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Case 6-2022: A 68-Year-Old Man with Fatigue, Weight Loss, and Hyperglycemia

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PRESENTATION OF CASE

Dr. Adith Sekaran (Medicine): A 68-year-old man with metastatic melanoma was evaluated in the oncology clinic of this hospital because of fatigue and weight loss.

Six years before the current evaluation, the patient received a diagnosis of superficial spreading melanoma of the left shoulder. He was treated with a wide local excision; a biopsy of the sentinel lymph node was negative for melanoma. One year before the current evaluation, the patient began to have slurred speech and weakness in the left hand. Imaging revealed a mass lesion in the parietal lobe of the brain and another mass in the hilum of the left lung. Craniotomy with resection of the brain mass was performed; pathological examination of the resected specimen revealed findings consistent with melanoma, as did a biopsy of the lung mass. Seizures developed postoperatively, and treatment with levetiracetam was initiated. Further treatment included radiation therapy targeting the parietal resection cavity and the administration of pembrolizumab.

Four months before the current evaluation, after seven cycles of pembrolizumab, the blood thyrotropin level was 9.4 μIU per milliliter (reference range, 0.4 to 5.0) and the free thyroxine level 0.9 ng per deciliter (12 pmol per liter; reference range, 0.9 to 1.8 ng per deciliter [12 to 23 pmol per liter]); treatment with levothyroxine was initiated. Three months before the current evaluation, after eight cycles of pembrolizumab, exertional angina developed, and the patient underwent coronary catheterization with placement of two drug-eluting stents. Pembrolizumab treatment was resumed 1 month later.

When the patient presented to the oncology clinic for a planned infusion of pembrolizumab, he reported a 3-week history of fatigue and a 2-week history of increased thirst and nocturia, with a need to urinate as many as three times each night. Although there was no change in appetite or eating habits, he had lost 5 kg of weight in the previous 3 weeks. There was no headache or change in vision.

On examination, the temperature was 36.4°C, the heart rate 75 beats per minute, the blood pressure 128/66 mm Hg, the respiratory rate 18 breaths per minute, and the oxygen saturation 100% while the patient was breathing ambient air. The

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Table 1. Laboratory Data.*

Variable	Reference Range, Adults†	On Admission
Blood		
Sodium (mmol/liter)	135–145	133
Potassium (mmol/liter)	3.4–5.0	4.5
Chloride (mmol/liter)	100–108	92
Carbon dioxide (mmol/liter)	23–32	21
Anion gap (mmol/liter)	3–7	20
Urea nitrogen (mg/dl)	8–25	20
Creatinine (mg/dl)	0.60–1.50	0.92
Glucose (mg/dl)	70–110	505
Calcium (mg/dl)	8.5–10.5	9.6
β-Hydroxybutyrate (mmol/liter)	<0.4	2.6
Venous blood gases		
pH	7.30–7.40	7.39
Partial pressure of carbon dioxide (mm Hg)	38–50	38
Partial pressure of oxygen (mm Hg)	35–50	69
Urine		
Color	Yellow	Yellow
Clarity	Clear	Clear
pH	5.0–9.0	5.0
Specific gravity	1.001–1.035	1.037
Glucose	Negative	3+
Ketones	Negative	2+
Bilirubin	Negative	Negative
Leukocyte esterase	Negative	Negative
Nitrite	Negative	Negative
Blood	Negative	Negative
Protein	Negative	Negative

* 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 calcium to millimoles per liter, multiply by 0.250.

† 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.

body-mass index (the weight in kilograms divided by the square of the height in meters) was 29.0. Heart sounds were regular, with no murmur. Lung sounds were normal. There was no leg edema. Muscle bulk was normal, as was strength in the arms and legs. There was no rash, bruising, or change in skin tone. Other history included hyperlipidemia, hypothyroidism, and coronary artery disease. Medications included aspirin, atorvastatin, clopidogrel, levetiracetam, levothyroxine, metoprolol, and pembrolizumab. He did not smoke tobacco, drink alcohol, or use illicit drugs. The patient lived in New England and was a retired police officer. His father, sister, and brother had had melanoma. There was no family history of diabetes.

A complete blood count, the results of liver-function tests, and the blood thyrotropin level were normal. The blood glucose level was 505 mg per deciliter (28.03 mmol per liter; reference range, 70 to 110 mg per deciliter [3.89 to 6.11 mmol per liter]). Other laboratory test results are shown in Table 1.

The patient was sent to the emergency department of this hospital, and management decisions were made.

DIFFERENTIAL DIAGNOSIS

Dr. Jonathan R. Wing: This 68-year-old man with metastatic melanoma presented for a routine clinic visit, where he reported a several-week history of fatigue, weight loss, polyuria, and polydipsia; blood testing revealed marked hyperglycemia. The hyperglycemia occurred in the context of ongoing cancer therapy and two recent episodes of illness: hypothyroidism and symptomatic coronary disease. I am confident that the patient's current constellation of symptoms can be attributed to hyperglycemia. He meets American Diabetes Association criteria for new-onset diabetes mellitus, which include classic symptoms of hyperglycemia or hyperglycemic crisis and a random plasma glucose level of 200 mg per deciliter (11.10 mmol per liter) or higher.[1]

NEW-ONSET DIABETES

To construct an initial differential diagnosis for this patient's new-onset diabetes, it is helpful to recall the mechanisms of glucose homeostasis. The blood glucose level is mainly regulated by insulin (secreted by pancreatic beta cells in response to hyperglycemia) and glucagon (secreted by pancreatic alpha cells in response to hypoglycemia). Glucagon often acts in concert with other, nonpancreatic counterregulatory hormones, such as cortisol, epinephrine, and growth hormone. This patient's hyperglycemia may have been caused by insulin deficiency, insulin resistance, an excess of counterregulatory hormones, or a

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combination of these mechanisms, given that some conditions result in hyperglycemia through more than one of these mechanisms.

INSULIN DEFICIENCY

Insulin deficiency can be absolute (with complete loss of insulin production) or relative (with inadequate insulin production relative to the body's needs). Immune-mediated destruction of pancreatic beta cells eventually leads to complete loss of insulin production, resulting in type 1 diabetes mellitus. This can occur in isolation or as part of a polyglandular autoimmune syndrome associated with other endocrinopathies, such as adrenal insufficiency, thyroid disease, or hypogonadism. Although hypothyroidism had recently been identified in this patient, he did not have clinical features that would be consistent with adrenal insufficiency due to polyglandular autoimmune syndrome type 2.

Other causes of beta-cell destruction and insulin deficiency include conditions that lead to global pancreatic dysfunction, such as hemochromatosis, cystic fibrosis, chronic pancreatitis, or extensive pancreatic resection. However, this patient did not have symptoms that would be consistent with pancreatic exocrine insufficiency, such as abdominal cramping or steatorrhea. Defects in genes that regulate beta-cell function, insulin production, or insulin secretion can lead to clinical diabetes. The phenotypes and penetrance of these defects vary widely, but this patient's older age and absence of a family history of diabetes make this possibility unlikely.

INSULIN RESISTANCE

Insulin resistance is the body's inability to adequately respond to secreted insulin. Although several genetic and environmental contributors have been described, insulin resistance often occurs in conjunction with obesity, hypertension, and dyslipidemia, as part of metabolic syndrome.[2] Over time, insulin resistance contributes to beta-cell dysfunction and a relative insulin deficit, which manifest as hyperglycemia and lead to type 2 diabetes mellitus. This patient had hypertension, cardiovascular disease, and a body-mass index of 29.0, features of metabolic syndrome that make the development of type 2 diabetes a possible explanation for his current presentation. In rare cases, the presence of genetic mutations that affect the insulin receptor or the formation of autoantibodies against the insulin receptor can lead to a functionally insulin-resistant state. These causes of insulin resistance are most often seen in middle-aged women who have other autoimmune disorders,[3] so they are unlikely diagnoses in this patient.

EXCESS OF COUNTERREGULATORY HORMONES

Glucagon, cortisol, epinephrine, and growth hormone are key hormones that are normally secreted to increase serum glucose levels as a protective mechanism against hypoglycemia. Individually, each of these hormones can be produced inappropriately by hormone-secreting tumors or after failure of homeostatic feedback loops. This patient did not have the classic features of glucagonoma, Cushing's syndrome, pheochromocytoma, or acromegaly (syndromes caused by excessive production of glucagon, cortisol, epinephrine, and growth hormone, respectively), so these primary endocrinopathies are unlikely to explain his presentation. Up-regulation of these hormones can also occur in the context of critical illness. Although this patient was ill, his presenting symptoms can be attributed to hyperglycemia; there is no convincing evidence that an antecedent illness was causing hyperglycemia.

MEDICATION USE

The use of certain medications can cause hyperglycemia by inducing insulin deficiency, insulin resistance, or an excess of counterregulatory hormones. The use of glucocorticoids, which have effects that mimic those of endogenous cortisol, is a very common cause of hyperglycemia. This patient was not taking any glucocorticoids, but he was taking metoprolol, a beta-blocker that can cause a moderate degree of insulin resistance. He was also taking pembrolizumab, a monoclonal antibody against the programmed death 1 (PD-1) receptor expressed by T lymphocytes. Pembrolizumab and other immune checkpoint inhibitors (ICIs) amplify the body's immune response, and a myriad of adverse events can be attributed to ICI-induced autoimmunity. These immune-related adverse events can affect nearly every organ system and range in severity from mild to life-threatening.[4] Among the several ICI-related endocrinopathies that have been described, ICI-induced diabetes is very rare. When it does occur, patients typically have an acute presentation with ketoacidosis, a low or

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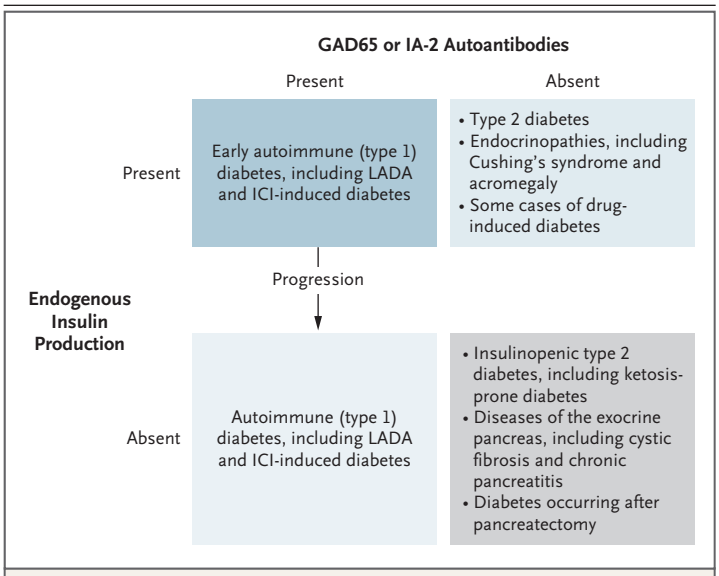

Figure 1. Subtypes of Diabetes According to the Detection of Autoantibodies and Endogenous Insulin Production.

Some subtypes of diabetes are listed according to the presence or absence of glutamic acid decarboxylase 65 (GAD65) or islet antigen 2 (IA-2) autoantibodies and according to the presence or absence of endogenous insulin production (beta-cell function), which is based on the C-peptide level. Tests for autoantibodies may be positive or negative in patients with immune checkpoint inhibitor (ICI)–induced diabetes. LADA denotes latent autoimmune diabetes in adults.

undetectable level of C-peptide, and in approximately half of cases, a detectable level of pancreatic autoantibodies.[5] ICI-induced thyroid dysfunction is much more common, and it is possible that this patient's recent hypothyroidism had been related to his treatment with pembrolizumab.

KETOGENESIS

The presence of ketones in serum and urine and an elevated serum anion gap suggests the generation of ketoacids. Ketogenesis occurs when cells cannot use glucose and instead rely on the metabolism of free fatty acids. This process can be associated with chronic alcoholism and severe malnutrition, two conditions in which glycogen stores are depleted, gluconeogenesis is impaired, and counterregulatory hormones are up-regulated. However, this patient did not drink alcohol or have evidence of severe malnutrition.

A third cause of ketogenesis is a nearly complete lack of insulin, a state that prevents cells from taking up glucose from the bloodstream. In patients with autoimmune (type 1) diabetes mellitus, acute hyperglycemia with ketosis is a common first presentation; subsequently, beta-cell destruction leads to absolute insulin deficiency. By contrast, patients with syndromes of insulin resistance and relative insulin deficiency rarely present with ketosis. It is worth noting that this patient, despite his elevated anion gap and serum ketone level, did not have acidemia. However, the venous blood gas analysis and serum bicarbonate level are consistent with an excess of bicarbonate, suggesting that a concurrent metabolic alkalosis (of unclear cause) kept the serum pH in a normal range.

In this patient, who had an acute presentation with new hyperglycemia and associated ketosis, autoimmune diabetes is the leading diagnosis. Patients with classic type 1 diabetes mellitus typically first present during childhood or adolescence, and this patient was 68 years of age at symptom onset. Pembrolizumab treatment is his most compelling risk factor for new-onset autoimmune diabetes; I suspect that the diagnosis is ICI-induced diabetes. There is no definitive diagnostic test to confirm this diagnosis, but it would be helpful to check blood levels of glycated hemoglobin, islet-cell autoantibodies, and — after treatment with insulin and stabilization of blood glucose levels — C-peptide.

DR. JONATHAN R. WING'S DIAGNOSIS

Immune checkpoint inhibitor–induced diabetes.

DIAGNOSTIC TESTING

Dr. Allison Kimball: The patient's glycated hemoglobin level had risen from 5.7% to 11.0% (reference range, 4.3 to 5.6) over a period of 3 months. This increase in the glycated hemoglobin level and the rapid development of diabetes, in the absence of weight gain (which is associated with type 2 diabetes mellitus) and of risk factors for pancreatic insufficiency, strongly supported a diagnosis of autoimmune diabetes. It is helpful to characterize the main subtypes of diabetes according to the detection of autoantibodies and endogenous insulin production (Fig. 1). This patient presented with positive tests for ketones in serum and urine, findings suggestive of insulin deficiency. The C-peptide level is a helpful marker of endogenous insulin production, but it

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may be falsely low in the presence of chronic hyperglycemia; therefore, measurement of the C-peptide level is typically reserved for the outpatient setting when diabetes is controlled. The next best diagnostic test is measurement of autoantibody levels. In this case, tests for glutamic acid decarboxylase 65 (GAD65) and islet antigen 2 (IA-2) autoantibodies were negative, which ruled out latent autoimmune diabetes in adults. Tests for autoantibodies may be positive or negative in patients with ICI-induced diabetes.[6] ICI-induced diabetes is the most likely diagnosis.

LABORATORY DIAGNOSIS

Immune checkpoint inhibitor–induced diabetes.

DISCUSSION OF MANAGEMENT

INITIAL MANAGEMENT

Dr. Kimball: The first step in the initial treatment of this patient was to determine whether he had diabetic ketoacidosis. The underlying mechanism of diabetic ketoacidosis is insulin deficiency, which explains why this finding is commonly present in patients with type 1 diabetes at the time of diagnosis. There are several ways in which insulin deficiency and a relative excess of glucagon can lead to hyperglycemia, including reduced glucose uptake by insulin-sensitive tissues and increased glucose output from the liver through gluconeogenesis and glycogenolysis. Lipolysis ensues, and the free fatty acids released are available for ketogenesis by the liver. As ketones (acetoacetate and β-hydroxybutyrate) accumulate, anion-gap metabolic acidosis develops, and a profound decrease in the pH can occur in some patients. The management of diabetic ketoacidosis includes aggressive fluid resuscitation and electrolyte repletion to counteract the osmotic diuresis that occurs with hyperglycemia. Insulin therapy is required to halt ketogenesis; although intravenous insulin has long been considered the treatment of choice, there is evidence supporting the use of subcutaneous insulin for the treatment of mild or moderate diabetic ketoacidosis (pH, >7.00).[7]

This patient's initial laboratory test results showed hyperglycemia, ketosis, and anion-gap metabolic acidosis, findings consistent with diabetic ketoacidosis. The classification of diabetic ketoacidosis as mild, moderate, or severe is based on the degree of acidemia. The classification can be challenging to determine if concurrent alkalosis is present, which was the case in this patient, given the normal venous pH. The patient was presumed to have mild diabetic ketoacidosis and was therefore treated with subcutaneous insulin.

The second step in the initial treatment of this patient was to decide whether long-term therapy with insulin would be necessary. Because the most likely diagnosis was ICI-induced diabetes, long-term management with insulin was anticipated. In the emergency department, the patient received fluid resuscitation and started a regimen of basal insulin plus rapid-acting insulin at meals. Repeat laboratory tests performed 12 hours later revealed a decrease in the blood glucose level to 131 mg per deciliter (7.27 mmol per liter), an increase in the carbon dioxide level to 22 mmol per liter, and a decrease in the anion gap to 17 mmol per liter. The patient was discharged home while receiving this insulin regimen, with a plan to attend an endocrinology follow-up visit.

LONG-TERM MANAGEMENT

Dr. Michelle Rengarajan: We have two major considerations regarding long-term treatment in this patient. First, how should we manage the newly diagnosed diabetes? Second, should the administration of pembrolizumab be continued?

Data driving these decisions are limited, largely because ICI-induced diabetes is rare. An early meta-analysis of 38 clinical trials showed only 13 cases among 7551 participants — a rate of 0.2%.[8] Although subsequent retrospective analyses have estimated slightly higher rates of ICI-induced diabetes,[9-11] the collective number of cases still remains small. As such, our understanding of the heterogeneity of ICI-induced diabetes is still evolving. Therefore, long-term management requires careful consideration of the specific glycemic characteristics of each individual patient.

ICI-induced diabetes is caused by immune-mediated destruction of beta cells, and the clinical manifestations result from decreased insulin production. Therefore, treatment requires insulin, although there is some flexibility in the specific regimen administered. The earliest reported cases of ICI-induced diabetes occurred in patients who presented with diabetic ketoacido-

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sis and rapidly progressive diabetes, with negative tests for endogenous insulin production and frequently with positive tests for islet-cell autoantibodies.[12] However, another retrospective study showed that only 4 out of 10 patients with ICI-induced diabetes presented with diabetic ketoacidosis.[9] This characterization is more consistent with this patient's presentation. Although he had mild diabetic ketoacidosis at the time of presentation, he had a normal C-peptide level 2 months after his diagnosis, a finding that indicates preserved endogenous insulin production.

It is possible that increasing awareness of ICI-induced diabetes has led to earlier diagnosis, with less severe clinical manifestations. The use of ICIs, particularly inhibitors of PD-1 and programmed death ligand 1, has increased exponentially over the past 10 years.[13,14] Along with this increased use has come heightened awareness of immune-related adverse events, including ICI-induced diabetes, particularly among oncology teams.[15-18] Now, ICI-induced diabetes may be identified in patients during the presymptomatic or dysglycemic phase,[19] whereas in the past, ICI-induced diabetes was considered only in patients who presented with fulminant symptoms. If the disease is identified earlier, in the dysglycemic phase, we would expect the patient to progressively lose beta-cell mass and endogenous insulin production.

Alternatively, we may now be observing previously unreported heterogeneity of ICI-induced diabetes. There is some evidence of this among described cases. In one cohort of 27 patients with ICI-induced diabetes identified between 2012 and 2018, 60% of the patients did not have a positive test for islet-cell autoantibodies.[10] It is possible that patients with and those without autoantibodies have different immunologic insults with distinct clinical courses. Of note, heterogeneity has been increasingly reported in patients with type 1 diabetes mellitus, particularly adult-onset disease.[20] Heterogeneity of immune-related adverse events is more evident in patients with ICI-induced thyroiditis, a common event that occurred in this patient. Patients with ICI-induced thyroiditis can present with diverse phenotypes, including transient hyperthyroidism followed by permanent hypothyroidism, transient hyperthyroidism followed by transient hypothyroidism, transient hyperthyroidism only, and permanent hypothyroidism only.[21]

If increased reporting of cases of ICI-induced diabetes has uncovered heterogeneity of the disease, perhaps we should reconsider the use of a basal–bolus insulin regimen in this patient. If islet-cell destruction is self-limited and a sufficient pancreatic reserve is present, we might consider a simpler insulin regimen, such as premixed insulin or basal insulin only. For this patient, I thought that the rationale for the basal–bolus insulin regimen outweighed the benefits of a simpler regimen. At the time, I was concerned about the possibility of evolving islet-cell destruction that might result in a more dramatic insulin deficiency in the near future.

The second consideration regarding long-term treatment in this patient is whether the administration of pembrolizumab should be continued. In general, because endocrine immune-related adverse events are defined by functional loss rather than inflammation, we suspect that the damage is done at the time of diagnosis. Therefore, permanently stopping ICI therapy is unlikely to change the course of ICI-induced diabetes, and treatment with the ICI can resume once the patient's condition is clinically stable. This may be an oversimplification; it is possible that patients in whom the disease has been caught early, in the dysglycemic phase, may have ongoing immune-mediated destruction that could be slowed or stopped with cessation of the ICI. However, even in that case, ICI-induced diabetes can be managed with insulin, so the development of this condition would not be a reason to stop a potentially lifesaving cancer therapy. Shortly after this patient received the diagnosis of ICI-induced diabetes, elevated aminotransferase levels developed, which suggested the possibility of ICI-induced hepatitis. The administration of pembrolizumab was discontinued, with a plan to restart treatment if the cancer relapses.

It has been 3 years since the patient received the diagnosis of ICI-induced diabetes. His melanoma is currently stable, and pembrolizumab therapy has not been restarted. He continues to have good glycemic control while receiving the basal–bolus insulin regimen; he has been taking a stable dose of 44 units total per day since his diagnosis. He has not had any diabetes-related hospitalizations or complications.

A physician: Is there a role for glucocorticoids in the management of ICI-induced diabetes?

Dr. Rengarajan: In contrast with other immune-

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related adverse events, such as myocarditis or colitis, ICI-induced diabetes is not treated with antiinflammatory doses of glucocorticoids. As noted previously, the rationale is that irreversible damage to beta cells has already occurred at the time of diagnosis of ICI-induced diabetes, so immunomodulatory therapies, such as glucocorticoids, are unlikely to alter the disease process. Furthermore, glucocorticoids may have a detrimental effect in patients with newly diagnosed ICI-induced diabetes; by causing hyperglycemia, high-dose glucocorticoids may impair beta-cell function.

FINAL DIAGNOSIS

Immune checkpoint inhibitor–induced diabetes.

This case was presented at the Medicine Case Conference.

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

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