JCEM Case Reports, 2023, **1**, 1–4
https://doi.org/10.1210/jcemcr/luad104
Advance access publication 13 September 2023
Case Report

Type B Insulin Resistance Syndrome: A Rare Cause of Hypoglycemia

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Abstract

We describe a case of a Black female patient with a history of type 2 diabetes mellitus and systemic lupus erythematosus, who had a subacute onset of severe hypoglycemia that persisted after cessation of insulin therapy. Biochemical testing revealed hyperinsulinemic hypoglycemia, normal serum triglycerides, and high-normal serum adiponectin levels. Abdominal imaging demonstrated an 11-mm cystic pancreatic lesion. Her clinical history and biochemical test results raised suspicion for type B insulin resistance syndrome (TBIRS), which was confirmed on anti-insulin receptor antibody testing. The patient's hypoglycemia was managed with dietary modification therapy and continuous glucose monitoring. The severity and frequency of hypoglycemic episodes decreased spontaneously. We describe TBIRS and its uncommon hypoglycemic presentation, analyze factors that put TBIRS among the differential diagnosis, and discuss the treatment of TBIRS-associated hypoglycemia.

Key Words: autoimmune hypoglycemia, type B insulin resistance syndrome, anti-insulin receptor antibody, diabetes mellitus, pancreatic cyst

Abbreviations: AIRA, anti-insulin receptor antibody; CGM, continuous glucose monitor; SLE, systemic lupus erythematosus; TBIRS, type B insulin resistance syndrome.

Introduction

Non-therapy-related hypoglycemia is rare in patients with diabetes mellitus. Type B insulin resistance syndrome (TBIRS), typically associated with severe hyperglycemia, can paradoxically cause hyperinsulinemic hypoglycemia as an uncommon presentation. Differentiation from insulinoma in the presence of a pancreatic lesion can be challenging; however, clinical context and biochemical assessments provide valuable assistance.

Case Presentation

A 59-year-old Black woman presented to our hospital with a venous blood glucose of 44 mg/dL (2.44 mmol/L) and symptoms of confusion, somnolence, and slurred speech. The patient was treated with IV dextrose, which improved her symptoms and her blood glucose to 135 mg/dL (7.49 mmol/L). This was her first ever known episode of hypoglycemia. She reported approximately 45 kg of unintentional weight loss over a year but otherwise was in her usual state of health with a normal appetite. Her medical history is significant for type 2 diabetes mellitus, systemic lupus erythematosus (SLE), hypertension, and recovered primary hyperparathyroidism after parathyroidectomy. Two years before presentation, she was diagnosed with type 2 diabetes mellitus based on a screening blood test (hemoglobin A1C at diagnosis not known) and was started initially on metformin and on insulin treatment shortly thereafter. Her insulin regimen was titrated to a daily dose of 0.8 units/kg because of uncontrolled hyperglycemia. Her premeal and bedtime fingerstick blood glucose readings at home had previously ranged between 70 and 100 mg/dL (3.88-5.55 mmol/L). Hemoglobin A1C on admission was 7.7% (60.7 mmol/mol) (reference: 4.0%-5.6% or 20.2-37.7 mmol/mol). SLE was diagnosed 1 year before current presentation and was managed by her rheumatologist with hydroxychloroquine. Her medication list included: metformin, glargine, Novolin-R, gabapentin, losartan, furosemide, and hydroxychloroquine. The family history was unknown.

On physical examination, she was afebrile, had a blood pressure of 101/48 mm Hg, a heart rate of 95 beats/min, and a body mass index of 29.3 kg/m^2. Her head and neck examination were notable for gingival hyperplasia with multiple missing teeth and acanthosis nigricans (Figs. 1 and 2). On axillary examination, there was painless, mobile lymphadenopathy. Skin examination was otherwise unremarkable. The joint examination was notable for bilateral metacarpophalangeal joint edema and proximal interphalangeal joint tenderness. No hyperandrogenic features were noted.

Despite the discontinuation of all antidiabetic medications on admission, the patient continued to have episodes of fasting hypoglycemia with blood glucose readings in the range of 40 to 50 mg/dL (2.22-2.77 mmol/L). However, for the rest of the day, her blood glucose ranged between 150 and 300 mg/dL (8.32-16.65 mmol/L), with patterns of postprandial hyperglycemia.

Received: 30 June 2023. **Editorial Decision:** 8 August 2023. **Corrected and Typeset:** 13 September 2023

Figure 1. Mild acanthosis nigricans of the neck.

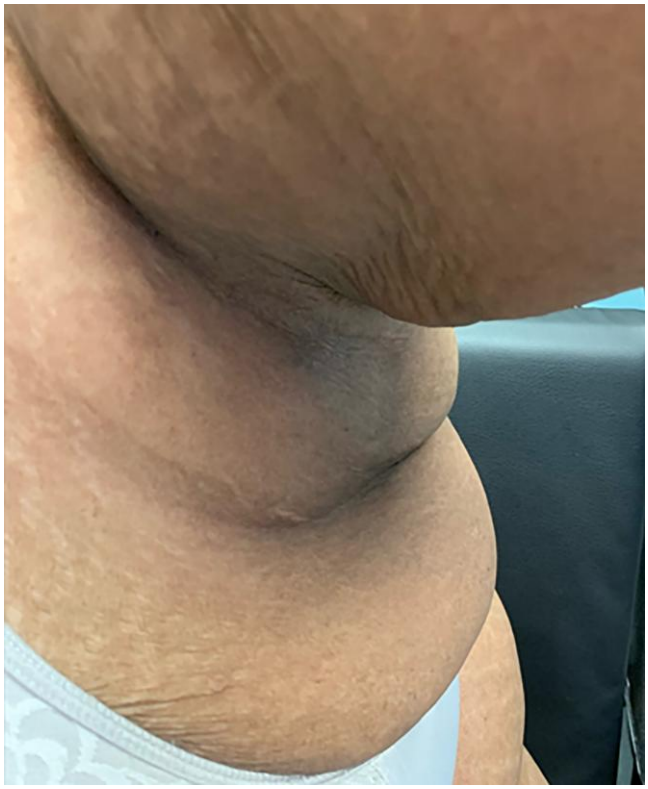

Figure 2. Acanthosis nigricans of the axillae.

Diagnostic Assessment

Initial laboratory workup showed blood glucose of 44 mg/dL (2.44 mmol/L) (drawn at 5 AM, after at least 12 hours of fast), C-peptide 1.72 ng/mL (0.57 nmol/L) (reference: <0.6 ng/mL or <0.2 nmol/L at the time of hypoglycemia), insulin 55.1 mcU/mL (330.6 pmol/L) (reference: <3 mcU/mL or <18 pmol/L), and proinsulin 21.9 pmol/L (reference: ≤5 pmol/L), confirming hyperinsulinemic hypoglycemia. Laboratory evaluation done when the blood glucose was 252 mg/dL (13.98 mmol/L) (reference: 71-99 mg/dL or 3.9-5.5 mmol/L) showed C-peptide 10.02 ng/mL (3.33 nmol/L) (reference: 0.8-3.85 ng/mL or 0.26-1.27 nmol/L), and insulin 1078 mcU/mL (6468 pmol/L) (reference: 2.6-24.4 mcU/mL or 15.6-146.4 pmol/L). Sulfonylurea screen and insulin autoantibody titers were negative. Additional workup included: total cholesterol 118 mg/dL (3.05 mmol/L) (reference: ≤200 mg/dL or ≤5 mmol/L), triglyceride 71 mg/dL (0.8 mmol/L) (reference: ≤150 mg/dL or ≤1.6 mmol/L), high-density lipoprotein 59 mg/dL (1.52 mmol/L) (reference: ≥40 mg/dL or ≥1 mmol/L), low-density lipoprotein 44 mg/dL (1.13 mmol/L) (reference: ≤130 mg/dL or ≤3.4 mmol/L), adiponectin level 28 ug/mL (reference: 5-28 µg/mL) and normal creatinine, liver function test, TSH, and morning cortisol level. Given gingival hyperplasia, lymphadenopathy, and history of SLE, our patient underwent hematologic and rheumatologic workup. Her serum electrophoresis and urine electrophoresis did not show monoclonal gammopathy. She had high titers of RNP IgG and Smith IgG (both were greater than quantifiable amounts), Ro52 IgG 1580 units (reference: <20 units), and antinuclear antibodies 1:640. dsDNA antibody was negative. She underwent computed tomography of the chest, abdomen, and pelvis with contrast that showed axillary, mediastinal, and right perihilar bulky adenopathy and mildly enlarged bilateral external iliac and inguinal lymph nodes. A core needle biopsy of her lymph nodes showed a reactive lymph node with follicular hyperplasia. Magnetic resonance imaging/magnetic resonance cholangiopancreatography with and without contrast showed an 11-mm cystic lesion in the pancreas with radiographic features most consistent with intraductal papillary mucinous neoplasm. Based on coexisting SLE, unintentional weight loss, unusually elevated insulin levels, high normal adiponectin, and normal triglyceride, we had a high suspicion for TBIRS. Anti-insulin receptor antibodies (AIRAs) were checked, which came back highly positive and confirmed the diagnosis (Table 1). Of note, insulin AIRAs were tested in a research laboratory because the assay is not commercially available [1].

Treatment

To manage the patient's hypoglycemia, we discontinued insulin but continued a low-dose metformin for her postprandial hyperglycemia. Although she had a small 11-mm lesion in the pancreas, our suspicion for insulinoma was low given the clinical picture, the imaging characteristics of the lesion, and significantly elevated insulin levels; thus, a biopsy was not pursued.

Because our patient's hypoglycemia showed spontaneous improvement, we jointly decided to continue conservative treatment with a structured dietary plan and the use of a continuous glucose monitor (CGM). She was advised to eat frequent meals and a bedtime snack consisting of complex carbohydrates with protein and fat. If she became hypoglycemic but not symptomatic, she was advised to treat it with a complex carbohydrate snack as opposed to simple sugar to avoid a sudden surge in blood glucose. Initially, our patient was having daily fasting hypoglycemia and postprandial hyperglycemia after lunch and dinner. At 3 months, her glucose level became more stable with fasting hypoglycemia occurring about once every 3 days. She also had less severe postprandial hyperglycemia. At 4 months, she had a lupus flare and was started on prednisone 10 mg daily by her

rheumatologist, which was tapered to a maintenance dose of 5 mg daily. Because her lupus symptoms were mild, she was not started on any other immunosuppressive therapy.

Outcome and Follow-up

During this time, she developed an increased appetite and progressive weight gain with continued improvement of hypoglycemia. At the 1-year follow-up, she had gained 37 kg of weight. She was having much less frequent severe hypoglycemia occurring about once a month confirmed on fingerstick and she no longer had hyperglycemia. Repeat laboratory tests also showed improved insulin and C-peptide levels (glucose 73 mg/dL or 4.1 mmol/L, insulin 37.5 mcU/mL or 225 pmol/L, C-peptide 3.25 ng/mL or 1.07 nmol/L, hemoglobin A1C 5.4% or 20.2 mmol/mol).

Discussion

TBIRS is a rare autoimmune syndrome characterized by extreme insulin resistance, with less than 120 cases reported per systematic review published in 2019 [2]. It often requires daily insulin doses of more than 3 units/kg/day. Insulin sensitizers may be considered in the treatment of TBIRS while monitoring blood glucose levels closely. AIRAs are the pathognomonic feature of TBIRS. The mechanism of insulin resistance is thought to involve direct blockade of insulin binding, increased insulin receptor internalization, and allosteric inhibition [3].

TBIRS most commonly occurs in middle-aged Black women. It has a strong association with autoimmune diseases such as SLE, mixed connective tissue disease, and hematologic malignancies such as multiple myeloma [3]. In contrast to those with metabolic syndrome, patients with TBIRS are typically nonobese and have unintentional weight loss. Up to 80% of the patients have signs of insulin resistance such as skin tags and acanthosis nigricans, including in unusual areas such as periocular, perioral, and labia. In women, features of hyperandrogenism such as polycystic ovaries, elevated testosterone levels, and ovarian hyperthecosis may also be present. Lipid laboratory results may reveal low to normal triglycerides. Interestingly, in TBIRS, adiponectin levels are elevated, contrary to what is typically seen in metabolic syndromes [2].

Hypoglycemia is an uncommon presentation of TBIRS, seen in 25% to 42% of patients. Hypoglycemia typically occurs following a period of insulin resistance and hyperglycemia, but it can also be an initial presentation (13%-22%) [2, 3]. The timing of hypoglycemia can vary, with fasting hypoglycemia being more prominent, as in our patient. Hypoglycemia confers a higher risk of mortality in patients with TBIRS [2, 3]. Pathophysiology of hypoglycemia in TBIRS is thought to be a result of differential activation of the insulin receptor by AIRAs. AIRAs are polyclonal and can have both agonistic and antagonistic activity [4]. Rat models have shown that lower concentrations of AIRAs have a hypoglycemic effect, whereas higher concentrations result in insulin resistance [5]. Increased frequency of hypoglycemia was noted in patients treated with immunosuppressive regimens who had decreasing antibody titers, although the role of insulin dosing mismatch with decreasing requirements could not be ruled out [2, 3].

Our patient had a pancreatic lesion, which raised suspicion of an insulinoma. Differentiating between TBIRS and insulinoma can be a diagnostic challenge. The lesion was an 11-mm cystic pancreatic mass with no T-2 hyperintensity, favoring an intrapapillary mucinous neoplasm. Insulinomas are characterized by solid, low-intensity T1 and high-intensity T2

Table 1. Anti-insulin receptor antibody testing shows significantly elevated BI in our patient (Pt. 1) compared with normal BI in control patient (Pt. 2), both compared with negative control

Serum	RLU-1	RLU-2	BI
Background	160	139	0.58
Negative control	266	252	1.00
Positive control	10 053	9785	38.30
Pt. 1	63 581	64 893	248.0
Pt. 1	66 575	63 871	251.8
Pt. 1	60 376	67 697	247.2
Pt. 2	330	295	1.21
Pt. 2	245	241	0.94
Pt. 2	251	226	0.92

BI >10 suggests high degree of positivity for insulin receptor antibody.
Abbreviations: BI, binding index; RLU, relative light unit.

Table 2. Clinical characteristics differentiating between type B insulin resistance syndrome, insulin autoimmune syndrome, and insulinoma

Characteristics	Type B insulin resistance syndrome	Insulin autoimmune syndrome	Insulinoma
Hypoglycemia	Typically fasting	Fasting, postprandial, or both	Typically fasting
Hyperglycemia	Common. Typically requires a very high dose of insulin to treat insulin resistance	Not common. If present, it is typically mild and postprandial	Rare
Insulin level	↑/↑ ↑	↑/↑ ↑	↑
C-peptide level	↑/↑ ↑	↑/↑ ↑	↑/Inappropriately normal
Insulin autoantibody	Negative	Positive	Negative
Insulin receptor antibody	Positive	Negative	Negative
Imaging	Negative	Negative	Positive
Common racial background	Black	Asian	Variable
Association with autoimmune diseases	Yes	Yes	No
Association with hematologic diseases (lymphoma, multiple myeloma)	Yes	Yes	No

lesions on magnetic resonance imaging. Cystic insulinomas are extremely rare [6]. Coexistence of insulinoma and hyperglycemia is also extremely rare [7]. Patients with insulinoma tend to gain weight because of frequent ingestion of carbohydrates over time. For our patient, the clinical/biochemical picture (history of weight loss, SLE, the pattern of dysglycemia with high adiponectin, low triglycerides) and cystic nature of the pancreatic lesion made TBIRS the more likely diagnosis. Other features differentiating hypoglycemia in TBIRS from insulinoma include much higher levels of insulin, C-peptide, and pro-insulin in TBIRS compared with insulinoma [8] (Table 2). In a patient with a history of autoimmune disease, primary adrenal insufficiency, and insulin autoimmune syndrome (Hirata syndrome) (characterized by anti-insulin autoantibodies causing abnormal insulin release dynamics) should be considered and were ruled out in our patient. Testing for AIRAs is diagnostic for TBIRS. Antibody testing is not commercially available and is financially and logistically difficult to obtain. Easier and more readily available assays are being designed to diagnose this rare condition [1].

Management of TBIRS depends on the severity of the insulin resistance, dysglycemia, and the presence of underlying autoimmune disease. Some patients (20%) can have spontaneous remission and thus hypoglycemia can be managed conservatively with a special meal program and CGM use as was the case in our patient. CGM is an essential tool in patients with hypoglycemia, providing an alert system and predictive information regarding future glucose trends and allowing patients to treat themselves when blood glucose levels drop into the hypoglycemic range. It can also help by educating patients on what kind of food works best for them to treat hypoglycemia.

In severe cases, immunosuppressants are used to target autoimmunity and AIRA production. Malek et al at the National Institutes of Health published the results of treatment of 7 patients with TBIRS with a protocol consisting of 2 cycles of dexamethasone, cyclophosphamide, and rituximab followed by maintenance therapy with azathioprine or cyclosporine [9]. All 7 patients achieved remission defined as improvement in hyperglycemia, discontinuation of insulin therapy, and resolution of hyperandrogenism with an average time to remission of 8 months.

Learning Points

- Type B insulin resistance syndrome (TBIRS) is a rare cause of hyperinsulinemic hypoglycemia in a patient with diabetes mellitus.
- TBIRS is associated with other autoimmune conditions, particularly systemic lupus erythematosus
- Anti-insulin receptor antibody testing is diagnostic of TBIRS. However, anti-insulin receptor antibody testing is currently not commercially available.
- Treatment of hypoglycemia in TBIRS includes continuous glucose monitor use, dietary changes, and immunosuppressant therapy.

Acknowledgments

The authors thank Dr. Lutz Schomburg, Professor at Charité – Universitätsmedizin Berlin, for testing our patient's serum for anti-insulin receptor antibody in his laboratory, which has developed a specific assay.

Contributors

All authors made individual contributions to the manuscript. S.Z.B., S.L., A.S., and A.H.H. were involved in the diagnosis and management of this patient and writing and reviewing the manuscript. All authors reviewed and approved the final draft.

Funding

No public or commercial funding.

Disclosures

The authors have nothing to disclose and do not report any conflict of interest.

Informed Patient Consent for Publication

Signed informed consent obtained directly from the patient.

Data Availability Statement

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

References

1. Minich WB, Abel BS, Schwiebert C, *et al*. A novel in vitro assay correlates insulin receptor autoantibodies with fasting insulin in type B insulin resistance. *J Clin Endocrinol Metab*. Published online March 3, 2023. doi:10.1210/clinem/dgad125
2. Martins LM, Fernandes VO, Carvalho MMD, Gadelha DD, Queiroz PC, Montenegro Junior RM. Type B insulin resistance syndrome: a systematic review. *Arch Endocrinol Metab*. 2020;64(4):337-348.
3. Arioglu E, Andewelt A, Diabo C, Bell M, Taylor SI, Gorden P. Clinical course of the syndrome of autoantibodies to the insulin receptor (type B insulin resistance): a 28-year perspective. *Medicine (Baltimore)*. 2002;81(2):87-100.
4. De Pirro R, Roth RA, Rossetti L, Goldfine ID. Characterization of the serum from a patient with insulin resistance and hypoglycemia. Evidence for multiple populations of insulin receptor antibodies with different receptor binding and insulin-mimicking activities. *Diabetes*. 1984;33(3):301-304.
5. Dons RF, Havlik R, Taylor SI, Baird KL, Chernick SS, Gorden P. Clinical disorders associated with autoantibodies to the insulin receptor. Simulation by passive transfer of immunoglobulins to rats. *J Clin Invest*. 1983;72(3):1072-1080.
6. Ahrendt SA, Komorowski RA, Demeure MJ, Wilson SD, Pitt HA. Cystic pancreatic neuroendocrine tumors: is preoperative diagnosis possible? *J Gastrointest Surg*. 2002;6(1):66-74.
7. Kamocki ZK, Wodyńska NA, Pryczynicz A. Co-existence of insulinoma and diabetes: a case report. *Oncol Lett*. 2014;8(4):1697-1700.
8. Lupsa BC, Chong AY, Cochran EK, Soos MA, Semple RK, Gorden P. Autoimmune forms of hypoglycemia. *Medicine (Baltimore)*. 2009;88(3):141-153.
9. Malek R, Chong AY, Lupsa BC, *et al*. Treatment of type B insulin resistance: a novel approach to reduce insulin receptor autoantibodies. *J Clin Endocrinol Metab*. 2010;95(8):3641-3647.