Pseudohypoaldosteronism following Kidney Transplantation

Renal Division, Mount Sinai School of Medicine, New York, NY, USA Jaime Uribarri, M.D.

A 56-year-old woman with ESRD of unknown etiology received a kidney transplant from her son. Following transplantation her serum creatinine became stable at 1.1 mg/dL. Her progress was good until 5 months later when she was admitted to the hospital with complaints of weakness and anorexia for 2-3 weeks. She denied vomiting and diarrhea. On admission her medications included azathioprin 50mg qd and prednisone 30mg qd. She had been taking furosemide for several months but this medication was discontinued 3days prior to admission.

Physical examination revealed marked dehydration and mild signs of hyperadrenocorticism. Blood pressure was 100/60 mmHg supine and 90/50mm Hg sitting. Laboratory data on admission showed: serum Na 115 mmol/L, serum K 6.3 mmol/L, BUN 92 mg/dl and serum creatinine 2.6 mg/dl. The 24-hour urine excretion of Na was 62 mmol and of K 43 mmol. After intravenous infusion of 0.9% NaCl, her clinical state improved and serum electrolytes and GFR returned toward normal. She demonstrated a gain in weight of 1.8 kg in 2 days, a decreased in hematocrit from 40 to 24% in 3 days, and a rise in blood pressure to its usual value, 120/80 mmHg.

A presumptive diagnosis of mineralocorticoid deficiency was made and blood was drawn for measurement of plasma renin activity(PRA : greater than 26 ng/ml/hr) and plasma aldosterone(PA : 375 ng/dL). The pituitary-adrenal axis was not tested in view of her chronic treatment with prednisone. Treatment was started with Florinef(9 alpha-fluorohydrocortisone) 0.1 mg/day and 4 days later she left the hospital.

One week later she was readmitted to the hospital because of weakness and anorexia. She stated emphatically that she had been taking Florinef at home. Physical signs and laboratory data were similar to those of the previous admission. The 24-hour urinary excretion of Na was 120 mmol and of K 51 mmol. The dose of Florinef was increased to 0.2 mg/day and the salt intake to 15 g daily. She repeatedly refused readmission for evaluation of her renin-aldosterone axis under controlled conditions.

Questions :

1. Which one of the following is the most likely explanation for this patient's hyperkalemia?
   a) diuretic-induced volume contraction with decreased delivery of sodium into the distal tubule
   b) renal insufficiency
   c) hyporeninemic hypoaldosteronism
   d) pseudohypoaldosteronism

2. How do you make the diagnosis of salt-losing nephropathy?

3. Where in the nephron is the lesion which explains this patient's findings?

DISCUSSION

Transplanted kidneys frequently manifest abnormalities of function including: diabetes insipidus, renal tubular acidosis and defects in potassium secretion[1-4]. This report describes a patient with transient apparent unresponsiveness to aldosterone following kidney transplantation, characterized by hyperkalemia and renal salt wasting with marked elevation of plasma renin activity and plasma aldosterone. The cause of this defect is not clear but some of the evidence implicates graft rejection. The presence of a marked defect in sodium reabsorption distinguishes the present case from those previously reported with hyperkalemia following renal transplantation who were regarded as having isolated defects in potassium secretion[4].

The diagnosis of tubular unresponsiveness to aldosterone was made at the time of this patient's first postoperative admission because she had extremely high levels of PRA and PA despite clinical signs and laboratory data suggesting hyperkalemia, inappropriately high urinary sodium excretion and inappropriately low urinary potassium excretion. Tubular unresponsiveness to mineralocorticoid is a syndrome very well described in children[5]. The term pseudohypoaldosteronism type I has been used to characterize this syndrome which usually occurs in infancy, responds well to salt supplementation but not to mineralocorticoids, and which usually clears during the first few years of life. In contrast it has generally been thought that this syndrome is almost non-existing in adults. In 1983, however, we reviewed the world literature on salt wasting nephropathy and the analysis of the data suggests that the majority of these patients had tubular unresponsiveness to aldosterone as the mechanism of renal salt wasting[6].

Table 1 shows the results of this analysis which included a total of 57 case reports. Evidence for tubular unresponsiveness to aldosterone and normal glucocorticoid function included; a) necropsy report describing the pathology of adrenal glands in 18 cases: enlarged and/or hyperplastic in 10 and normal in 8 cases; b) aldosterone excretion rate was measured in 4 patients : high in 3 and normal in 1 patient. Plasma renin activity and plasma aldosterone were measured simultaneously in 4 patients : high in all 4; c) the response to exogenous aldosterone was assessed in 28 cases with no significant response; d) glucocorticoid metabolism was evaluated in 22 patients: normal. The nature of the underlying kidney disease was determined by autopsy and/or biopsy in 30 cases. Of these, 27 patients had diseases involving primarily the tubulointerstitial region of the kidney : chronic pyelonephritis(9); acute interstitial nephritis(2); renal tuberculosis(3); medullary cystic disease(7); papillary necrosis(1); extensive renal candidiasis(1); bilateral cystic disease(1); nephrocalcinosis(2); polyarteritis nodosa(1). Only 3 patients had a primarily glomerular disease : chronic glomerulonephritis.

Salt-losing nephropathy was defined as a clinical syndrome with all of the following characteri

Table 1.

Parameter	Mean±SD	Range	Comments
Serum Na(mmol/L)	115±43	108-145	Data only in 34. Na>140 only in 4
Serum K(mmol/L)	6.05±1.7	2.0-9.1	Data only in 32. K>5 in 25
Serum CO2(mmol/L)	15±6	5.6-26.5	

stics : (a) The development of severe volume and sodium depletion caused by renal salt wasting. Renal salt wasting is documented either by demonstrating a urinary sodium excretion greater than 80 mmol/day despite volume depletion, or by the presence of volume depletion despite a salt intake greater than 5 g/daily without extrarenal salt loss. (b) The absence of evidence for salt-losing mechanisms other than renal disease such as diuretic therapy or adrenal insufficiency. (c) Evidence of intrinsic renal disease. The term salt-losing nephropathy should be used only in patients who meet all of the above criteria and not to describe the mild-to-moderate salt-losing tendency which is almost universally present in chronic renal failure.

All the available evidence, plasma renin activity, plasma aldosterone, adrenal gland hypertrophy, and lack of response to mineralocorticoid, indicates that lack of aldosterone is seldom the problem in patients with salt-losing nephropathy. Defective salt reabsorption must therefore be caused either by a tubular defect not related to aldosterone or by unresponsiveness to aldosterone. The former mechanism has as its clinical prototype-Bartter's syndrome; a disorder in which a defect in salt reabsorption is proximal to the potassium exchange site and therefore predictably leads to pronounced hypokalemia. Since most patients in this series have hyperkalemia, a separate defect in potassium secretion would have to be postulated.

Hyperkalemia in salt-losing nephropathy has not been generally evaluated as an indication of the pathogenic mechanism but mostly attributed to either renal failure or acidosis. However, the degree of renal failure was usually not severe enough to cause hyperkalemia suggesting that indeed there is a defect in potassium secretion combined with a proximal defect in sodium reabsorption or a primary abnormality of electrolyte transport in the distal nephron are required to satisfy all the findings. Since lack of aldosterone does not seem to be present, unresponsiveness to aldosterone is very likely

High levels of plasma renin activity and plasma aldosterone represent a nonspecific response to volume contraction and are not by themselves proof that the tubules are unresponsive to aldosterone, but impairment of potassium secretion which persists after volume is replenished is more persuasive evidence. Severe unresponsiveness to aldosterone is not a characteristic of progressive renal failure. Although most patients with chronic renal failure manifest some diminution in response to exogenous mineralocorticoid aldosterone retains an important physiologic role in this condition.

Significant advances in molecular nephrology in the last decade have allowed the characterization of the genetic defect in a variety of renal tubular abnormalities. We now know the syndrome of pseudohypoaldosteronism type I may exist in 2 forms. An autosomal recessive form which is caused by loss-of-function mutations in genes encoding subunits of the amiloride-sensitive epithelial sodium channel. The autosomal dominant form seems to be the result of mutations in the mineralocorticoid receptor gene[7]. No such studies are available for patients with the acquired form of the syndrome

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