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CASE REPORT

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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 adrenectomy. After administration of glecaprevir/pibrentasvir was started, her transaminase levels normalized promptly and a rapid virological response also was achieved. Laparoscopic left adrenectomy was then performed safely.

KEYWORDS

acute exacerbations, chronic hepatitis C, Cushing's syndrome, reactivation

1 | INTRODUCTION

Reports of reactivation of hepatitis C virus (HCV) and acute exacerbation of chronic hepatitis C associated with immunosuppressive therapy and cancer drug therapy are rarer than for hepatitis B virus (HBV) 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.

2 | 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 tests showed low ACTH and HCV antibody positivity, and she was referred to our hospital because she was suspected of having Cushing's syndrome and chronic hepatitis C. 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/m^2. 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. Testing showed the amount of cortisol by 24-hour urine collection was 62.1 μg/day, and this level of cortisol secretion was maintained. In an overnight low-dose dexamethasone suppression test, cortisol after loading was 6.61 μg/dL, which exceeded 5 μg/dL,

TABLE 1 Laboratory data on admission

Hematology			Chemistry					
WBC	6100	/μL	TP	8.2	g/dL	DHEA-S	48	/μL
RBC	526 x 10^4	/μL	Alb	3.4	g/dL	PRA	0.7	ng/mL/h
Hb	15.8	g/dL	T-Bil	0.3	mg/dL	ALD	189	pg/mL
Ht	49.1	%	AST	33	U/L			
PLT	25.5 x 10^4	/μL	ALT	46	U/L	Serological tests		
			LDH	201	U/L	CRP	<0.10	mg/dL
			ALP	292	U/L	HBsAg	(-)	
			γ-GTP	77	U/L	anti-HBs	(-)	
Coagulation			BUN	13	mg/dL	anti-HBc	(+)	
PT	126.1	%	Cr	0.63	mg/dL	HBeAg	(-)	
APTT	27.5	sec	HbA1c	6.2	%	anti-HBe	(+)	
			Cortisol	7.46	μg/dL	anti-HCV	(+)	
			ACTH	<1.5	pg/mL			
			FBS	82	mg/dL	Genetic tests		
			Na	138	mmol/L	HBV DNA	Undetectable	
			Cl	105	mmol/L	HCV RNA	4.1	LogIU/Ml
			K	3.6	mmol/L	HCV genotype	2	
			Ca	9.0	mg/dL			

Abbreviations: Hematology: WBC, white blood cells; RBC, red blood cells; Hb, hemoglobin; Ht, hematocrit; PLT, platelets.

Coagulation: PT, prothrombin time; APTT, activated partial thromboplastin time.

Chemistry: TP, total protein; Alb, albumin; T-Bil, total bilirubin; AST, aspartate transaminase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; ALP, alkaline phosphatase; γGTP, γ-glutamyl transpeptidase; BUN, blood urea nitrogen; Cr, creatinine; HbA1c, Hemoglobin A1c; FBS, fasting blood sugar; Na, sodium; Cl, chlorine; K, potassium; Ca, calcium; DHEA-S, dehydroepiandrosterone sulfate; PRA, plasma renin activity; ALD, aldosterone.

Serological tests: CRP, C-reactive protein; HBsAg, hepatitis B surface antigen; anti-HBs, hepatitis B surface antibody; anti-HBc, hepatitis B core antibody; HBeAg, hepatitis B e antigen; anti-HBe, hepatitis B e antibody; anti-HCV, hepatitis C virus antibody.

Genetic tests: HBV DNA, hepatitis B virus deoxyribonucleic acid; HCV RNA, hepatitis C virus ribonucleic acid.

suggesting that cortisol was autonomously secreted. Her contrast-enhanced CT scan (Figure 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" (Figure 2A) and decreased signal in the "out of phase" (Figure 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 (Figure 3). HBV DNA was undetectable at the time of liver injury, but the HCV RNA concentration increased to 6.4 logIU/mL. Therefore, an acute exacerbation of chronic hepatitis C was suspected, and a percutaneous liver biopsy was performed. The biopsy revealed an inflammatory cell infiltration, mostly composed of lymphocytes and plasma cells and mainly in the portal vein area (Figure 4). Fibrosis and interface hepatitis were also observed, and spotty necrosis was evident in the hepatic lobule. No clear fat deposits were found in the hepatocytes, ruling out NASH or

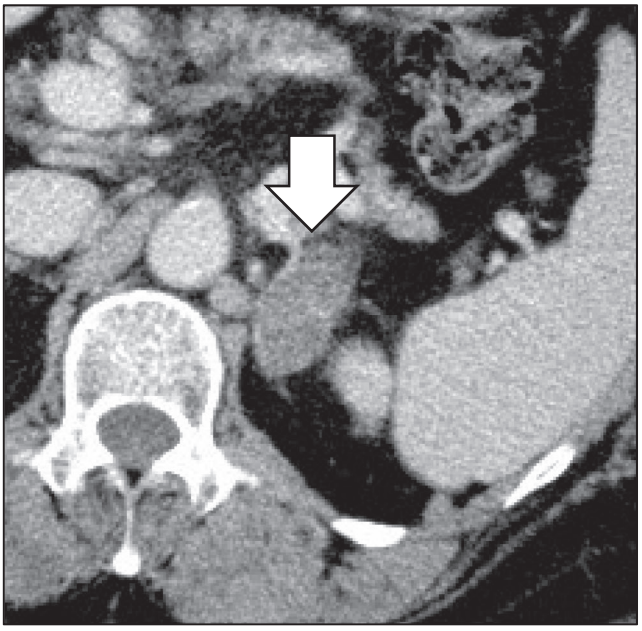

FIGURE 1 Contrast-enhanced CT examination. Contrast-enhanced CT examination revealed a tumor (arrow) with a major axis of about 30 mm in the left adrenal gland

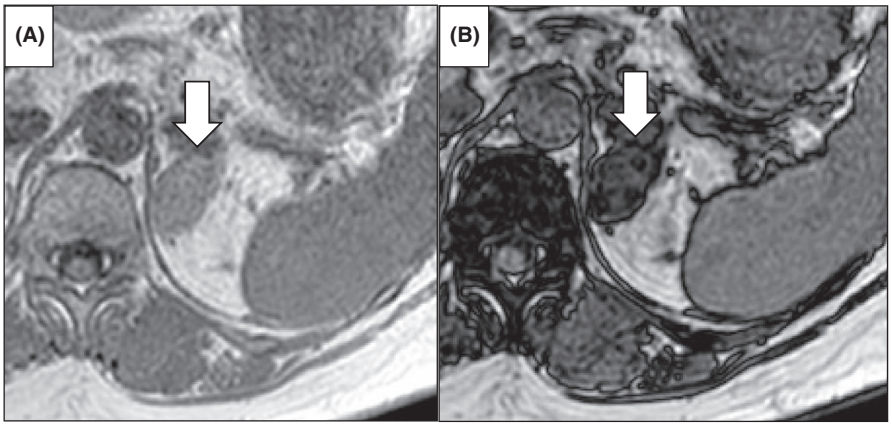

FIGURE 2 MRI image of the adrenal lesion. MRI showed mild hyperintensity in the "in phase" (A) and decreased signal in the "out of phase" (B), suggesting adrenocortical adenoma (arrow)

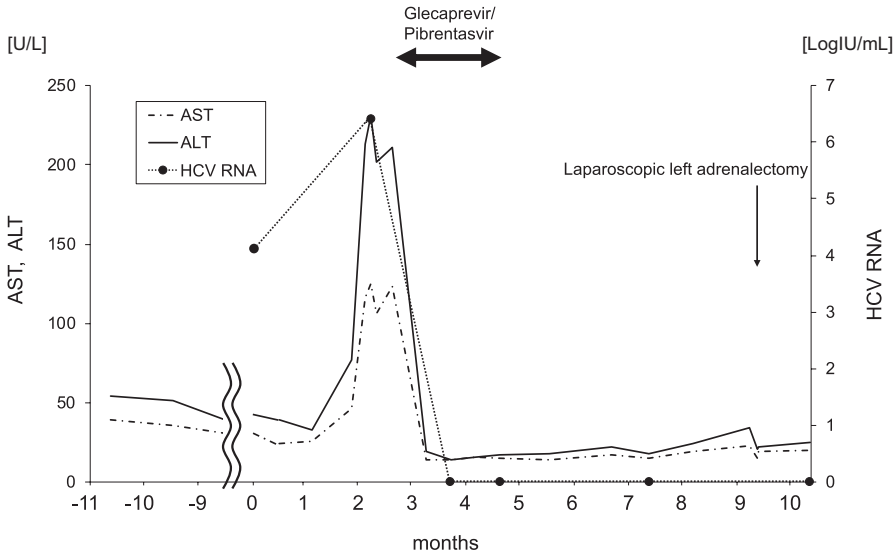

FIGURE 3 Changes in serum transaminase and HCV RNA levels. All showed rapid improvement by administration of direct acting antivirals. ALT: alanine aminotransferase, AST: aspartate transaminase, HCV RNA: hepatitis C virus ribonucleic acid

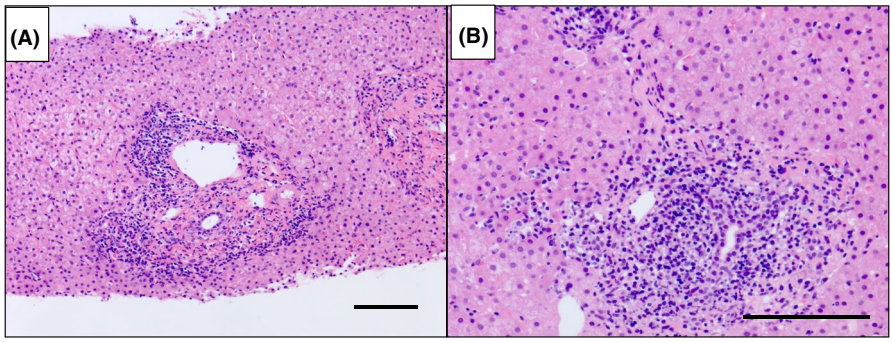

FIGURE 4 Pathological findings of tissues obtained by percutaneous liver biopsy. Infiltration of inflammatory cells, which was mostly composed of lymphocytes and plasma cells and a small number of neutrophils, was observed mainly in the portal vein area. This was accompanied by fibrous enlargement and 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; ×100, b; ×200, scale bar = 500 μm)

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 (Figure 3). Subsequently, HCV RNA remained negative, no liver damage was observed, and laparoscopic left adrenectomy was safely performed nine months after the initial diagnosis. The pathological findings were adrenal adenoma, and no atrophy was observed in the attached normal adrenal cortical gland. After the operation, hypertension improved and weight loss was obtained (92.6 kg (BMI: 34.2 kg/m^2) before the operation, but 77.0 kg (BMI: 28.5 kg/m^2) 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 2 years after the completion of DAA therapy, and the follow-up continues.

3 | DISCUSSION

Reactivation of HBV 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 fewer reports of the reactivation of HCV, and many aspects of the pathophysiology of HCV reactivation remain unclear. 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[3–5] have defined an increase of HCVRNA 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 patients.[3] 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 failure.[4] 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 C.[7–10] 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 factor.[4] In addition, there are reports of acute exacerbation of chronic hepatitis C due to corticosteroids administered as antiemetics and as immunosuppressive therapy.[12-14] 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 glucocorticoids,[4] enhancement of HCV infectivity by upregulation of viral receptor expression on the hepatocyte surface,[15] and enhanced viral replication.[16] 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.[17–19] 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 B.[13] 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 similar cases may be latent. Among the reports of acute exacerbation of hepatitis B due to adrenal Cushing's syndrome, there is a case in which the liver damage and viral load were improved only by adrenalectomy.[17] Therefore, it is also possible that hepatitis C was improved by adrenal resection in this case. However, general anesthesia associated with adrenalectomy and the use of various drugs used for postoperative physical management should be avoided, if possible, in situations where some severe liver damage is present. In addition, reactivation of immunity due to rapid depletion of glucocorticoid, following resection of an adrenal tumor, may lead to exacerbation of liver damage. In this case, the amount of HCV and hepatic transaminase levels were improved rapidly by glecaprevir/pibrentasvir treatment, and the operation could be performed safely. If Cushing's syndrome is complicated by an acute exacerbation of hepatitis C, clinicians should consider including treatment strategies such as in this case. Summarizing the above, 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. Treatment with DAAs may then be considered to be effective for reactivation of HCV and acute exacerbation of chronic hepatitis.

4 | 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 excess, 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 were collected and analyzed the data and wrote and edited the manuscript. KH, ST, HO, KT, KM, and JK were involved in the patient's care and provided advice on the preparation of this case report.

ETHICAL APPROVAL

This study complied with the standards of the Declaration of Helsinki and the current ethical guidelines.

CONSENT

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

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study

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