Case Report

Insulin Receptor Autoantibody–mediated Hypoglycemia in a Woman With Mixed Connective Tissue Disease

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Abbreviations: CGM, continuous glucose monitor; SLE, systemic lupus erythematosus.

Abstract

Autoantibodies to the insulin receptor are rare and typically cause severe insulin resistance and hyperglycemia, a condition termed *type B insulin resistance*. Uncommonly, antibodies to the insulin receptor can cause hypoglycemia. We present the case of a woman who developed recurrent severe hypoglycemia and myopathy, was found to have insulin receptor autoantibodies and mixed connective tissue disease, and had resolution of hypoglycemia with immunosuppression. A 55-year-old woman with a history of obesity, hypertension, and prior hemorrhagic stroke presented with recurrent severe hypoglycemia. A diagnostic fast resulted in hypoinsulinemic hypoketotic hypoglycemia. Adrenal function was intact. Progressive myopathy had developed simultaneously with her hypoglycemia, and rheumatologic evaluation revealed mixed connective tissue disease. The plasma acylcarnitine profile was normal, extensive oncologic evaluation including insulin-like growth factor 2 measurement was unrevealing, and anti-insulin antibody testing was negative. Ultimately, anti-insulin receptor antibodies were found to be present. The patient was treated with glucocorticoids and rituximab. Eight weeks after initiation of immunosuppression, the insulin receptor antibody titer had decreased and hypoglycemia had resolved. Eight months after diagnosis, the patient remained free of severe hypoglycemia despite tapering of glucocorticoids to a near-physiologic dose. Though antibodies to the insulin receptor typically cause severe insulin resistance, this patient had no evidence of insulin resistance and instead presented with recurrent

severe hypoglycemia, which responded to glucocorticoids and rituximab. The diagnosis of insulin receptor antibody–mediated hypoglycemia is rare but should be considered in patients with systemic autoimmune disease, including mixed connective tissue disease, in the appropriate clinical context.

Key Words: autoimmune hypoglycemia, anti-insulin receptor antibody, type B insulin resistance, mixed connective tissue disease

Autoimmune causes of hypoglycemia are rare [1]. Two major forms of autoimmune hypoglycemia have been described: the insulin autoimmune syndrome and type B insulin resistance. Insulin autoimmune syndrome, also known as Hirata disease, is caused by antibodies to insulin that bind insulin after its postprandial secretion and subsequently release it with kinetics independent of glycemia, predisposing to hypoglycemia [2]. First described in Japan in 1970, most published case series of insulin autoimmune syndrome are in East Asian populations [2-4]. Type B insulin resistance is caused by antibodies to the insulin receptor. These antibodies typically inhibit the binding of insulin to the insulin receptor and decrease cellular responsiveness to insulin, resulting in severe insulin resistance with associated hyperglycemia, acanthosis nigricans, and polycystic ovarian syndrome [1, 5, 6]. However, an estimated 24% of patients with type B insulin resistance will develop autoimmune-mediated hypoglycemia during their clinical course, and some patients with autoantibodies to the insulin receptor develop pure hypoglycemia without any evidence of insulin resistance or hyperglycemia [1, 5, 7]. The mechanism of hypoglycemia in such cases is insulin receptor agonism [5].

Insulin autoimmune syndrome and type B insulin resistance are both associated with systemic autoimmune disease. Insulin autoimmune syndrome is associated with Graves disease (and with the use of methimazole to treat Graves disease), systemic lupus erythematosus (SLE), and rheumatoid arthritis [1]. Type B insulin resistance is strongly associated with SLE, with up to half of patients in published case series meeting diagnostic criteria for SLE [7]. Typically, the development of clinical systemic autoimmune disease precedes the development of type B insulin resistance [1].

Here, we describe a case of a 55-year-old woman who presented with severe recurrent hypoglycemia and subacute muscle weakness, was diagnosed with mixed connective tissue disease, and was ultimately found to have high-titer autoantibodies to the insulin receptor. She had durable resolution of hypoglycemia and reduction of antibody titer with glucocorticoids and rituximab.

Case Report

A 55-year-old White woman with history of obesity, hypertension, and a prior hemorrhagic stroke with mild residual right-sided weakness was evaluated for severe recurrent hypoglycemia and progressive diffuse weakness.

Four months before admission, she had a first episode of hypoglycemia. The patient's husband noted confusion and decreased level of arousal during the night and she was found by emergency medical services to have hypoglycemia; symptoms and hypoglycemia resolved with oral dextrose.

She was evaluated in the outpatient setting by an endocrinologist and was admitted twice to her community hospital. Evaluation during those admissions is summarized in Table 1. Diagnostic fasting revealed hypoinsulinemic hypoglycemia. On abdominal magnetic resonance imaging, there were no lesions compatible with insulinoma noted in the pancreas or foregut. Abnormal serum transaminase levels prompted a liver biopsy, which revealed only focal, mild steatosis. In an attempt to decrease the risk of severe hypoglycemic episodes, hydrocortisone 10 mg twice daily was started despite normal Cosyntropin stimulation testing. Frequent small meals were recommended, and she began to eat every 4 hours.

Despite these interventions, the frequency and severity of hypoglycemic episodes increased over the next 3 months. Episodes occurred both in fasting and postprandial states.

The patient also developed progressive muscle weakness, which was first noted around the time of her first bout of hypoglycemia. Over the next 3 months, as her hypoglycemia was becoming more frequent and severe, her muscle weakness also progressed with eventual inability to rise from a seated position or climb stairs. Dysphagia for solids, which progressed to dysphagia for solids and liquids, also developed during this time. She endorsed Raynaud phenomenon.

One week before admission, progressive dyspnea on exertion developed. The day of admission, spontaneous hypoglycemia to 13 mg/dL occurred at home. She was admitted to her community hospital where repeated bouts of hypoglycemia to 30 to 40 mg/dL occurred. Ultimately, a continuous dextrose infusion was started and the patient was transferred to an academic medical center for further evaluation.

The past medical history included hypertension, obesity, depression, and a hemorrhagic left thalamic stroke 5 years before admission that required frontal ventriculostomy

Table 1. Test results before index hospitalization

Diagnostic fast		Result	Reference range
Plasma glucose, mg/dL		52	70-199
Plasma insulin, µU/mL		< 1	2.6-25
Plasma C-peptide, ng/mL		< 0.1	1.1-4.4
Plasma cortisol, mcg/dL		15.5	Not defined
Sulfonylurea screen		Negative	Negative
Anti-insulin antibody		Negative	Negative
Cosyntropin stimulation testing, 250 mcg			
Cortisol, base, mcg/dL	Cortisol, 30 min, mcg/dL	Cortisol, 60 min, mcg/dL	Reference range
13.3	17.2	19.0	> 18
Imaging			
MR abdomen w/wo contrast	No hypervascular lesions noted in the pancreas. Pancreas has a normal appearance without focal abnormalities. Mild hepatic steatosis. Adrenals have a normal appearance.		
Pathology			
Liver, needle-core biopsy	Focal, mild steatosis. Iron, PAS, and trichrome stains negative		

Abbreviations: MR, magnetic resonance; PAS, periodic acid–Schiff; w, with; wo, without.

placement. That hospitalization was complicated by difficulty weaning from mechanical ventilation prompting tracheostomy. The tracheostomy was later reversed. Mild residual weakness in the right lower extremity persisted following stroke recovery. The past surgical history also included tubal ligation and carpal tunnel release surgery. She had smoked approximately one half-pack of cigarettes daily for 15 years and stopped at the time of her stroke 5 years before admission. She had previously consumed up to 6 drinks nightly but also stopped consuming alcohol after her stroke. She did not use other nonprescribed substances. Family history included a mother with prior myocardial infarction and heart failure, a deceased father who had traumatic brain injury, 2 siblings without known medical problems, and 2 adult daughters without medical problems. There was specifically no family history of diabetes mellitus, hypoglycemic disorder, SLE, or any other known systemic autoimmune disease. The patient had no known allergies. Home medications before admission included bupropion, cetirizine, diltiazem, escitalopram, ferrous fumarate, folic acid, gabapentin, and hydrocortisone (10 mg twice daily). On review of systems, she had had menopause at age 50 but had previously had regular monthly menses.

Pertinent findings on physical examination included hand stiffness and reduced extension range of motion at the metacarpophalangeal joints. The fingers were puffy and cool and transient Raynaud phenomenon was present. Muscle strength was 3 of 5 in the bilateral finger abductors, 4 of 5 in the bilateral triceps, 3 of 5 in the bilateral hip flexors, and 5 of 5 in the bilateral deltoids, trapezii, sternocleidomastoids, knee flexors, knee extensors, and ankle dorsi/plantar flexors. No rash was present. Acanthosis nigricans was not present. The body mass index was 32.3 kg/m^2 and the body surface area was 1.89 m^2.

Initial laboratory testing on admission and selected subsequent laboratory results are shown in Table 2. This workup was remarkable for elevated serum transaminases (with negative viral hepatitis serologies and normal ceruloplasmin and α-1–antitrypsin), and elevated aldolase and creatine kinase levels with low serum complement C3 and markedly positive antinuclear antibody, anti-Sm antibody, and anti–U1-RNP antibody titers.

A continuous intravenous dextrose infusion was started on admission and adjusted to maintain euglycemia (Fig. 1). Hydrocortisone was continued at physiologic replacement dosing of 10 mg each morning and 5 mg each evening. The frequency of her hypoglycemic episodes and the presence of hypoglycemia unawareness necessitated transfer to the medical intensive care unit. A continuous glucose monitor (CGM) was placed at the bedside to enhance recognition of impending hypoglycemia. A diagnostic fast was performed and after 4 hours resulted in hypoinsulinemic hypoglycemia with low β-hydroxybutyrate (see Table 2). The serum glucose rose from 53 mg/dL to 87 mg/dL 30 minutes after administration of 1-mg glucagon.

The finding of hypoinsulinemic hypoketotic hypoglycemia on diagnostic fasting, in which insulin-mediated suppression of ketogenesis appeared intact despite hypoinsulinemia, guided further diagnostic evaluation. Differential diagnostic considerations included insulin-like

Table 2. Testing during index hospitalization

Admission laboratory testing	Result	Reference range
Sodium, mmol/L	138	135-145
Potassium, mmol/L	3.8	3.3-4.9
Chloride, mmol/L	106	97-110
Carbon dioxide, mmol/L	28	22-32
Anion gap, mmol/L	4	2-15
Blood urea nitrogen, mg/dL	5	8-25
Creatinine, mg/dL	0.76	0.60-1.10
Glucose, mg/dL	60	70-199
Calcium, mg/dL	8.6	8.5-10.3
Bilirubin, total, mg/dL	0.3	0.1-1.2
Protein, total, g/dL	5.8	6.5-8.5
Albumin, g/dL	3.2	3.5-5.0
Alkaline phosphatase, U/L	122	40-130
Aspartate aminotransferase, U/L	296	10-45
Alanine aminotransferase, U/L	227	7-45
Gamma glutamyltransferase, U/L	46	5-35
Magnesium, mg/dL	1.6	1.4-2.5
Phosphorus, mg/dL	3.1	2.3-4.5
Aldolase, U/L	109.7	0.1-8.0
Creatine kinase, U/L	5777	30-200
Ceruloplasmin, mg/dL	18.9	16.0-45.0
α-1–Antitrypsin, mg/dL	140	90-200
HIV 1/2 antibody + p24 antigen	Nonreactive	Nonreactive
Hepatitis B surface antigen	Nonreactive	Nonreactive
Hepatitis B surface antibody	Nonreactive	Nonreactive
Hepatitis B core antibody IgM/IgG	Nonreactive	Nonreactive
Hepatitis C antibody	Nonreactive	Nonreactive
Glycated hemoglobin A_{1c}, %	4.3	4.0-5.6
TSH, µU/mL	3.31	0.30-4.20
Total cholesterol, mg/dL	112	30-199
LDL cholesterol, mg/dL	53	< 129
HDL cholesterol, mg/dL	38	> 40
Plasma triglycerides, mg/dL	104	< 149

Diagnostic fast	Result	Reference range
Serum glucose, mg/dL	53	70-199
Insulin, µU/mL	0.9	2.6-25.0
C-peptide, ng/mL	0.4	1.1-4.4
β-hydroxybutyrate, mmol/L	0.2	0.0-0.5
Proinsulin, pmol/L	6.9	3.6-22
Serum glucose 30 min after 1 mg glucagon, mg/dL	87	70-199

Additional hypoglycemia testing	Result	Reference range
Insulin antibody	Negative	Negative
Hypoglycemic agent screen[a]	Negative	Negative
Insulin-like growth factor 1, ng/mL	10	40-210
Insulin-like growth factor 2, ng/mL	315	333-967
Plasma acylcarnitine profile[b]	Normal	Normal

Table 2. Continued

Immunologic testing	Result	Reference range
Erythrocyte sedimentation rate, mm/h	41	1-30
C-reactive protein, mg/L	3.2	< 10
Complement C3, serum, mg/dL	88.0	90.0-180.0
Complement C4, serum, mg/dL	17.3	10.0-40.0
Antinuclear antibody titer	1:5120, homogeneous	Negative
dsDNA antibody, IU/mL	1.0	< 4.0
Sm antibody index	> 8.0	< 0.9
SS-A antibody index	< 0.2	< 0.9
SS-B antibody index	< 0.2	< 0.9
Jo-1 antibody index	< 0.2	< 0.9
Scl-70 antibody index	< 0.2	< 0.9
Anti-U1RNP antibody, U	80	< 20
Antimitochondrial antibody	Negative	Negative
Antismooth muscle antibody	Negative	Negative
Myeloperoxidase antibody index	< 0.2	< 0.9
Proteinase-3 antibody index	< 0.2	< 0.9
Urine protein/creatinine ratio, mg/g	307.3	0-180

Abbreviations: dsDNA, double-stranded DNA; HDL, high-density lipoprotein; Ig, immunoglobulin; LDL, low-density lipoprotein; TSH, thyrotropin.
[a]The hypoglycemic agent screen used in this case assayed serum by liquid chromatography–tandem mass spectrometry for glyburide, glipizide, repaglinide, glimepiride, acetohexamide, chlorpropamide, and tolbutamide.
[b]The plasma acylcarnitine assay used in this case assayed plasma by electrospray-tandem mass spectrometry for C2, C3, C3-DC, C4, C4-OH, C5, C5-OH, C5-DC, C6, C6-OH, C8, C8:1, C10, C10:1, C12, C12:1, C12-OH, C14, C14:1, C14:1-OH, C16, C16:1, C16-OH, C16:1-OH, C18, C18:1, C18:2, C18:1-OH, and C18:2-OH species.

growth factor 2–mediated nonislet cell tumor hypoglycemia, disorders of fatty acid oxidation, and autoimmune hypoglycemia. The serum insulin-like growth factor 2 level was not elevated, and an extensive oncologic evaluation, including bone marrow examination and flow cytometry and contrast-enhanced computed tomography of the chest, abdomen, and pelvis, did not reveal any neoplastic disease. A plasma acylcarnitine profile was normal, making a disorder of fatty acid oxidation unlikely. The normal response to glucagon after the diagnostic fast also made a disorder of fatty acid oxidation less likely. Anti-insulin antibodies were undetectable twice.

Additional workup of the patient's myopathy included magnetic resonance imaging of the lower extremities demonstrating diffuse myositis and electromyogram with irritable myopathy. A deltoid muscle biopsy revealed mild myopathic changes including excess fiber size variation, scattered small atrophic fibers, scattered necrotic fibers undergoing myophagocytosis, regenerative fibers, and an increase in the number of internalized nuclei. In the setting

of high-titer antinuclear antibodies, positive U1-RNP antibodies, Raynaud phenomenon, and puffy digits with inflammatory myopathy, the patient was diagnosed with mixed connective tissue disease. Predominant features of polymyositis with inflammatory myositis and SLE with positive anti-Sm antibodies and mild complement C3 hypocomplementemia were present.

Given high clinical suspicion and extensive unrevealing workup, testing for insulin receptor antibodies was performed as described [8]. While this was pending, treatment with glucocorticoids (methylprednisolone 1.5 mg/kg daily for 2 d, followed by prednisone 1 mg/kg daily) was initiated. The continuous dextrose infusion was gradually weaned off over the subsequent 7 days. A slow taper of prednisone by 5 mg/day each week was begun. The patient was monitored for several days off the continuous dextrose infusion and severe hypoglycemia did not recur. During this time, insulin receptor antibody testing was completed, revealing the presence of autoantibodies to the insulin receptor (Fig. 2). Discharge to home with physical therapy and a CGM system was arranged. Rituximab, at a dose of 1 g, was administered 1 day before discharge and again 3 weeks after discharge.

Seen in follow-up 6 weeks after hospital discharge, the patient reported modest improvements in strength and complete resolution of hypoglycemia. The prednisone dose was 0.5 mg/kg daily. CGM data revealed an average sensor glucose of 131 mg/dL and no episodes of severe hypoglycemia of less than 54 mg/dL over the 6-week interval. Repeat insulin receptor antibody titers were decreased (see Fig. 2). By 90 days after hospital discharge, the prednisone

dose had been tapered to 10 mg daily. CGM interrogation revealed sustained euglycemia with average sensor glucose 132 mg/dL, 0.07% of total time less than 54 mg/dL, no excursions of less than 54 mg/dL for greater than 30 minutes, and no episodes of severe hypoglycemia requiring external assistance (Fig. 3). Seven months after hospital discharge, a second cycle of rituximab was begun. Eight months
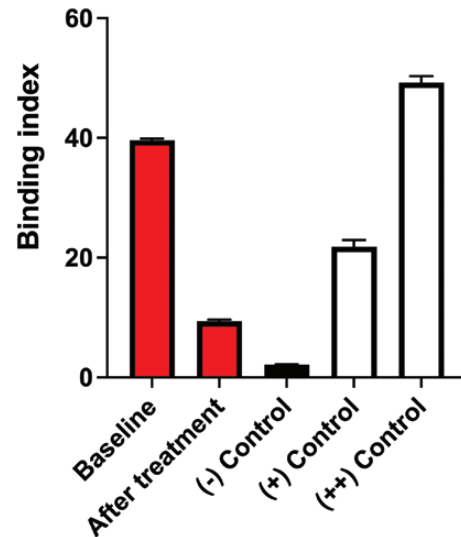
Figure 2. Insulin receptor antibody titers. Patient serum drawn during the hospital admission—4 days after initiation of high-dose glucocorticoids, but before rituximab initiation—was assayed for anti-insulin receptor antibody ("Baseline"). Eight weeks after initiation of high-dose glucocorticoids and 6 weeks after initiation of rituximab, patient serum was redrawn and assayed using the same method ("After treatment"). Negative control, moderately positive control, and strongly positive control patient serum samples were also assayed. Insulin receptor binding index is expressed as mean ± SEM of 2 to 4 technical replicates.
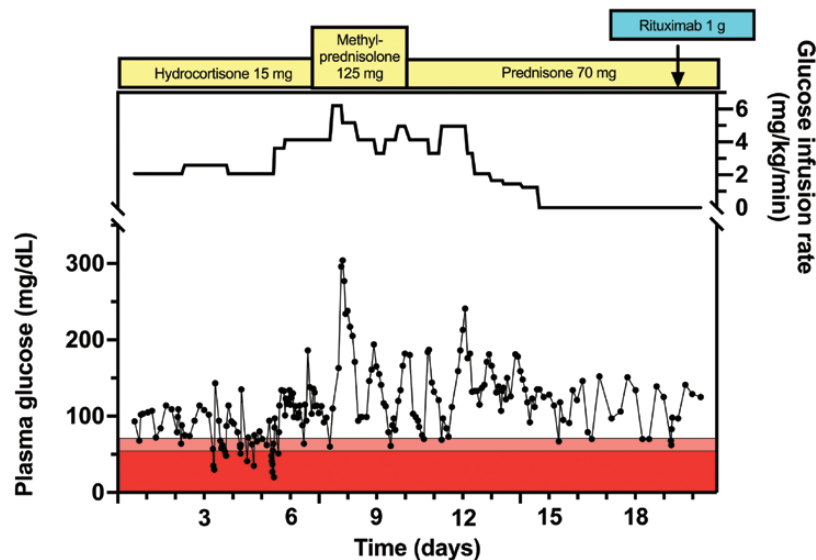
Figure 1. Plasma glucose and glucose infusion rate during the index hospitalization. Point-of-care capillary blood glucose and serum glucose values are graphed on the left y-axis throughout the 20-day admission. Level 1 hypoglycemia, less than 70 mg/dL, is shaded light red. Level 2 hypoglycemia, less than 54 mg/dL, is shaded dark red. The intravenous glucose infusion rate is graphed on the right y-axis. Glucocorticoids (shown as total daily dose during the indicated periods) are shown in yellow. Rituximab was administered on the day prior to discharge.
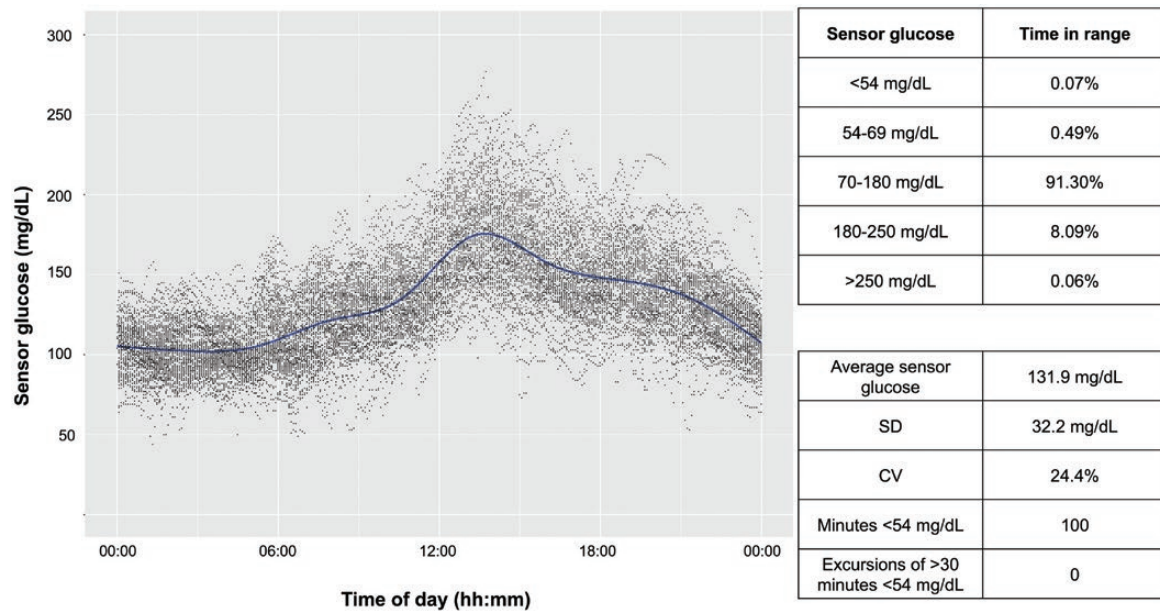
Sensor glucose	Time in range
<54 mg/dL	0.07%
54-69 mg/dL	0.49%
70-180 mg/dL	91.30%
180-250 mg/dL	8.09%
>250 mg/dL	0.06%

Average sensor glucose	131.9 mg/dL
SD	32.2 mg/dL
CV	24.4%
Minutes <54 mg/dL	100
Excursions of >30 minutes <54 mg/dL	0

Figure 3. Continuous glucose monitor data. All sensor glucose data from the first 90 days of continuous glucose monitoring (CGM) after hospital discharge are shown. Downloaded CGM data were analyzed using the R package cgmanalysis [22]. The aggregate daily overlay with Loess smoothing is overlaid on all individual sensor glucose data points. Summary measures of glycemic time in range and hypoglycemic events are shown at right. During this time, the prednisone dose was tapered by 5 mg/day each week and was 10 mg/day by the end of the 90-day period. CV, coefficient of variation.

after diagnosis, the patient remained free of any symptomatic hypoglycemia with CGM time at less than 54 mg/dL of 0.1%.

Discussion

The diagnosis of insulin receptor antibody–mediated hypoglycemia is challenging owing to its rarity and the lack of availability of commercial testing for insulin receptor antibodies in the United States. In this case, the clinical suspicion for insulin receptor antibody–mediated hypoglycemia was high owing to the simultaneous onset of systemic autoimmune disease and extensive unrevealing laboratory workup focused on hypoinsulinemic hypoglycemia.

The patient has had durable resolution of hypoglycemia with immunosuppression. High-dose glucocorticoids ameliorate hypoglycemia regardless of the underlying cause, and thus the patient's initial response to glucocorticoids does not provide evidence for insulin receptor antibodies as the cause of hypoglycemia. However, the patient's sustained freedom from severe hypoglycemia after immunosuppression with tapering glucocorticoids and rituximab, taken together with the decreased titer of anti-insulin receptor antibodies following treatment, indicates that the cause of the patient's recurrent severe hypoglycemia was insulin receptor antibody production.

Autoantibodies to the insulin receptor typically cause severe insulin resistance [9]. However, this patient displayed no evidence of insulin resistance. Specifically, there was no hyperinsulinemia, acanthosis nigricans, or polycystic ovarian syndrome. Insulin receptor antibody–mediated hypoglycemia has been described both as the sole manifestation of insulin receptor autoantibody production [5] and as a distinct phase of the type B insulin resistance syndrome in which the clinical course shifts from severe insulin resistance to refractory hypoglycemia [10]. The inverse clinical course, in which refractory hypoglycemia is the initial manifestation and a transition to severe insulin resistance occurs later, has also been described [11]. Hypoglycemia is thought to result from partial agonist activity at lower insulin receptor antibody titers, whereas type B insulin resistance is thought to result from downregulation of cellular insulin receptors at higher antibody titers [6]. An alternative hypothesis for the observation that some patients with insulin receptor autoantibodies develop insulin resistance while others develop hypoglycemia is the existence of polyclonal antibody populations with different biologic activities [12].

Type B insulin resistance is strongly associated with SLE and has a female predominance [7]. This patient was diagnosed with mixed connective tissue disease, which has also been described in patients with type B insulin resistance [6, 13-16]. The presence of detectable insulin receptor antibody titers in SLE is uncommon; in one study, 1 of 26 patients with SLE was found to have an asymptomatic positive insulin receptor antibody titer [17]. Antibodies to the insulin receptor have also been described as a paraneoplastic phenomenon in the setting of multiple myeloma and Hodgkin lymphoma [7]; however, extensive oncologic evaluation in this patient was unrevealing.

The prognosis for patients with type B insulin resistance is historically guarded, with mortality rates greater than 50% in older case series [7]. Serologic remission can be temporary, and fatal hypoglycemia following plasmapheresis-and-glucocorticoid-induced remission has been described [7]. The development of CGM systems with hypoglycemia alarm capability was a major advance for patients at risk of severe hypoglycemia of any cause and has been an invaluable diagnostic and therapeutic tool in this case. In addition, advances in immunosuppression including rituximab have resulted in improved rates of remission in the literature [6, 18, 19]. The role of maintenance immunosuppression (eg, azathioprine) following remission is unknown, but has been used in some reports [6, 19].

Interestingly, the patient had no antecedent history of connective tissue disease but developed insulin receptor antibody–mediated hypoglycemia at the same time that symptoms of her overlap connective tissue disorder began. Insulin receptor antibody–mediated disease (either type B insulin resistance or insulin receptor antibody–mediated hypoglycemia) typically develops in a patient with known systemic autoimmune disease [1]. In one case series, symptoms of an underlying systemic autoimmune disease preceded the development of insulin receptor antibody–mediated disease in 95% of cases [7]. However, insulin receptor antibody–mediated hypoglycemia as the first manifestation of SLE has rarely been described [20, 21].

In conclusion, we describe a case of insulin receptor antibody–mediated hypoglycemia that has been successfully managed with rituximab and glucocorticoids. Some aspects of this case are typical of insulin receptor antibody–mediated disease: the patient's female sex, autoimmune connective tissue disease, and response to immunosuppression. The most unusual aspect of the case is the development of autoimmune hypoglycemia as the first clinical manifestation of a connective tissue disease that soon progressed to involve additional systems. Another atypical aspect of the case is isolated hypoglycemia without any evidence of type B insulin resistance, though it will be important to remain vigilant for the development of this complication in the future.

Acknowledgments

Additional Information

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