Treatment of Aldosteronoma with Superselective Intraarterial Injection of Absolute Ethanol

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無水エタノールの超選択的動注による原発性アルドステロン症の治療

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良性副腎腺腫による原発性アルドステロン症患者4例に対し，無水エタノールを使用した超選択的副腎動脈塞栓術を行った．CT，副腎シンチグラフィ，副腎静脈採血により一側性副腎腺腫の確認を行った後，栄養動脈である副腎動脈の小分枝を，二重管法によるマイクロカテーテルを用いて無水エタノール1～2 mlで塞栓した．3例では2回の塞栓術を施行した．全例で施行直後に一過性の腹・腰部痛を，1例で血圧不安定がみられたが，いずれも対症的治療にて消失し，重篤な副作用は認められなかった．治療効果として，2例で血中アルドステロン値・レニン活性値および血圧の正常化が得られ，残りの2例では検査値の正常化と高血圧の軽減を1例に，検査値の改善と高血圧の軽減を1例に認めた．本法施行後，最長例で10カ月間効果が持続しており，今後長期の経過観察も必要であるが，本法は外科的摘出術に匹敵する治療法となる可能性が考えられた．

Research Code No. : 523.4

Key words : *Absolute ethanol, Primary aldosteronism, Adrenal tumor, Embolization, Coaxial technique*

Received Jul. 19, 1993; revision accepted Oct. 27, 1993

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Introduction

Adrenal embolization of the arterial or venous supply has been used to decrease tumor bulk or vascularity, suppress tumor hormonal function, or relieve pain in patients with functioning pheochromocytomas[1),2),3)], ACTH-dependent Cushing's syndrome[4),5)], adrenal cortical carcinoma, and metastatic adrenal tumors[6)]. To our knowledge, there has been no attempt to deactive an aldosteroma by adrenal embolization. We describe our initial experience with the intraarterial injection of absolute ethanol (AE) in treating 4 patients with aldosteronoma.

Materials and Methods

Four patients (one man and 3 women, age range 28 to 65 years) were included in this study (Table 1). Each patient had hypertension due to primary aldosteronism due to an adrenal adenoma. They variously exhibited hypokalemia, hypernatremia, high plasma levels of aldosterone, low plasma renin activity after furosemide stimulation, and normal urinary concentrations of 17-KS and of 17-OHCS. The unilaterality of the tumor and its location were confirmed by computed tomography (CT), adrenocortical scintigram with 131-iodocholesterol and venous sampling of blood with analysis of serum levels of aldosterone.

Informed consent for panticipation in this

study was obtained from each patient, in that they had refused, or were reluctant to undergo, surgical resection of the tumor. The initial angiogram was performed to identify the arteries that fed the adenoma ; an aortogram and arteriograms of the renal and inferior phrenic arteries were obtained to analyze the targeted branches that fed the adrenal adenoma. Therapeutic angiography was performed one week after the first diagnostic angiogram. A catheter was introduced into the inferior adrenal artery. The latter originated from the renal artery in 3 cases, and the inferior phrenic artery in one case. We used a 5 Fr catheter in the shape of duck head, or cobra type, as an outer catheter using the coaxial technique. When tumor staining was observed by angiography for these arteries using an outer catheter, their small branches were catheterized by the coaxial technique using a microcatheter (Tracker 18 catheter, Target Therapeutics, San Jose, CA, USA) to select the target arteries for embolization. The dose of absolute ethyl alcohol (AE) was administered at approximately the same volume as that of the water-soluble contrast medium (Iopamidol 300) used to fill the adenoma to produce tumor staining. A volume of 1 to 2 ml of AE was administered slowly as a single injection, at a rate of approximately 1 ml/min, by hand, while the blood pressure was monitored. Angiography was then repeated to confirm the status of the occlusion at the same microcatheter position. When the targeted branches had been completely occluded, angiogram of the inferior adrenal or inferior phrenic arteries were obtained with the outer catheter after withdrawing the microcatheter to locate any another feeding branches originating from these arteries. Vital signs such as blood pressure and body temperature, as well as neurological findings and the patient's complaints were closely monitored from postoperative days 1-28. All patients were administered 5 mg of phentlamine intravenously to avoid severe complications immediately before the procedure. Followup CT, laboratory and hormonal measurements were performed at one, two weeks and again at one month postoperatively in the inpatient. Studies were performed every month after discharge. Adrenocortical scintigrams were also obtained after therapy.

Results

The procedures was successful in embolizing the tumor without major complications in all 4 patients. However, the treatment had to be repeated in 3 patients because of a lack of, or of only partial efficacy, as determined by the plasma levels of aldosterone.

The plasma levels of aldosterone, renin activity, and other laboratory abnormalities caused by the adenoma returned to the normal range

Table 1 Patient list

Patient			Adrenal tumor		Blood pressure before therapy (mmHg)	Plasma concentration	
No.	Age	Sex	Location	Diameter on CT (mm)		※ Aldosterone	※※ Renin activity
1	44	F	right	9	190/120	34	< 0.1
2	65	F	right	15	180/110	66	< 0.1
3	43	M	right	10	170/110	56	< 0.1
4	28	F	left	20	200/120	61	< 0.1

※ Normal range ; 2-12 ng/dl

※※ After furosemide stimulation, normal range ; 0.1-2.0 ng/ml/h

within 7 days of treatment in 3 patients. In these patients, the normal hormonal and laboratory data have continued for 3,4 and 10 months, respectively following treatment (Fig. 1). Although the plasma level of aldosterone immediately declined after treatment, a gradual elevation was observed in one patient (case 4), even after a second treatment.

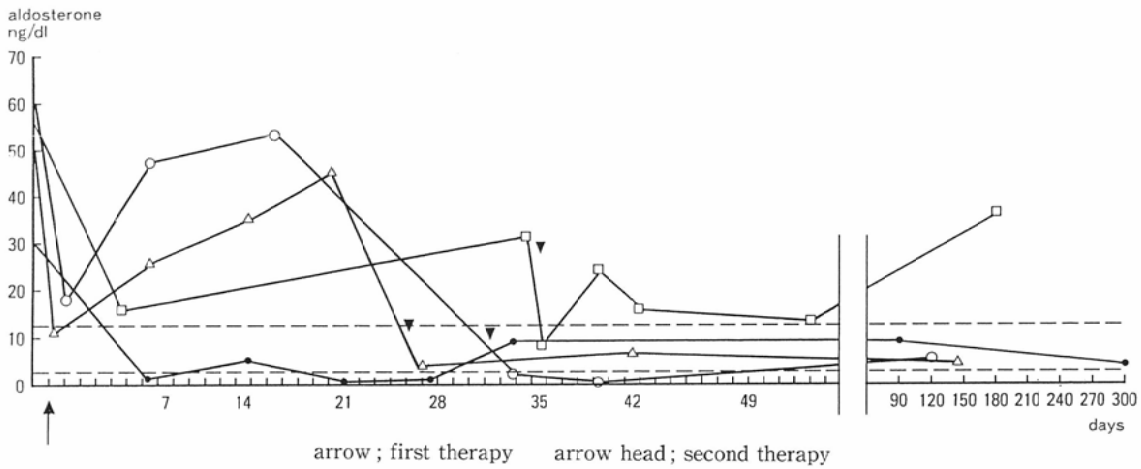
Normotension was achieved in 2 patients (cases 1 and 2) and a decrease in hypertension severity was observed in 1 patient (case 3). Blood pressure normalized more gradually as compared with the hormonal response (Table 2). Normotension continued after the treatment in 3 of the 4 patients.

All patients complained of transient abdominal or back pain immediately after the AE infusion. However, the pain disappeared within a few hours without treatment. Three of 4 patients experienced fever (37.0-38.5℃) which disappeared within 3 days. In 1 of the 4 patients (case 1), variable changes in blood pressure (116/68 ~180/106 mmHg) was observed immediately after the procedure. This instability improved within 3 days without medications. No other severe complications or side effects were observed.

Two representative cases are presented.

Case Reports

Case 1 This 44-year-old woman with a 10-year history of hypertension and headache was hospitalized for diagnosis and treatment. Her blood pressure was markedly elevated (200/110 mmHg). Laboratory and hormonal studies revealed hypokalemia (plasma K, 3.0 mEq/l;



arrow; first therapy arrow head; second therapy
●; case 1 ○; case 2 △: case 3 □; case 4

Fig. 1 Serial changes of serum aldosterone levels after AE injection therapy

Table 2 Blood pressure before and after therapy

Patient No.	Blood Pressure (mmHg)		
	Before	After	
		3 weeks	3~6 months
1	190/120	130/75	140/90
2	180/110	158/100	130/85
3	170/110	150/100	150/100
4	200/120	170/110	220/140

normal range, 3.6-5.1), hypernatremia (plasma Na, 150 mEq/l ; 135-146), high plasma aldosterone (34 ng/dl ; 2-12) and low plasma renin activity after furosemide stimulation (below 0.1 ng/ml/h ; 0.1-2.0). These findings led to the diagnosis of primary aldosteronism. Analysis of venous blood sampled from the adrenal revealed a plasma level of aldosterone of 125.8 ng/dl in the right adrenal vein and 34.5 ng/dl in the left adrenal vein. Findings on CT and an adrenal cortical scintigram performed with 131-iodocholesterol suggested an adenoma present in the right adrenal gland (Fig. 2 (A), (E)). The right renal angiogram revealed tumor staining in the right adrenal artery and in one branch of the right renal artery. Angiography of the right inferior adrenal artery showed a hypervascular mass that was fed by small branches of the inferior adrenal artery, suggestive of a benign adenoma (Fig. 2 (C)). Two small branches were occluded respectively by the slow injection of 0.5 ml of AE with superselective catheterization using a Tracker 18 catheter as the inner catheter. No tumor staining was observed 15 minutes after the embolization (Fig. 2 (D)). The patient complained of transient abdominal pain immediately after the injection of AE, which disappeared within a few hours without medication. Her blood pressure varied from 116/68 to 180/106 mmHg and she had a slight fever (body temperature,37.0 to 38.2℃) for 3 days after the procedure. Laboratory abnormalities returned to the normal range within 7 days : plasma aldosterone concentration : 5.6 ng/dl, plasma renin actitity : 1.4 ng/ml/h, plasma K value : 4.6 mEq/l, and Plasma Na value : 144 mEq/l. A followup CT on the 7 th day demonstrated a reduction in tumor density (Fig. 2 (F)). An adrenocortical scan obtained one month post-procedure showed a reduction in activity of the right adrenal gland (Fig. 2 (B)). She has experienced no recurrence of symptoms, and the laboratory findings remained normal during 10 months of outpatient observation.

Case 4 This 28-year-old woman was found to be hypertensive in a routine health screen performed at her work place. Her blood pressure was markedly elevated (200/110～220/130 mmHg) but she had no symptoms. Laboratory evalution, including hormonal studies, performed on admission, revealed a high plasma level of aldosterone (61 ng/dl) ; low plasma renin activity follwing furosemide stimulation (below 0.1 ng/ml/h) ; hypokalemia (plasma K, 3.5 mEq/l), and hypernatremia (plasma Na, 148 mEq/l). These findings led to a diagnosis of primary aldosteronism. CT showed an area of low density messuring 2.0 cm in diameter in the left adrenal gland, with a normally appearing right adrenal gland (Fig. 3 (A)). Tumor staining was observed in the left superior adrenal artery, and in one branch of the left inferior phrenic artery. The left middle and the inferior adrenal arteries could not be visualized by aortography. Angiography of the left superior adrenal artery identified a hypervascular mass fed by small branches of the superior adrenal artery which suggested a benign adenoma (Fig. 3 (C)). Embolization of the left inferior phrenic artery was done at an area that was more peripheral than the orifice of the superior adrenal branch. We used a microcoil (Target Therapeutics,CA,USA) to prevent the overflow of AE into the peripheral part of the inferior phrenic artery. A branch of the adrenal artery was occluded by slow injection of 2.0 ml of AE with superselective catheterization, using a Tracker 18 catheter as the inner catheter. The tumor stain was disappeared 15 minutes after embolization (Fig. 3 (D)). The patient complained of transient abdominal pain immediate-

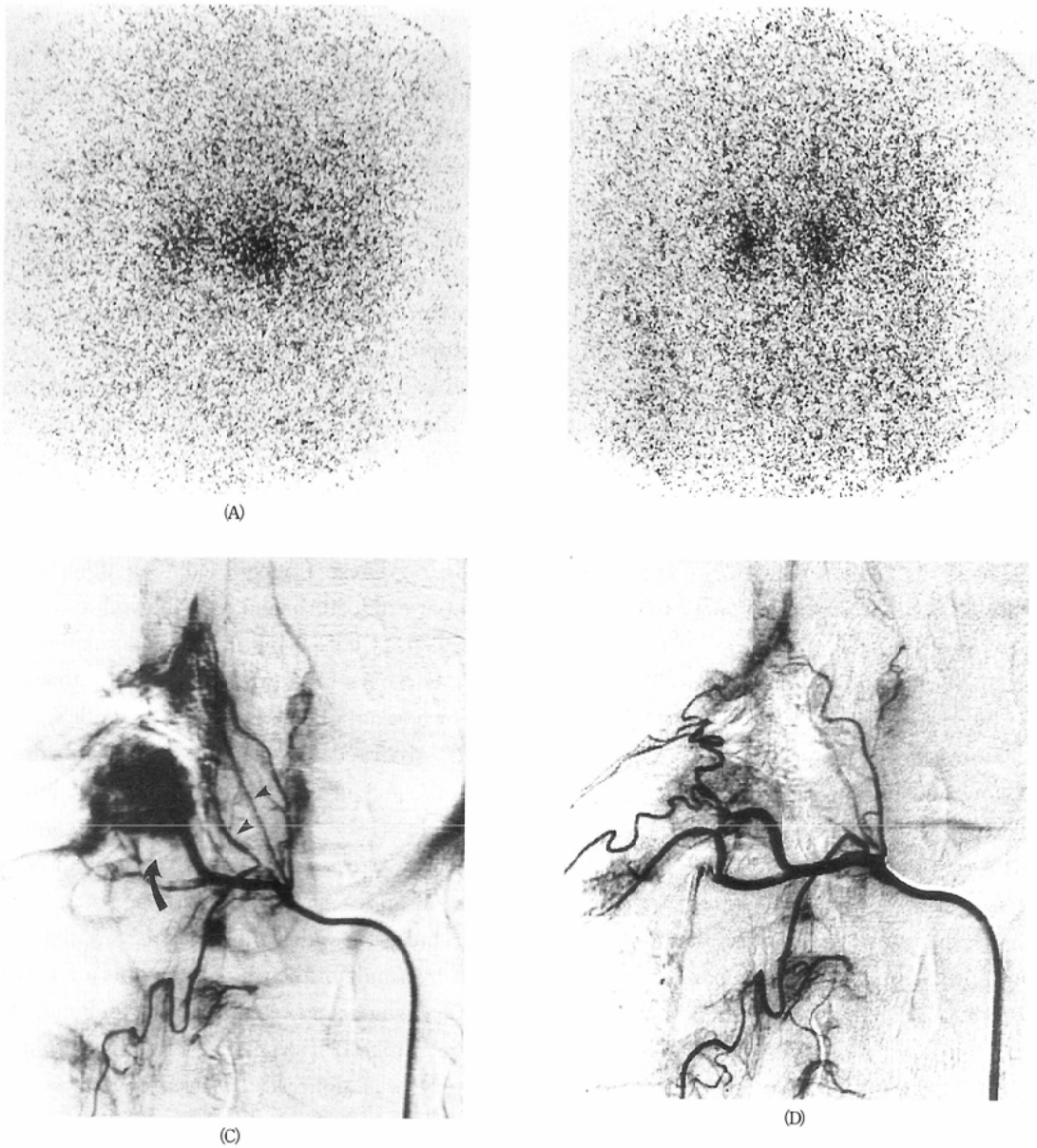
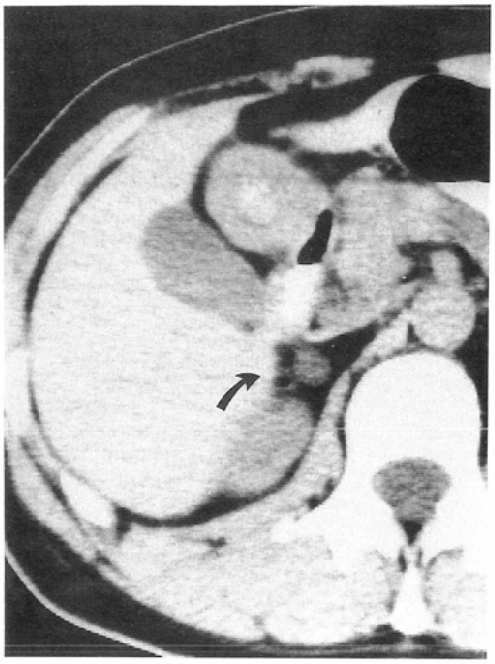


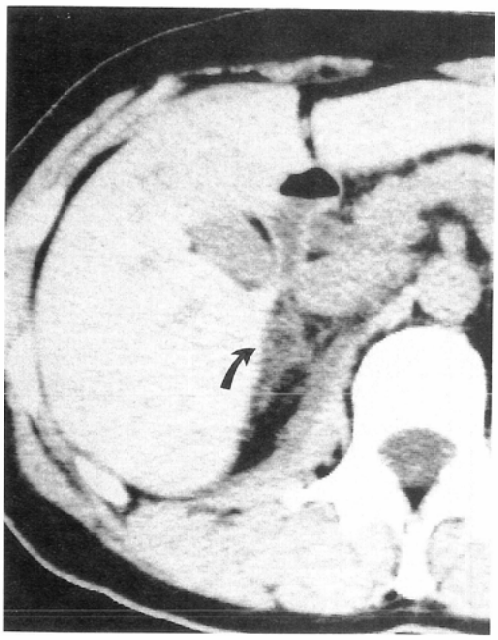
Fig. 2 A 44-year-old woman with right aldosteronoma (case 1) : Adrenocortical scans with intravenous I-131-iodocholesterol before (A) and one month after AE injection therapy (B). Radioactivity of the right adrenal gland decreased after the therapy.

The inferior adrenal angiograms before (C) and 15 min after the therapy (D). The inferior adrenal artery was one of the branches of the renal artery. The tip of the guiding catheter was placed at the orifice of inferior adrenal artery. Before the therapy the tumor stain was seen in the central part of the right adrenal gland ((C), arrow). After the injecton of each 0.5 ml of AE into 2 branches using a Tracker 18 catheter with coaxial system ((D)), the tumor stain disappeared almost completely. A soft tissue density mass with approximately 1 cm in diameter was demonstrated in the rightadrnal gland on the pretreatment CT ((E), arrow). Seven days after ethanol infusion the density of tumor become lower, suggesting necrotic change ((F), arrow).

She has experienced no reccurence of symptoms and laboratory data have remained in normal range during 10 months after the single therapy.

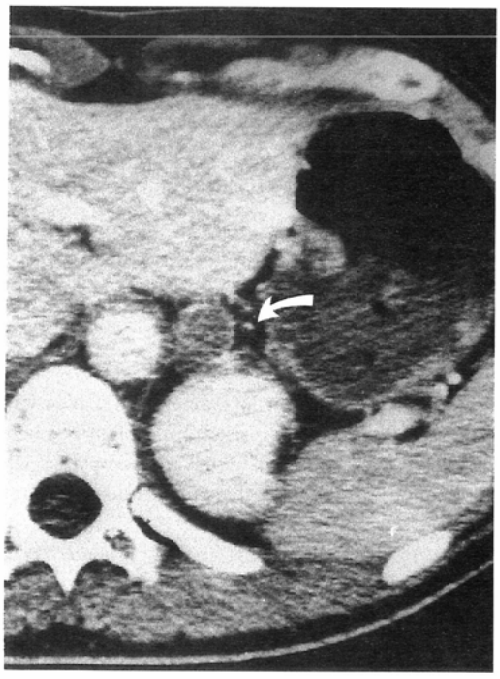


(E)

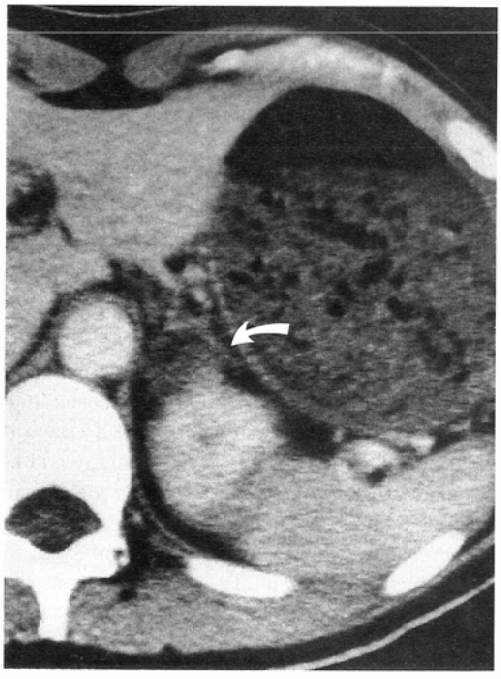


(F)

Fig. 2

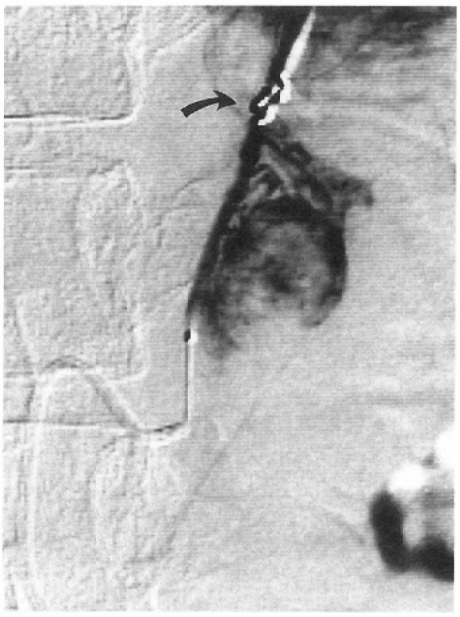


(A)

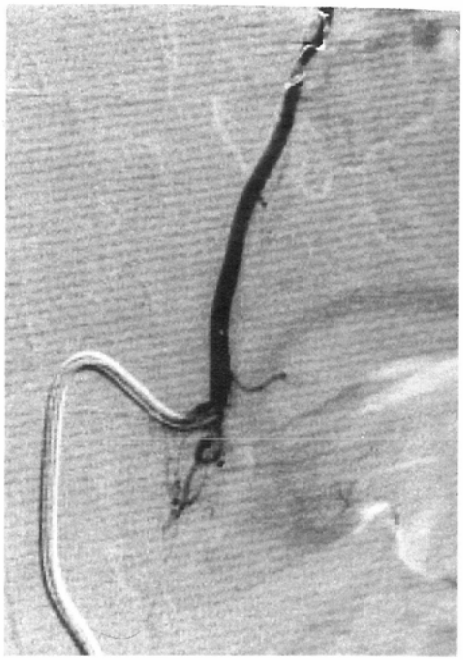


(B)

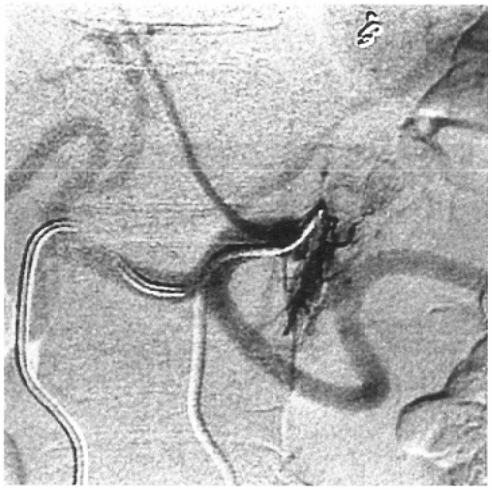
Fig. 3



(C)



(D)



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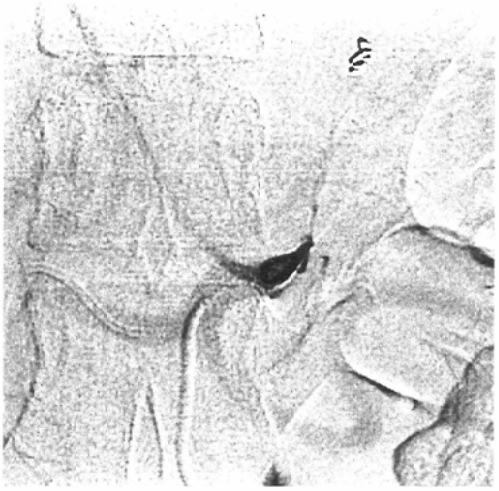

(F)

Fig. 3 A 28-year-old woman with left aldosteronoma (case 4). She received twice of intraarterial AE injection. Computed tomography taken before (A) and 7 days after the first therapy (B). Adrenal arteriograms performed before (C) and immediately after (D) the first therapy and before (E) and immediately after (F) the second therapy.

Computed tomography demonstrated a low density area with a diameter of 2.0 cm suggesting an adenoma in the left adrenal gland (A). The density of the adenoma became lower after the first therapy (B).

An adrenal branch was occluded by 2.0 ml of AE with superselective catheterization using a microcatheter. The left inferior phrenic artery was also occluded by a microcoil to avoid the overflow of AE into the peripheral part (arrow). After the first therapy, the tumor stain (C) disappeared (D) and the plasma aldosterone level decreased to 17 ng/dl, about 1/3 of the pretreatment level. However, hypertension was not improved and gradual elevation of the plasma aldosterone level was observed.

Gradual elevation of plasma aldosterone was observed, even after the second therapeutic angiography was performed with 0.5 ml of AE ((E),(F)).

ly after the injection of AE, but disappeared within a few hours without medication. In seven days after, the plasma level of aldosterone decreased to 17 ng/dl. On the 7th day follow-up CT demonstrated a decrease in tumor density (Fig. 3 (B)). However, the hypertension did not improve and there was a gradual elevation of the plasma aldosterone concentration (29 ng/dl, 30 days after the first treatment). We considered that the left superior adrenal artery would recanalize, and a second therapeutic angiography was performed 35 days after the first procdure. The orifice of the inferior phrenic artery was occluded and a feeder was seen in the normal adrenal tissue around the adenoma (Fig. 3 (E)). No other feeding arteries were discovered. Therefore, the inferior phrenic artery was embolized using 0.5 ml of AE to protect the recurrence of the tumor. After the procedure the plasma levels of aldosterone returned to the normal range, but the hypertension did not improve, and the plasma aldosterone concentration gradually rose (24 ng/dl, 7 days after the second therapy). We considered that the aldosteronoma was only partially deactivated. This patient continues to be followed as an outpatient.

Discussion

Despite the wide use of arterial embolization in treating other tumors, adrenal arterial embolization of the adrenal artery is infrequently reported. However, adrenal arterial embolization is sometimes used to decrease tumor bulk or vascularity so as to facilitate a subsequent adrenalectomy, to suppress hormonal function of the tumor or to relieve pain, especially in such inoperable adrenal lesions as a functioning pheocromocytoma[1)-3)], ACTH-dependant Cushing's syndrome[4),5)], adrenal carcinoma, and metastatic tumors of the adrenal[6)]. However, we know of no attempt at adrenal embolization has been made to deactivate an operable benign adenoma. All patients in our study had refused, or were reluctant to receive, surgical resection of the tumor. We therefore tried to perform adrenal arterial embolization to suppress hormonal function, after we had obtained informed consent.

The complexity of the adrenal supply is a problem with the present method and renders catheterization both time-consuming and difficult. This problem may be overcome by using a coaxial technique and a microcatheter. In our study, the superior, middle and inferior adrenal arteries were not always visualized despite the performance of angiography before the treatment to detect the feeding vessels. This may be attributed to normal vessel variants. In addition, several branches arose from the inferior adrenal artery in 3 patients, and from the inferior phrenic artery in one patient. However, the small branches of the feeding arteries were easily catheterized by the coaxial technique using a microcatheter. Therefore, a nearly complete deactivation of the aldosteronoma was achieved in all but one patient (case 4).

AE is an effective occlusive agent with long-term effects,is being used to embolize tumors of the kidney[7)] and the adrenals in patients with severe ACTH-dependent Cushing's syndrome[4)]. Massive catecholamine release can occur from the normal adrenal tissue following the adrenal venous and arterial injection of AE[8)]. Timmis et al reported that during the four weeks proceding the adrenal embolization of a pheochromocytoma, their patient had received an α-adrenergic antagonist, and immediately before the procedure 5 mg of phentolamine had been injected intravenously[3)]. We also administered 5 mg of phentolamine intravenously to avoid severe complications. Should a hypertensive

crisis be induced by an overdose of AE, phentolamine would effectively control it[3]. We selected the volume of AE suitable for injection by measuring the volume of the water-soluble contrast medium needed to fill the adenoma to produce tumor staining. We consider that the 3 patients who received the AE injection twice had received a less than optimal reguired to completely deactivate the aldosteronoma. The suitable volume of AE remains to be resolved. Furthermore, the entry of blood flow from the abdominal aorta or renal arteries may be interrupted by the outer catheter. Overflow into the normal adrenal tissue and damage of normal adrenal tissue can therefore be avoided. During the arterial infusion of AE, we closely monitored the vital signs, especially the blood pressure, and were prepared to administer emergency treatment. However, no serious complications such as hypertensive crisis or deterioration of symptoms occurred.

If the source of the aldosteronoma is unilateral, an unilateral adrenalectomy is generally indicated. However, the successful surgical removal of an aldosteronoma produced normotension in 70% of the patients with a significant lowering of blood pressure, but not to normal values, in 25%, and a lack of improvement in 5%[9]. Although additional long-term follow-up is required, superselective embolization using AE to deactivate an aldosteronoma may be an useful alternative to surgery, especially in patients who refuse, or who are not candidates, for surgical treatment.

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