Tumor-Dependent Hypertension

Principal Discussant
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Case Presentation

A 34-year-old woman presented with a 1-month history of nocturia, constipation, and abdominal and back pain. Her blood pressure was recorded 6 months earlier as 100/60 mm Hg, and she was always said to be normotensive.

First Admission

The patient’s blood pressure was found to be 150/110 mm Hg, and pelvic exam revealed a large pelvic mass. Intravenous pyelogram showed normal kidneys and collecting system; a pelvic soft tissue mass indented the bladder. Serum potassium was 2.8 mEq/liter, random peripheral plasma renin activity (PRA) was 52 ng angiotensin I (ANG I)/ml/hr (normal upper limit on a low salt diet = 9.1 ng ANG I/ml/hr), and urine vanillylmandelic acid (VMA) was 8.2 mg/24 hr (upper limit of normal = 8 mg/24 hr). An exploratory laparotomy revealed a tumor in the fallopian tube with peritoneal involvement. Manual exploration of the upper abdomen including the liver, diaphragm, and periaortie nodes showed no evidence of tumor. The pathologic diagnosis was poorly differentiated fallopian tube adenocarcinoma with peritoneal micrometastases. The patient underwent total abdominal hysterectomy and bilateral salpingo-oophorectomy and was subsequently treated with pelvic and abdominal irradiation for a total dose of 5900 rads over the subsequent 2 months. Six months after presentation, her blood pressure was normal, the serum potassium was 3.8 mEq/liter, and a repeat laparoscopy revealed no evidence of recurrent malignancy.

Second Admission

Three months later, the patient’s blood pressure was 200/120 mm Hg. Therapy with hydrochlorothiazide, triamterene, metoprolol, and hydralazine was initiated. Because of persistent hypertension, she was hospitalized 3 months later with a blood pressure of 170/120 mm Hg. The fundi were normal. There were no cardiac murmurs, no abdominal bruit, and no clinical evidence of residual pelvic tumor. Serum sodium was 127 mEq/liter, and serum potassium was 2.9 mEq/liter. Values for creatinine, complete blood count, peripheral smear, and urinalysis were normal. Intravenous pyelogram (IVP) demonstrated a slightly delayed appearance of contrast on the right side, but a renal arteriogram and nephrogram revealed normal renal vessels. Abdominal CT scan showed three peripheral abnormalities within the liver consistent with metastatic tumor and no evidence of tumor within the kidney or pelvis. Venous sampling for PRA revealed that the PRA of the infrarenal inferior vena cava was 63 ng ANG I/ml/hr; that of the right lower pole was 61; of the right upper pole, 64; of the left lower pole, 227; and of the left upper pole, 83 ng ANG I/ml/hr. Renal arteriogram showed normal renal arteries on both sides with no interparenchymal defects. Nephrogram also showed relatively smooth contours of the kidneys, and no overt mass or blush suggestive of tumor. During the late phase, the collecting system on the right side appeared to show minimal dilation and only minor blunting of the individual calyces. The left collecting system was normal. At this point, Dr. Corvol will discuss the case.
**Discussion**

**Dr. Corvol:** This young woman suffered from both fallopian tube carcinoma and relapsing hypertension. The nature of her hypertension is of interest in that her blood pressure was normal 3 months before presenting with a blood pressure of 150/110 mm Hg and low serum potassium concentration. This is an indication of severe hyperaldosteronism, either primary or secondary. It is interesting to note that the first cases of renin-producing tumors in the literature were thought to be primary aldosteronism because, at that time, PRA measurement was not available. Subsequently, determination of PRA has led to the accurate diagnosis of secondary hyperaldosteronism. This patient was suffering from back and abdominal pain as well as high renin hypertension. The discovery of a fallopian tube adenocarcinoma leads one to suspect participation of the tumor in the genesis of hypertension. Two main causes could explain this tumor-dependent hypertension: 1) renal artery compression or alteration in the kidney excretory function by infiltrated lymph nodes or metastatic tumor; or 2) an ectopic renin-producing tumor that could have recurred a few months after surgery and abdominal irradiation. However, the renal arteriogram was normal, and the IVP did not show evidence of hydrenephrosis, although there was some dilation of the collecting system. In any case, hypertension caused by hydrenephrosis is usually associated with volume expansion and low PRA. It is interesting that this patient had a low plasma sodium level (127 mEq/liter), which was indicative of very severe secondary aldosteronism.

**Dr. David Levenson (Hypertension Unit, Brigham & Women’s Hospital, Boston, Massachusetts):** Isn’t it true that most patients with primary hyperaldosteronism have a high-normal serum sodium concentration?

**Dr. Corvol:** Patients with secondary aldosteronism induced by renin tumors consistently have a low sodium concentration and hemoconcentration, probably because there is some sodium loss due to the pressure natriuresis. Another possibility is elevated plasma vasopressin concentration stimulated by high plasma angiotensin levels. The sodium concentration in this patient was low and, in fact, was lower than in renovascular hypertension. The extremely high PRA of this patient also indicated a renin-producing tumor. In our experience, a PRA above 50 ng ANG I/ml/hr is due to either an infarcted kidney or renal-producing tumor. We have very rarely seen a case of renovascular hypertension with a PRA greater than 50 ng ANG I/ml/hr. When we did see higher values, it was renovascular hypertension complicated by kidney infarction. Under these circumstances, there is a huge release of renin by the necrotic tissue. However, when you follow these patients, you can sometimes see a decrease in PRA with time.

Now, I would like to discuss the PRA value itself in patients with renin-producing tumors. We might underestimate the PRA value because of a very high renin secretion, and, therefore, we might be dealing with a limiting amount of plasma renin substrate. So we should be very careful in saying that this patient had a PRA of 50 ng ANG I/ml/hr. She might have had a higher PRA, which we did not detect just because we were not dealing in a correct zero-order kinetic reaction. The plasma renin concentration of the patient was, in fact, 3000 ng ANG I/ml/hr; a normal value is about 10 ng ANG I/ml/hr. It would be interesting to have determined the total renin value (both active and inactive renin) in this patient, because the presence of excessive inactive renin has been found in several renin-producing tumors.1-3 We do not know the nature of inactive renin exactly, but in renal and ectopic renin-producing tumors it is markedly elevated and relatively more so than in other types of renin-dependent hypertension. We have observed three renal renin-producing tumors in our clinic.1 We have found a discrepancy in the results of direct renin radioimmunoassay, which measures both active and inactive renin, and of the enzymatic assay of renin-producing tumors. This discrepancy is probably due to the presence of some immunoreactive renins which cannot be fully processed into the active enzyme and which are secreted as an inactive, partially activable form.

**Dr. Victor Dzau (Hypertension Unit, Brigham & Women’s Hospital):** I believe that Atlas and co-workers reported that patients with extrarenal renin-secreting tumors had higher concentrations of plasma inactive renin than patients with tumors of renal origin. Has this been your experience?

**Dr. Corvol:** We have studied two extrarenal renin-secreting tumors, a pulmonary cancer, and a parovarian cancer. We found that the tissue itself contained at least 50% inactive renin, whereas in normal kidneys, inactive renin constituted only 10% to 15% of the total renin concentration. It is possible that such tumors lack some of the processing enzymes needed for cleaving the inactive precursor to the active enzyme.

Renal vein renins may sometimes be helpful in distinguishing extrarenal renin-secreting tumors from renin-secreting tumors of renal origin or from renal ischemia. In the present case, I have no explanation for the higher PRA levels at the lower pole of the left kidney except that they may have been due to ischemia in that part of the kidney. However, the arteriogram did not substantiate this. Another possibility is that a local metastatic lesion drained into that vein. Alternately, residual primary tumor may have drained into the renal vein through the ovarian vein. We must also keep in mind that the anatomical relationship may have been distorted by prior surgery.

Another diagnostic test is a saralasin infusion. I would be very careful to use a very low dose of saralasin or captopril since dramatic hypotensive re-
response can be anticipated. The fact that the plasma sodium was also low is a likely indicator of sodium depletion and would accentuate the blood pressure decrease. However, long-term blood pressure control with captopril is variable. Some patients were not controlled by chronic captopril administration, whereas they were completely cured by excision of the tumor. Now I am interested to know the diagnosis and course of this patient.

Dr. David Levenson: Over the 6 months after the arteriogram, the hypertension was treated with metoprolol, spironolactone, and minoxidil. Chemotherapy was initiated with cytoxan, adriamycin, and cisplatinum, which reduced the size of the liver metastases and also resulted in a modest decrease in blood pressure so that the antihypertensive therapy could be reduced. At one point when the patient was off all medication, her blood pressure was 150/120 mm Hg, and peripheral PRA was 177 ng ANG I/ml/hr. Over the subsequent year, the hepatic metastases grew despite chemotherapy, and the hypertension became more difficult to control. When the patient received a single oral dose of 12.5 mg of captopril, her blood pressure fell dramatically to 70/40 mm Hg. This lasted for several hours. At that time, the PRA was 78 ng ANG I/ml/hr (upper limit of normal, 9), and the plasma concentration of active renin was 3700 ng ANG I/ml/hr. The inactive renin concentration as determined by activation with trypsin was approximately 26,000; 87% of the total plasma renin concentration was in the inactive form.

Three months later, the patient died. Postmortem examination showed abdominal carcinomatosis with extensive hepatic involvement by the tumor and extension into the base of the lower lobe of the right lung. The kidney showed intimal fibrosis of small- and medium-sized arterioles, interstitial fibrosis, and occasional glomeruli with focal segmental necrosis. There was no tumor identified within the kidneys, but retroperitoneal tumor below the level of the kidneys produced a moderate degree of hydronephrosis, slightly greater on the left than on the right. Dr. Carr will discuss the histology of the tumor.

Dr. Clayton Carr (Department of Pathology, Massachusetts General Hospital): The tumor is moderately differentiated and contains both papillary and glandular elements. The stroma is vascular with delicate fibrous bands running throughout the tumor. The nuclei are of medium size and variable in shape with irregular contours. Figure 1 is a close-up of an area with glandular differentiation and provides more detail of the nuclei. The tumor sampled at autopsy had a similar appearance to the primary adenocarcinoma.

Dr. David Levenson: Unfortunately, we obtained the tissues 24 hours after the patient’s death. There was much autolysis. As a result, satisfactory electron microscopic and immunohistochemical studies were not possible. However, we do have biochemical analysis of this tissue. The tissue was homogenized and extracted. Renin concentration was measured both in the fallopian tube tumor itself and in the patient’s kidneys. Normal plasma renin concentration is 5 to 10 ng ANG I/ml/hr, whereas the patient’s active plasma renin concentration was approximately three orders of magnitude higher, that is, \(3.7 \times 10^3\) ng ANG I/ml/hr. Normal plasma inactive renin concentration is perhaps twice as high and accounts for about 67% of the total, whereas in this patient it was markedly elevated and, as we mentioned, accounted for 88% of the total. In the tumor there were again extremely high levels of inactive and active renin compared to those in human cadavers, perhaps 10 to 100 times higher. The inactive renin concentration in the tumor was much higher than in the patient’s kidney and than in the normal kidney.

Dr. Corvol: It’s interesting that the kidney of this patient still contained renin. This renin was probably not secreted.

Dr. David Levenson: The pathology of the kidney had two findings. The first was the hydronephrosis; the second was some focal necrosis of glomeruli. Do intrinsic renal diseases like focal sclerosis or other...
kinds of glomerulonephritis produce these high levels of renin? Could focal necrosis or severe necrosis within the kidney cause elevated renin levels of this magnitude?

Dr. Corvol: No, I have never seen such high renin levels in chronic glomerulonephritis or lesions of this type. But, what is interesting here is that the patient developed this lesion probably because of the short-term hypertension associated with high levels of ANG II or because of the effect of the high blood pressure itself. I would be surprised, however, if she had developed so many lesions after only 3 to 6 months of hypertension just because of elevation of blood pressure.

Dr. David Levenson: One question that interests us is a follow-up on the issue of angiotensin as the mediator of vascular injury. Are captopril or other agents that reduce ANG II to be preferred in the treatment of high renin hypertension because they eliminate the offending toxin ANG II?

Dr. Corvol: I think that's a very good point that can only be solved by an experimental model. Unfortunately, we do not yet have experimental renin tumors to answer this question.

Dr. Victor Dzau: Can you review with us the origin and pathology of tumors associated with ectopic renin production?

Dr. Corvol: There are five cases of ectopic renin-secreting cancer. Two cases were lung cancer. One case was from a paraovarian tumor that was not very well described in terms of its origin, another a liver hepatoma, and an orbital hemangiopericytoma. I am not aware of any uterine tumors, for example, that produce renin or inactive renin. In the lung cancer, at least one of the two cancers was an oat cell cancer. Despite the fact that all of the tumors were renin-producing, their histological characteristics and the patients' clinical presentations were variable.

Dr. C. Ronald Kahn (Joslin Clinic and Brigham & Women's Hospital): Was the tumor renin in this case more like renal or uterine renin?

Dr. Victor Dzau: The tumor in our case was immunologically recognized by renin antibody. Its enzymatic activity was completely inhibited by antirenin. It had similar isoelectric points as renal renin but a higher molecular weight. Thus, the tumor renin had similar isoelectric points as renal renin but a higher molecular weight. This results in higher circulating levels of the inactive form. It looks like this may be the case in this situation, that is, inactive renin may have a longer half-life so that the serum actually contains a higher percentage of inactive renin than the tumor.

Acknowledgments

The author gratefully acknowledges the contributions of Dr Clayton Carr and Dr. David Levenson in the preparation of this case presentation.

References

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Hypertension. 1984;6:593-596
doi: 10.1161/01.HYP.6.4.593

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1984 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/6/4/593.citation

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