamyl transpeptidase (γ-GTP), 44 IU/l; lactate dehydrogenase (LDH), 149 IU/l; zinc sulfate turbidity test (ZTT), 21.8; total bilirubin, 1.13 mg/dl; total protein, 7.68 g/dl; and albumin, 4.47 g/dl. Antibody to HCV (anti-HCV) was positive and serum HCV RNA was detected. The serum HCV RNA level quantified by Roche Amplicor Monitor assay and HCV genotype was 660 kIU/ml, and 1b, respectively. The serum was negative for hepatitis B surface antigen (HBsAg) and anti-nuclear antibody. Ultrasonographic examination, computerized tomography, and MRI scans of the abdomen performed in the outpatient clinic revealed a hepatic shape similar to that in chronic hepatitis, while multiple hemangiomas in segments eight (S8), five (S5), and six (S6), and liver cysts in S5 and S6 were observed as intrahepatic space-occupying lesions, but HCC was not observed. The spleen was enlarged. Regarding this patient who underwent liver biopsy, grading and staging of liver tissues were diagnosed as F2A1 according to the new Inuyama classification (23).

The patient was admitted to the Second Department of Medicine in our university hospital for treatment of chronic hepatitis C on April 9, 2003. The schedule of his treatment for chronic liver disease was as follows: initial administration of IFNβ [Feron®, at a dose of 6 million units (MU)/day] for 2 week, then administration of IFNα-2b (Intron A®, at a dose of 6 MU/day for 2 weeks and thereafter 3 times a week for 22 weeks) and ribavirin (600 mg/day for 24 weeks). On April 18, 2003, the patient started to receive injections of IFN, and started to take ribavirin at a dose of 600 mg/day from May 2. The dose of ribavirin was reduced to 400 mg/day from May 15 because of vomiting and anorexia, and ribavirin was discontinued for 3 weeks, from May 27 to June 17, because of anemia. At the beginning of May, hoarseness developed and it was diagnosed histopathologically as leukoplakia of the right vocal cord. He underwent inhalation therapy by nebulizer. The erosive OLP lesion was not widely aggravated by application of steroids agent during the 7 weeks after IFN

Figure 2. Exacerbation of lichen planus of the buccal mucosa and lip during administration of interferon and ribavirin as shown in Fig. 5B. The patient's oral pain and hemorrhagic crusts on the lower lip became severe and impaired his intake of food.