Elevated Endothelin-1 Levels and Persistent Stage IV Hypertension in a Nonvolume Overloaded Anephric Patient

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Persistent hypertension after nephrectomy is in most cases due to increased fluid volume. Endothelin-1 is a potent endogenous vasoconstrictor peptide. Its role in the development and maintenance of hypertension is not completely understood, but it might be significant in some cases. We report a case of stage IV hypertension after nephrectomy with elevated endothelin-1 levels and no volume overload. Am J Hypertens 1996;9:935–937

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Persistent hypertension in anephric patients, termed renopriapal hypertension, is almost always due to volume overload. After bilateral nephrectomy, the blood pressure usually becomes normal, and remains so with adequate volume control. This might be in part due to lower sympathetic nervous system activity. Circulating levels of plasma renin, angiotensin I and II are lower post nephrectomy, but may play a role in poor blood pressure control in some patients. Alteration of the whole body autoregulation has also been suggested for maintaining high blood pressure in the anephric state, whereas the absence of renal vasodepressive substances is not felt to play a major role.

Endothelin-1, synthesized by a variety of cells, is a potent endogenous vasoconstrictor peptide. Its vasoactive effect is associated with the activation of phospholipase C, which leads in several steps to the increase of the intracellular calcium concentration. Endothelin-1 potentiates the vasoconstriction caused by norepinephrine, while catecholamines increase the action of endothelin-1. The vasoconstricting effects of endothelin-1 are heightened in atherosclerotic vessels, in which the opposing effect of nitric oxide is lost.

CASE PRESENTATION

The patient was a 31 year old Mexican-American woman with a history of nephrotic syndrome due to focal segmental glomerulosclerosis (FSGS). The patient exhibited massive proteinuria, measured at 10 g/24 h with resultant severe anasarca. Blood urea nitrogen (BUN) was measured at 37 mg/dL and serum creatinine at 4.9 mg/dL. In addition, the patient had several episodes of hypertensive crises requiring admission to the Medical Intensive Care Unit at the Maricopa Medical Center. Medical management for FSGS with steroids and cytotoxic agents was felt to have failed when the patient's massive proteinuria persisted and her serum albumin had fallen to 1.3 g/dL. Therefore, the patient underwent bilateral nephrectomy to control the proteinuria. Afterwards, the patient began thrice weekly hemodialysis. Surprisingly, despite remaining at or near her dry weight in between hemodialysis treatments, she remained hypertensive, requiring the use of a four to five drug
antihypertensive regimen that included minoxidil. When attempts were made to remove 0.5 to 1 L of fluid during hemodialysis, the patient complained of cramps, nausea, and lightheadedness. Hemodialysis was unsuccessful in lowering her blood pressure. In addition, the patient had several occurrences of hypertensive emergencies with systolic blood pressures between 197 and 208 mm Hg and diastolic blood pressures between 122 and 134 mm Hg, including an episode of hypertensive encephalopathy (Figure 1). On each admission, the patient presented without signs of volume overload. An ectopic source of renin production was sought for. However, plasma renin activity was measured at <0.1 (ng/mL)/h. Plasma aldosterone was measured at 4 ng/dL. Spot serum catecholamine and thyroid stimulating hormone level determinations were within normal limits. Plasma endothelin-1 levels were measured predialysis at 3.4 pg/mL and were elevated postdialysis at 11.9 pg/mL, with the normal range being between 4.5 and 8.5 pg/mL.

**DISCUSSION**

Sodium retention is the postulated mechanism underlying hypertension in the majority of patients with renoprival hypertension. Removal of the native kidneys has been advocated as a method to control severe hypertension in patients who have undergone cadaveric renal transplantation. Nephrectomy also lowers the rate of sympathetic nerve discharge, making overactivity of the sympathetic nervous system an unlikely etiology for the hypertension in anephric patients. Our patient remained hypertensive despite bilateral nephrectomy and lack of volume overload. De Santo et al reported on two patients who had undergone bilateral nephrectomy, and who were receiving erythropoietin therapy. Once these patients achieved their dry weight, neither developed hypertension as a result of erythropoietin therapy.

We detected high levels of circulating endothelin-1 in our patient. Endothelin-1 has been previously shown to produce sustained, salt-sensitive elevation of the mean arterial pressure in Sprague-Dawley rats. Endothelin-induced hypertension may involve the stimulation of the renin-angiotensin system, but not an increase in circulating angiotensin II concentration. Hypertension caused by endothelin-1 in animals has been demonstrated to respond to administration of angiotensin converting enzyme inhibitors. Our patient showed low plasma renin activity and serum aldosterone level. The patient received intravenous angiotensin converting enzyme inhibitors during her first hypertensive crisis, which had no effect on her blood pressure.

It is interesting to note that plasma endothelin-1 levels increased after hemodialysis. Wilkie et al found
that endothelin-1 levels were higher posthemodialysis in patients in whom dialysis was performed through an arterial-venous fistula. Hemodialysis was performed in our case through an arteriovenous graft. Carlini et al. found that endothelin-1 levels increase after hemodialysis in patients given intravenous, but not subcutaneous, recombinant human erythropoetin. Our patient received erythropoetin intravenously.

Plasma endothelin-1 concentrations are usually normal in essential hypertension, and there is little evidence that endothelins play a role in the development or maintenance of essential hypertension. However, they might be important in some other forms of hypertension. A patient with hemangiopericytoma has been reported to have hypertension and elevated plasma endothelin-1 levels. Similarly, plasma endothelin-1 concentrations have been shown to be increased in patients with preeclampsia.

We think that elevated plasma endothelin-1 levels may have contributed to hypertension in our patient. The cause of the elevation of endothelin-1 level in our case is likely multifactorial, probably in part due to hemodialysis and intravenous erythropoetin administration.

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REFERENCES