Use of Gadolinium Contrast Adrenal Venography for the Assessment of Primary Aldosteronism in a Patient with Iodine Allergy

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Abstract. Primary aldosteronism is a relatively common cause of secondary hypertension. It is often important to diagnose this disease accurately, since appropriate surgical therapy may result in cure of the disease. Assessment of the laterality of adrenal hyperfunction is possible using adrenal venous sampling of steroid hormones, but this procedure may not be feasible in patients with allergy to iodinated radiocontrast agents. In this paper, we report a patient with primary aldosteronism who was found to have bilateral adrenal tumors on CT. Because preoperative localization of the hyperfunctioning tumor was important, adrenal venous sampling and venography was performed by a highly-experienced radiologist using the MRI contrast agent gadolinium. After reviewing the data, the patient received a right adrenalectomy. This case report demonstrates that it was possible to perform adrenal venography using gadolinium in this patient, however the safety and efficacy should be re-assessed in individual cases.

Key words: Gadolinium, Venography, Primary aldosteronism

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PRIMARY aldosteronism is a major cause of secondary hypertension which is characterized by excess secretion of aldosterone resulting in hypertension, hypokalemia, metabolic alkalosis and a variety of other metabolic changes. Recent studies have suggested that the incidence of this disease may be greater than expected previously, and can occur in the absence of the classical signs of disease [1].

Primary aldosteronism can be caused by both unilateral (for example, adrenal adenoma, unilateral adrenal hyperplasia, unilateral multiple micronodules, adrenal carcinoma) and bilateral lesions (for example, idiopathic hyperaldosteronism, primary adrenal hyperplasia, bilateral adrenal adenomas). It is possible to

distinguish unilateral lesions from bilateral lesions to some extent from the hormonal data with or without stimulation/suppression, however definitive diagnosis requires demonstration of laterality in the hormonal function of the two adrenals. One way to demonstrate the laterality is with the iodinated radioisotope [¹²⁵I]iodocholesterol. However, the most reliable method remains adrenal venography with adrenal venous hormone sampling.

The use of radiocontrast agents is required for the visualization of the adrenal veins in order to direct the sampling of venous blood at different locations. However, patients with allergy to iodinated contrast agents present a major clinical dilemma, because the use of these agents could result in an anaphylactic reaction, which can be severe in some cases [2]. Recent reports have suggested that, in the case of arterial angiography, the use of an MRI contrast agent (gadolinium) can be used as an alternative contrast agent in patients with renal failure or iodine allergy [3–5]. In this

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paper, we report the use of gadolinium for adrenal venography in the assessment of unilateral adrenal adenoma.

Case Report

A thirty-three-year-old woman presented with muscle weakness. The weakness started in the lower extremities but spread to the upper body. On visiting a local clinic, the serum potassium was found to be 1.8 mEq/L, so the patient was referred to this hospital. The patient had a family history of hypertension, and had previously been told that she was hypertensive, however she had avoided treatment. On physical examination, the patient's height was 165 cm and weight was 97.6 kg. The blood pressure was 176/102 mmHg, and the pulse was 80/min, regular. Muscle strength was grossly normal, and there were no neurological deficits or remarkable findings in heart, lung or abdomen.

The laboratory data were as follows: the complete blood count and coagulation tests were within the normal range. Serum total protein was 6.9 g/dL, total cholesterol was 204 mg/dL, blood urea nitrogen was 5.5 mg/dL, creatinine was 0.4 mg/dL, uric acid was 5.0 mg/dL, sodium was 140.8 mEq/L, potassium was 2.4 mEq/L, chloride was 99 mEq/L, calcium was 7.7 mg/dL, glucose was 188 mg/dL, and creatinine kinase was 1660 IU/L. The patient was admitted for evaluation. Blood gas analysis at room air was pO₂ 83.2 torr, pCO₂ 43.5 torr, pH 7.479, HCO₃⁻ 32.0 mmol/L. In the 24 hour urine collection, urine volume was 2500 mL, creatinine was 1.53 mg/day, sodium was 306.5 mEq/day, potassium was 25.5 mEq/day, chloride was 175 mEq/day. Hormone data on admission are presented in Table 1.

In summary, the patient had hypertension, hypokalemia, metabolic alkalosis, with an increase in plasma aldosterone (Aldo) and urine aldosterone with suppression of plasma active renin concentration (ARC), suggesting the diagnosis of primary aldosteronism. Various hormonal tests were therefore performed to investigate the possibility that the patient had primary aldosteronism due to adrenal adenoma or hyperplasia. The results of these tests are summarized in Table 2. Firstly, the response of ARC and Aldo to furosemide injection was investigated, and it was found that ARC remained suppressed after furosemide injection.

Table 1. Endocrine studies (1)

	Patient values	Normal range
Plasma hormones		
Active renin (ARC)	<u>2.6 pg/mL</u>	3.6–36.2
Aldosterone (Aldo)	<u>496 pg/mL</u>	50–200
ACTH	10 pg/mL	7–56
Cortisol	16.1 ug/dL	3.5–18.4
DHEA-S	78.0 ug/dL	50–270
24-hour urine hormones		
Aldosterone	<u>54.0 ug/day</u>	0.6–9.0
Free cortisol	38.5 ug/day	11.2–80.3
17-OHCS	7.6 mg/day	2.6–9.0
17-KGS	12.5 mg/day	6.1–16.2
17-KS	4.4 mg/day	2.4–11.4
Adrenaline	6.3 ug/day	5.4–17.4
Noradrenaline	88.2 ug/day	38.1–144.7
Dopamine	663 ug/day	316–1272
VMA	2.9 mg/day	1.4–4.9
HVA	2.9 mg/day	1.6–5.5
Metanephrine	0.06 mg/day	0.05–0.20
Normetanephrine	0.19 mg/day	0.10–0.28
Androsterone	0.77 mg/g Cr	0.30–3.46
Etiocolanolone	0.58 mg/g Cr	0.25–2.93
11-oxoandrosterone	0.03 mg/g Cr	0.00–0.07
11-oxoetiocolanolone	0.34 mg/g Cr	0.03–0.71
11-hydroxyandrosterone	0.77 mg/g Cr	0.23–1.46
11-hydroxyetiocolanolone	0.24 mg/g Cr	0.02–0.57
DHEA	0.54 mg/g Cr	0.03–3.94

Table 2. Endocrine studies (2) (furosemide test and diurnal variation)

	Before furosemide	After furosemide	
Aldosterone (Aldo, pg/mL)	469	343	
Active renin (ARC, pg/mL)	<2.5	<2.5	
	7 am	4 pm	11 pm
Cortisol (ug/dL)	16.1	8.6	5.1
ACTH (pg/mL)	17	6	6
Aldosterone (Aldo, pg/mL)	469	343	270
Active renin (ARC, pg/mL)	<2.5	<2.5	<2.5

The diurnal variations in adrenocortical steroids were also examined, and values of cortisol and Aldo at 11 pm (cortisol 5.1 ug/dL, Aldo 270 pg/mL) were found to be slightly reduced compared to the values at 7 am (cortisol 16.1 ug/dL, Aldo 469 pg/mL) (Table 2).

Various imaging studies were performed to localize the source of the excess aldosterone secretion. On abdominal ultrasound, a 17 mm hypoechoic mass was found in the right adrenal. Similarly, the abdominal

MRI revealed a mass of about 20 mm of fatty density above the right kidney, compatible with an adrenal adenoma. On the other hand, the abdominal CT showed a 20 mm mass which was poorly enhanced after contrast enhancement, and also revealed a similar 8 mm mass in the left adrenal (Fig. 1). After the contrast-enhanced CT examination, the patient developed wheezing and dyspnea. Piping sounds were also heard on auscultation. The timing of these symptoms was thought to be consistent with an allergic reaction to the iodinated radiocontrast agent.

Fig. 1. Abdominal CT scan of this patient. The 20 mm right adrenal tumor and the 8 mm left adrenal tumor are shown with arrows.

The investigations so far suggested the possibility of primary aldosteronism due to adrenal adenoma. However, since adrenal tumors were found in both the right and left adrenals by CT scan, the source of the excess aldosterone secretion was unclear. A full discussion was performed with the patient, the internal medicine team, and the radiology team. After explaining the risks and benefits, the patient requested the use of gadolinium as a radiocontrast agent to guide adrenal venous sampling. The results of this investigation are shown in Figs. 2 and 3. The technical aspects of the

Fig. 3. Results of adrenal venous sampling. Aldo: aldosterone concentration (pg/ml); Cortisol: cortisol concentration (ug/dL).

Right adrenal venography

Left adrenal venography

Fig. 2. Representative photograph of the gadolinium-contrast adrenal venography in this patient.

procedure will be discussed elsewhere. The right and left adrenal veins were visualized using a total of 6 mL of sodium gadodiamide, and adrenal vein sampling was performed. The Aldo/cortisol ratio was markedly increased in the right adrenal vein.

No side effects were seen after this study. As a result of this study, the patient elected to have surgery on the right adrenal tumor. Laparoscopic adrenalectomy was performed on the right adrenal tumor, and the postoperative course was unremarkable. Photomicrographs of the excised cortical adenoma and surrounding adrenal tumor tissue are shown in Fig. 4. On histological examination, tumor cells with foamy-appearing cytoplasm with oval nuclei were visible in an alveolar pattern, and sinusoid vessels were seen in the interstitium. Some fat cells and compact cells were seen (<10%), but no evidence of malignancy was found. The surrounding adrenal tumor tissue was not atrophic. These findings were considered by the pathologist to be compatible with primary aldosteronism due to adrenal adenoma. When the patient was last seen in this hospital's outpatient clinic one month after the operation, her blood pressure had fallen to 125/80 mmHg (on valsartan 20 mg/day), and her potassium ARC and Aldo were within the normal range (sodium 137.8 mEq/L, potassium 4.5 mEq/L, chloride 100 mEq/L, ARC 42 pg/mL, Aldo 42 pg/mL, ACTH 43 pg/mL, cortisol 13.0 ug/dL).

Discussion

Iodinated radiocontrast agents are routinely used for angiography. Although there are wide variations between different reports, it has been estimated that the incidence of anaphylactoid reactions to ionic hyperosmolar radiocontrast agents ranges from 0.1% to 5%, with lower values (less than 0.5%) for non-ionic lower osmolar preparations [6–8]. Symptoms of radiocontrast allergy include dermatologic symptoms such as rash, itching, erythema, urticaria, gastrointestinal symptoms such as nausea, vomiting, and respiratory symptoms such as wheezing and dyspnea. In some cases, more severe symptoms such as anaphylactic shock, convulsions, and even death have been reported.

In one series, Lang *et al.* reported that the incidence of such allergic reactions was 73 out of 5264 patients (1.39%) [2]. Of interest, more of the patients (51 versus 22 men) were female, and women were also more susceptible to severe reactions [2]. The patient in this study was also female, and was suspected to have allergy to iodinated compounds because of the typical symptoms and clinical course after her contrast-enhanced CT scan. This was a problem, because it was important to determine the functionality of the two tumors in this patient, because the patient did not want to continue anti-hypertensive medication since she was thinking of having a child in the future. However, it was unclear which of the two tumors was producing the excess aldosterone in this patient.

Adrenal tumor tissue

Adjacent adrenal tissue

100 μ m

Fig. 4. Photomicrographs of adrenal tumor and adjacent adrenal tissue histology. Hematoxylin-eosin stain. Original magnification $\times 200$.

One potential method of determining the laterality of adrenal function is adrenal scintigraphy using [^{131}I]-iodocholesterol. The amount of iodine in the injected [^{131}I]-iodocholesterol is almost negligible, and it may be possible to use this radioisotope in patients with iodine allergy. However, the drug information sheet listed a contraindication in patients with allergy to iodinated compounds, so the test was discontinued. A more reliable method to diagnose unilateral hyperfunction is adrenal venous sampling. However, the patient obviously was anxious about the possibility of recurrence of an anaphylactoid reaction.

One potential method to treat such patients is to use premedication before angiography [7, 9]. Marshall and Lieberman compared three pretreatment protocols to prevent anaphylactoid reactions to radiocontrast media in patients with a previous anaphylactoid reaction. Patients were pretreated with either prednisone and intramuscular diphenhydramine, or prednisone, diphenhydramine, and cimetidine, or prednisone, diphenhydramine, cimetidine and ephedrine before the procedure. Despite these pretreatments 6–8% of the patients in each of the treatment groups experienced a repeat anaphylactoid reaction [9].

Recent reports have suggested that gadolinium chelates may be a useful alternative to iodinated contrast media for angiography and interventional radiology. Kinno *et al.* first reported the use of gadolinium chelate for intraarterial DSA in 1993 [4]. Subsequently, Spinosa *et al.* reported the use of gadolinium for percutaneous transluminal angioplasty of patients with renal failure due to renal artery stenosis [5, 10]. Kaufman *et al.* successfully performed carotid arteriography in patients with a serum creatinine of about 1.5 mg/dL, and reported that renal function was not decreased by the contrast media [3, 11]. These reports highlighted the fact that gadolinium chelates can be used relatively safely in patients with renal dysfunction or renal failure. CO_2 gas has also been used as a radiocontrast agent. Similar to gadolinium, CO_2 can be used in patients with renal dysfunction or radiocontrast allergy. However, CO_2 gas is technically difficult to use, and the image resolution may be inferior [12].

To our knowledge, there are few reports at present concerning the use of gadolinium chelates for venography of the adrenal veins. However, in this case we

used this agent because diagnosis of the hyperfunctioning adrenal tumor was important for the diagnosis, and because of the request of the patient to use this agent. As a result of the study, the most probable source of excess aldosterone was assessed to be the right adrenal tumor. The possibility that the left adrenal also produced aldosterone could not be completely ruled out. Nevertheless, the patient elected to receive laparoscopic adrenalectomy.

Several caveats are required in the application of the results of this case report to other patients. Firstly, although no adverse reactions were noted in this patient, the possibility that a reaction to gadolinium may occur should be considered, and the risk/benefit assessed in individual cases. For example, Cochran *et al.* reported that the adverse reaction rate to gadolinium contrast material was 0.06% [8]. Similarly, Murphy *et al.* reported that out of 74,275 gadodiamide injections, 11 (0.015%) nonallergic and 12 (0.016%) mild allergy-like reactions occurred [13]. The incidence of adverse events after injection of MR contrast agents was much higher (15%) in a Chinese population, but most of these were non-specific adverse events [14]. Secondly, the procedure was performed by a skilled radiologist who was experienced in locating the adrenal veins, and the amount of contrast required (about 6 mL of 32.3% gadodiamide hydrate, infused by slow injection (approximately 1 mL/second)) was less than the normal dose used, for example, in gadolinium MR angiography (8–20 mL). Visualization of the adrenal vein was much less clear than the image obtained using conventional iodinated contrast material, so it is unclear whether this method is suitable for more inexperienced radiologists. In fact, the cortisol concentration in the left adrenal vein was lower than in the right adrenal vein, which could suggest the possibility that the catheter inserted in the left adrenal vein was dislodged or poorly positioned, however the positioning of the catheter was constantly confirmed by direct visualization. Therefore this method should be considered only by experienced radiologists. Thirdly, the cost of the radiocontrast agent could not be provided by the health insurance. For these reasons, it is best that the risks and benefits are assessed, and the patient's full consent is obtained before considering this procedure, in accordance with institutional guidelines.

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