A Woman with Diabetes Mellitus Complicated by Insulin Antibody Interactions

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The patient is a 43-year-old, Spanish-speaking female with a 20-year history of depressive symptoms and a 16-year history of diabetes mellitus type II. She had been treated originally with oral hypoglycemic agents, but, due to poor efficacy, is being treated with insulin.

The patient has become known to the psychiatric consult service at the local major metropolitan hospital after repeated incidences of loss of consciousness due to severe hypoglycemia evidenced by blood glucose levels in the low 20s. During the most recent such occurrence, the patient was referred to the consult-liaison services in preparation for an involuntary admission to the inpatient psychiatric unit based on suspicions of surreptitious insulin use in the context of food restriction and preoccupation with weight loss.

PRESENTATION

The patient is a polite, reserved and soft-spoken woman who was born and raised in Mexico. She has a close-knit family of modest means and Catholic traditions. She has a sixth-grade education. The patient moved to the American Southwest at the age of 20 years, and is single, never married, and without children despite efforts to conceive. She resides with her adult siblings and has worked as a nanny and housekeeper.

The patient is on disability for depression that was first diagnosed at the age of 21 years. The patient reported that she had been
depressed all of her life and started to realize at the age of 18 years that, “something wasn’t right.” She described episodes of difficulty in getting out of bed, in taking a shower, and in finding pleasure in activities she used to enjoy, such as going to church. She also experienced decreased energy and appetite. The patient denied problems with sleep and reported that symptoms worsened in the morning. She reported no personal history of suicide attempts; psychosis; mood episodes; anxiety; psychiatric admissions; cigarette, alcohol, or drug use. She has five other siblings, all of whom suffer from depression, including a brother with bipolar disease.

Aside from insulin-dependent diabetes mellitus (IDDM), her medical history is significant for hypothyroidism, hypercholesterolemia and gastroesophageal reflux disease (GERD).

Previously, the patient was treated unsuccessfully with mirtazapine, escitalopram, venlafaxine, paroxetine, and fluoxetine. On these medications, she complained of agitation; crying spells; difficulty getting along with other people; and recurrent thoughts and wishes of death. The patient stated that the only treatment that worked was sertraline 200 mg, which she had started at the mental health center 2 years earlier.

During the course of her most recent hospitalization, there were no remarkable findings on physical exam. Her laboratory values were normal, including complete blood count, electrolytes, and liver function studies. Adrenocorticotropic (ACTH) stimulation test was also normal, and c-peptide levels were undetectable at glucose levels 30 mg/dL to 200 mg/dL.

Consistent with findings of hypoglycemia, HbA1c was 5.3% with a body mass index (BMI) of 17 and prealbumin of 12.6.

Psychiatric symptoms she reported included poor appetite, depression, fatigue, indecisiveness, hopelessness, and, at times, lying in bed all day not wanting to shower or prepare meals. She acknowledged a change in behavior during the previous 4 months, during which she became afraid of leaving the house by herself; she would not go to church, the supermarket, or appointments unless accompanied by a sibling.

The patient could not identify any triggers, but complained that “something is wrong,” and acknowledged difficulty thinking clearly and an excessive fear of hyperglycemia, leading to restriction of carbohydrates. She denied preoccupation with death or thoughts of suicide. On exam, the patient appeared demoralized and presented with markedly restricted intensity and decreased range and reactivity.

On admission to the inpatient unit at the mental health center, she appeared to be depressed with notable cognitive slowing confirmed on screening with MADRS 30 and refusal to complete MOCA. She was described as, “brittle, and her behavior categorized as delusional and obsessive phobia surrounding insulin management controlling carbohydrate intake and insulin, possible characterologic issues aggravating symptoms with cognitive disorder of unknown etiology placing the patient at high risk for grave passive neglect.”

In the unit, additional laboratory findings revealed that HIV antibody was nonreactive and Treponema pallidum antibodies were negative.

**DIFFERENTIAL DIAGNOSES**

At that time, the differential diagnoses included major depressive disorder (MDD) recurrent and severe with psychotic features, obsessive-compulsive disorder (OCD), and eating disorder NOS. In the unit, she was treated with nutritional rehabilitation, behavioral and milieu therapy, psychotherapy, and pharmacotherapy.

Her family was involved, concerned, and provided consent within state regulations. In accordance with unit protocols for patients
with eating disorders, the patient was kept under strict observation 24 hours a day. Her meals were supervised with strict PO monitoring, and her toileting activity after meals was restricted to minimize risk of purging. Her weight was measured three times weekly.

**TREATMENT**

Treatment with low-dose mirtazapine was started by the consult service to target sleep and appetite and was continued after transfer. Olanzapine augmentation was started to target psychosis and enhance appetite.

The patient remained on the unit for an extended hospitalization, since the treatment team and her family were concerned for her safety and well-being. Accordingly, her family consented to an extended inpatient treatment. Despite a 48-day hospitalization, the patient’s condition warranted transfer to the state hospital. The magistrate granted a 30-day extension of her involuntary admission.

All laboratory values were within normal levels, her BMI was 19, and prealbumin was 22.8. She was tolerating a combination of medications that included mirtazapine now titrated to 45 mg. Augmentation with olanzapine was discontinued due to worsening hyperlipidemia on laboratory findings.

Treatment was started with aripiprazole, an atypical agent, with decreased metabolic burden that was titrated to 10 mg daily. After 3 weeks, she was discharged from the state hospital on the same combination of mirtazapine, now titrated to 45 mg, and aripiprazole 10 mg daily.

During the next few months, she continued to experience episodes of life-threatening hypoglycemia, which necessitated emergency treatment, and four other hospitalizations in the medical unit, despite multiple efforts by the diabetic care team to stabilize her glucose levels.

Questions surfaced surrounding the suspected surreptitious use of insulin, given her extensive psychiatric history and history of inappropriate insulin dosing. Thus, a multi-disciplinary meeting that included endocrinology, medicine, and psychiatry was held in conjunction with the family.

The patient and the family signed a contract agreeing that her sister would be responsible for prefilling syringes and providing all her daily insulin doses. In addition to storing the syringes in a locked box, the agreement stipulated that empty syringes were collected daily in a sharps container to ensure appropriate administration of all medications, and at the correct dosage.

During the next several weeks, glucose levels remained difficult to control and the endocrinologists became suspicious about other etiologies that caused severe episodes of hypoglycemia. Because the patient had a remote history of positive antinuclear antibody, immunologic resistance became highly suspect. Several changes were made to her insulin regimen, and she was started on a low dose of prednisone. Laboratories performed in clinic for sulfonylurea screening and urine dip stick for ketones were all negative.

The patient continued to experience episodes of “difficulty thinking clearly, increasing somnolence and fatigue, dizziness, polyuria, polydipsia, and headache.” A switch to a low-dose regimen of short-acting insulin, depending on carbohydrate load, led to 4 days in which she experienced progressive hyperglycemia with blood sugars in the high 400s, necessitating 63 sporadic units of Lantus and NovoLog over 18 hours.

At that point, other diagnoses started climbing to the top of the differential list. When the results of insulin antibodies levels were markedly elevated (5.5, where normal is 0.5), it became evident that autoantibodies were binding to insulin. It was postulated by the endocrinology service that these antibodies had been formed against exogenous insulin.1
case challenge

D I A G N O S I S

Insulin Antibody Interaction

The patient was admitted to the intensive care unit and placed on a continuous glucose monitor with inconsistent responses to insulin. She was experiencing levels of hyperglycemia despite escalating insulin to 60 to 80 units within 12 hours. Laboratory test results revealed insulin levels greater than 1,500 uIU/mL with total insulin levels of 61 and free insulin levels of two. Thus, 97% of her insulin was bound to antibodies.

Insulin antibody interactions are rare and responsible for causing distinct episodes of hypoglycemia and hyperglycemia determined by the equilibrium between free insulin and bound insulin complex. When the antibody is unbound to the insulin molecule, episodes of hypoglycemia ensue; when the antibody binds to insulin, the result is episodes of hyperglycemia.

DISCUSSION

There is no consensus on the optimal treatment of hypoglycemia and hyperglycemia caused by insulin antibody interactions. Discontinuation of subcutaneous insulin is not realistic. Treatment options include short-acting insulin formulations that mimic intermediate-acting insulin, immunosuppression, and plasmapheresis. In this case, treatment with insulin lispro and a concomitant prednisone burst started at 60 mg was not effective and the patient continued to have severe hypoglycemia.

There is case-based evidence of the therapeutic applications of plasmapheresis to remove antibodies and immune complexes. Due to the severity of fluctuating glucose levels, a trial of therapeutic plasmapheresis was initiated with the goal of achieving improved glycemic control.

TABLE

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<th>Total Free- and Percentage-Bound Insulin</th>
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Source: Diaz NA and Apfeldorf W. Reprinted with permission.

FIGURE

Six Plasmapheresis Treatments Over 11 Days

Figure 1. A simple line graph delineating a rise in free insulin levels with a concomitant decrease in the percentage of insulin bound by autoantibody over the course of six plasmapheresis treatments in 11 days. Source: Diaz NA and Apfeldorf W. Reprinted with permission.

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In addition, after testing normal for TMPT enzyme activity, treatment with azathioprine 50 mg daily was initiated with the goal of augmenting the decreased production of antibodies to insulin. Treatment with prednisone was tapered down to 5 mg daily.

There were no complications from treatment and the patient experienced no adverse effects. After six rounds of pharesis treatment in 11 days, the percentage of insulin bound to antibodies decreased by 85% and the levels of free insulin increased by 94% (see Table and Figure, page 120).

Four days after discharge from the hospital, an examination at the diabetes comprehensive care clinic revealed the patient was stable with no episodes of severe hypoglycemia or hyperglycemia. Her lowest blood sugar levels since discharge were in the 70s with highs in the 300s and average glucose levels between 100 and 200. In addition, HbA1c was found to be 7.7%, a marked improvement from 9.4% 3 months prior. Treatment with plasmapheresis had resulted in glycemic stability.

Five months after discharge, the patient continues to do well and is currently stable on a regimen of short-acting and intermediate forms of insulin. Her episodes of glycemic instability are rare with daily variable glucose levels in the 80s to 100s. HbA1c continues to trend downward and is currently at 6.8%. She is stable on immunosuppression therapy with azathioprine 50 mg daily and prednisone 5 mg.

At the Mental Health Center Outpatient Clinic, she no longer complains of “difficulty thinking clearly, somnolence, fatigue, hopelessness, lying in bed all day, not wanting to shower, or fear of leaving her house.” On examination, the patient does not appear demoralized, and she reports “good” mood that is congruent with markedly improved range and reactivity. She is stable on serotonin–norepinephrine reuptake inhibitors (SNRI) therapy at 120 mg daily and augmentation with an atypical antipsychotic, aripiprazole 5 mg daily.

When asked about her stay in the unit, she reports: “It saved my life because my depression was very bad and I did not realize that my behaviors where placing me at risk of death. I could not understand what was happening to me.” She expressed gratitude for her recovery, walks three times per week and is currently considering volunteer opportunities in the community after spending the holidays with her family.

CONCLUSION

The importance of ruling out psychiatric consequences of general medical conditions cannot be overemphasized. This case presents compelling evidence of the importance of maintaining a high level of clinical suspicion when treating patients with co-occurring chronic diseases such as depression and diabetes mellitus that is further complicated by insulin antibody interactions.

REFERENCES