CASE RECORDS of the MASSACHUSETTS GENERAL HOSPITAL

Case 1-2023: A 49-Year-Old Man with Hypokalemia and Paranoia

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PRESENTATION OF CASE

Dr. David J. Bozym (Medicine): A 49-year-old man was admitted to this hospital because of hypokalemia and paranoid thoughts.

Six months before the current admission, discomfort on the right side of the chest developed, and the patient was evaluated at another hospital.

Dr. Mark C. Murphy: Computed tomography (CT) of the chest (Fig. 1), performed after the administration of intravenous contrast material, revealed a nodule in the upper lobe of the left lung that measured 2.1 cm by 1.9 cm, as well as bulky mediastinal and hilar lymphadenopathy.

Dr. Bozym: An endobronchial ultrasound–guided transbronchial needle aspiration of a mediastinal lymph node was performed. Cytologic examination of the specimen revealed small-cell carcinoma.

Five months before the current admission, the patient sought a second opinion in the oncology clinic of this hospital. The patient was counseled about the diagnosis of small-cell lung cancer and the need for additional imaging before consideration of chemotherapy, radiation therapy, or immunotherapy. Additional imaging was scheduled, along with a follow-up appointment. The patient did not undergo additional imaging and did not attend follow-up visits at the oncology clinic of either this hospital or the other hospital.

Six weeks before the current admission, the patient noticed swelling of both legs. Ten days before this admission, the swelling had not abated, and he was evaluated in the emergency department of this hospital.

In the emergency department, the patient described himself as generally healthy and did not report any chronic health conditions. He reported no fever, chills, shortness of breath, or pain. Additional history was obtained from the patient's brother. The patient had been pursuing alternative treatment for small-cell lung cancer that included a strict diet and intravenous infusions, and he had not shared the diagnosis of small-cell lung cancer with his family until several days earlier. The patient's brother believed that the patient was in denial about the diagnosis.

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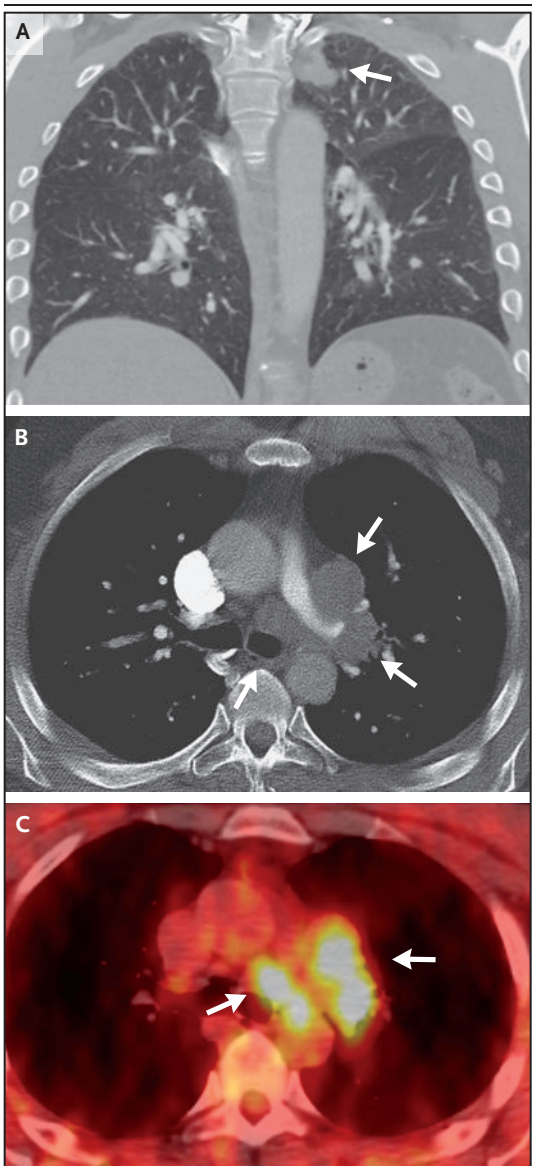

Figure 1. Images Obtained 6 Months before Current Admission.

A coronal image from CT pulmonary angiography (Panel A) shows a nodule (arrow) in the paramediastinal apical segment of the upper lobe of the left lung that measures 2.1 cm by 1.9 cm. An axial image from CT pulmonary angiography (Panel B) shows bulky left hilar and left paratracheal mediastinal lymphadenopathy (arrows), with lymph nodes measuring up to 2.9 cm in diameter. An axial image from a positron-emission tomographic–CT fusion scan (Panel C) shows intense radiotracer uptake (arrows) that corresponds to the lymphadenopathy.

When the patient was 12 years of age, he had received a diagnosis of non-Hodgkin's lymphoma, which had been treated with radiation therapy and splenectomy. Fifteen years before this presentation, ischemic colitis had been treated with small-bowel resection. One year before this presentation, deep-vein thrombosis had been treated with a 4-month course of anticoagulation. There was no history of psychiatric disease. He took no medications and had no known drug allergies; he did not disclose details about the infusions that he had received as alternative treatment for small-cell lung cancer. The patient lived in a suburban area of New England with his parents. He was divorced and frequently visited his children. He worked part-time as a skilled tradesman. Family members reported that he was a lifelong nonsmoker.

The temporal temperature was 36.7°C, the blood pressure 167/95 mm Hg, the pulse 80 beats per minute, the respiratory rate 18 breaths per minute, and the oxygen saturation 94% while the patient was breathing ambient air. The patient was alert and appeared well, but he looked thinner than he had looked during his evaluation at the oncology clinic 5 months earlier. The abdomen had a healed surgical scar, and the legs had symmetric 1+ edema. The blood potassium level was 2.6 mmol per liter (reference range, 3.6 to 5.1); the white-cell count was 14,630 per microliter (reference range, 4000 to 11,000). Other laboratory test results are shown in Table 1. Ultrasonography of the legs revealed no evidence of deep-vein thrombosis.

Dr. Murphy: CT pulmonary angiography of the chest (Fig. 2A and 2B), performed after the administration of intravenous contrast material, revealed a marked increase in the size of the left-lung mass, which now measured 9.3 cm by 4.6 cm, as well as enlargement of the mediastinal and hilar lymphadenopathy. CT of the abdomen and pelvis (Fig. 2C), performed after the administration of intravenous contrast material, showed numerous new ill-defined rim-enhancing hepatic lesions, which measured up to 8.0 cm in diameter; an adrenal mass, which measured 4.1 cm by 3.4 cm; and thrombosis of the branches of the right portal vein. Magnetic resonance imaging (MRI) of the head was normal.

Dr. Bozym: Supplemental potassium was administered intravenously and orally, and the patient was admitted to this hospital. During the next 3 days, additional supplemental potassium was administered. During follow-up interviews, the patient acknowledged the diagnosis of small-

Table 1. Laboratory Data.*

Variable	Reference Range, Adults†	10 Days before Current Admission	On Current Admission
Blood			
Hemoglobin (g/dl)	13.5–17.5	11.4	12.0
Hematocrit (%)	41.0–53.0	33.6	35.6
Platelet count (per μl)	150,000–450,000	231,000	213,000
White-cell count (per μl)	4000–11,000	14,630	13,530
Differential count (per μl)			
Neutrophils	1800–7700	12,200	12,050
Lymphocytes	1000–4800	1670	850
Monocytes	200–1200	330	380
Eosinophils	0–900	0	0
Basophils	0–300	20	30
Sodium (mmol/liter)	136–145	135	142
Potassium (mmol/liter)	3.6–5.1	2.6	2.2
Chloride (mmol/liter)	98–107	90	94
Carbon dioxide (mmol/liter)	22–32	34	37
Urea nitrogen (mg/dl)	6–20	26	19
Creatinine (mg/dl)	0.60–1.30	0.94	0.87
Glucose (mg/dl)	65–99	221	165
Calcium (mg/dl)	8.9–10.3	8.7	9.2
Magnesium (mg/dl)	1.7–2.4	2.1	2.4
Phosphorus (mg/dl)	2.4–4.7	2.1	1.4
Anion gap (mmol/liter)	3–17	11	11
Alanine aminotransferase (U/liter)	10–50	202	196
Aspartate aminotransferase (U/liter)	15–41	134	115
Alkaline phosphatase (U/liter)	32–100	505	451
Total bilirubin (mg/dl)	0.0–1.2	1.0	2.0
Globulin (g/dl)	1.9–4.1	3.3	3.4
Albumin (g/dl)	3.5–5.2	2.4	2.4
Ammonia (μmol/liter)	12–48	—	51
C-reactive protein (mg/liter)	0.0–0.8	26.6	—
Erythrocyte sedimentation rate (mm/hr)	0–13	51	—
Ferritin (μg/liter)	20–300	1058	—
Prothrombin time (sec)	11.5–14.5	13.2	—
International normalized ratio	0.9–1.1	1.0	—
D-dimer (ng/ml)	150–400	3119	—
Fibrinogen (mg/dl)	150–400	465	—

* To convert the values for urea nitrogen to millimoles per liter, multiply by 0.357. To convert the values for creatinine to micromoles per liter, multiply by 88.4. To convert the values for glucose to millimoles per liter, multiply by 0.05551. To convert the values for magnesium to millimoles per liter, multiply by 0.4114. To convert the values for phosphorus to millimoles per liter, multiply by 0.3229. To convert the values for bilirubin to micromoles per liter, multiply by 17.1. To convert the values for ammonia to micrograms per deciliter, divide by 0.5872.

† Reference values are affected by many variables, including the patient population and the laboratory methods used. The ranges used at Massachusetts General Hospital are for adults who are not pregnant and do not have medical conditions that could affect the results. They may therefore not be appropriate for all patients.

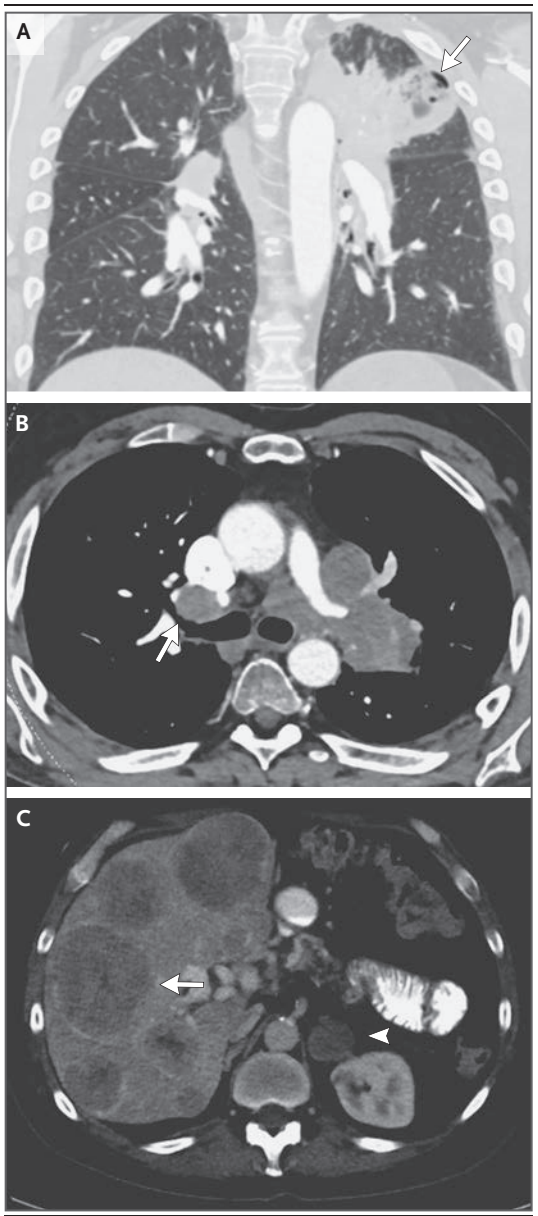

Figure 2. Images Obtained on Current Admission.
A coronal image in lung windows from CT pulmonary angiography (Panel A) shows a radiologically significant increase in the size of the left-lung mass, which now measures 9.3 cm by 4.6 cm. There is new mixed ground-glass opacification and cavitation in the peripheral left upper lobe (arrow). An axial image in soft-tissue windows from CT pulmonary angiography (Panel B) shows enlargement of the left hilar and mediastinal lymphadenopathy, with lymph nodes measuring up to 3.8 cm in diameter, as well as new right hilar lymphadenopathy (arrow), with lymph nodes measuring up to 1.9 cm in diameter. An axial image in soft-tissue windows from CT of the abdomen and pelvis (Panel C) shows multiple new rim-enhancing lesions involving all segments of the liver. The largest lesion (arrow), in liver segment 8, measures 8.0 cm in diameter. There is also a new lesion (arrowhead) in the body of the left adrenal gland that measures 4.1 cm by 3.4 cm.

cell lung cancer, but he did not explain why he had not shared the diagnosis with his family or provide details about the alternative treatment that he had pursued. On the fourth hospital day, the blood potassium level increased, and the patient asked to go home. He stated that he was willing to attend follow-up visits at the oncology clinic, but he was evasive when chemotherapy and immunotherapy were discussed. The patient was discharged.

One week after discharge, and 1 day before the current admission, the patient's father accompanied the patient to receive massage therapy and an intravenous infusion as alternative treatment. During the infusion, the patient abruptly became volatile, agitated, and angry. On the drive home, he refused to close the window and stared into the distance. He stated that doctors had cast spells on him during his recent hospitalization and that he had killed his oldest child, which was not true.

The next day, the patient borrowed his brother's car without permission and drove across the state. After he returned home, family members brought the patient to the emergency department of this hospital for evaluation.

In the emergency department, the patient stated that he was "embarrassed" for being in the hospital. He initially reported no symptoms, but on specific questioning, he acknowledged fatigue, weight loss, generalized weakness, decreased appetite, and ongoing leg swelling. He reported that he did not feel confused, afraid, or worried and that he had no suicidal or homicidal thoughts or auditory or visual hallucinations. Additional history was obtained from the patient's family members. The patient had not slept for several days. His aggressive and erratic behavior and delusions were not typical, although he could become easily angered and had a long-standing belief that his doctors had administered radiation therapy for non-Hodgkin's lymphoma to make money.

The temporal temperature was 36.4°C, the blood pressure 194/106 mm Hg, and the pulse 87 beats per minute. The patient alternated between being alert and lethargic, and he could

state the names of his children but not their ages. He was cooperative but intermittently paused and stared; he was not distracted by external stimuli, but he seemed to be responding to internal stimuli. He spoke only a couple of words at a time and answered most questions by nodding or shaking his head. There was generalized weakness, which was most pronounced in the proximal muscle groups. The leg edema was unchanged, and the skin appeared abnormally tan; there was no scleral icterus, sublingual jaundice, or asterixis.

The blood potassium level was 2.2 mmol per liter, the carbon dioxide level 37 mmol per liter (reference range, 22 to 32), and the ammonia level 51 μmol per liter (87 μg per deciliter; reference range, 12 to 48 μmol per liter [20 to 82 μg per deciliter]). The white-cell count was 13,530 per microliter. Urinalysis was normal, and urine and blood toxicologic testing was negative. Other laboratory test results are shown in Table 1. CT of the head, performed without the administration of contrast material, was normal. Supplemental potassium was administered intravenously and orally, and the patient was admitted to the hospital. On the second hospital day, the blood potassium level was 2.2 mmol per liter.

A diagnostic test was performed.

DIFFERENTIAL DIAGNOSIS

Dr. Chad W. Vokoun: This 49-year-old man had recently received a diagnosis of small-cell lung cancer. He had pursued alternative treatment and then presented to this hospital with evidence of metastatic disease. There was also hypokalemia, hypertension, proximal muscle weakness, and darkening of his skin. Altered mental status with paranoia prompted family members to bring him to the hospital and was one of the more striking aspects of his presentation. I will begin by considering the differential diagnosis for his altered mental status.

INTOXICATION OR WITHDRAWAL

Among patients presenting to the hospital, a common cause of altered mental status is intoxication or withdrawal from alcohol, benzodiazepines, or barbiturates. An intoxication or withdrawal syndrome is unlikely in this patient because he had no history of substance use disorder and had normal results on urine and blood toxicologic testing. Some medications can cause altered mental status, but this patient was not taking any prescribed medications.

METABOLIC DISORDERS

Electrolyte abnormalities such as hypernatremia, hyponatremia, hypercalcemia, and hypoglycemia can cause altered mental status, but these abnormalities were ruled out on initial laboratory testing. A hyperosmolar hyperglycemic state can result in varying degrees of neurologic impairment.[1] This patient had an elevated blood glucose level but not of the magnitude that would cause a hyperosmolar state. He also had clinically significant hypokalemia, which can be associated with constipation, palpitations, fatigue, and weakness but not with altered mental status.

Uremic encephalopathy was ruled out on initial laboratory testing, which showed normal renal function. Hepatic encephalopathy and acute liver failure are important considerations in this patient because he most likely had metastatic cancer involving the liver. However, acute liver failure due to malignant infiltration of the liver is uncommon,[2] and the results of liver-function tests were consistent with mild liver injury, not liver failure. Hepatic encephalopathy with mildly abnormal results on liver-function tests can be observed in patients with cirrhosis, but this patient did not have underlying cirrhosis. The elevated blood ammonia level is unhelpful; measurement of the ammonia level should not be used as either an initial diagnostic test or a test to direct therapy in patients with suspected hepatic encephalopathy.[3] Furthermore, asterixis, which would suggest hepatic encephalopathy, was not present on examination in this case.

PRIMARY PSYCHIATRIC DISORDERS

The patient's family members reported that the patient had long-standing concerns regarding his doctors' motivations for administering radiation therapy for non-Hodgkin's lymphoma, but whether this belief reflects a delusion is difficult to determine. No previous episodes of hallucinations or depressed mood had been reported. Although schizophrenia and schizoaffective disorder are possible causes of the patient's current paranoia, other causes of altered mental status need to be ruled out before a primary psychiatric illness can be considered.

CENTRAL NERVOUS SYSTEM PROCESSES

This patient had mild leukocytosis on presentation, which could indicate an infection involving the central nervous system, such as meningitis or encephalitis. However, such infections are unlikely in the absence of fever. Paranoia can be caused by brain metastases, which develop in 40 to 50% of patients with small-cell lung cancer during the course of illness.[4] However, MRI of the head showed no evidence of metastatic disease. The patient had elevated blood pressure on presentation, and sudden increases in blood pressure can cause hypertensive encephalopathy. Hypertensive encephalopathy should be considered in patients who have markedly elevated blood pressure that abates rapidly with treatment.

EFFECTS OF ALTERNATIVE TREATMENT

This patient was receiving alternative treatment for small-cell lung cancer, but the specific type of treatment was unknown. Alternative therapy for lung cancer can include the use of a high dose of vitamin C, a strict alkaline diet, insulin potentiation therapy, and intermittent hyperthermia treatment. Laetrile, which is a synthetic form of amygdalin and a cyanogenic glycoside compound,[5] has been described as an alternative cancer therapy since the 1950s, but its use has been banned by the Food and Drug Administration. During the degradation of laetrile, cyanide is released and is thought to have anticancer properties.[5] Although it is possible that this patient was using laetrile as an alternative therapy, he did not have other symptoms of cyanide poisoning, such as nausea, headache, or seizure.

PARANEOPLASTIC SYNDROMES

Small-cell lung cancer is the cancer that is most frequently associated with paraneoplastic syndromes, which can be hormone-associated or immune-mediated.[6] The paraneoplastic syndrome that best fits with this patient's clinical presentation is Cushing's syndrome caused by ectopic secretion of adrenocorticotropic hormone (ACTH). Patients with Cushing's syndrome can present with several neuropsychologic manifestations, including psychosis. This patient also had hypokalemia, hypertension, metabolic alkalosis, proximal muscle weakness, and skin hyperpigmentation (which is associated with Cushing's syndrome only when it is ACTH-dependent). Taken together, all these clinical features are consistent with the diagnosis of Cushing's syndrome. To establish the diagnosis in this case, I would obtain serum cortisol and ACTH levels.

DR. CHAD W. VOKOUN'S DIAGNOSIS

Cushing's syndrome due to ectopic secretion of adrenocorticotropic hormone from small-cell lung cancer.

DIAGNOSTIC TESTING

Dr. Melanie S. Haines: This patient had a random serum cortisol level of 81.5 μg per deciliter (2249 nmol per liter). For context, random serum cortisol levels obtained from patients in the intensive care unit (ICU), in whom maximal activation of the hypothalamic–pituitary–adrenal axis is expected, range from 5.3 to 40.7 μg per deciliter (146 to 1123 nmol per liter).[7] We confirmed that the patient had had no exogenous glucocorticoid exposure.

Cortisol is a hormone that is secreted in a pulsatile manner under the direction of pituitary ACTH and according to a diurnal cycle, with the level reaching a nadir at approximately 12 a.m.[8] In patients with Cushing's syndrome, diurnal variation is lost and late-night cortisol levels are inappropriately elevated. In the outpatient setting, a late-night serum cortisol level of 7.5 μg per deciliter (207 nmol per liter) or greater has high sensitivity and specificity for distinguishing Cushing's syndrome from physiologic hypercortisolism.[9] We therefore recommended obtaining a serum cortisol level at 12 a.m., with the understanding that physiologic hypercortisolism is greater in the hospital setting than in the outpatient setting. The 12 a.m. serum cortisol level in this patient was 84.7 μg per deciliter (2337 nmol per liter), a finding that confirmed the diagnosis of Cushing's syndrome.

Cushing's syndrome could explain most, if not all, of this patient's presenting symptoms and signs: neuropsychiatric disturbances, including psychosis and insomnia; cardiovascular and mineralocorticoid effects, including hypertension, hypokalemia, and edema; hyperglycemia; and proximal myopathy, which can be worsened by hypokalemia.[10] Hypokalemic metabolic alkalosis, which was also present in this patient,

occurs in 10 to 15% of patients with Cushing's syndrome due to secretion of ACTH from a pituitary tumor and in more than 95% of patients with Cushing's syndrome due to ectopic secretion of ACTH from a nonpituitary tumor.[11] In the kidney, the hormone 11β-hydroxysteroid dehydrogenase 2 (11β-HSD2) inactivates cortisol to cortisone, thus preventing it from activating the mineralocorticoid receptor. However, very high cortisol levels overwhelm the activity of 11β-HSD2, enabling cortisol to activate the mineralocorticoid receptor, which results in sodium resorption and potassium excretion.

Among patients with Cushing's syndrome, the risk of venous thromboembolism is approximately 18 times as high as the risk in the general population.[12] This patient had a history of deep-vein thrombosis, although it had occurred 1 year before the current admission and 6 months before the diagnosis of small-cell lung cancer. Cushing's syndrome typically causes truncal obesity, but patients with ectopic Cushing's syndrome due to cancer can present with weight loss. Cushing's syndrome has been associated with hyperpigmentation, including darkening of the skin in areas that are not exposed to the sun, that occurs when high levels of ACTH precursors stimulate melanocyte receptors. In addition, Cushing's syndrome can cause neutrophil-predominant leukocytosis.

After the diagnosis of Cushing's syndrome was established in this patient, the next step was to determine whether he had ACTH-dependent or ACTH-independent Cushing's syndrome. We had a very high clinical suspicion for Cushing's syndrome due to ectopic secretion of ACTH, both because it is a known paraneoplastic syndrome associated with small-cell lung cancer and because of the severity of the patient's presentation.

This patient had plasma ACTH levels of 264 pg per milliliter and 223 pg per milliliter (reference range, 6 to 76), findings that confirmed the diagnosis of ACTH-dependent Cushing's syndrome. Typically, MRI of the pituitary gland would be the next step because ACTH-secreting pituitary adenomas are more common than ectopic sources of ACTH. However, recent imaging of the head in this patient had revealed no obvious sellar abnormality. Ectopic secretion of corticotropin-releasing hormone can stimulate pituitary secretion of ACTH, but because this process is exceedingly rare and would not change our management approach, we determined that ectopic secretion of ACTH was the most likely cause of this patient's ACTH-dependent Cushing's syndrome.

CLINICAL DIAGNOSIS

Cushing's syndrome due to ectopic secretion of adrenocorticotropic hormone from small-cell lung cancer.

DISCUSSION OF ENDOCRINOLOGY MANAGEMENT

Dr. Haines: In cases of life-threatening hypercortisolism due to Cushing's syndrome, medical therapy should not be delayed once samples have been obtained for measurement of the ACTH level. Several clinical manifestations in this case, including steroid-induced psychosis and hypokalemia, prompted immediate management. Since the patient had widely metastatic small-cell lung cancer, our goal was to rapidly normalize cortisol secretion or function with medical therapy.

Drugs that were considered in this case included adrenal steroid synthesis inhibitors (Fig. 3). Many of these drugs are used off-label for the treatment of Cushing's syndrome. Adrenal enzyme inhibitors include ketoconazole[15] and the more potent levoketoconazole,[16] as well as metyrapone[17] and the more potent osilodrostat.[18] Ketoconazole and levoketoconazole normalize the cortisol level over a period of weeks in most patients with Cushing's syndrome. However, the use of these drugs is contraindicated in patients with elevated levels on liver-function tests, and these drugs have several known interactions with other drugs. Metyrapone and osilodrostat are more likely than ketoconazole to normalize the cortisol level with dose adjustment over a period of weeks in patients with Cushing's syndrome, but the use of these drugs may worsen hypertension and hypokalemia, given the build-up of cortisol precursors with mineralocorticoid activity.

Other adrenal steroid synthesis inhibitors include mitotane and etomidate. Mitotane has an effect that has been described as "medical adrenalectomy," but it has a slow onset of action[19]

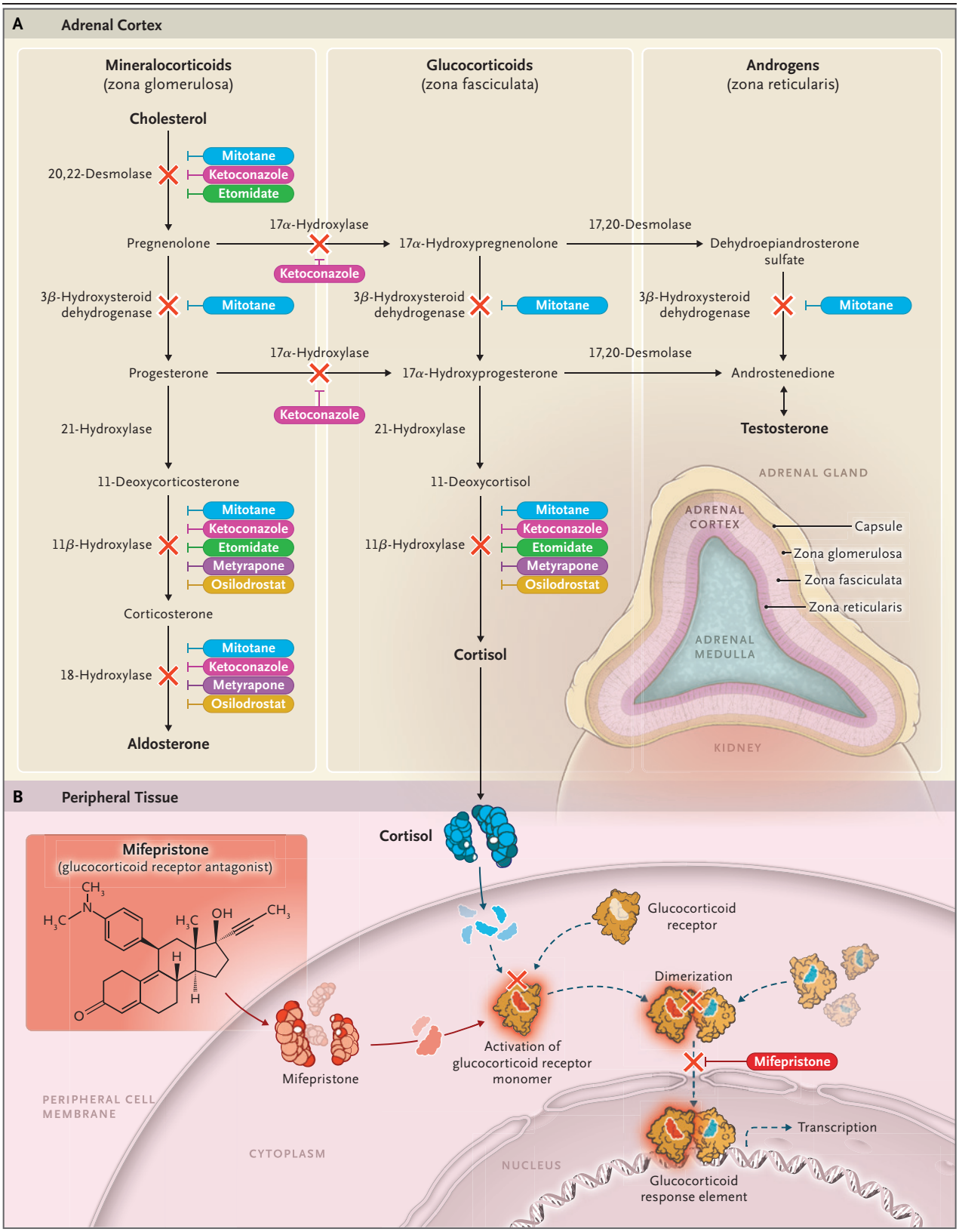

Figure 3 (facing page). Sites of Action of Adrenal Steroid Synthesis Inhibitors and Glucocorticoid Receptor Antagonists.

Panel A shows the sites of action of adrenal steroid synthesis inhibitors. The synthesis of mineralocorticoids, glucocorticoids, and adrenal androgens occurs in the zona glomerulosa, zona fasciculata, and zona reticularis of the adrenal cortex, respectively. Mitotane and ketoconazole inhibit several enzyme steps in adrenal steroid production. Etomidate, an anesthetic drug, inhibits the initial step in the synthesis of pregnenolone from cholesterol and also inhibits 11β-hydroxylase. Metyrapone and osilodrostat are potent inhibitors of 11β-hydroxylase and, to a lesser degree, 18-hydroxylase, and such inhibition results in the build-up of cortisol precursors with mineralocorticoid activity, such as 11-deoxycorticosterone. Panel B shows the sites of action of glucocorticoid receptor antagonists, specifically mifepristone. Mifepristone inhibits the binding of cortisol to the glucocorticoid receptor, thus preventing nuclear translocation and downstream gene interaction of the receptor. Adapted from Feelders et al.[13] and Cohan.[14]

and therefore was not further considered in this case. Etomidate normalizes the cortisol level within hours, but it is administered as an intravenous infusion that requires ICU care[20] and therefore is best considered as bridge therapy for critically ill patients who are unable to take oral medications.

Cushing's syndrome can be treated by blocking glucocorticoid action at the receptor level with mifepristone, an antiprogestin drug that acts as a glucocorticoid receptor antagonist at higher doses.[21] After the administration of mifepristone, the serum cortisol level remains elevated and therefore cannot be used to guide therapy, but clinical manifestations — such as altered mental status, hypertension, and hyperglycemia — typically abate within days. The effects of cortisol and its precursors on the mineralocorticoid receptor remain present, so hypokalemia may not abate, but hypertension may decrease if it is being mediated in part by the direct effect of cortisol on the vasculature. Excessive blockade of the glucocorticoid receptor can precipitate acute adrenal insufficiency; high-dose dexamethasone should be given immediately to overcome the blockade if clinical manifestations of an acute adrenal crisis (e.g., hypotension, nausea, and vomiting) develop. Given that mifepristone is immediately available for use on the general medical floor and has a rapid onset of action, we recommended the initiation of mifepristone in this patient.

DISCUSSION OF ONCOLOGY MANAGEMENT

Dr. Kerry L. Reynolds: Small-cell lung cancer accounts for 10 to 15% of lung cancers and is known for its rapid doubling time, aggressive nature, and often very advanced disease at presentation. There are two disease stages: limited and extensive. Paraneoplastic syndromes can appear before the cancer diagnosis in patients with small-cell lung cancer and can occur even with limited-stage disease, so it is unclear how long the ectopic Cushing's syndrome had been present in this patient.

The patient initially presented with limited-stage disease, with malignant cells confined to the ipsilateral hemithorax, which can be safely encompassed by a radiation field. At the time of the initial diagnosis, he was in excellent health and had a good performance status and a minimal burden of illness. Therefore, standard therapy would have been platinum-based chemotherapy with radiation therapy, an approach associated with an initial response rate of 70 to 90% among patients with limited-stage small-cell lung cancer, which is highly sensitive to initial chemotherapy.[22,23] Unfortunately, the 5-year survival rate in this patient population is only 31 to 34% because a substantial number of patients have a relapse after standard therapy; the median overall survival is 25 to 30 months. Despite having several conversations with multiple oncologists at the time of the initial diagnosis, the patient declined all cancer treatments at that time.

When the patient was hospitalized 6 months later, he had extensive-stage disease, with malignant cells detected beyond the ipsilateral hemithorax, as well as paranoia in the context of Cushing's syndrome. After treatment with mifepristone and spironolactone, there was improvement in the patient's glucose level, blood pressure, white-cell count, and potassium level (Fig. 4). The altered mental status abated, and he no longer had paranoia or delusions. The patient, along with family members, engaged in discussions about his diagnosis and options for treatment. At that point, he was offered systemic

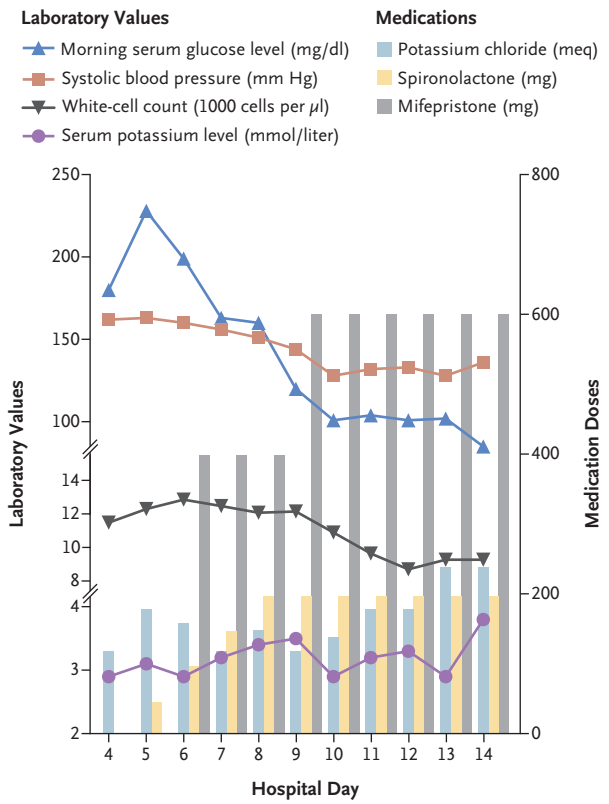

Figure 4. Laboratory Values after Treatment with Mifepristone.

Before hospital day 6, the patient was receiving up to 200 meq of potassium chloride per day and escalating doses of spironolactone, and his serum potassium levels were approximately 3 mmol per liter. On hospital day 6, treatment with mifepristone was started, and after 3 days of treatment, the dose was increased. Over the course of a week, there was a decrease in the morning serum glucose level, systolic blood pressure, and white-cell count. As expected, blockade of the mineralocorticoid receptor with spironolactone, along with aggressive potassium repletion, led to an increase in the serum potassium level.

therapy alone, with the goals of palliation and prolonged survival. Two clinical trials — the CASPIAN trial[24] and the IMpower133 trial[25] — have ushered in a new paradigm for the treatment of extensive-stage small-cell lung cancer that involves the use of platinum-based chemotherapy and an immune checkpoint inhibitor, a monoclonal antibody targeting programmed death ligand 1. The patient consistently declined to commit to any treatment plan. His primary goal was to be discharged from the hospital. Ultimately, the patient's wishes were honored, and on hospital day 14, he was discharged home with his family and palliative care support. Seven weeks later, he died at home.

FAMILY'S PERSPECTIVE

The Patient's Family: It was difficult to see our family member decline treatment. It was very clear that the team tried to engage him in the decision-making process and to address his concerns, worries, and fears, but he continued to decline treatment. We had hoped that, once he improved medically, he would accept therapy. We believe that he trusted the team, but in the end, he could not commit to regular treatment out of both denial and fear. All we could do was try to keep him as comfortable as possible. We are now left with complicated grief, but we are choosing to focus on his children. We are very thankful to see that so many in the medical field are learning from his case.

DISCUSSION

Dr. Kathy M. Tran (Medicine): Dr. Haines, was adrenalectomy considered?

Dr. Haines: Bilateral adrenalectomy can be an effective option to surgically stop glucocorticoid production. However, daily glucocorticoid and mineralocorticoid supplementation is necessary after surgery. Our concerns about proceeding with surgery in this patient were that he had very advanced small-cell lung cancer with a poor prognosis that was limited to weeks to months, that he might have had difficulty with adherence to daily steroid supplementation, and that this option did not fit best with his goals and desires. Therefore, medical management was chosen.

FINAL DIAGNOSIS

Cushing's syndrome due to ectopic secretion of adrenocorticotropic hormone from small-cell lung cancer.

This case was presented at the Medicine Grand Rounds.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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