

Hepatitis C Virus and Oral Cancer - Extrahepatic Manifestations

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Abstract

Hepatitis C virus (HCV) is associated with a broad spectrum of clinical and biological extrahepatic manifestations. Oral lichen planus (OLP) is common among HCV-infected patients in Japan. Some studies reported a possible link between oral squamous cell carcinoma and HCV. The improvement of the extrahepatic manifestations by elimination of HCV is expected because interferon-free direct-acting antivirals (DAAs) therapy is introduced for hepatitis C mainly in Japan.

Keywords: Hepatitis C virus (HCV); Extrahepatic manifestations; Oral cancer; Oral lichen planus

Commentary

Extrahepatic manifestations

Hepatitis C virus (HCV) causes not only severe liver damage but also extrahepatic manifestations, including glomerular disease, hematologic diseases such as cryoglobulinemia and lymphoma, autoimmune disorders and dermatologic conditions such as oral lichen planus (OLP) [1]. HCV can be considered as a virus with a triple tissue tropism (hepatotropism, lymphotropism and sialotropism) and extrahepatic tissues might act as a reservoir for HCV. HCV may be detected in tissue from OLP, oral cancer and salivary glands [2,3].

Oral squamous cell carcinoma and HCV

An association between HCV and head and neck cancer (HNCs) has been reported [4-8]. Most recently, Mahale et al. reported that HCV is associated with nonoropharyngeal HNCs and human papillomavirus (HPV)-positive oropharyngeal cancers [6]. The prevalence of HCV infection was shown to be higher in patients with oropharyngeal cancer than control subjects (14.0%), particularly patients with HPV-positive oropharyngeal cancer (16.9%). The authors showed that HCV was associated with HNCs (particularly nonoropharyngeal and HPV-positive oropharyngeal cancers), which is a clinically important finding impacting the treatment of HNCs.

My colleagues and I previously reported an association between HCV and oral squamous cell carcinoma (OSCC) [4], and provided evidence for head and neck squamous cell carcinoma (SCC) at the national level in Japan [5]. The subjects included 305 patients with head and neck SCC and 276 patients with non-malignant disease (the control group: dental caries, periodontal disease, fractures, cysts, benign tumors and odontogenic infection) from five geographically-distinct institutions. We reported that the incidence of HCV infection in Japanese OSCC patients and head and neck SCC were 24.0% and 16.7%, respectively [4,5].

Multiple Primary Cancers (MPCs) and HCV

We demonstrated a high incidence of multiple primary cancers (MPCs) in HCV-infected OSCC patients [9]. Serum HCV antibodies (anti-HCV) and HCV RNA were detected in 36.7% and 28.6%, respectively, of the OSCC patients with MPCs. Moreover, we evaluated the occurrence of MPCs between 1992 and 2008 [10]. The incidence of MPCs in HCV-infected OSCC cases was 62.5% ($P < 0.01$ vs. the non-HCV-infected OSCC group), compared to 25% of cases without HCV infection. Hepatocellular carcinoma was the most common outcome

of MPCs in HCV-infected patients. In logistic regression analysis, the adjusted odds ratios for staging IV, anti-HCV positivity, and age over 70 years were 15.50, 13.45 and 4.46 respectively. Furthermore, the HCV-infected patients with MPCs had hyperinsulinemia. Insulin resistance may be involved in the development of MPCs in patients with HCV infection, although the mechanisms are unclear.

Malignant transformation of HCV-infected OLP

OLP is considered premalignant. It was reported that HCV infection increased the risk of malignant transformation in OLP with patients [11]. We reported a case of oral verrucous carcinoma arising from OLP-coexisting vulvo-vaginal-gingival syndrome and esophageal SCC in a patient with HCV-related liver cirrhosis [12]. The factors thought to be responsible for the development of malignant transformation are the long-lasting presence of symptomatic OLP, persistent HCV infection, advanced age and hyperinsulinemia.

HCV-infected oral manifestations by Direct-Acting Antivirals (DAAs) therapy

Branched chain amino acid (BCAA) supplementation is reported to improve insulin resistance and can promote liver regeneration [13,14]. We reported that BCAA intake is useful for adherence to and effect of interferon therapy for patients with chronic hepatitis C [13]. Currently, direct-acting antivirals (DAAs) are used for interferon free treatment of HCV infection. The treatment of HCV infection has changed dramatically with the rapid advent of new antiviral agents such as DAAs. Treatments using DAAs have few side effects and high sustained virological response (SVR) rates are expected for, not only liver disease, but also the extrahepatic manifestations of HCV, particularly extrahepatic malignant tumors and precancerous lesions.

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