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CASE REPORT

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Treatment of refractory oral lichen planus using direct antiviral agents in a patient with chronic hepatitis C: A case report

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Abstract

Oral lichen planus (OLP) is a chronic inflammatory and immunologically mediated mucocutaneous disease with a high prevalence in hepatitis C virus (HCV)-infected patients. Interferon (IFN)-free direct-acting antiviral drugs (DAA) have been recommended for the treatment of patients with extrahepatic manifestations of HCV infection. Herein, we present the case of a 65-year-old woman who was diagnosed with OLP and chronic hepatitis C. She received DAA treatment with sofosbuvir (SOF) and ribavirin (RBA) at 75 years of age, which led to partial disappearance of the OLP and complete eradication of HCV. Thus, the patient was effectively treated without any major side effects.

KEYWORDS

direct-acting antivirals, extrahepatic manifestation, hepatitis C virus, oral lichen planus

1 | INTRODUCTION

Oral lichen planus (OLP) is a common mucocutaneous inflammatory disease with a low potential for malignant transformation.[1,2] Approximately 1%–2% of OLP cases develop into oral squamous cell carcinoma.[3] The precise cause of OLP remains uncertain, although it is believed to be an autoimmune disorder. Immune dysregulation is thought to play an important role in the development of this disease. T ($CD4^+$ and $CD8^+$) lymphocyte-mediated local immune responses have a major role in the pathogenesis of OLP; CD8+T-cells trigger the apoptosis of oral epithelial cells at the basal layer.[4–7]

Hepatitis C virus (HCV) infection is one of the major health problems worldwide for patients with chronic liver disease.[8] Globally, about 130-170 million people are infected with HCV, and approximately 3-4 million new cases of infection are reported every year.[9] In Japan, about 1.5 million people are chronically infected with HCV.[10] Treatment with interferon (IFN) has long been accepted as the standard therapy for the eradication of HCV.[11,12] In recent years, IFN-free direct-acting antivirals (DAA) with high sustained virological response (SVR) rates and few side effects are used for the treatment of hepatitis C markedly.[13–15]

HCV induces liver disease and disorders of other organs and tissues; additionally, it has been reported that HCV causes several extrahepatic manifestations, including mixed cryoglobulinemia, B-cell non-Hodgkin lymphoma, membranoproliferative glomerulonephritis, lichen planus, and porphyria cutanea tarda.[16–21] Epidemiological cohort studies in northern Kyushu[19–21] and Hiroshima[22,23] prefectures showed that approximately 10%–20% of Japanese individuals with HCV infection developed OLP.

While the mechanism of HCV-related OLP remains unknown, Nagao *et al* reported that single-nucleotide polymorphisms (SNPs) can be used to identify patients who are at risk for OLP in a genome-wide association study of Japanese patients with HCV infection, followed by a replication analysis in an Italian population.[24] The authors also reported the successful use of DAA in patients with HCV-associated OLP.[25–27] Several articles by other authors have

also documented the usefulness of DAA treatment in improving or resolving HCV-associated oral and cutaneous lichen planus.[28,29] Herein, we report a case of refractory OLP that had partially disappeared after eradication of HCV via DAA treatment, which was recommended to the patient by a dentist.

2 | CASE REPORT

A 65-year-old Japanese woman visited the Department of Oral and Maxillofacial Surgery of Yamaguchi University Hospital (Ube, Japan) in May 2009 with a complaint of discomfort and tingling sensations in the buccal mucosae on the left and right sides. Characteristic lacy white lesions were observed bilaterally on buccal mucosae, and the lesions were clinically and histopathologically diagnosed as OLP. The patient suffered from hepatitis C, but had never received antiviral treatment. Alternatively, anti-inflammatory therapy using ursodeoxycholic acid was provided to the patient for about 10 years. There was no history of blood transfusion, tattooing, injection drug use, smoking, or habitual alcohol consumption. Topical steroids were provided and a vitamin A agent was administered to the patient followed by the removal of the dental crowns. However, the tingling sensations and the lacy white lesions did not disappear completely. Symptomatic treatment was provided as prescribed by a family internal medicine doctor following which, the OLP flared up repeatedly for the next 8 years.

In April 2017, she visited our department again with a chief complaint of bleeding from the lower lip, and lesions and tingling sensations in the lower lip. Bleeding and lesions were observed on the lower lip (Figure 1A); as well as reddish, lacy white region, and weak tingling sensations were recognized on the bilateral buccal mucosa (photos are not available). The patient was informed that OLP could be an extrahepatic manifestation of HCV infections and that IFN-free DAA was the standard treatment for chronic hepatitis C in Japan at that time. On April 28, 2017, the patient was referred to the Department of Gastroenterology and Hepatology of our hospital. She was diagnosed with chronic hepatitis C (genotype 2a), and received DAA treatment involving a 12-week course of sofosbuvir (SOF; 400 mg; Sovaldi®; Gilead Sciences Inc, Foster City, CA, USA) and ribavirin (RBA; 600 mg; Rebetol®; MSD., Merck & Co., Inc, Kenilworth, NJ, USA) from May 19, 2017 to August 21, 2017. The lesions on the lower lip were gradually improved within 9 weeks of the DAA therapy (Figure 1B); also the lesions on the bilateral buccal mucosa decreased. The OLP lesion on the lower lip shrank and became less conspicuous (Figure 1C), and the lesions on the bilateral buccal mucosa appeared to reduce in size (photos are not available) a week after the DAA therapy (12-week course) was finished. The lesion on the lower lip (Figure 1D), and OLP lesion on the bilateral buccal mucosa almost disappeared after Sustained Virological Response for 24 weeks (SVR24; 24 weeks after finishing the DAA therapy). However, the erythema and mild epithelial lesions still remained on the lower lip lesions. Then, the patient had very faint uncomfortable feeling on the lower lip lesions. The patient used topical steroids for the treatment of OLP previously (10 years ago), but it was not effective. Therefore, in this time, topical treatment such as steroids was not recommended. The patient was asked to use petroleum jelly for the lower lip lesions several times per day during DAA therapy. She was satisfied with the petroleum jelly treatment because of its soothing effect. The patient also used commercially available lip balms occasionally when petroleum jelly was not available to her. We did not instruct the patient not to take any stimulants; there was no restriction on any kind of food or drink.

Moreover, liver function was gradually improved, and level of HCV RNA was dramatically decreased (5.9 log IU/mL on 28th April

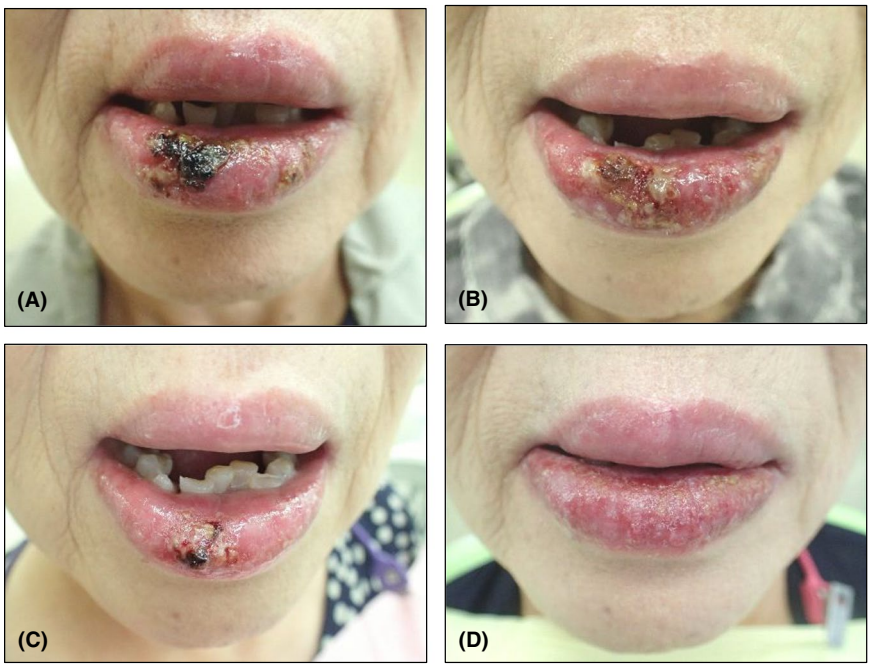

FIGURE 1 Clinical appearance of oral lichen planus. A, OLP lesions were observed on the lower lip of a 75-year-old woman before DAA therapy (in 2017). The patient complained about bleeding and tingling sensations in the lower lip. B, The OLP lesions on the lower lip were gradually improved within 9 weeks of DAA therapy. C, The OLP lesion on the lower lip shrank in size and reduced 1 week after finishing the DAA therapy (12-week course). D, The OLP lesion had almost disappeared after SVR24 (24 weeks after finishing the DAA therapy). However, the erythema and mild epithelial lesions still remained. SVR24; Sustained Virological Response for 24 weeks

2017, 1.2 log IU/mL on 6th June 2017, and 0 log IU/ml from 14th July 2017 to 27th July 2018) (Table 1).

DAA treatment reduced the severity of the symptoms of OLP in spite of its repeated recurrence; however, the tingling sensations in the lower lip remained the same over the years.

3 | DISCUSSION

The prevalence of HCV infection in patients with OLP varies between 0.5% and 35%.[30] This variation may be attributed to the geographical location, race, age, SNPs, and testing methods used in various studies. The rates of HCV infection are particularly high in Japan and Italy.[17,24,31]

Approximately 50% of the population of Japan has been screened for hepatitis, and some of the infected individuals do not receive appropriate treatment for the disease. The introduction of DAA for HCV treatment has led to higher rates of HCV eradication; nonetheless, issues regarding the pick-up and follow-up of people infected with hepatitis virus continue to remain. In recent years, retrospective and prospective studies have shown that a number of patients who visited the general dental clinics have been diagnosed with viral infections by the dentists, and untreated hepatitis C patients have been advised to undergo the appropriate treatment.[32–34] Similarly, in the present case report, the latest information about hepatitis and extrahepatic manifestations were provided to the patient by a dentist, which led to the provision of the appropriate antiviral therapy.

HCV infection is associated with various extrahepatic manifestations, most of which can be reversed by viral elimination with a concomitant reduction in mortality[35–37] and cost.[38] In a recent meta-analysis, Cacoub *et al* demonstrated that achieving SVR was associated with higher complete remissions and objective responses in patients with cryoglobulinemia vasculitis and malignant B-cell lymphoproliferative diseases, respectively. Moreover, SVR achievement was associated with reduced insulin resistance at follow-up and a protective effect on the incidence of diabetes.[37] El-Serag *et al* reported that successful DAA treatment resulting in SVR was associated with significant reductions in the future risk of conditions, including mixed cryoglobulinemia, glomerulonephritis, and lichen planus.[39]

To date, 2 of 146 OLP patients who visited our hospital were infected with HCV (data not shown); one of the two patients is presented in this case report. The oral symptoms in the patient were present for 8 years, but improved significantly due to partial eradication of HCV indicating that IFN-free DAA treatment can successfully reduce the severity of OLP. After DAA therapy, the lesions on the lower lip and the bilateral buccal mucosa were gradually improved, then reduced and finally disappeared (Figure 1). In addition, the liver function of the patients was gradually improved after DAA therapy; as well as the level of HCV RNA was dramatically decreased over time (Table 1). Briefly, all these findings indicate that DAA therapy was effective for the treatment of OLP in this patient; although the tingling sensations in the lower lip remained.

Although some OLP patients are prone to or present with HCV infections, they do not receive the appropriate treatment for the condition. Therefore, it is important for a dentist to refer such patients to a liver specialist and advise them to seek the appropriate treatment.

TABLE 1 Comparison of the laboratory data

	Normal range	First visit of Department of Gastroenterology & Hepatology	Before DAA treatment	SVR24
Anti-HCV	Negative	Positive		
HCV genotype	-	2a		
Level of HCV RNA, log IU/mL	-	5.9		Not detected
HBsAg	Negative	Negative		
AST, U/l	13-30	136	85	30
ALT, U/l	7-23	117	96	35
ALP, U/l	106-322	411	400	375
γ-GTP, U/l	9-32	51	48	33
AFT, ng/dL	0.0-10.0	19.5	-	5.2
TP, g/dL	6.6-8.1	7.7	7.6	8.3
Alb, g/dL	4.1-5.1	4.0	3.8	4.3
WBC,/μL	3,300-8,600	4,400	5,460	6,830
RBC, × 10^4/μL	386-492	473	452	494
Hb, g/dL	11.6-14.8	14.5	14.2	15.3
Plt, × 10^4/μL	15.8-34.8	14.1	14.5	17.9

Abbreviations: SVR24, sustained virological response for 24 weeks; AST, aspartate aminotransferase; ALT, serum alanine aminotransferase; AFP, alpha-fetoprotein; TP, total protein; Alb, albumin; RBC, red blood cell; Hb, hemoglobin; Plt, platelet.

In conclusion, the patient with HCV-associated OLP in this case report was treated using IFN-free DAA, which led to the improvement of the OLP. Long-term follow-up studies are needed to elucidate the therapeutic effects of DAA therapy and to understand whether it can be used for the complete eradication of HCV-related OLP.

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CONFLICT OF INTEREST

Isao Hidaka has received honoraria from Gilead Sciences, Inc All other authors declare no conflict of interest.

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