Mysterious Hyperglycemia: Disease Versus Device

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Case Presentation

A 77-year-old Latina woman was referred to our center for a second opinion regarding poorly controlled type 2 diabetes, with the specific question of an underlying neuroendocrine neoplasm as a possible secondary cause. Diabetes had been diagnosed >30 years earlier, and the patient was initially treated with oral agents alone for several years but had been using insulin injections for as long as she could remember. There was no history of diabetic ketoacidosis or other hyperglycemic emergency and no known history of definitive diabetes microvascular or macrovascular complications.

Most recently, her regimen consisted of the combination of saxagliptin and metformin 2.5/1,000 mg twice daily, glargine 50 units at bedtime, and lispro 28 units three times daily before meals. The patient usually self-administered her insulin, although at times her son administered it when she visited his home to share a meal. For many years, her A1C had hovered in the low 7% range. Approximately 2 years before our evaluation, the patient noted a relatively abrupt increase in her blood glucose levels, as determined by fingerstick glucose monitoring and as corroborated by an increasing A1C into the 9–10% range.

The patient had recently been under the care of an endocrinologist in another city who had added the oral agents to her insulin regimen and aggressively increased her insulin doses, seemingly to no avail. In the 1–2 months before her visit with us, her capillary blood glucose levels, checked four times daily, had been consistently in >200 mg/dL, with frequent excursions to >300 mg/dL. The patient had had no recent hypoglycemia, although occasionally she noted improved glucose control for 1–2 days that was unexplained. The patient and her family were becoming increasingly frustrated by her seeming inability to achieve the quality of glycemic control to which she had become accustomed earlier in the course of her disease.

The patient's adherence to dietary recommendations was reasonably good. In fact, her children, who were becoming more diligent participants in their mother's care, reported that she was avoiding most concentrated sweets and was successful in her attempts at moderating carbohydrate intake and avoiding excessive dietary fats. Her weight had declined by ~30 lb in the past 2 years, which was presumed to be the result of her uncontrolled hyperglycemia and her more rigid diet. Never obese until recently, she had maintained a BMI in the range of 29 kg/m^2 for years.

Except for mild symptoms of hyperglycemia, including polyuria, the patient reported otherwise feeling well, without fever, headaches, visual disturbance, diaphoresis, change in facial characteristics or weight distribution, rash, palpitations, chest discomfort, abdominal pain, alteration in bowel habits, muscle

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weakness, edema, arthralgia, tremor, or focal neurological deficits. Aside from her frustration with her glycemic control, she denied recent stress or depressive symptoms. There had been no other changes in her nondiabetes medications and specifically no treatment with any glucocorticoids or psychiatric medications.

Although her physical examination at the time revealed no findings to suggest any infection or new disease state, the patient's endocrinologist had undertaken an appropriate comprehensive search for secondary causes of her deteriorated glycemic control. This included routine chemistries, which ruled out any development of either renal or hepatic disease and included normal lipase and thyroid function test results and a normal complete blood count (CBC). A 24-hour urine free cortisol measurement was normal, and assessment of urinary catecholamine metabolites was also within range. Imaging studies, particularly directed at the pancreas, were then undertaken. Both ultrasound and computed tomography of the abdomen were normal, save for benign-appearing renal cysts. Specifically, there were no pancreatic, hepatic, or adrenal masses. Rare neuroendocrine syndromes were next considered. A chromogranin A level was mildly elevated at 27 ng/mL (normal range 9–15 ng/mL) but the cancer antigen 19-9 level was normal. The high chromogranin level prompted an octreotide-labeled scintigraphy study, which suggested mildly increased activity in the mid-upper abdomen. This finding led to re-imaging of the abdomen with magnetic resonance, again demonstrating no abnormal findings in this region. Finally, an endoscopic ultrasound found no evidence of pancreatic lesions.

The patient's medical history was additionally notable for diabetic retinopathy with preserved vision, diabetic somatosensory peripheral neuropathy, hypertension and hyperlipidemia (both well controlled), and gastroesophageal reflux disease. Her surgical history was remarkable only for a laparoscopic cholescystectomy several years earlier.

In addition to insulin and oral antihyperglycemic agents, the patient had been treated with valsartan 160 mg once daily, rosuvastatin 10 mg once daily, omeprazole 20 mg once daily, and aspirin 81 mg once daily, the latter for cardiovascular prophylaxis. She reported no drug allergies and specifically had not noted any swelling, redness, or itching at insulin injection sites.

Her family history was positive for diabetes (mostly type 2) in multiple members. Her granddaughter had type 1 diabetes. There was no family history of other endocrine disease or pancreatic tumors.

The patient's social history was remarkable for no use of tobacco, alcohol, or illicit substances. She was retired and living alone in an urban apartment. Her two children visited her frequently and helped with her care, especially by handling routine shopping tasks. The family reported no suspicion of nonadherence to insulin injections or diet. She maintained a fair amount of physical activity in her daily life but was not engaging in regular exercise.

On physical examination, this was an elderly woman who appeared somewhat fatigued. There were no stigmata of hyperthyroidism, Cushing syndrome, or acromegaly. Her blood pressure was 150/65 mm Hg, with a pulse of 64 bpm and respiratory rate of 18 breaths/min; she was afebrile. Her skin demonstrated no rashes or lesions. Specifically, there was no flushing, striae, ecchymosis, or violaceous eruptions in the groin or buttocks. Insulin injection sites showed no areas of lipoatrophy or lipohypertrophy. Her pupils were equal and reactive, extra-ocular movements were full, and the fundoscopic exam showed some background retinopathy. Her pharynx was not injected, and she was edentulous. The thyroid gland was not enlarged and contained no nodules. There was no cervical, axillary, or inguinal lymphadenopathy. The lungs were clear to auscultation and percussion. The cardiac sounds were normal, with no murmur or gallop. The abdomen was soft and nontender, without organomegaly or masses. The extremities were not edematous. The musculoskeletal exam was notable only for some osteoarthritic changes in the hands. The neurological exam was without focality.

Additional laboratory assessments included a normal comprehensive medical panel, except for a nonfasting glucose of 499 mg/dL. Amylase and lipase were normal. The complete blood count was notable for a normal white blood cell count of 7,300 and no left shift. The A1C was 13.4%. Urine spot microalbumin was mildly elevated at 54 µg/mg creatinine.

Extensive evaluation of this woman's 2-year history of deteriorated glycemic control was unrevealing except for a mildly elevated chromogranin A level, but that was likely attributable to her proton pump inhibitor. We considered other rare conditions, including glucagonoma and somatostatinoma, but each of these seemed unlikely based on her overall clinical presentation, especially the multiple negative imaging studies. The abrupt nature of the worsening hyperglycemia was perplexing, and we considered whether subtle changes in her self-management habits could be the underlying cause. In retrospect, she recalled that she may have switched the delivery device of her insulin from syringe and vial to pen ~1.5 years earlier.

A referral to our diabetes educator/nurse practitioner was made to further explore her insulin injection technique and other self-management skills. Therapeutically, we advised the patient to advance her insulin doses by ~10% and asked her to adjust her prandial rapid-acting insulin analog progressively for premeal hyperglycemia. We also added pioglitazone 15 mg daily in an attempt to improve

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what appeared to be worsening insulin resistance, although even that assessment was not fully concordant with her presentation. At this point, she was taking glargine 50 units twice daily and lispro 40–50 units with each meal.

One week later, at the initial nurse practitioner visit, the patient had noted no improvement in her glycemic control despite the recommended changes. Her glucose readings were now routinely >300 mg/dL and occasionally >400 mg/dL. During one day, however, her glycemic control became markedly improved, and, in fact, a single blood glucose reading of 40 mg/dL was noted, during which the patient felt extremely weak.

During that visit, the patient stated that she used one 300-unit pen of rapid-acting insulin for "many weeks." This did not correspond with the total daily number of units prescribed for meals, which should have been ~150 units/day. She was asked to demonstrate her injection technique. The patient dialed up the appropriate dose and inserted the pen needle perfectly into the subcutaneous fat of the abdomen. However, instead of depressing the plunger button to inject the insulin, she proceeded to dial down the insulin dose to zero units. No insulin was delivered. Having never been instructed to use the insulin pen device, she assumed this was the proper technique. Upon further questioning, her normal glucose readings (and recent hypoglycemia) occurred on days when she visited her son, who injected his mother's insulin during those visits. His daughter had type 1 diabetes, so he was well versed in the use of insulin pens. Interestingly, the patient, despite having used insulin for >30 years, remained somewhat squeamish about injections, especially when they were administered by another person; she had a tendency to look away when her son injected her, never observing his proper technique. Amusingly, she remarked that she now realized why her insulin pens "lasted so long!"

The patient, after being instructed on the proper use of the insulin pen, was asked to reduce her glargine to 25 units, to discontinue, at least temporarily, all her mealtime lispro injections, and to stop the pioglitazone. The saxagliptin-metformin combination was continued. She was advised to continue checking capillary blood glucose four times daily and to report any hypoglycemia to our center as soon as possible.

Over the next several weeks, the patient easily achieved fasting glucose levels in the mid-100 mg/dL range and postprandial glucose levels in the low-200 mg/dL range. Within 2 months, her A1C had fallen to 10.6%, and after 6 months, her A1C was 7.5%. Eventually, she was thought to require some prandial insulin and was placed back on premeal lispro. Her current dosing is 15 units of glargine daily and 3–4 units of lispro three times per day.

Questions

1. What are the illnesses that present with altered glucose control?
2. In cases of severe, persistent hyperglycemia, what self-care practices need to be examined?
3. How did the need for continuing diabetes self-management education significantly affect this patient's health?

Commentary

This case underscores the importance of proper patient education and self-management training in the treatment of diabetes, particularly in those using insulin injections. Although insulin pens have been deemed "intuitive" by the manufacturers, injecting insulin with a pen device is a skill that must be demonstrated and then reviewed with each patient.

Type 2 diabetes is known to be a progressive disease, with the tendency for blood glucose levels and A1C to increase slowly over time, requiring intensification of therapy. Not infrequently, however, clinicians are faced with a patient whose glycemic control has deteriorated in either an acute or subacute manner. In such cases, the differential diagnosis is very broad. The possibility of changes in lifestyle, such as diet and activity level, should first be considered. Proper adherence to prescribed antihyperglycemic medications must be thoroughly explored, especially if there have been any recent lapses in insurance coverage or financial difficulties. At times, patients may reduce or stop a medication if they feel they have reached their glycemic targets, not understanding that the medications need to be continued to maintain that level of glycemic control. The possibility of degraded insulin formulations should also be considered, given the propensity for insulin solutions or suspensions to be rendered inactive when mishandled (e.g., exposed to extreme heat.) Other technical issues, such as injection technique (e.g., correctly attaching the pen tip needle and priming the pen), especially if the change in control correlates temporally with the use of a new delivery device. Injection into lipohypertrophic areas also has been known to decrease insulin absorption.

After lifestyle and management issues are ruled out, clinicians must consider the interval development of an intercurrent illness, especially acute infection. Through the activation of counterregulatory stress hormones, especially cortisol and catecholamines, infectious illnesses can increase insulin requirements. Other medical considerations include abrupt increases in emotional stress levels, which can similarly aggravate underlying insulin resistance. Although not classically acute (but occasionally subacute), the development of steatosis, especially in type 2 diabetes, may also reduce insulin action and can be easily excluded by assessment of liver function tests. Less common medical causes include the development of hormonal syndromes associated with hyperglycemia in nondiabetic individuals (i.e., secondary diabetes), which can certainly lead to significant

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increases in blood glucose in patients with previously well-controlled diabetes. These syndromes include, classically, hyperthyroidism (especially in type 1 diabetes), Cushing syndrome, pheochromocytoma, and acromegaly—each working primarily through reduced insulin sensitivity. Rarely, the development of insulin antibodies can result in less effective glucose lowering from insulin injections.

Our case also underscores the importance of adequate patient education and skills training. Specifically, proper insulin injection technique must be ensured, given the important safety considerations when using this potent glucose-lowering agent. In this case, the patient truly believed she was properly injecting the insulin and had not had the opportunity to review the use of the insulin pen or to demonstrate the technique she used for injection. Health care providers can never assume that patients' duration of disease and number of years in self-care management will translate into the proper use of a new technique or device. To incorporate the new skill, particularly one as important as self-administration of insulin, into the self-care regimen, a patient must be able to demonstrate mastery in a "teach back" session. Unfortunately, as medical appointment visits are shortened, time for patient education is limited. Diabetes therapy relies on self-care management; therefore, self-management education is integral in the successful implementation of a prescribed medical regimen. This case clearly demonstrates this principle.

Clinical Pearls

- Even the most "intuitive" device will require hands-on patient education to ensure proper use.
- Understanding a patient's diabetes self-care management regimen is essential to assessing any change in health and well-being.
- In spite of the duration of disease and self-care experience, every patient needs to be routinely evaluated for the safe and proper use of the various diabetes devices.

Duality of Interest

Ms. Spollett has served as an advisory board member for and received honoraria for speaking engagements from Sanofi and has been a consultant to AstraZeneca. Dr. Inzucchi has served as an advisor, consultant, or clinical trial committee member for AstraZeneca, Boehringer Ingelheim, Janssen, Novo Nordisk, and Sanofi/Lexicon. No other potential conflicts of interest relevant to this article were reported.

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