Elevation of Plasma Renin Activity during Pregnancy and Rupture of a Dissecting Aortic Aneurysm in a Patient with Primary Aldosteronism

Akihiko SHIMIZU, M.D., Wataru AOI, M.D., Masazumi AKAHOSHI, M.D., Toshinori UTSUNOMIYA, M.D., Yutaka DOI, M.D., Shin SUZUKI, M.D., Morio KURAMOCHI, M.D., and Kunitake HASHIBA, M.D.

SUMMARY

This is a case report of a 37-year-old Japanese woman with primary aldosteronism who was found to have high plasma renin activity during toxemia of pregnancy and who died of a dissecting aneurysm of the aorta about 2 years later. The autopsy findings showed cystic medial necrosis in the aorta and a right adrenocortical adenoma. The dissecting aneurysm in this case is probably related to hypertension and cystic medial necrosis. A definite diagnosis of primary aldosteronism cannot be made during toxemia of pregnancy, and it is necessary to do serial determinations of plasma renin activity and plasma aldosterone concentration after delivery to confirm the diagnosis.

Additional Indexing Words:
Primary aldosteronism Plasma renin activity Toxemia of pregnancy Dissecting aneurysm of the aorta Cystic medial necrosis

NORMAL pregnancy is characterized by elevation of plasma renin activity and plasma aldosterone concentration. Primary aldosteronism has been reported only rarely as a complication of pregnancy. It has been reported that plasma renin activity in a pregnant woman with primary aldosteronism is suppressed to subnormal levels as compared with that of normal pregnancy or of normal non-pregnant subjects. Therefore, a definite diagnosis of primary aldosteronism can be made during pregnancy, using the usual criteria.

The essential hypertensive patient with low plasma renin activity has
been reported to have a conspicuously low level of vascular complications of hypertension. It is commonly held that primary aldosteronism is a relatively benign form of hypertension. Therefore, the occurrence of vascular damage in a patient with primary aldosteronism has rarely been reported.

All of these cases had cerebral vascular accidents and ischemic heart disease.

In the past dissecting aneurysm of the aorta has been held to occur almost exclusively in older individuals particularly in the presence of hypertension. However, Schnitaker et al reported a case of dissecting aneurysm of the aorta occurring in a 22 year old female without hypertension, and that dissecting aneurysms seen in young females were frequently associated with pregnancy.

As far as we know, no case of primary aldosteronism with high plasma renin activity during pregnancy has been reported. We have recently encountered a patient with primary aldosteronism who had been found to have high plasma renin activity during toxemia of pregnancy and who subsequently developed a dissecting aneurysm of the aorta about 2 years after delivery.

**MATERIALS AND METHODS**

The plasma renin activity was measured by the radioimmunoassay of angiotensin I released during incubation at pH 7.4 (CEA-IRE-SOLIN, Italy). The plasma aldosterone concentration was determined by radioimmunoassay. Serum electrolytes were measured by autoanalyser.

**CASE REPORT**

A 37-year-old Japanese housewife was admitted to the Third Department of Internal Medicine, Nagasaki University Hospital on May 14, 1981, because of an oppressive feeling in the chest and back pain. She was the product of a normal pregnancy and delivery. The patient had no previous history of hypertension, proteinuria or edema even during normal pregnancies in 1969 and 1971. During the seventh month of her third pregnancy in 1974 the patient noticed the gradual onset of generalized edema. One month later she was found to be hypertensive (200/100 mmHg) by an attending physician and entered the hospital. However, her baby died following premature separation of the placenta. One week after delivery, the patient became normotensive and the generalized edema disappeared without additional treatment.

In 1976 she again became pregnant, and her blood pressure was 160/100 mmHg at the fifth month of pregnancy. In the last month of preg-
In May 1978, during her fifth pregnancy she was seen by an obstetrician who recorded a blood pressure of 184/124 mmHg with pretibial edema and no proteinuria. In June, during the seventh month of pregnancy, she was admitted to the Gynecological Department of the Nagasaki University Hospital because of hypertension (190/100 mmHg) and proteinuria. Despite initiation of treatment with α-methyl-dopa and hydralazine and a low salt diet (5 Gm/day), she was found to have a blood pressure of 240/130 mmHg with facial edema and vomiting. Eleven days later, she was transferred to the Third Department of Internal Medicine for the control of her blood pressure.

On the day of admission, as shown in Fig. 1, plasma renin activity in the supine position was 5.69 ng/ml/hr on a low salt diet (5 Gm/day) (normal range-recumbent with normal diet; 0.48–1.98 ng/ml/hr). The plasma aldosterone concentration in the supine position was 560 pg/ml on a low salt diet (normal range-recumbent with normal diet; 30–80 pg/ml). At 7 A.M. after remaining recumbent and fasting overnight her plasma renin activity in the supine position was 3.40 ng/ml/hr on a low salt diet (5 Gm/day). The plasma aldosterone concentration in the supine position was 603 pg/ml on a low salt diet. The serum potassium was 2.7 mEq/L (Fig. 1). The patient received additional treatment with propranolol and spironolactone. On funduscopy cotton wool patches were found but there was no retinal hemor-
An electrocardiogram was normal except for an abnormal U wave. Roentgenogram of the chest disclosed blunting of the right costophrenic angle, but no cardiac enlargement.

On July 12, 1978, the patient delivered a premature baby after induction of labor because of accelerated hypertension. One month after delivery she was normotensive while under treatment with antihypertensive drugs such as hydralazine, α-methyl-dopa, propranolol and spironolactone. At that time, plasma renin activity was 0.09 ng/ml/hr, plasma aldosterone concentration 440 pg/ml, and serum potassium 3.4 mEq/L (Fig. 1), which led to a diagnosis of primary aldosteronism. However, she refused further examinations. In September 1978, the patient was discharged and treatment continued with the above antihypertensive drugs. From April to August 1979, her blood pressure ranged from 130/70 to 150/90 mmHg, despite receiving only 75 mg/day of spironolactone. During out-patient clinic visits, suppressed plasma renin activity, high plasma aldosterone concentration, and decreased serum potassium were found repeatedly, which reinforced the diagnosis of primary aldosteronism (Fig. 1). To our disappointment, she stopped attending the out-patient clinic because she was asymptomatic and did not receive any antihypertensive drugs after August 1979.

Subsequently the patient had remained asymptomatic until 11 May, 1981, when while housekeeping, she first suddenly noted a sensation of heavy pressure in the sternal area and back pain for about 10 min. The oppressive feeling in the chest occurred intermittently and tended to become of longer duration and more intense on 12 and 13 May. However this did not prevent the patient from sleeping or working. At 7 P.M. on 14 May, she experienced sudden continuous chest pain in the sternal area and extending to the back, which was so severe as to prevent the patient from working. At 11 P.M., the patient was admitted to the Nagasaki University Hospital by ambulance because of these symptoms.

Physical and laboratory examination on the second admission:

Her height was 152 cm and body weight was 44 Kg. The radial pulse was 56/min and regular. The blood pressure was 180/98 mmHg. There was no difference in the blood pressure between the two arms. There was a grade 2 bruit on the right side of neck and a grade 3 bruit on the left side of neck. There was a grade 3 systolic and diastolic murmur in the left third inter-costal space (this murmur was not heard on the first admission). The liver was palpable two fingerbreadths below the costal margin in the right midclavicular line, and was tender. Neurological examination was negative except for the presence of Trousseau’s sign. There was no muscle weakness.
Funduscopic examination was classified as Keith-Wagner II.

Laboratory examination showed a hemoglobin of 10.5 g/dl and a white cell count of 8,900, with 19% banded neutrophils, 67% neutrophils, and 14% lymphocytes. The serum potassium was 2.4, sodium 154, chloride 106 and carbon dioxide 29.5 mEq/L. Plasma renin activity was undetectable with the patient on a normal diet without any antihypertensive drugs. However, plasma aldosterone concentration in the supine position was 1,430 pg/ml on a normal diet. The blood Wassermann and TPHA were negative. The electrocardiogram disclosed left ventricular hypertrophy.

The chest roentgenogram did not reveal an increased heart shadow or dilatation of the aorta.

Clinical course after the second admission:

On the second admission, the extreme chest pain and auscultatory findings led to probable diagnosis of dissecting aneurysm. The chest and back pain gradually subsided after about 3 hours following treatment with nifedipine, and at that time the blood pressure was 162/86 mmHg. However, control of blood pressure was difficult. Despite treatment with spironolactone 150 mg/day, furosemide 40 mg/day, nifedipine 140 mg/day, and α-methyl-dopa 750 mg/day which were prescribed after the second admission, the blood pressure remained 150–200 mmHg systolic and 80–100 mmHg diastolic. For the next 5 days, the patient did not complain of severe chest pain while at bed rest. Although computerized tomography was scheduled in order to confirm the diagnosis, the patient suddenly felt faint at rest at 5:06 P.M. on 19 May. The patient’s respiratory rate was 18/min, and blood pressure 116/72 mmHg. She remained conscious without chest pain but vomited brown material at this time. Eleven min after the onset of faintness, she suddenly lost consciousness and exhibited moderate cyanosis and marked distention of the neck veins. There was no radial pulse at this time. Resuscitation was begun immediately (cardiac massage, norepinephrine and atropine). Thirty min later her blood pressure rose to 102/76 mmHg and she regained consciousness.

As it was thought that she probably had a tamponade secondary to a hemopericardium, an echocardiogram was done to confirm the diagnosis. The echocardiogram showed a massive pericardial effusion, which led to the diagnosis of hemopericardium with dissecting aneurysm of the aorta. At 7:00 P.M., a roentgenogram of the chest disclosed dilatation of the aorta and an increase in the size of the cardiac shadow. The next day at 0:05 A.M., the patient again went into shock induced by cardiac tamponade. She regained consciousness after 15 min at which time her blood pressure was
96/72 mmHg. In spite of treatment with dopamine her blood pressure remained under 100 mmHg systolic 24 hours after the vascular accident, and acute renal failure developed. About 36 hours after going into shock her blood pressure increased to 120/90 mmHg. The patient improved gradually without hemodialysis. Beginning at 5:30 P.M., on 21 May, 1981, trimetaphan was administered because blood pressure gradually rose to 150/100 mmHg. The blood pressure was maintained at less than 120/80 mmHg with this treatment. However, the chest film on 23 May showed complete radio-opacity of the left hemithorax and marked increase in the size of the heart shadow. At noon on 28 May, the blood pressure increased to 170/110 mmHg in spite of an increased dose of trimetaphan. Unfortunately, the patient suddenly lost consciousness and died of cardiac tamponade.

**Autopsy findings:**

Two hundred ml of bloody fluid were present in the pericardial sac and 500 ml of bloody fluid were in the left pleural cavity. The heart weighed 570 Gm. The aorta showed a sharp longitudinal tear (1.5 cm) in the intima near the root of brachiocephalic artery, as if it had been cut with a knife. A dissecting aneurysm extended proximally to above the orifice of the coronary

![Fig. 2. Demonstration of the very sharp, knife-like tear at the root of the brachiocephalic artery. The open arrow shows the longitudinal sharp tear. The closed arrow shows a site of dissection filled with recently clotted blood.](image-url)
artery and distally to the renal arteries but did not include them. The site of the dissection was filled with recently clotted blood (Fig. 2). The dissection did not extend into the arterial walls of the arms or neck. The intima of the aorta did not show any abnormal changes except for minute atherosclerosis. There was a right adrenocortical adenoma surrounded by normal adrenal tissue (Fig. 3). The size of the adenoma was 15×15×10 mm. The lungs, liver, spleen and kidneys showed only passive congestion.

Microscopic findings:

The thoracic and abdominal aorta showed slight intimal thickening. There was marked variation with regard to the amount of basophilic material, which ranged from small pools of mucopolysaccharides with minute cysts that did not interrupt the arrangement, to large pools with confluent cyst-like spaces resulting in disruption of the lamellar build of the aortic media. This feature has frequently been termed "cystic medial necrosis". As shown in Fig. 4a, the cysts were large and extended over more than one lamellar unit in the media of the non-dissecting abdominal aorta. In Fig. 4b, focal fragmentation of the elastic lamellar in the aortic media was present, and the cells showed disarray. Fig. 4c shows a slightly increased amount of basophilic material that had been stained with Alcian blue, but not with PAS. This indicates that the cyst contained a mucoid substance. The adenoma was composed of small packets with clear and somewhat foamy cytoplasm, which was consistent with the histological findings of primary aldosteronism.
Fig. 4. Histologic findings of non-dissected media of the abdominal aorta. a. Note the cysts in the media of the non-dissecting abdominal aorta (Hematoxylin-Eosin ×200). b. Note the focal fragmentation of elastic lamellae in the aortic media (Elastic van Gieson ×400). c. Note the basophilic substance in the cyst (Alcian blue ×400).

**DISCUSSION**

The characteristic findings in this case are as follows: (1) elevated plasma renin activity during pregnancy in spite of primary aldosteronism, and (2) occurrence of a dissecting aneurysm of the aorta about 2 years after
delivery. The diagnosis of primary aldosteronism was confirmed by the presence of suppressed plasma renin activity, elevated plasma aldosterone and normal glucocorticoid function (17KS and 17-OHCS). In 1964 Conn reported that plasma renin activity in primary aldosteronism was severely suppressed and that measurements of plasma renin activity were of great importance in making the diagnosis of primary aldosteronism and in making the distinction between primary aldosteronism and secondary aldosteronism associated with renal abnormalities.

Plasma renin activity and plasma aldosterone concentration have only rarely been reported in pregnant women with primary aldosteronism. Under these circumstances, plasma renin activity, rather than being elevated as in normal pregnancy, was suppressed to subnormal levels. In our patient plasma renin activity was lower but plasma aldosterone concentration was higher in comparison with that seen during the corresponding period (seventh month) of a normal pregnancy. Plasma renin activity and plasma aldosterone concentration in the postpartum period usually return to normal within 2 weeks. In our patient, plasma renin activity was obviously low (0.09 ng/ml/hr) and plasma aldosterone concentration was clearly elevated (440 pg/ml) even 1 month after delivery. This low level of plasma renin activity and high plasma aldosterone concentration continued. As mentioned above, we felt that this patient already had primary aldosteronism at the time of her first admission. Her plasma aldosterone concentration gradually decreased from 440 pg/ml to 165 pg/ml during follow-up at the out-patient clinic. This was thought to be due to inhibition of aldosterone secretion by spironolactone.

Although plasma renin activity increases in normal subjects and hypertensive patients without adrenal adenoma during periods of extended sodium restriction, it remains clearly subnormal in primary aldosteronism. However, in our patient plasma renin activity and plasma aldosterone concentration on a low salt diet (5 Gm/day) were clearly elevated during the third-trimester of pregnancy, and suppressed plasma renin activity and elevated plasma aldosterone concentration were observed beginning 1 month after delivery. The mechanism by which plasma renin activity increased during pregnancy in our patient is not clear. However, there are several possible explanations for this. One is that this patient had been found to have accelerated hypertension during pregnancy and developed toxemia of pregnancy, which was possibly related to elevated plasma renin activity. The case reported here had primary aldosteronism with toxemia of pregnancy, whereas the patient described by Gordon et al did not have toxemia of pregnancy. Although plasma renin activity was found to be significantly lower in hypertensives and
in patients with toxemia of pregnancy \(^{21}\) as compared with normal pregnant women, toxemia of pregnancy might cause an increase in plasma renin activity due to high levels of progesterone which were, however, not measured in this patient. Another possibility is that the gravid uterus might be the source of the elevated plasma renin activity of pregnancy. \(^{22}\) However, Gordon et al reported that uterine renin might be suppressible as a part of the physiopathology of primary aldosteronism without toxemia of pregnancy and, therefore, there is no possibility that the gravid uterus might be the source of the renin in our case. A third possibility is that the malignant hypertension was caused by the primary aldosteronism. Baglin reported primary aldosteronism with malignant hypertension with elevated plasma renin activity and renal insufficiency. \(^{23}\) Plasma renin activity is elevated in 36% of patients with malignant hypertension. \(^{24}\) But our case did not have malignant hypertension as evidenced by her stage II hypertensive retinopathy (Keith-Wagner II) and lack of renal insufficiency. Furthermore, the patient improved after delivery without removal of the adrenal adenoma.

As mentioned above, a definite preoperative diagnosis of primary aldosteronism during toxemia of pregnancy was impossible, using the usual criteria, because plasma renin activity is not suppressed to subnormal levels in patients such as ours with primary aldosteronism during toxemia of pregnancy. The mechanism for this remains unexplained.

Generally, the occurrence of vascular damage in a patient with primary aldosteronism has only rarely been reported. \(^{12}\) Our case exhibited a dissecting aneurysm of the aorta with histologic findings of cystic medial necrosis of the aorta including that portion without dissection. Today, the diagnosis of cystic medial necrosis is generally made on the basis of the presence of cysts with basophilic substances. Erdheim claimed that cystic medial necrosis played an important role in dissecting bleeds. \(^{25}\) Gore \(^{26}\) and Kunita \(^{27}\) described the aortic media as showing medial degeneration of the elastic laminae in dissecting aneurysms in patients under 40 years of age, which was in general consistent with the histologic findings of Marfan's syndrome. Nevertheless, Schlatmann et al \(^{28}\) and Carlson et al \(^{29}\) reported the presence of cystic medial necrosis in the human ascending thoracic aorta, which showed a striking correlation with age and might represent the normal histologic aging process of the aorta. Furthermore, it has been reported that dissecting aneurysms in young females were frequently associated with pregnancy, \(^{13}\) and that there was marked fragmentation of the reticulum fibers and a decrease in acid mucopolysaccharides in the aortic media of pregnant women. \(^{30}\) On the contrary, Kinney et al found that pregnancy did not appear to influence the frequency of aortic dissection. \(^{31}\) However, in our patient, cystic medial
necrosis of the non-dissecting abdominal aorta was observed, which was consistent with the histologic findings reported by Manalo-Estrella. Therefore, in our case, the dissecting aneurysm of the aorta was probably related to hypertension due to primary aldosteronism and cystic medial necrosis of the aorta which was probably induced by toxemia of pregnancy.

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