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【 CASE REPORT 】

Immune Checkpoint Inhibitor Can Reduce HCV-RNA without Liver Damage

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Abstract:

Recently, immune checkpoint inhibitors (iCIs) have been used to treat cancers. Once some of the iCIs for the treatment of hepatocellular carcinoma (HCC) are certified in clinical trials, they are likely be administered to HCC patients with hepatitis C virus (HCV). However, the immunopathogenesis of HCV after the administration of iCIs has not been clarified. We experienced a lung cancer patient with HCV infection treated by nivolumab, programmed cell death 1 (PD-1) antibody. HCV-RNA gradually decreased after the start of nivolumab treatment. However, no increase in transaminase was observed during the decline of HCV-RNA. It was thought that HCV-specific cytotoxic T lymphocytes (CTLs) were activated by iCIs.

Key words: iCIs, nivolumab, PD-1, CTLs

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Introduction

Recently, immune checkpoint inhibitors (iCIs) have been used for the treatment of various kinds of cancers (1-11). In addition, clinical trials of various kinds of iCIs for hepatocellular carcinoma (HCC) are underway. It has been reported that some of them may have good anti-tumor effects (12). Once some of the iCIs for the treatment of HCC are verified in clinical trials, iCIs are likely to be administered to HCC patients with viral hepatitis B (HBV) and/or C. However, there have been few patients with chronic viral hepatitis, since patients with viral hepatitis have been considered ineligible due to the exclusion criteria for iCIs clinical trials (13).

The immunopathogenesis of hepatitis virus after the administration of iCIs has not been clarified. Recently, another group reported that hepatitis C virus (HCV)-RNA could be decreased by iCIs (12). However, the relationship between the anti-tumor effects and the anti-viral effects after the administration of iCIs has not been clarified.

We herein report the case of a chronic hepatitis C (CH-C) patient who achieved a reduction of the viral load without alanine transaminase (ALT) elevation after receiving iCIs.

Case Report

A 75-year-old man with advanced squamous cell lung cancer, cStageIVB [T2aN3M1c (BRA)] was found to have HCV infection at the diagnosis of lung cancer. However, since we considered the treatment of HCV infection not to affect the prognosis of this patient, we decided to start treatment while carefully monitoring the liver damage and HCV viral load. The HCV-RNA titer was first evaluated in June 20XX, and the patient showed 4.5 log IU/mL HCV RNA. The genotype of HCV was 1b.

The patient started receiving nivolumab as a third-line treatment in October 20XX+1 (first-line was carboplatin+nab-paclitaxcel). Transaminase levels before nivolumab treatment were within the normal range. Among the tumor markers, CYFRA was high at 5.1 ng/mL. The clinical data of this case are summarized in Table. HCV-RNA gradually decreased after the start of nivolumab treatment.

However, no increase in transaminase levels was observed during the decline of HCV-RNA (Fig. 1). Two months after starting nivolumab monotherapy, the patient suffered from radiation pneumonitis. After that, his general condition worsened, and nivolumab treatment was discontinued.

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Table. **Blood Test at First Visit.**

Factor (normal range)	Values
WBC (3,000-9,500)	6,200 /μL
Hb (13-17)	16.3 g/dL
Plt (15-38)	12.4×10^4 /μL
T-Bil (0.23-1.28)	0.51 mg/dL
AST (8-40)	28 U/L
ALT (4-42)	34 U/L
ALP (105-340)	215 U/L
γ-GTP (0-78)	44 U/L
BUN (8-20)	11.6 mg/dL
Cre (0.4-1.1)	0.69 mg/dL
ALB (3.8-5.3)	3.5 g/dL
PT-INR	0.94
M2BPGi (0-0.9)	3.73
Cryoglobulin	(-)
HCV antibody	(+)
HCV-RNA (0-1.0)	4.5 log IU/mL
HCV genotype	1b
CYFRA (0-3.5)	6.2 ng/mL
AFP (0-10.0)	2.3 mg/mL
CEA (0.1-5.0)	3.0

The patient had 4.5 log IU/mL HCV RNA. The genotype of HCV was 1b. Transaminase before Nivolumab treatment were within normal range. Among the tumor markers, only CYFRA was high, which was 6.2 ng/mL. WBC: White Blood Cell, Hb: Hemoglobin, PLT: platelet, T-Bil: total billirubin, AST: Aspartate transaminase, ALT: alanine aminotransferase, γ-GTP: γ-glutamyl transpeptidase, BUN: blood urea nitrogen, Cre: Creatinine, ALB: albumin, PT-INR: prothrombin time-International normalized ratio, M2BPGi: Mac-2 binding protein, HCV: hepatitis C virus, CYFRA: cytokeratin subunit 19 fragment, AFP: alpha fetoprotein, CEA: Carcinoembryonic antigen

HCV-RNA titers decreased after the discontinuation of nivolumab treatment, reaching 2.1 log IU/mL at 1 year after the start of nivolumab administration. The patient did not suffer any adverse effects from nivolumab. The primary lesion was stable until four months after the start of nivolumab administration (two months after discontinuation of nivolumab administration). However, tumor progression was observed at one year after the start of nivolumab administration (Fig. 2). HCV-RNA titers continued to decrease, regardless of the tumor progression.

Discussion

In this case, there were two important findings. First, HCV-RNA titers were decreased without liver damage after the start of nivolumab treatment. Second, the decline in the HCV-RNA titers was observed regardless of the anti-tumor effect. An increase in ALT can reportedly achieve good response during interferon/ribavirin treatment in CH-C patients, since the immune response might contribute to the eradication of HCV-infected hepatocytes (14). In contrast, an excessive immune response to HCV might induce liver damage. Some patients infected with viruses, such as with HCV, HBV and human immunodeficiency virus (HIV), might have exhausted cytotoxic T lymphocytes (CTLs) and therefore be unable to eradicate viruses (15-17). One important mechanism underlying CTL exhaustion is the programmed cell death 1 (PD-1)/programmed cell death ligand 1 pathway (18). In the present case, nivolumab, anti-PD-1 antibody, might recover the exhausted HCV-specific CTLs. It has been reported that the administration of immune checkpoint blockers to HIV-infected individuals on antiretroviral therapy might facilitate latency disruption (19). Another

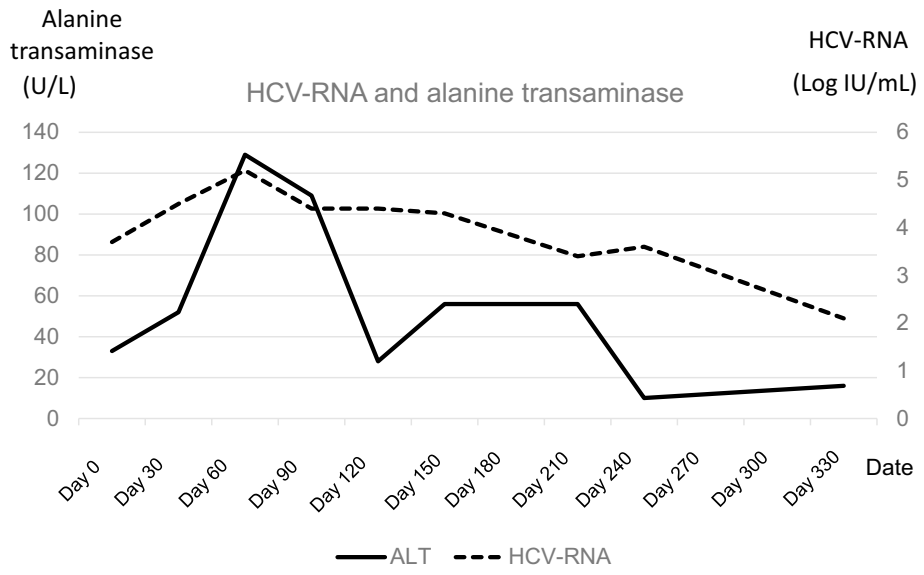

Figure 1. **The sequential data of HCV-RNA and transaminase. The dotted line indicates the titer of HCV-RNA. The solid line indicates the serum amount of ALT. HCV-RNA declined without ALT elevation. After two months of administration, nivolumab was discontinued. HCV: hepatitis C virus, ALT: alanine transaminase**

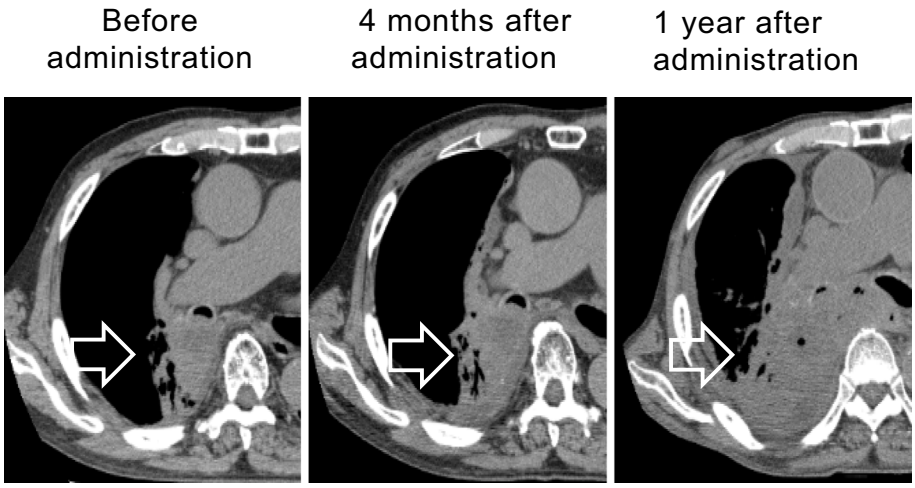

Figure 2. **Plain computed tomography (CT) scanning of lung cancer (primary lesion). Three time points of CT scanning for lung cancer are shown. The arrow indicates the main tumor in the right S6 lesion extending to the right main bronchus. The primary lesion was stable until four months after starting nivolumab administration (two months after the discontinuation of nivolumab administration). One year after starting treatment, the tumor was judged to be progressive disease.**

group also reported the safety with an efficacy signal during treatment of PD-1 inhibitor for cancers with HIV (20). In a metastatic melanoma patient, nivolumab might induce inflammation of seborrheic keratoses by PD-1 inhibition reactivating virally driven T lymphocytes (21). Furthermore, CTLs can control viruses non-cytotoxically via interferon-γ production (22). Therefore, the viral load may have been decreased without liver damage by HCV-specific CTLs in this case.

The other important finding was that the HCV-RNA still decreased even as the lung cancer progressed. It was previously reported that adverse events appeared regardless of cancer progression. Furthermore, adverse events can appear at any time after the start of iCI administration (23). It was believed that HCV-specific CTLs were activated by iCIs, and this activation was sustained even after the discontinuation of iCI administration. In the present case, lung cancer-antigen specific CTLs might not have been activated, or else the activation of the lung cancer-antigen specific CTLs was not sufficient to suppress the cancer progression due to various kinds of immune suppressive reactions. However, HCV-specific CTLs were able to be activated by nivolumab, and the activation of HCV-specific CTLs persisted even after the discontinuation of nivolumab administration.

Our literature search failed to turn up any papers describing the changes in liver enzyme levels and tumor progression during the decline in the HCV-RNA titer. iCIs reduced HCV-RNA titers without causing liver damage in this case. Furthermore, the HCV-RNA also continued to decrease even as the lung cancer progressed. When administering iCIs to HCV-infected patients with cancer, periodic testing of the RNA level should be done. The above phenomenon might also occur in chronic viral diseases other than HCV. When we administer iCIs for such viral antigens as HBV, we should evaluate the liver damage carefully.

In conclusion, we experienced a case of CH-C with a decline in HCV-RNA after the administration of anti-PD-1 antibody. The characteristics of such cases and the progression of other chronic viral diseases need to be explored through the accumulation of further cases.

The authors state that they have no Conflict of Interest (COI).

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