

A case of acute exacerbation of chronic hepatitis C during the course of adrenal Cushing's syndrome

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Abstract

A 50-year-old woman with adrenal Cushing's syndrome and chronic hepatitis C developed an acute exacerbation of chronic hepatitis C before adrenalectomy. After administration of Glecaprevir/Pibrentasvir was started, her transaminase levels normalized promptly and a rapid virological response also was achieved. Then laparoscopic left adrenalectomy was performed safely.

CASE REPORT

A case of acute exacerbation of chronic hepatitis C during the course of adrenal Cushing's syndrome

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Patient consent statement

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy

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Abstract

A 50-year-old woman with adrenal Cushing's syndrome and chronic hepatitis C developed an acute exacerbation of chronic hepatitis C before adrenalectomy. After administration of Glecaprevir/Pibrentasvir was started, her transaminase levels normalized promptly and a rapid virological response also was achieved. Then laparoscopic left adrenalectomy was performed safely.

Key Clinical Message

This is the first report of Cushing’s syndrome causing acute exacerbation of chronic hepatitis C. Acute exacerbation of hepatitis C should be listed as a differential disease for liver disorders in patients with Cushing’s disease.

key words: acute exacerbations, reactivation, chronic hepatitis C, Cushing’s syndrome

Introduction

Reports of reactivation of hepatitis C virus and acute exacerbation of chronic hepatitis C associated with immunosuppressive therapy and cancer drug therapy are rarer than for hepatitis B virus, but have been made occasionally. In HBV infection, viral reactivation and acute hepatitis caused by an excess of endogenous cortisol due to Cushing’s syndrome have been reported, but no acute exacerbation of chronic hepatitis C has been reported so far. Here, we report a case of acute exacerbation of chronic hepatitis C during the course of adrenal Cushing’s syndrome.

Case Report

A woman in her 50s underwent a CT scan at a nearby hospital to investigate treatment-resistant hypertension and was found to have a left adrenal mass. Her blood test showed low ACTH and Cushing’s syndrome was suspected, so she was referred to the endocrinology department of our hospital. She was diagnosed with adrenal Cushing’s syndrome but was referred to our department because she was found to be HCV antibody positive. There is nothing special to note about her medical or family history. She had never smoked and drank very little. Her physical findings on admission were 164.5 cm tall, 92.6 kg in weight, and a BMI of 34.2 kg/m². Her blood pressure was 179 / 73 mmHg, pulse 64 /min (rhythmic), body temperature 36.8°C, and respiratory rate 12 /min. She had findings of central obesity, moon face, buffalo hump, and red skin stretch marks. Her blood test findings (Table 1) showed an increase in ALT, HCV antibody positivity, and an HCV RNA concentration of 4.1 log IU/ml. The virus was genotype 2. Cortisol was within the reference range but ACTH was as low, less than 1.5 pg/ml. Her bedtime cortisol level was 7.07 µg/dl, which was above her reference of 5 µg/dl, suggesting the loss of diurnal variation in cortisol secretion. In an overnight low-dose dexamethasone suppression test, cortisol after loading was 6.61 µg/dl, which exceeded 5 µg/dl, suggesting that cortisol was autonomously secreted. Her contrast-enhanced CT scan (Fig. 1) revealed a tumor with a major axis of about 30 mm in her left adrenal gland. MRI scans showed mild hyperintensity in the “in phase” (Fig. 2a) and decreased signal in the “out of phase” (Fig. 2b), suggesting her adrenal mass was an adenoma. Based on the above test results, she was diagnosed with chronic hepatitis C and adrenal Cushing’s syndrome. She agreed to receive treatment with direct acting antiviral agents (DAAs) after resection of the left adrenal tumor. However, two months later, she had liver dysfunction with AST 116 U/L and ALT 213 U/L (Fig. 3). Because the HCV RNA concentration had increased to 6.4 logIU/mL, she was suspected to have an acute exacerbation of chronic hepatitis C and underwent percutaneous liver biopsy. The biopsy revealed an inflammatory cell infiltration, mostly composed of lymphocytes and plasma cells and mainly in the portal vein area (Fig. 4). Fibrosis and interface hepatitis also were observed and spotty necrosis was evident in the hepatic lobule. No clear fat deposits were found in the hepatocytes, ruling out NASH or NAFLD. According to the New Inuyama classification, hepatitis equivalent to A2-3 / F1-2 was considered. Because HBV DNA was not detected, no new drug was used and no cause of liver damage, such as biliary atresia, was found; the patient was diagnosed with liver damage due to reactivation of HCV, with acute exacerbation of chronic hepatitis C. The treatment policy was changed, in order to treat hepatitis C before the left adrenal resection, and administration of Glecaprevir / Pibrentasvir was started. A blood test two weeks after the start of treatment confirmed normalization of AST and ALT, and a rapid virological response was achieved (Fig. 3). Subsequently, HCV RNA remained negative, no liver damage was observed, and laparoscopic left adrenalectomy was safely performed nine months after the initial diagnosis. The pathological findings were adrenal adenoma. After the operation, hypertension improved and weight loss was obtained (92.6 kg (BMI: 34.2 kg/m²) before the operation, but 77.0 kg (BMI: 28.5 kg/m²) one year after the operation). ACTH increased, and the adrenal Cushing’s syndrome was considered to have been

cured. Regarding HCV infection, the sustained virological response has been maintained to date, more than two years after the completion of DAA therapy, and the follow-up continues.

Discussion

Reactivation of hepatitis B virus can cause serious liver damage. Therefore, it is recommended to check the HBV infection status before starting anticancer chemotherapy or immunotherapy and to continue monitoring for the presence or absence of reactivation thereafter^{1, 2}. On the other hand, there are few reports of the reactivation of hepatitis C virus, and there are many unclear points about the pathophysiology. In this case, it is possible that chronic hepatitis C was acutely exacerbated due to endogenous cortisol secretion in Cushing's syndrome. Although the definition of HCV reactivation has not been defined, several studies^{3, 4, 5} have defined an increase of HCV RNA of 1.0 log IU/ml or more as HCV reactivation. In addition, the definition of acute exacerbation of chronic hepatitis C is that ALT increases to more than three times the upper limit of the reference range^{3, 4, 6}. Mahale et al. reported a retrospective study in which acute exacerbation of chronic hepatitis C due to cancer medication was seen in 11% of 308 patients³. Torres et al. also reported that, in a prospective study of 100 patients with cancer medication, HCV reactivation was found in 23%⁴. Given these reports, HCV reactivation potentially could occur quite frequently. However, Torres et al. reported that only 10% of all patients had acute exacerbations, none of which led to liver failure⁴. Such data suggest that HCV reactivation may often be overlooked in actual cases without aggravation. Thus, the frequency of aggravation due to hepatitis virus reactivation is thought to be lower for HCV than for HBV. However, there are some reports of deaths from acute exacerbation of chronic hepatitis C⁷⁻¹⁰. In addition, if severe hepatitis develops following viral reactivation, mortality rates have been reported to be similar for HBV and HCV^{8,11}. Thus, reactivation of HCV is considered to be a pathological condition that requires caution, similar to HBV. Torres et al. reported that administration of rituximab or corticosteroids is a significant independent risk factor⁴. In addition, there are reports of acute exacerbation of chronic hepatitis C due to corticosteroids administered as antiemetics and as immunosuppressive therapy^{12, 13, 14}. Therefore, excess cortisol can reactivate not only HBV but also HCV. The mechanism by which HCV is reactivated with cortisol is assumed to be decreased cell-mediated immunity due to rapid apoptosis of circulating T cells caused by steroids⁴, enhancement of HCV infectivity by upregulation of viral receptor expression on the hepatocyte surface¹⁵, and enhanced viral replication¹⁶. In addition, there is a report that genotype 2 is more common in cases with acute exacerbation of chronic hepatitis C^{4, 13}, which is consistent with this case.

Regarding HBV reactivation due to Cushing's syndrome, three cases of acute exacerbation of chronic hepatitis B have been reported^{17, 18, 19}. It is believed that Cushing's syndrome caused a decrease in cell-mediated immunity and humoral immunity due to an endogenous excess of cortisol, resulting in an acute exacerbation of chronic hepatitis B¹³. As described above, because an excess of cortisol can cause reactivation of HCV, it is considered that a decrease in immunocompetence due to Cushing's syndrome, which is an excess of endogenous cortisol, can also cause reactivation of HCV and acute exacerbation of chronic hepatitis. However, as far as we can determine, no cases of Cushing's syndrome causing HCV reactivation or acute exacerbation of chronic hepatitis C have been reported, and this is the first report. In addition, this case, in which good results were obtained by treatment with DAAs, is considered to be very helpful in deciding treatment policy. In the future, when liver damage appears in HCV-infected patients with Cushing's syndrome, it will be necessary to distinguish the acute exacerbation and reactivation of chronic hepatitis C. Then, treatment with DAAs may be considered to be effective for reactivation of HCV and acute exacerbation of chronic hepatitis.

Conclusion

We report a case of chronic hepatitis C with acute exacerbation during the course of Cushing's syndrome. At the time of cancer drug therapy and in the state of endogenous and extrinsic corticosteroid hyperplasia, it is necessary to pay attention not only to acute exacerbation of chronic hepatitis B but also to hepatitis C.

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CONFLICT OF INTEREST

The authors have no conflict of interests.

AUTHOR CONTRIBUTIONS

TO and KM: collected and analyzed data and wrote and edited the manuscript. KH, ST, HO, KT, KM and JK: involved in the patient's care.

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Figure Legends

Figure 1. Contrast-enhanced CT examination. Contrast-enhanced CT examination revealed a tumor (arrow) with a major axis of about 30 mm in the left adrenal gland.

Figure 2. MRI image of the adrenal lesion. MRI showed mild hyperintensity in the "in phase" (a) and decreased signal in the "out of phase" (b), suggesting adrenocortical adenoma (arrow).

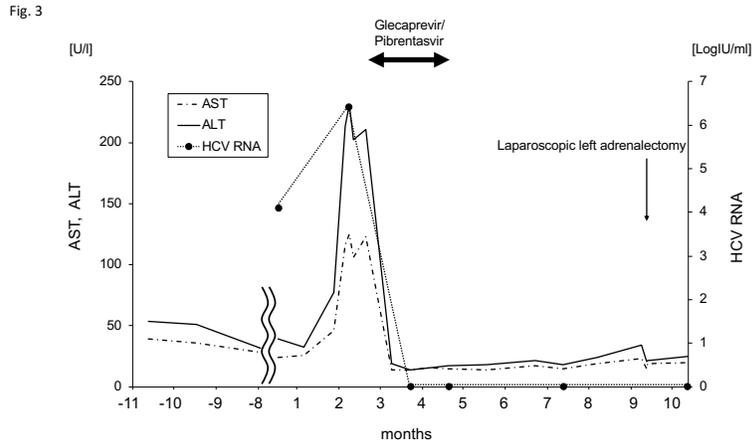
Figure 3. Changes in serum transaminase and HCV RNA levels. All showed rapid improvement by administration of direct acting antivirals. ALT: alanine aminotransferase, AST: aspartate transaminase, HCV RNA: hepatitis C virus ribonucleic acid.

Figure 4. Pathological findings of tissues obtained by percutaneous liver biopsy. Infiltration of inflammatory cells, which was mostly composed of lymphocytes and plasma cells and a small number of neutrophils, was observed mainly in the portal vein area. This was accompanied by fibrous enlargement and interface hepatitis. Although the arrangement of hepatocytes was maintained in the hepatic lobule, spotty necrosis was observed in some parts. No clear fat deposits were found in the hepatocytes, and NASH or NAFLD was a negative finding. According to the new Inuyama classification, hepatitis equivalent to A2-3 / F1-2 was considered. (a; x100, b; x200, scale bar=500µm)

Table

Table 1. Laboratory data on admission

Figure2 CCR Osuga et al.pptx available at <https://authorea.com/users/360546/articles/548019-a-case-of-acute-exacerbation-of-chronic-hepatitis-c-during-the-course-of-adrenal-cushing-s-syndrome>



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Figure4 CCR Osuga et al.pptx available at <https://authorea.com/users/360546/articles/548019-a-case-of-acute-exacerbation-of-chronic-hepatitis-c-during-the-course-of-adrenal-cushing-s-syndrome>