refractory to K^+ replacement in the absence of Mg^{2+} repletion. Again, however, this patient had not previously developed significant hypokalemia, despite periodic hypomagnesemia, such that other factors must have caused the severe hypokalemia.

The associated hypertension in this case suggested an increase in mineralocorticoid activity, causing increased activity of ENaC channels in principal cells, NaCl retention, hypertension, and hypokalemia. The increase in ENaC-mediated Na^+ transport in principal cells would have led to an increase in the lumen-negative potential difference in the connecting tubule and cortical collecting duct, driving an increase in K^+ secretion through apical K^+ channels (Fig. 64e-1). This explanation is compatible with the very high TTKG, i.e., an increase in K^+ excretion that is inappropriate for the plasma K^+ concentration.

What caused an increase in mineralocorticoid activity in this patient? The patient had bilateral adrenal metastases, indicating that primary hyperaldosteronism was unlikely. The clinical presentation (hypokalemia, hypertension, and alkalosis) and the history of small-cell lung cancer suggested Cushing's syndrome, with a massive increase in circulating glucocorticoids, in response to ectopic adrenocorticotropic hormone (ACTH) secretion by his small-cell lung cancer tumor. Confirmation of this diagnosis was provided by a very high plasma cortisol level, high ACTH level, and increased urinary cortisol (see the laboratory data above).

Why would an increase in circulating cortisol cause an apparent increase in mineralocorticoid activity? Cortisol and aldosterone have equal affinity for the mineralocorticoid receptor (MLR); thus, cortisol has mineralocorticoid-like activity; however, cells in the aldosterone-sensitive distal nephron (the distal convoluted tubule [DCT]), connecting tubule (CNT), and collecting duct are protected from circulating cortisol by the enzyme 11β-hydroxysteroid dehydrogenase-2 (11βHSD-2), which converts cortisol to cortisone **(Fig. 64e-2)**; cortisone has minimal affinity for the MLR. Activation of the MLR causes activation of the basolateral Na^+/K^+-ATPase, activation of the thiazide-sensitive Na^+-Cl^- cotransporter in the DCT, and activation of apical ENaC channels in principal cells of the CNT and collecting duct (Fig. 64e-2). Recessive loss-of-function mutations in the *11βHSD-2* gene lead to cortisol-dependent activation of the MLR and the syndrome of apparent mineralocorticoid excess (SAME), comprising hypertension, hypokalemia, hypercalciuria, and metabolic alkalosis, with suppressed plasma renin activity (PRA) and suppressed aldosterone. A similar syndrome is caused by biochemical inhibition of 11βHSD-2 by glycyrrhetinic/glycyrrhizinic acid (found in licorice, for example) and/or carbenoxolone.

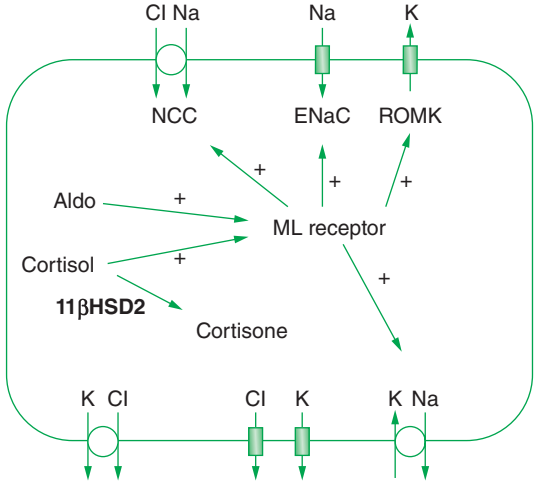

FIGURE 64e-2 11β-Hydroxysteroid dehydrogenase-2 (11βHSD-2) and syndromes of apparent mineralocorticoid excess. The enzyme 11βHSD-2 protects cells in the aldosterone-sensitive distal nephron (the distal convoluted tubule [DCT], connecting tubule [CNT], and collecting duct) from the illicit activation of mineralocorticoid receptors (MLR) by cortisol. Binding of aldosterone to the MLR leads to activation of the thiazide-sensitive Na^+-Cl^- cotransporter in DCT cells and the amiloride-sensitive epithelial sodium channel (ENaC) in principal cells (CNT and collecting duct). Aldosterone also activates basolateral Na^+/K^+-ATPase and, to a lesser extent, the apical secretory K^+ channel ROMK (renal outer medullary K^+ channel). Cortisol has equivalent affinity for the MLR to that of aldosterone; metabolism of cortisol to cortisone, which has *no* affinity for the MLR, prevents these cells from activation by circulating cortisol. Genetic deficiency of 11βHSD-2 or inhibition of its activity causes the syndromes of apparent mineralocorticoid excess (see Case 8).

In Cushing's syndrome caused by increases in pituitary ACTH, the incidence of hypokalemia is only 10%, whereas it is ~70% in patients with ectopic secretion of ACTH, despite a similar incidence of hypertension. The activity of renal 11βHSD-2 is reduced in patients with ectopic ACTH compared with Cushing's syndrome, resulting in SAME; the prevailing theory is that the much greater cortisol production in ectopic ACTH syndromes overwhelms the renal 11βHSD-2 enzyme, resulting in activation of renal MLRs by unmetabolized cortisol (Fig. 64e-2).

Why was the patient so weak? The patient was profoundly weak due to the combined effect of hypokalemia and increased cortisol. Hypokalemia causes hyperpolarization of muscle, thereby impairing the capacity to depolarize and contract. Weakness and even ascending paralysis can frequently complicate severe hypokalemia. Hypokalemia also causes a myopathy and predisposes to rhabdomyolysis; notably, however, the patient had a normal creatine phosphokinase (CPK) level. Cushing's syndrome is often accompanied by a proximal myopathy, due to the protein-wasting effects of cortisol excess.

The patient presented with a mixed acid-base disorder, with a significant metabolic alkalosis and a bicarbonate concentration of 44 meq/L. A venous blood gas was drawn soon after his presentation; venous and arterial blood gases demonstrate a high level of agreement in hemodynamically stable patients, allowing for the interpretation of acid-base disorders with venous blood gas results. In response to his metabolic alkalosis, the P_{CO_2} should have increased by 0.75 mmHg for each 1-meq/L increase in bicarbonate; the expected P_{CO_2} should have been ~55 mmHg. Given the P_{CO_2} of 62 mmHg, he had an additional respiratory acidosis, likely caused by respiratory muscle weakness from his acute hypokalemia and subacute hypercortisolism.

The patient's albumin-adjusted AG was $21 + ([4 - 2.8] \times 2.5) = 24$; this suggests a third acid-base disorder, AG acidosis. Notably, the measured AG can increase in alkalosis, due to both increases in plasma protein concentrations (in hypovolemic alkalosis) and to the alkalemia-associated increase in net negative charge of plasma proteins, both causing an increase in unmeasured anions; however, this patient was neither volume-depleted nor particularly alkalemic, suggesting that these effects played a minimal role in his increased AG. Alkalosis also stimulates an increase in lactic acid production, due to activation of phosphofructokinase and accelerated glycolysis; unfortunately, however, a lactic acid level was not measured in this patient. It should be noted in this regard that alkalosis typically increases lactic acid levels by a mere 1.5–3 meq/L and that the patient was not significantly alkalemic. Regardless of the underlying pathophysiology, the increased AG was likely related to the metabolic alkalosis, given that the AG had decreased to 18 by hospital day 2, coincident with a reduction in plasma bicarbonate.

Why did the patient have a metabolic alkalosis? The activation of MLRs in the distal nephron increases distal nephron acidification and net acid secretion. In consequence, mineralocorticoid excess causes a saline-resistant metabolic alkalosis, which is exacerbated significantly by the development of hypokalemia. Hypokalemia plays a key role in the generation of most forms of metabolic alkalosis, stimulating proximal tubular ammonium production, proximal tubular bicarbonate reabsorption, and distal tubular H^+/K^+-ATPase activity.

APPROACH TO MANAGEMENT

The first priority in the management of this patient was to increase his plasma K^+ and magnesium concentrations rapidly; hypomagnesemic patients are refractory to K^+ replacement alone, resulting in the need to correct hypomagnesemia immediately. This was accomplished via the administration of both oral and intravenous K^+-Cl^-, giving a total of 240 meq over the first 18 h; 5 g of intravenous magnesium sulfate was also administered. Multiple 100-mL "minibags" of saline containing