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Case 17-2013: A 56-Year-Old Woman with Poorly Controlled Diabetes Mellitus and Fatigue

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PRESENTATION OF CASE

Dr. Harshabad Singh (Medicine): A 56-year-old woman with diabetes mellitus was admitted to this hospital because of hyperglycemia and chest pain.

The patient had been well, with a history of diabetes mellitus for which she took oral medication, until the previous year when glucose levels became increasingly difficult to control. Approximately 6 months before this admission, vague symptoms developed, including nausea, metallic taste, headache, throat pain, chest discomfort, and "indigestion." Omeprazole, lansoprazole, and antacids were administered, with partial relief. Three weeks before admission, she was seen in the clinic for evaluation of her symptoms. The weight was 74.4 kg and the lips were dry; the vital signs and the remainder of the examination were normal. The capillary blood glucose level was 314 mg per deciliter (17.4 mmol per liter); other results are shown in Table 1. The patient was referred to the diabetes clinic.

On examination 3 days before admission, the blood pressure was 128/76 mm Hg, the pulse 100 beats per minute, the weight 73.8 kg, the height 174 cm, and the body-mass index (the weight in kilograms divided by the square of the height in meters) 24.4. The lungs were clear, there was trace edema of the legs, and pedal pulses were 2+ bilaterally. Ultrasonography of the abdomen revealed a moderately fatty liver, pancreatic atrophy, and a cyst in the right kidney. The administration of metoclopramide was begun for presumed dysmotility. On the day of admission, the patient came to the emergency department at this hospital because of persistent discomfort in the throat, chest, and epigastrium that increased when she was in a supine position, interrupted her sleep, and was associated with postprandial abdominal fullness and nausea. She reported generalized malaise for 1 week and a metallic taste in her mouth. She reported no chest pain on exertion and no dyspnea, diaphoresis, light-headedness, palpitations, vomiting, diarrhea, melena, or blood in her stool.

Approximately 3.5 years before this admission, a diagnosis of diabetes mellitus type 2 had been made after polyuria and polydipsia had developed; metformin was administered. Glycated hemoglobin levels were 7.4% or lower when measured 1 year earlier; 4 months before admission, the level rose to 10.4% and glimepiride was added.

Table 1. Laboratory Data.*

Variable	Reference Range, Adults†	3 Wk before Admission, Outpatient	On Admission	3 Mo after Admission	5 Mo after Admission
Hematocrit (%)	36.0–46.0	38.3	34.0	38.6	39.2
Hemoglobin (g/dl)	12.0–16.0	13.0	11.8	13.0	13.0
White-cell count (per mm^3)	4500–11,000	9100	7000	13,600	12,000
Differential count (%)					
Neutrophils	40–70		85		83
Lymphocytes	22–44		10		11
Monocytes	4–11		4		5
Basophils	0–3		1		1
Sodium (mmol/liter)	135–145	137	133	134	139
Potassium (mmol/liter)	3.4–4.8	3.0	3.0	4.6	4.4
Chloride (mmol/liter)	100–108	91	90	98	97
Carbon dioxide (mmol/liter)	23.0–31.9	27.4	23.0	22.2	28.9
Plasma anion gap	3–15	19	20	14	13
Glucose (mg/dl)	70–110	282	435	175	310
Glycated hemoglobin (%)	3.80–6.40	12.30	13.70	6.60	
Urea nitrogen (mg/dl)	8–25	27	23	34	41
Creatinine (mg/dl)	0.60–1.50	1.15	1.23	1.19	1.03
Estimated glomerular filtration rate (ml/min/1.73 m^2)	≥60 (if black, multiply result by 1.21)	52	48	50	55
Protein (g/dl)					
Total	6.0–8.3		6.8	5.7	6.1
Albumin	3.3–5.0		3.9	3.7	4.1
Globulin	2.3–4.1		2.9	2.0	2.0
Phosphorus (mg/dl)	2.6–4.5	2.6	2.9		
Magnesium (mmol/liter)	0.7–1.0	0.6	0.5		
Calcium (mg/dl)	8.5–10.5	10.2	9.2		
Alkaline phosphatase (U/liter)	30–100		88	99	220
Aspartate aminotransferase (U/liter)	9–32		21	21	23
Alanine aminotransferase (U/liter)	7–30		22	35	28
Iron (μg/dl)	30–160		16		
Total iron-binding capacity (μg/dl)	230–404		204		
Ferritin (ng/ml)	10–200		582		
Thyrotropin (μU/ml)	0.40–5.00				0.89
γ-Glutamyl transferase (U/liter)	5–36				88
5′Nucleotidase (U/liter)	0–15				23

* To convert the values for glucose to millimoles per liter, multiply by 0.05551. 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 phosphorus to millimoles per liter, multiply by 0.3229. To convert the values for magnesium to milligrams per deciliter, divide by 0.4114. To convert the values for calcium to millimoles per liter, multiply by 0.250. To convert the values for iron and iron-binding capacity to micromoles per liter, multiply by 0.1791.

† 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.

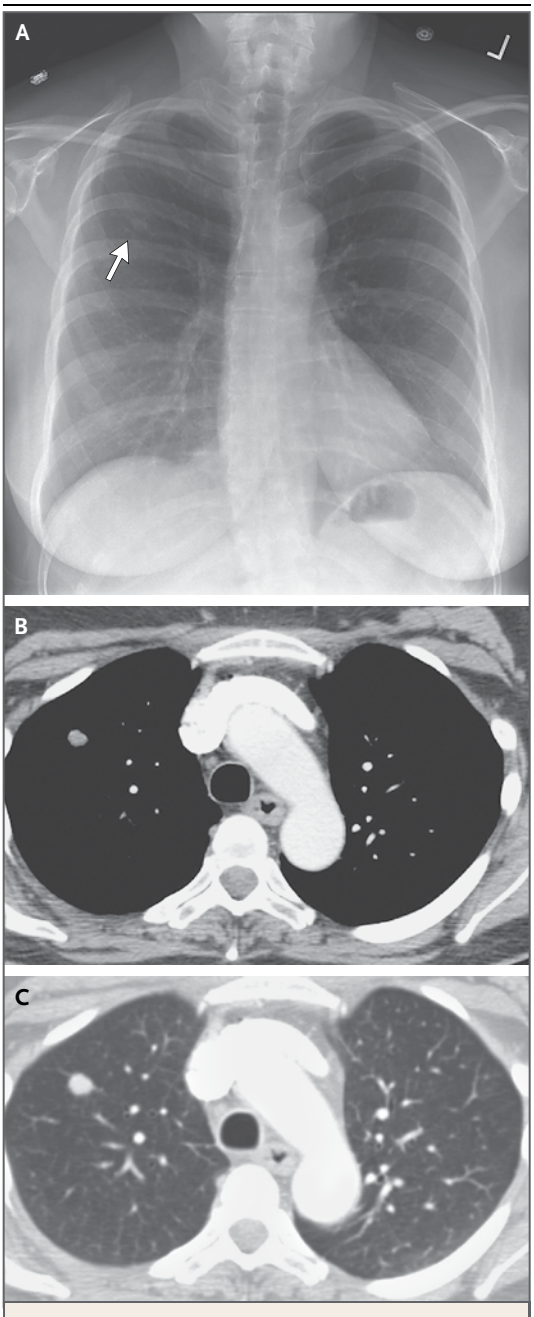


Figure 1. Initial Chest Images.

A chest radiograph obtained 4 years before admission incidentally reveals a small pulmonary nodule in the right upper lobe (Panel A, arrow). A CT image of the chest obtained 3.5 years before admission shows a well-defined, noncalcified, nonenhancing nodule, 8 mm by 10 mm, in the right upper lobe (Panel B, soft-tissue window; and Panel C, lung window).

Dr. Jo-Anne O. Shepard: A chest radiograph obtained 4 years before admission showed a small pulmonary nodule in the right upper lobe (Fig. 1A). A follow-up computed tomographic (CT) scan of the chest obtained 3.5 years before admission, after the administration of contrast material, showed a well-defined, noncalcified pulmonary nodule, 8 mm by 10 mm, in the right upper lobe and no mediastinal lymphadenopathy (Fig. 1B and 1C).

Dr. Singh: The patient had had headaches since a fall 6 months before this admission. She also had undergone lithotripsy for nephrolithiasis, a bilateral salpingo-oophorectomy 6 years earlier for an ovarian cystic teratoma (dermoid cyst), and a postsurgical herniorrhaphy. Medications included metformin, glimepiride, sodium citrate dehydrate, and magnesium oxide, as well as naproxen as needed. She had no known allergies; amiloride had been stopped because of urinary frequency. She lived alone and worked at a health care facility. She did not smoke, drink alcohol, or use illicit drugs. Her mother had transient ischemic attacks, and her father had died at 85 years of age, having had heart disease, renal failure with minimal-change disease, and borderline diabetes mellitus; he and other paternal relatives had a history of colon cancer. The patient's siblings were healthy.

On examination, the blood pressure was 153/80 mm Hg, the pulse 120 beats per minute, the respiratory rate 20 breaths per minute, and the oxygen saturation 96%; the temperature was 37.4°C and rose to 38.2°C. The remainder of the examination was normal. The platelet count and blood levels of total and direct bilirubin, lipase, creatine kinase, and troponin T were normal. Screening for troponin I was negative; other test results are shown in Table 1. Urinalysis revealed clear, yellow urine; the pH was 5.5, with 3+ glucose (≥1000 mg per deciliter), 1+ bilirubin, 2+ ketones, and trace blood by dipstick; and there were few bacteria and squamous cells per high-power field.

Dr. Shepard: A chest radiograph obtained on admission showed patchy opacities at the lung bases, a finding that was consistent with pneumonia, and a nodular opacity in the right upper lobe overlying the interspace of the posterior

fifth and sixth ribs, which was increased in size from 4 years earlier (Fig. 2A).

Dr. Singh: An electrocardiogram showed left atrial enlargement and was otherwise normal. The patient was admitted to this hospital, and insulin glargine, levofloxacin, azithromycin, ceftriaxone, dalteparin, lisinopril, potassium chloride, albuterol by inhaler, magnesium oxide, metoclopramide, antacids, normal saline (intravenously), thiamine, folic acid, and acetaminophen as needed for pain or fever were administered. During the first 3 days, dyspnea and a nonproductive cough developed, the temperature rose to 39.1°C, and oxygen saturation decreased to 82% while the patient was breathing ambient air. Oxygen was administered. Blood cultures drawn on admission were sterile; a urine culture was consistent with contamination. Testing for influenza A virus antigen was positive.

Dr. Shepard: CT of the chest performed according to the pulmonary-embolism protocol revealed no evidence of embolism, but it did reveal a pulmonary nodule, 11 mm by 13 mm, in the right upper lobe that was increased in size from the previous CT examination (Fig. 2B and 2C). Multifocal pneumonia was noted bilaterally, as were small pleural effusions.

Dr. Singh: Antimicrobial therapy was changed to vancomycin, cefepime, levofloxacin, metronidazole, and oseltamivir, with gradual improvement. Upper gastrointestinal imaging revealed normal motility, a small hiatal hernia, and moderate-to-severe gastroesophageal reflux. The patient was discharged home on the 12th day on moxifloxacin, insulin glargine, lisinopril, magnesium supplements, spironolactone, potassium chloride, omeprazole, prochlorperazine maleate, aspirin, a multivitamin, primidone at bedtime, and lorazepam as needed for anxiety. She was advised to return for follow-up within 1 week; however, she did not return. Eleven days after discharge, testing for anti–islet-cell cytoplasmic antibodies was positive at 0.11 nmol per liter (reference range, ≤0.02), and testing for islet-cell antigen 512 (also known as islet antigen 2) antibodies was negative.

During the next 3 months, the patient was seen in the emergency department and in the urgent-care psychiatry unit at this hospital because of increasing tremulousness and anxiety;

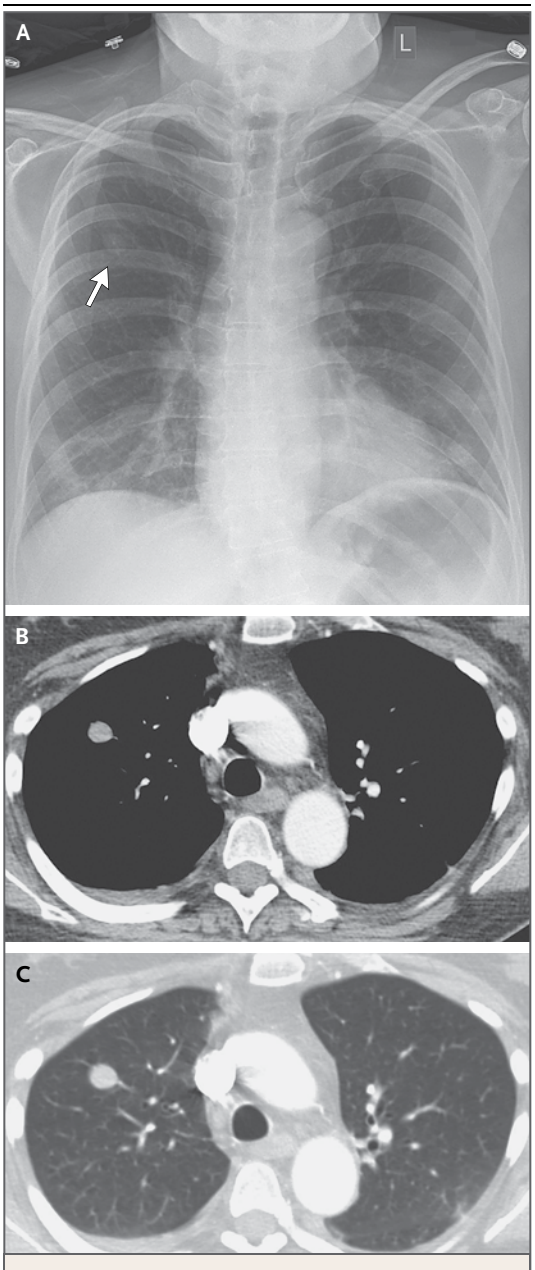


Figure 2. Chest Images on Admission.

A chest radiograph obtained on admission shows an increase in the size of the nodule in the right upper lobe (Panel A, arrow) as compared with 4 years earlier, as well as new consolidations at the lung bases that are consistent with pneumonia. A CT image of the chest shows a soft-tissue nodule, 11 mm by 13 mm, in the right upper lobe, increased in size from the previous CT scan (Panel B, soft-tissue window; and Panel C, lung window). Small pleural effusions were present bilaterally, along with bilateral pneumonia (not shown).

she was seen once in the diabetes clinic for hyperglycemia. Three months after discharge, she saw her primary care physician; the blood pressure was reportedly low, and the weight was 64.9 kg; test results are shown in Table 1. She was instructed to stop lisinopril, primidone, and the potassium supplement and to decrease the dose of spironolactone. The next month, she noted marked fatigue and rising blood-sugar levels. Her blood level of thyrotropin was 1.1 μU per milliliter (normal).

Approximately 5 months after discharge, the patient presented to her primary care physician with persistent fatigue, thinning hair, and a few weeks of "tired" legs, as well as worsening edema in her legs. Test results are shown in Table 1. Atenolol was administered for essential tremor. Two weeks later, she underwent a routine follow-up chest CT with the administration of contrast material, which revealed a noncalcified nodule, 11 mm by 13 mm, in the right upper lobe, unchanged from the previous study; subsegmental atelectasis in the lingula, right middle lobe, and both lower lobes; scattered mediastinal lymph nodes measuring less than 1 cm; and bilateral renal cysts, with resolution of the bilateral airspace disease and pleural effusions. The adrenal glands were diffusely enlarged, a finding consistent with hypertrophy. Six months after admission, she was seen in the medical walk-in clinic at this hospital because of increasing leg edema, new swelling of her face and abdomen, leg weakness and difficulty arising from a chair, and a 7-kg weight gain during 2 weeks, without changes in diet.

Diagnostic tests were performed.

DIFFERENTIAL DIAGNOSIS

Dr. Jose C. Florez: This 56-year-old woman presented with progressive, difficult-to-control diabetes mellitus, an enlarging solitary pulmonary nodule, hypokalemia, susceptibility to infection, nausea, abdominal discomfort, rapid weight gain, facial fullness, leg edema, new fatigue, and new proximal-muscle weakness. In formulating my differential diagnosis, I will first focus on the major features of this patient's presentation to see whether a unifying diagnosis can tie together these seemingly unrelated signs and symptoms. Then I will use pattern recognition to, I hope, arrive at the most likely answer.

UNCONTROLLED DIABETES

The differential diagnosis for uncontrolled diabetes includes undertreatment or misdiagnosis of the type of diabetes, a progressive course due to weight gain or advancing beta-cell failure, or a superimposed pathological process (e.g., pancreatitis, pancreatic cancer, hemochromatosis, cystic fibrosis, acromegaly, lipodystrophy, medication use, or high levels of endogenous or exogenous glucocorticoids). Undertreatment is unlikely in this case, since the patient's glycated hemoglobin levels had been stable for years, yet she had a sudden loss of glycemic control. Misdiagnosis of the type of diabetes might lead to an inappropriate treatment strategy. Monogenic forms of diabetes (e.g., neonatal diabetes[1] or maturity-onset diabetes of the young[2]) are often misdiagnosed as type 1 diabetes or type 2 diabetes, leading to the initiation of insulin therapy or metformin therapy, respectively; however, patients with monogenic forms of diabetes tend to be exquisitely sensitive to sulfonylureas.[3,4] Latent autoimmune diabetes in adults is an autoimmune form of diabetes that, like type 1 diabetes, is characterized by the presence of anti–glutamic acid decarboxylase antibodies or anti–islet-cell antibodies; however, patients present with this condition later in life, typically after 30 years of age, and the disease has a less rapid course, with a nonketotic onset and a delay of several months before insulin therapy is required.[5,6] This patient was not obese at the time of her diagnosis in adulthood, she has evidence of islet autoimmunity, and the glycemia became uncontrolled despite escalation of oral therapy with both metformin and a sulfonylurea (glycated hemoglobin range, 10.4 to 13.7%); glycemic control was restored with the initiation of insulin glargine (glycated hemoglobin level, 6.6%), confirming the diagnosis of latent autoimmune diabetes.[5,7]

Despite the use of insulin glargine and an initial satisfactory response in this case, hyperglycemia recurred, with a change in the clinical picture. Of particular concern is the rapid onset of various symptoms concurrent with a subtle enlargement of a known pulmonary nodule.

SOLITARY PULMONARY NODULES

Isolated pulmonary nodules identified incidentally can be benign or malignant. Benign nodules include nonspecific granulomas, hamartomas, infectious granulomas due to fungal or mycobacterial infection, or dirofilariasis, which is the dog heartworm that is transmitted from dogs through mosquito vectors. Neoplastic nodules include carcinoid tumors and either primary or metastatic carcinoma.

Benign nodules typically are less than 5 mm in diameter, have smooth borders, and appear dense or solid, with a concentric, central, or homogeneous pattern of calcification. Benign nodules tend to double in size either very rapidly (in <1 month) or very slowly (in >1 year). Features of nodules that are worrisome for cancer include a diameter greater than 10 mm, the presence of irregular or spiculated borders, a nonsolid ground-glass appearance, the absence of calcifications or the presence of eccentric calcifications, and a doubling time between 1 month and 1 year. Additional clinical factors incorporated in treatment algorithms include smoking history, age, and a personal cancer history. This patient's pulmonary nodule was not particularly worrisome on her initial presentation and was appropriately followed with serial imaging. However, the size of the nodule began to increase, and this change was associated temporally with the development of the other abnormalities noted during her presentation. Therefore, I suspect the definitive diagnosis in this case will be determined after recognizing a pattern that ties all these signs and symptoms together.

REACHING A UNIFYING DIAGNOSIS: PATTERN RECOGNITION

One approach to reaching a diagnosis is to construct exhaustive differential diagnoses for each set of related signs and symptoms and look for their confluence into a single clinical entity, assuming that the most parsimonious explanation must account for the full picture. A complementary approach involves pattern recognition, which is based on clinical intuition rooted in personal or learned experience. The various symptoms and physical findings are recognized as components of a delineated syndrome, and further exploration is focused on the generation of confirmatory positive or negative data points that help establish the diagnosis.

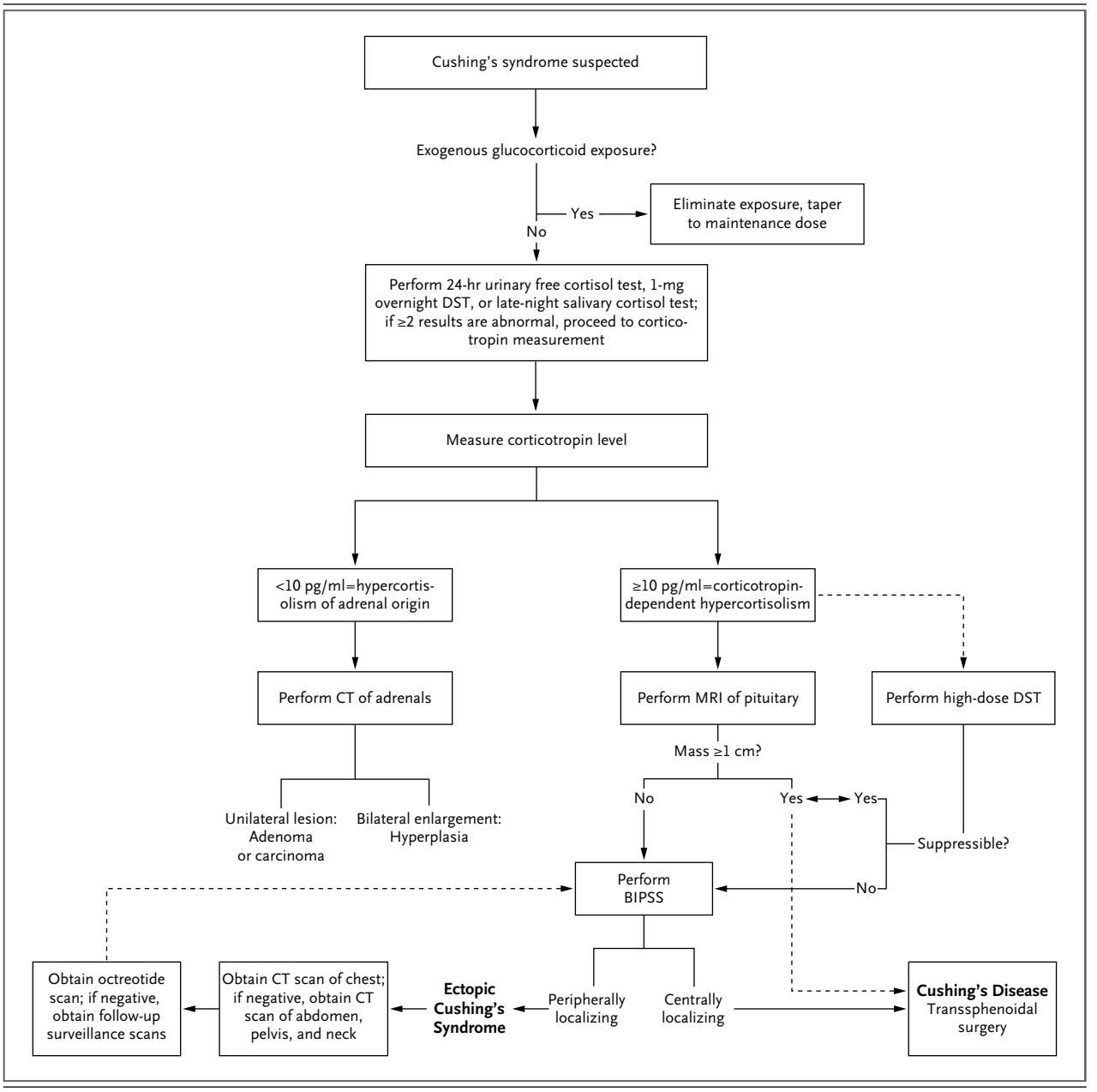
In this case, progressive diabetes despite adequate therapy, rapid weight gain in a central distribution, a complicated viral infection, hypokalemia, new edema, facial fullness, hypertension, hair thinning, fatigue, documented proximal-muscle weakness, and various psychological symptoms all point to hypercortisolism (Cushing's syndrome). Many of the clinical features of Cushing's syndrome (e.g., obesity, hypertension, hyperglycemia, edema, hypokalemia, fatigue, mood disorders, and insomnia) are common and nonspecific; others (e.g., easy bruising, purple striae, facial plethora, and proximal-muscle weakness) are more specific and helpful in reaching a clinical diagnosis. Patients with nonpathological forms of hypercortisolism (e.g., pregnancy, depression, alcohol abuse, morbid obesity) can present with similar features, and we should keep these in mind as potential causes of abnormal laboratory values when evaluating a patient.

EVALUATION OF CUSHING'S SYNDROME

On the basis of her medical history and physical examination, I suspect that this patient had hypercortisolism, but this must be confirmed biochemically (Fig. 3). The first step is to rule out the administration of supraphysiologic glucocorticoids. We have no knowledge that this patient had ever taken exogenous steroids, and therefore an excess seems unlikely.

The next step would be to document endogenous hypercortisolism. Although several testing strategies are available,[8] I would obtain a 24-hour urine collection for a measurement of the free cortisol level. If the level is elevated, I would confirm this finding by performing a late-night salivary cortisol test.

If this patient did have biochemical hypercortisolism, we would next determine whether it is corticotropin-dependent or corticotropin-independent. A plasma corticotropin level that is below the normal range (<10 pg per milliliter [2.2 pmol per liter]) would suggest primary hypercortisolism of an adrenal origin, with suppression of pituitary corticotropin release through negative feedback. The patient's enlarging pulmonary nodule and the hypertrophic appearance of her adrenal glands, without evidence



of discrete adenomas, make me suspect that she had an abnormally high level of corticotropin for the serum cortisol level, which would indicate corticotropin dependence. Corticotropin-dependent hypercortisolism can have a pituitary source (Cushing's disease) or an ectopic source (Cushing's syndrome).

The usual next step would be to obtain an image of the pituitary gland with magnetic resonance imaging. However, given the existence of a known pulmonary nodule and its enlargement coincident with the recrudescence of the patient's symptoms, I would bypass pituitary imaging and concentrate on obtaining biochemical proof of an ectopic source of corticotropin production by means of either a high-dose dexamethasone suppression test or sampling from the inferior petrosal sinuses bilaterally, which is more laborious and invasive.

Once ectopic Cushing's syndrome has been

Figure 3 (facing page). Algorithm for the Evaluation of Cushing's Syndrome.

Authorities disagree on the size criteria of a pituitary mass that would dictate either surgical resection or additional evaluation, since the prevalence of incidental pituitary masses is not trivial. At this hospital, the presence of a macroadenoma (a mass ≥1 cm in diameter) is sufficient grounds for neurosurgical referral, under the assumption that regardless of whether the mass represents Cushing's disease, it should be resected. This is because, over time, it is likely to cause mass effect on key adjacent structures, such as the cavernous sinus or the optic chiasm. A definitive diagnosis confirming or ruling out Cushing's disease can be attained at the time of pathological examination. The absence of a mass, or a mass of less than 1 cm in size, requires additional biochemical confirmation. This can be achieved through sampling from the inferior petrosal sinuses bilaterally, with or without stimulation with corticotropin-releasing hormone or arginine vasopressin; this procedure can also assist with lateralization. In facilities without magnetic resonance imaging (MRI) or specialized expertise in vascular radiology, the overnight or 2-day high-dose dexamethasone suppression tests can help distinguish pituitary Cushing's disease from ectopic Cushing's syndrome. Results of sampling from the inferior petrosal sinuses that show a gradient between central and peripheral corticotropin levels of less than 1.5 to 1 are suggestive of an ectopic source of corticotropin, as is the absence of suppression after the administration of high-dose dexamethasone. Localization by CT of the chest or, if that is unrevealing, of the abdomen, pelvis, and neck is indicated. When dedicated imaging does not yield a compatible lesion, a whole-body octreotide scintigraphy scan can be obtained. If all imaging procedures are unrevealing, the clinician can elect to continue periodic surveillance or take repeat samples from the inferior petrosal sinuses bilaterally, under the assumption that a central lesion may have been missed. The algorithm is a modification of algorithms from Nieman et al.,[8] Porterfield et al.,[9] and Boscaro and Arnaldi.[10] BIPSS denotes bilateral sampling from the inferior petrosal sinuses, and DST dexamethasone suppression test.

confirmed, I would recommend an excisional biopsy of the pulmonary nodule, which could be both diagnostic and therapeutic. Pathological examination of the specimen might reveal a pulmonary carcinoid tumor, and dedicated immunostaining for corticotropin would confirm the presence of corticotropin-secreting cells in the specimen. In rare cases, a pulmonary carcinoid tumor might produce corticotropin-releasing hormone instead,[11,12] which would make the results of bilateral sampling from the inferior petrosal sinuses seem as if there is a central (pituitary) corticotropin-secreting tumor; if the pulmonary specimen is negative on staining for corticotropin, I would then request staining for corticotropin-releasing hormone.

Dr. Hasan Bazari (Medicine): Dr. Singh, would you give us your initial impression when you evaluated this patient?

Dr. Singh: Given the patient's worsening diabetes control, proximal-muscle weakness, and facial edema, we were concerned about hypercortisolism. A 24-hour urinary free cortisol test was performed, and the result was a markedly elevated level, at 303 μg per 24 hours (836 nmol per day; normal range, 17 to 47 μg per 24 hours [47 to 130 nmol per day]). We confirmed the diagnosis of hypercortisolism with an overnight dexamethasone suppression test, which showed an elevated morning cortisol level of 32.8 μg per deciliter (905 nmol per liter). Subsequently, the serum corticotropin level was elevated at 188 pg per milliliter (41.4 pmol per liter; normal range, 6 to 76 pg per milliliter [1.3 to 16.7 pmol per liter]); this level was not suppressed after a high-dose dexamethasone suppression test. Thus, we had biochemical confirmation of ectopic Cushing's syndrome mediated by corticotropin secretion. Later, the patient underwent wedge resection of the pulmonary nodule in the right upper lobe.

CLINICAL DIAGNOSIS

Cushing's syndrome, probably caused by a corticotropin-secreting pulmonary nodule.

DR. JOSE C. FLOREZ'S DIAGNOSES

Autoimmune diabetes (latent autoimmune diabetes in adults).

Ectopic Cushing's syndrome, probably from a pulmonary carcinoid tumor.

PATHOLOGICAL DISCUSSION

Dr. Richard L. Kradin: The patient was electively admitted to this hospital for a wedge resection of the right upper lobe. A specimen from the lung resection shows a monomorphic tumor growing adjacent to a pulmonary interlobular septum (Fig. 4A). At higher magnification, the tumor consists of regular amphophilic cells with a low nuclear-to-cytoplasmic ratio (Fig. 4B). The nuclei

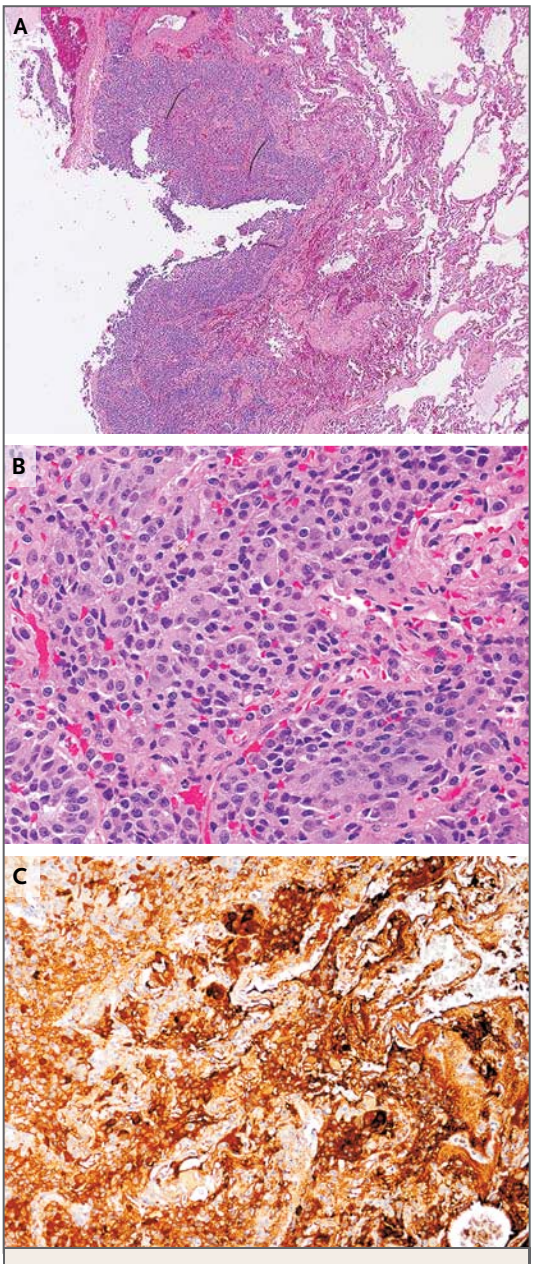


Figure 4. Pathological Evaluation of the Pulmonary Nodule.

At low magnification, the tumor is adjacent to the interlobular septum (Panel A, hematoxylin and eosin). At higher magnification (Panel B, hematoxylin and eosin), monomorphic amphophilic tumor cells with stippled chromatin are seen. These cells show no necrosis or mitotic activity. These findings are diagnostic of a typical carcinoid tumor. Immunostaining for corticotropin-releasing hormone shows that the tumor cells are strongly positive for corticotropin production (Panel C).

have the stippled chromatin pattern that is characteristically seen in cells with neuroendocrine differentiation. The absence of mitosis and necrosis indicates that this is a typical low-grade carcinoid tumor, with a favorable prognosis after resection. In view of the history of Cushing's syndrome in this case, the tumor was immunostained for corticotropin-releasing hormone, and the results showed strong antigenic expression that was consistent with a corticotropin-secreting carcinoid tumor (Fig. 4C).

FOLLOW-UP

Dr. Singh: After resection of the pulmonary nodule, the morning cortisol level dropped to 5.2 μg per deciliter (140 nmol per liter), and the corticotropin level decreased to 13 pg per milliliter (2.9 pmol per liter). The patient's glycemic control has improved markedly, and her weight has been stable while she has been taking relatively small doses of intermediate and rapid-acting (i.e., "70/30") insulin. The most recent glycated hemoglobin level was 5.6%. The hypertension, tremor, and bloating have all resolved. However, she continues to have some leg weakness, for which she is pursuing physical therapy.

Dr. Bazari: In a patient with diabetes and a pulmonary nodule, beyond ruling out a malignant condition, should one evaluate for a functioning nodule?

Dr. Florez: The co-occurrence of diabetes, which is a common disease, and a pulmonary nodule, which is also common, should not alter how one would treat either condition, unless there are unusual features. A solitary pulmonary nodule in the context of diabetes should be treated as a typical solitary pulmonary nodule. In this case, the rapid progression of the patient's symptoms appeared to be temporally associated with the change in the size of the pulmonary nodule and therefore warranted further investigation.

Dr. Thomas R. Spitzer (Medicine)*:* Did you choose carcinoid over small-cell cancer because of the indolence of the course?

Dr. Florez: Yes. The two features of this case that led me to choose carcinoid are the absence of a history of smoking and the stability of the nodule for about 3.5 years, without other worrisome features such as lymphadenopathy.

Dr. David A. Sallman (Medicine): If a patient has a new diagnosis of diabetes with some clinical symptoms of Cushing's syndrome, when should we think about pursuing a secondary workup?

Dr. Florez: Diabetes is very common, and Cushing's syndrome is relatively rare. It is estimated that approximately 0.6% of outpatients with type 2 diabetes have Cushing's syndrome.[13] Many features of diabetes, such as obesity and hypertension, are very common and not helpful for diagnosing Cushing's syndrome. I would pursue a secondary cause only in a scenario in which patients have diabetes that is very difficult to control — unless, of course, one starts noticing more of the findings specific to Cushing's syndrome, such as weakness in the proximal muscle groups, purple striae, or facial plethora.

Dr. Lloyd Axelrod (Medicine): The patient had hypomagnesemia and carried the presumed diagnosis of Gitelman's syndrome. Could the hypomagnesemia be related to the Cushing's syndrome instead?

Dr. Florez: In association with urinary potassium wasting, magnesium tends to also be wasted. We could invoke Gitelman's syndrome, but I am happy ascribing this finding to Cushing's syndrome and the hypokalemia. I would not chase some other esoteric diagnosis, unless the magnesium level continues to be low after effective treatment of Cushing's syndrome.

Dr. Axelrod: You listed several screening tests for Cushing's syndrome. We would prefer not to use all three tests all the time. When should we use one or another?

Dr. Florez: The most sensitive test is measurement of the 24-hour urinary free cortisol level. I would perform this test if I had a high clinical suspicion of Cushing's syndrome. However, there are a number of considerations: the urine volume must be adequate (if the volume is too high, it can lead to a false positive result), the patient must not be taking exogenous steroids that might interfere with the test, and the creatinine level should be normal. If the level of urinary free cortisol is higher than three times the upper limit of the normal range, it is diagnostic; if the level is high, but not to that extreme, you may consider repeating the test.

For the 1-mg overnight dexamethasone suppression test, the patient needs to take 1 mg of dexamethasone between 11 p.m. and midnight the night before the test. Then, the serum cortisol level should be measured at precisely 8 a.m. A level greater than 5 μg per deciliter (138 nmol per liter) is suggestive of Cushing's syndrome. To increase the sensitivity of the test, some advocate lowering the cutoff point to 1.8 μg per deciliter (50 nmol per liter). The 1-mg dexamethasone suppression test has a very good negative predictive value — a cortisol level less than 1.8 μg per deciliter effectively rules out Cushing's syndrome. The test is easy to perform in the outpatient setting; therefore, it is an avenue one can use in the clinic to lay a mild suspicion to rest.

The newer test is measurement of the salivary cortisol level. In this test, the patient chews on a cotton swab and deposits the saliva in a vial that can be sent back to the laboratory. Saliva is collected between 11 p.m. and midnight; therefore, the patient can perform the test at home.

ANATOMICAL DIAGNOSIS

Pulmonary carcinoid tumor, typical type, producing ectopic corticotropin.

This case was discussed at the medical case conference.

Dr. Florez reports receiving consulting fees from Pfizer, Eli Lilly, and Novartis. Dr. Shepard reports receiving consulting fees through her institution from AGFA and serving as an expert witness on behalf of physicians in legal cases involving chest imaging. Dr. Kradin reports serving as an expert witness on behalf of patients in cases involving asbestos and lung disease. No other potential conflict of interest relevant to this article was reported.

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

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