

Adrenal Tumors in Patients With Chronic Hepatitis C

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We report 3 patients with chronic hepatitis C associated with adrenal adenomas, 2 of which were functional. Hepatitis C can be associated with insulin resistance, which leads to hyperinsulinemia, and with increased serum levels of insulin growth factor (IGF); both substances have been reported to increase adrenal fasciculate cell growth in vitro. Thus, the hepatitis C virus may trigger adrenal tumorigenesis, which, in some cases, may lead to hyperaldosteronism. Accordingly, hyperaldosteronism may be one of the extrahepatic manifestations of chronic hepatitis C.

Infection with the hepatitis C virus is one of the most common causes of chronic liver disease. In addition to liver disease, chronic hepatitis C can be associated with extrahepatic manifestations, including mixed cryoglobulinemia, glomerulonephritis, porphyria cutanea tarda, lichen planus, Sjögren syndrome, and, recently, cardiomyopathy.^{1,2} In this report, we describe a series of 3 patients with chronic hepatitis C who were referred to the hepatologist for evaluation and treatment, and in whom adrenal adenomas were diagnosed. All relevant laboratory findings are reported in Table 1.

Case Series

Patient #1

A 54-year-old African-American man was referred to the hepatologist for treatment of chronic hepatitis C, which had not responded to standard therapy 12 years prior to the evaluation. His risk factor for hepatitis C virus infection had been remote intravenous drug use. He had had hypertension for at least 3 years that had been managed with a calcium channel and a beta blocker, an alpha 2

adrenergic agonist, and an angiotensin-converting enzyme (ACE) inhibitor, diabetes mellitus managed with a second-generation sulfonylurea, and schizophrenia managed with olanzapine. During the process of evaluation for hepatitis C treatment, the patient was admitted for treatment of hypokalemia. Investigations for hypertension associated with hypokalemia revealed findings consistent with hyperaldosteronism (see Table 1). An abdominal computed tomography (CT) scan revealed a right adrenal tumor less than 1 cm in size. The administration of spironolactone was associated with gradual correction of hypokalemia and control of blood pressure. The patient underwent laparoscopic resection of the adrenal tumor associated with resolution of his hypokalemia. The serum aldosterone concentration after surgery was 3 ng/dL. The patient remained hypertensive and was treated with a diuretic and an ACE inhibitor.

Patient #2

A 78-year-old white woman was admitted to the hospital because of pneumonia associated with a loculated empyema. She reported having hypertension for many years, which had been managed by an ACE inhibitor and a diuretic, and chronic obstructive pulmonary disease. The patient had received blood transfusions 30 years prior to admission. As part of her evaluation for pneumonia, she underwent a chest CT scan, which revealed a vascular lesion in the left lobe of the liver suggestive of hepatocellular carcinoma. A CT scan of the abdomen confirmed the presence of a vascular mass suggestive of hepatocellular carcinoma, which was supported by the presence of a serum alpha-fetoprotein concentration of 510.8 ng/mL. In addition, a 2.4-cm adrenal tumor was detected. Liver disease work-up revealed chronic hepatitis C (see Table 1). The patient's plasma aldosterone concentration, plasma renin activity, and plasma renin activity ratio were not consistent with hyperaldosteronism. The

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Table 1. Summary of Relevant Clinical Work-Up of Patients

Patient	Age (years)	Gender/race	Risk factors for hepatitis C	Hepatitis C		Adrenal gland findings by CT scan	Adrenal tumor investigations at diagnosis		
				Viral load (Log IU/mL)	Genotype		A (ng/dL)	PRA (ng/mL/hr)	A:PRA ratio
#1	54	Male/African American	Intravenous drug use	6.44	1A	Right mass, <1 cm	84	0.2	420
#2	78	Female/White	Blood transfusions	6.53	1A	Left mass, 2.4 cm	3	2.98	1.01
#3	43	Female/White	Intravenous drug use	7	1A	Left nodular adrenal lesion/left adrenal mass, 1.9 cm	32	<0.1	320

A=aldosterone; CT=computed tomography; PRA=plasma renin activity.

patient did not wish to pursue evaluation of the liver mass at the time of the admission but agreed to follow-up at a later time.

Patient #3

A 43-year-old white woman was referred to the clinic for evaluation of chronic hepatitis C. She reported having hypertension for 17 years and had been treated in various emergency rooms for hypokalemia. Her risk factor for chronic hepatitis C had been previous intravenous drug use. Due to the suspicion of primary hyperaldosteronism, relevant investigations were requested. The patient underwent a CT scan, which revealed a left adrenal tumor suggestive of adenoma. Her serum aldosterone concentration was 32 ng/dL, and her plasma renin activity was less than 0.1 ng/mL/hr, yielding an aldosterone:plasma renin activity ratio of 320, which was consistent with hyperaldosteronism (see Table 1). The patient was lost to follow-up, and efforts to find her were unsuccessful. One year later, she was hospitalized because of weakness associated with uncontrolled hypertension and hypokalemia. A CT and magnetic resonance imaging scan of the abdomen confirmed the diagnosis of an adrenal tumor. Adrenal vein sampling indicated that the left adrenal was the source of the hyperaldosteronism. The patient underwent resection of the tumor. Postoperatively, her serum aldosterone concentration decreased to 3 ng/dL and her serum potassium level was within normal limits. Her blood pressure was normal during the immediate perioperative period

but subsequently required medications to be controlled. She was discharged on a calcium channel blocker.

Discussion

We describe 3 patients with chronic hepatitis C and adrenal tumors, 2 of which were associated with hyperaldosteronism. Two of the patients had reported a history of hypertension and hypokalemia for several years. In 2 patients, the hypokalemia had been of sufficient magnitude that admissions to the hospital were required.

Two of the patients (patients #1 and #3) had used intravenous drugs, which was the identified risk for hepatitis C infection, and which preceded the diagnosis of hypertension. Patient #2 had received blood transfusions 30 years prior to the diagnosis of chronic hepatitis C, which might have been the mode through which she contracted the infection. In all of the patients, the activity identified as the likely risk for hepatitis C virus infection, and hence the infection, preceded the diagnosis of hypertension by several years, suggesting that the patients had already contracted the hepatitis C virus infection and that the virus might have stimulated the development of the adrenal adenoma.

In patient #2, the adrenal tumor had not been associated with hyperaldosteronism. Indeed, 70% of adrenal tumors are not functioning, and according to reported small series of patients, less than 20% of adrenal tumors followed over time become functional.³ The possibility of an adrenal metastasis in this patient, in whom hepatocel-

lular carcinoma was suspected, has to be considered in this discussion; however, the appearance on CT was most consistent with an adenoma, and the size (ie, less than 4 cm) was most suggestive of a benign tumor.³

The mechanism that mediates tumorigenesis and aldosterone production by adrenal adenomas is not known. Hepatitis C virus, however, has tropism for glandular tissue, as evidenced by its ability to cause hepatitis; thus, it is possible that what makes the virus thrive in the liver may be at play in its potential role in the formation of adrenal adenomas. In this regard, the immunoreactivities of IGF-I, insulin, and their respective receptors were reported to be expressed by adrenal tumors. In a published series of 23 tumors, 48% of adrenal adenomas expressed IGF-I and 56% expressed IGF-R immunoreactivities.⁴ In addition, insulin and insulin receptor immunoreactivities were detected in 69.5% and 100% of tumors, respectively.⁴ These results may suggest that IGF-I and insulin may mediate, to some degree, the growth of adrenal tumors. This idea may be relevant to the association of hepatitis C and adrenal tumors because it has been reported that serum levels of IGF are increased in patients with chronic viral hepatitis, including hepatitis C. Furthermore, insulin resistance, which has been reported in patients with chronic hepatitis C, is associated with an increase in secretion of insulin.⁵⁻⁷ Both insulin and IGF-I are growth factors that have been associated with increased cell growth in a culture system of adrenal fasciculate cells.⁸ These observations may suggest that IGF-I, and perhaps insulin, can trigger adrenal tumorigenesis.

A genetic predisposition to develop adrenal tumors in association with chronic hepatitis C may be required; however, the small number of patients in the series does not allow for a strong statement in regard to predisposing factors.

Summary

We report a case series of 3 patients with chronic hepatitis C and unilateral adrenal adenomas, of which 2 were functional. Primary hyperaldosteronism may be one of the extrahepatic manifestations of chronic hepatitis C virus infection and should lead to an expeditious diagnostic investigation to exclude this viral infection. The potential effect of interferon and ribavirin treatment, which is the standard of care for chronic hepatitis C, on adrenal tumorigenesis is unknown.

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Review

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Hepatitis C virus (HCV) infection has been associated with numerous different extrahepatic manifestations, including the endocrine diseases hypothyroidism and diabetes mellitus.^{1,2} In addition, several malignancies have been linked to HCV infection.³⁻⁵ Proving their association with HCV, however, would require large sample sizes.

Bergasa and associates⁶ describe a case series of 3 patients with HCV infection (1 African-American man and 2 white women) who had adrenal tumors. In their report, they discuss whether the adrenal tumors may be associated with HCV. They hypothesize that these tumors may be related to HCV infection due to HCV-associated hyperinsulinemia and increased levels of insulin growth factor. This theory is based upon the concept that hyperinsulinemia could lead to aberrant cell growth. However, a study of 173,643 diabetic veterans and 650,620 nondiabetic veterans did not find

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a general increase in malignancies among the diabetic patients versus the nondiabetic patients. In contrast, the researchers found that diabetes played a role in patients developing liver disease.⁷ The concept of hyperinsulinemia as reasoning link between adrenal tumors and HCV is further complicated by conflicting data on the prevalence of diabetes in the HCV population. Some studies have noted an even lower frequency of diabetes in the HCV-infected population compared to the control population.⁵

Recent data indicate that HCV's association with insulin resistance and associated hyperinsulinemia may be related specifically to genotype 1 infection, and less so with genotype 2 or 3. This was shown by the improvement of hyperinsulinemia when genotype 1–infected patients, but not genotype 2– or 3–infected patients, were cured of their HCV.⁸

All 3 patients treated by Bergasa and associates had genotype 1 infection. Thus, one could argue that this further supports the authors' notion of an association between adrenal tumors in these patients and HCV disease. However, genotype 1 is also the most prevalent HCV genotype in the United States, again limiting the conclusion that HCV is associated with adrenal tumors based upon HCV genotype. It is well established that the risk of hepatocellular carcinoma is also linked to the presence of insulin resistance, though this association has also been questioned recently.⁹

The concept of hyperinsulinemia as the basis for adrenal tumor development in these 3 patients is further questioned, as only 1 of the 3 patients is reported to be diabetic. Whether either of the other 2 patients has at least insulin resistance is not reported here. Epidemiologically, there is dominance in men and African Americans.¹⁰ Thus, the demographics of the patients in this case series do not fit into the expected epidemiologic pattern. Therefore, adrenal tumors may be associated with HCV, but there is neither sufficient evidence supporting this idea nor sufficient evidence against it.

Evaluating the association of HCV infection with this particular disease (adrenal tumors) would require 1 of the following 3 approaches: assessing the frequency of adrenal tumors in individuals with HCV to individuals without HCV; alternatively, assessing the frequency of HCV in individuals with adrenal tumors compared to individuals without adrenal tumors (this latter approach is likely more reasonable as a first step in evaluating HCV's association with adrenal tumors); and observing reversal of the disease upon clearance of HCV infection, as with follicular splenic lymphoma.¹¹

The prevalence of HCV infection in the US population has been described to be approximately 1.6%, with a confidence interval between 1.3% and 1.9%. If, for exam-

ple, the 3 patients in the case series were derived from a pool of 200 patients, the expected HCV frequency and the actual frequency would be the same. If the 3 patients were derived from a population of less than 58 patients with adrenal tumors, the 95% confidence interval would suggest a true increased association with HCV. Thus, it would likely be easiest to evaluate the association of HCV with adrenal tumors by assessing the prevalence of HCV among patients with adrenal tumors, as this would require a limited number of patients. In contrast, testing the association of HCV and adrenal tumors by assessing the prevalence of adrenal tumors among HCV-infected patients may require larger numbers of patients.

Examples of diseases where an association has been proven via the approach of assessing the frequency of HCV infection are porphyria cutanea tarda¹² and mixed cryoglobulinemia.¹³

In conclusion, the report by Bergasa and coworkers is an interesting addition to the literature of diseases potentially associated with HCV infection. It is, however, premature to conclude that HCV infection is associated with adrenal gland tumors based upon this case series. Further studies, as outlined above, are still needed.

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