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Case Report

Searching for the Culprit: When Diabetic Ketoacidosis Presents With Insulin Autoantibodies

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ABSTRACT

Objective: The main objective was to describe and review a unique case that presented with diabetic ketoacidosis, positive insulin autoantibodies (IAAbs, which are found in Hirata disease and are usually present with hypoglycemia), and laboratory findings characteristic of type B insulin resistance syndrome (TBIRS) and systemic lupus erythematosus. Confirmation of TBIRS was obtained in Germany as immunoassay for insulin receptor antibodies (IRAbs) is not available in the United States.
Methods: A literature review on TBIRS and cases that present with IAAbs and IRAbs simultaneously was conducted.
Results: We found 6 cases presenting with hypoglycemia, both antibodies, and treatment attempts with various management approaches that were different from the proposed National Institutes of Health (NIH) protocol for TBIRS. Our case is distinct because of the demographic background, presentation with diabetic ketoacidosis, comparatively lower insulin requirement, and no significant hypoglycemic episodes in the third phase.
Conclusion: We propose that access to IRAb immunoassays may be important for diagnosing milder cases of TBIRS, while IAAbs may provide prognostic and therapeutic insights. Despite completely different presentation from other TBIRS patients reviewed, we observed that the proposed NIH protocol consisting of dexamethasone, rituximab, and cyclophosphamide was successfully employed in our patient. Thus, we propose that our case and the findings regarding antibody testing and the NIH treatment regimen may assist clinicians with earlier recognition and effective management of milder cases of TBIRS.

Introduction

This is a case report describing a unique case that presented with diabetic ketoacidosis, positive insulin antibodies and insulin receptor antibodies. In addition, it provides a brief review of 6 cases[1] that presented with both antibodies simultaneously and treatment attempts with various management approaches that were different from the proposed National Institutes of Health protocol for type B insulin resistance syndrome.

Case Report

A 46-year-old Mexican female presented to us with a 3-day history of abdominal pain and weakness. She was diagnosed with diabetes mellitus by her primary doctor 1 week prior based on glycosylated hemoglobin of 15% (140 mmol/mol). Glycosylated hemoglobin 6 months prior was normal. She was started on degludec 10 units (U) subcutaneous daily and Lispro 3U subcutaneous premeals. She had been compliant with dietary restrictions and with her insulin regimen. Her medical history otherwise was significant only for hypertension, for which she had been on amlodipine and losartan for the past year. She denied personal or family history of autoimmune disease or endocrinopathy. She had 2

Abbreviations: DKA, diabetic ketoacidosis; IAAbs, insulin autoantibodies; IgG, immunoglobulin G; IRAbs, insulin receptor antibodies; SLE, systemic lupus erythematosus; TBIRS, type B insulin resistance syndrome; U, units.

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Table 1
Laboratory Values

Laboratory test	Values obtained	Reference range
Adiponectin	16.6 μg/mL	2.4-17.9 μg/mL
Albumin	2.6 g/dL	2.9-4.4 g/dL
Antinuclear antibody IFA	Positive	…
Anti-GAD 65 Abs	Negative	…
Anti-DNA DS Ab	1 IU/mL	<5: negative; >9: positive
Anti-Jo-1	<0.2	0.0-0.9
Antichromatin Abs.	7.4	0.0-0.9
Atypical pANCA	<1:20	<1:20: negative
Beta hydroxybutyrate	63 mg/dL	0.2-2.8 mg/dL
C-peptide	8.7 ng/mL	1.1-4.4 ng/mL
Cardiolipin immunoglobulin G and immunoglobulin M Ab	<9 MPL U/mL	<13: negative; >20: positive
Centromere Ab	<0.2	0.0-0.9
Complement C3 level	61 mg/dL	87-190 mg/dL
Complement C4 level	<8 mg/dL	18-55 mg/dL
CH50	35 U/mL	42-999 999 U/mL
Cytoplasm C-ANCA	<1:20	<1:20: negative
Gamma globulin	2.2 g/dL	0.4-1.8 g/dL
Glucose (fasting)	354 mg/dL	60-120 mg/dL
Insulin autoantibodies	9.2 μU/mL	<0.5 μU/mL
Immunoglobulin G	3017 mg/dL	635-1471 mg/dL
Immunoglobulin A	487 mg/dL	66-433 mg/dL
Insulin levels	Total: 6705 Free: 6256	Total insulin levels = free insulin plus antibody – bound insulin fractions
MPO Abs	<9.0 U/mL	0.0-9.0 U/mL
Pancreatic islet cells Abs	Negative	…
Perinuc P-ANCA	<1:20	<1:20: negative
Proteinase 3 PR3 Abs.	<3.5 U/mL	0.0-3.5 U/mL
RNP Abs	6.1	0.0-0.9
SCL-70 Abs.	0.2	0.0-0.9
Sjogrens SSA/SSB Ab.	<0.2	0.0-0.9
Smith Abs.	4.1	0.0-0.9
Speckled pattern	1:640	Strongly positive
Testosterone free	2.32 ng/dL	0.10-0.85 ng/dL
Testosterone total	249 ng/dL	8-48 ng/dL
Tryglycerides (fasting)	70 mg/dL	29-172 mg/dL, normal <160 mg/dL; average for type B insulin resistance syndrome patients: 54 ± 32 mg/dL
Thyroglobulin Ab.	<1.0 IU/mL	0.0-0.9 IU/mL
TPO Ab.	21 IU/mL	0-34 IU/mL
Thyroid stimulating hormone	0.944 μIU/mL	0.450-5.330 μIU/mL

Abbreviation: Ab = antibodies; C-ANCA = antineutrophil cytoplasmic antibodies; GAD = glutamic acid decarboxylase; IFA = Indirect fluorescent antibody; MPO = myeloperoxidase; P-ANCA = perinuclear anti-neutrophil cytoplasmic antibodies; RNP = ribonucleoprotein; SSA = Sjögren's-syndrome-related antigen A autoantibodies; SSB = Sjögren's syndrome type B autoantibodies.

living children, the last pregnancy 10 years prior, and no history of miscarriages. She denied any recent trauma, surgery, or pregnancy (urine human chorionic gonadotropin confirmed the latter). Lastly, she was rotating insulin injection sites at the abdomen and thigh areas as instructed by her primary doctor.

On presentation, the patient's blood pressure and heart rate were within normal limits, but she was tachypneic. Her body mass index was 29 mg/kg^2. She had periumbilical acanthosis nigricans, without signs of hyperpigmentation or rash elsewhere. There was also no evidence of hirsutism, acne, alopecia, frontal bossing, ring or shoe tightness, proximal muscle weakness, ecchymoses, or purple abdominal striae. Initial laboratory results were diagnostic of diabetic ketoacidosis (DKA) (Table 1) and our standard protocol was started. This protocol consists of aggressive intravenous hydration followed by maintenance fluids according to sodium and blood glucose levels. The patient was also given an initial insulin bolus of 0.1 U/kg followed by insulin infusion at a rate of 0.1 U/kg/h. The infusion goal was to reduce blood glucose by 50-75 mg/dL per hour. Upon further questioning, no triggering factors for DKA were found, including addition of new drugs or stressors that might have precipitated autoimmunity reactivation. Blood glucose was difficult to control but the anion gap closed 5 days later, and she was bridged to the combination of Levemir/Novolog insulin. Despite gap closure, severe hyperglycemia persisted, and she required up to a total of 3.2 U/kg daily. A few days later, the anion gap increased, and she was restarted on an insulin drip at 0.1 U/kg/h with Humulin R U-500 subcutaneous in addition to the Levemir/Novolog combination. No further responses in blood glucose to insulin adjustment despite the tripling of the total daily dosage over the course of 72 hours was observed.

Immunologic etiologies were sought in the differential diagnosis for this presentation of severe hyperglycemia in the setting of unremarkable clinical findings, and thus further workup revealed elevated insulin autoantibodies (IAAbs), C-peptide, and testosterone levels. Total and free insulin levels were elevated, but free insulin levels were lower than total, suggesting the presence of circulating insulin-binding antibodies. Lipid profile revealed inappropriately low triglycerides, and normal high- and low-density lipoprotein cholesterol concentrations. Lastly, adiponectin levels measured after initiation of treatment were at the upper limit of normal. Thyroid stimulating hormone as well as antithyroid peroxidase and thyroglobulin antibodies were normal (Table 1).

At this point, type B insulin resistance syndrome (TBIRS) was the working diagnosis due to its clinical tendency to present in patients with systemic lupus erythematosus (SLE) in most reported cases. An immunologic workup was obtained, showing positive antinuclear antibody (1:640, speckled), anti-Smith, anti-ribonucleoprotein, and antichromatin antibodies. In addition, total immunoglobulin G (IgG) and A levels were elevated, and C3, C4, and CH50 complements were low (Table 1). She met the 2019 European League Against Rheumatism and American College of Rheumatology diagnostic criteria for SLE with a score of 13 calculated from an antinuclear antibody titer of 1:80 or greater (entry criterion), leukopenia (3 points), low C3 and C4 levels (4 points), and positive anti-Smith antibody (6 points).[2]

After the aforementioned results, the patient was presumed to have TBIRS based on the presentation of severe resistant hyperglycemia, acanthosis nigricans, inappropriately high adiponectin levels, abnormally low levels of triglycerides, elevated IgG and testosterone levels, and newly diagnosed SLE.

The patient was initially treated with 60 g of intravenous immunoglobulin daily for 3 days and prednisone 10 mg daily to modulate the immune response.[3-5] However, this regimen proved to be unsuccessful in our patient as hyperglycemia persisted. Based on a proposed treatment protocol by Malek et al,[6] she was next trialed on an immunomodulating regimen consisting of rituximab 750 mg/m^2 intravenous daily for 2 days with dexamethasone 40 mg once daily for 4 days every 2 weeks with cyclophosphamide 100 mg oral daily. There was remarkable improvement in hyperglycemia 6 days after the first cycle of rituximab administration. The insulin requirement decreased from 47 U/kg to 10 U/kg with simultaneous improvement in the levels of IAAbs (Fig. 1 and 2). She was finally discharged on 420 U 3 times per day of Humulin R U-500. She received 2 more cycles of rituximab on a biweekly schedule after discharge. Right before the third cycle of rituximab, it was observed that her insulin requirement was decreased to less than 1.2 U/kg. Shortly after receiving this third dose of rituximab, she began having hypoglycemic episodes, at which point her insulin therapy was completely discontinued.

After insulin cessation, we were fortunately able to obtain and send blood samples to Dr. Professor Schomburg, located at the Institut für Experimentelle Endokrinologie in Germany, who measured the patient's serum for insulin receptor antibodies (Table 2). Thirteen samples were measured, out of which 11 were controls and 2 samples were from our patient. In comparison to

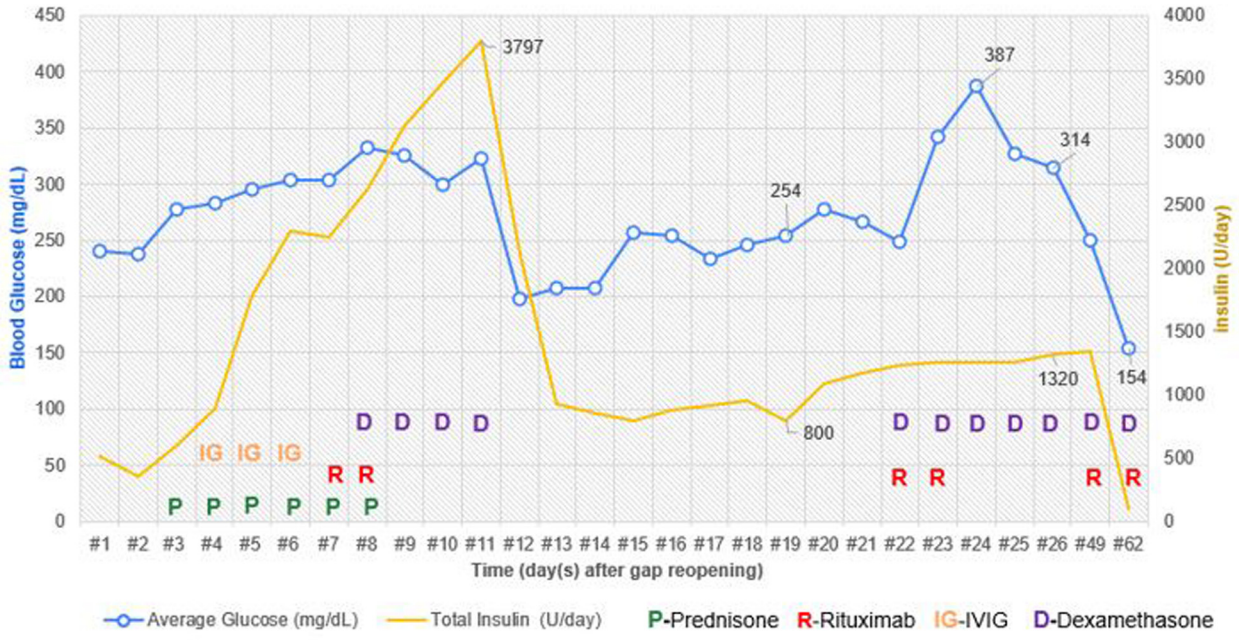

Fig. 1. Insulin versus glucose requirements with response to immunomodulator interventions. The glucose levels (blue curve, left vertical axis) and insulin requirements (yellow curve, right vertical axis) per day in response to the different immunomodulator treatments implemented after the gap reopened. The use of intravenous immunoglobulin and prednisone proved to be unsuccessful as both glycemia and insulin requirements increased. However, a dramatic decrease in both curves was appreciated 6 days after the first cycle with rituximab, dexamethasone, and cyclophosphamide. *D* = dexamethasone; *IVIG* = intravenous immunoglobulin; *P* = prednisone; *R* = rituximab.

healthy controls, samples of our patient (sample 12, 13) were highly positive even though the levels were low in comparison to those of patients with acute TBIRS. We attribute these relatively small elevations to the fact that the samples were obtained after 3 cycles of immunotherapy. In the assay for insulin receptor antibodies, a binding index is calculated for antibody binding (not biologic activity); when the binding index value exceeds 3, it is suggestive of autoantibody presence. Our patient's binding index was calculated to be 9.6, strongly indicating positive autoantibody binding. At the time of measurement of insulin receptor antibodies (IRAbs), IAAbs were also measured and yielded a negative result, as seen in Figure 2. Eventually, the patient became euglycemic with occasional fasting hypoglycemia after 4 months of insulin therapy, which was then discontinued accordingly. The patient currently remains euglycemic with no symptoms related to SLE.

Discussion

TBIRS is an immune-mediated disorder that leads to severe hyperglycemia and insulin resistance that may manifest as DKA, despite the presence of high insulin levels secondary to antibodies (IRAbs) that usually work antagonistically at the insulin receptor level to prevent appropriate insulin binding to its receptors. Per literature review, these IRAbs bind to a region located in the amino acids 540-601 of the C-terminal half of the alfa subunit of the receptor, and this decreases the capacity of insulin binding to its receptor by 5%-30%.[1,7,8] Based on the largest longitudinal cohort of patients with this syndrome (n = 38), a combination of a cohort published in 2002 by Arioglu et al[9] and revised in 2010 by Malek et al,[6] the syndrome predominates in females (86%) and in those of African-American ethnicity (70%). Patients have ranged in age from 17 to 64 years. Five of these patients were diagnosed with SLE and 2 with mixed connective tissue disorder. More importantly, although none of the other patients had a formal autoimmune diagnosis, they did have multiple positive antibodies.[6,9] Moreover, other autoimmune conditions related to TBIRS include primary biliary cirrhosis, scleroderma, dermatomyositis, and Hashimoto disease.[8] There are also several drugs associated with the development of TBIRS as evidenced by case reports, including pegylated interferon, ribavirin, and highly-active antiretroviral therapy; however, as per Censi et al,[10] there are no established triggers for the development of antibodies. For our patient, we were unable to identify drugs or a clinical sequela capable of inducing an autoimmune response. Acanthosis nigricans was reported in 88% of patients with periocular lesions as a distinctive feature along with signs of hyperandrogenism.[9] Hyperandrogenism was correlated to ovarian enlargement in 20 of the 24 patients reported by Arioglu et al,[9] and the speculated mechanism was endogenous insulin action as a growth factor for the ovaries. Interestingly, this phenomenon was not evident in our patient, which could suggest a milder form of the disease. Consequently, most of the aforementioned study's patients required upwards of 5000 U of daily insulin, which was significantly greater than our patient's maximal requirement of less than 4000 U per day.[9,11] It was also observed that all patients presented with hyperglycemia (fasting ranging from 200-500 mg/dL) and glycosylated hemoglobin values ranging from 6.8%-13.5% (53-130 mmol/mol).[6] Average fasting triglycerides were unusually low (58 mg/dL) while adiponectin levels were abnormally high in the reported patients.[6,9] The latter occurs secondary to insulin receptor dysfunction, and it helps differentiate TBIRS from type 2 diabetes in which triglycerides are high and adiponectin is low.[6,12] Lastly, all measured antibodies toward insulin receptors were found to be polyclonal with a predominance of the IgG class in these studies.[8,9]

Based on the findings reported, Willard et al[8] proposed that the "working" clinical diagnosis for TBIRS can be made with the biochemical triad of elevated fasting insulin and adiponectin levels, in conjunction with low/normal fasting triglyceride concentrations in an individual with severe hyperglycemia, acanthosis nigricans, and an underlying autoimmune disease. In addition, they also proposed that insulin-deficient individuals who require more than 3 U/kg per day of exogenous insulin with persistent hyperglycemia should raise clinical suspicion for TBIRS

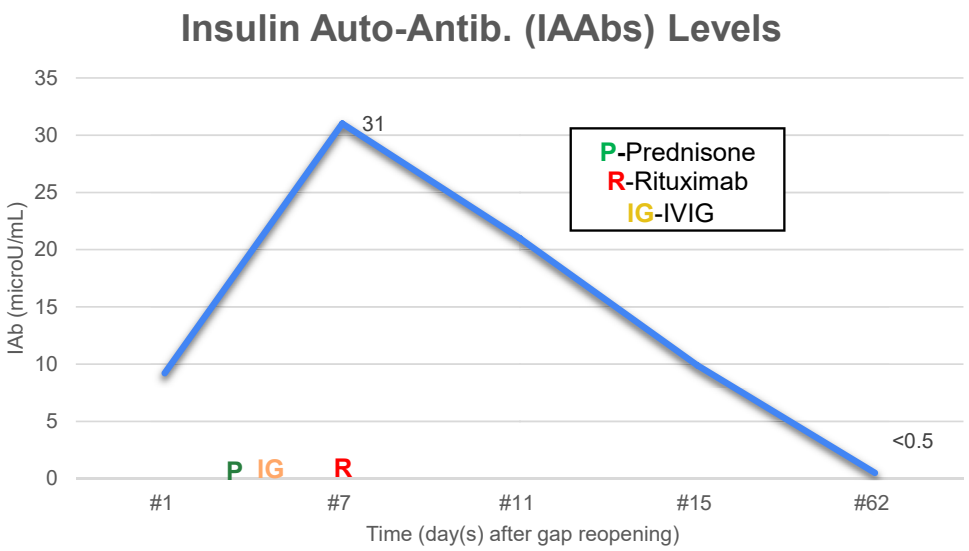

Fig. 2. Insulin autoantibody levels confirming the failure of prednisone and intravenous immunoglobulin levels increased after their administration but were nonexistent when measured after the third cycle of treatment. *IAAb* = insulin autoantibody; *IVIG* = intravenous immunoglobulin;

pathology.[13] The treatment of TBIRS has 2 components: 1 corresponds to glycemic control and the other to immunomodulation.[10] Glycemic control is obtained on high doses of insulin, with patients requiring several hundred to thousand units daily, and the dose is gradually reduced once euglycemia is achieved.[6] The most effective insulin is Humulin R-U 500; however, because IRAbs interfere with normal exogenous degradation, insulin has a prolonged half-life in these patients and closer monitoring is required.[8,14,15] On the other hand, both plasmapheresis and intravenous immunoglobulin have been effective in only a few cases.[3-5,7] Malek et al[6] proposed a regimen consisting of rituximab, cyclophosphamide, and steroids, on which all the treated patients underwent remission.

On the opposite spectrum of insulin-related immune-mediated disorders, Hirata disease presents with antibodies against insulin. Initially, insulin-IAAb complexes form and prevent insulin from appropriately binding its receptor postprandially, resulting in mild hyperglycemia. Subsequently, the insulin is released into the circulation from the insulin-IAAb complexes regardless of serum glucose level, thereby resulting in the hypoglycemia that patients typically present with.[16]

Usually IRAbs and IAAbs present as separate entities. However, upon review of case reports we found only 6 other studies describing the presence of both antibodies. Contrary to the majority of cases demonstrating hypoglycemia secondary to agonistic mechanisms seen when TBIRS presents with low titers, our case demonstrates initial presentation of DKA in the setting of persistent hyperglycemia during hospitalization. Additionally, while the other cases required an upwards average of almost 5000 U of insulin per day, our patient maximally needed less than 4000 U daily. We speculate that this could be attributed to mildness of disease and lower titers of IRAbs or coexisting IAAbs with the IRAbs.[13,17-20]

Table 2
Insulin Receptor Antibodies

Serum No.	RLU1	RLU2	Mean	Binding index[a]
1	2476	2176	2326	1.3
2	1945	2297	2121	1.1
3	2029	2240	2135	1.1
4	1804	1917	1861	1
5	1677	1708	1693	0.9
6	1805	1818	1812	1
7	1953	1844	1899	1
8	2378	2173	2276	1.2
9	2228	2406	2317	1.2
10	2227	2340	2284	1.2
11	2335	2327	2331	1.3
12	17457	18652	18055	9.7
13	16994	18864	17929	9.6
Positive insulin receptor antibodies	704292	804267	754280	405.7
WMi[b]	1882	1874	1878	1
WMi[b]	1840	1840	1840	1
Background	456	1932	1194	0.6

Abbreviation: RLU = relative light units of luciferase measurements.

[a] Thirteen samples were measured by Dr. Prof. Lutz Schomburg, out of which 11 were control and 2 were from our patient. As per Dr. Schomburg, in comparison to healthy controls, samples from our patients (sample 12, 13) were highly positive, though the levels are low as compared to patients with acute type B insulin resistance syndrome (TBRIS). We attribute this to the fact that samples were obtained after 3 cycles of immunotherapy. As per the assay, our patient's binding index was 9.6. A binding index indicates the fold positivity over negative controls, and more than 3 indicates positive autoantibodies. In addition, this immunoassay only measures for antibody binding and not for biological activity. However, in our case, the patient had clinically improved in terms of glycemic control and exogenous insulin requirements.

[b] WMi is a negative control, i.e., serum from the postdoc who conducted the measurements.

Conclusion

In conclusion, our patient did not have the classic severe hypoglycemic episodes of the resolution phase in the usually described TBIRS cases when IRAb titers decline. This can possibly be explained by the presence of coexisting IAAbs, as seen in our patient. Conversely, she did have mild hypoglycemic episodes once IAAbs were completely cleared, as proved by immunoassay testing. Thus, we propose that checking IAAb titers in suspected TBIRS cases may have clinical implications, because having these antibodies coexistent with IRAbs may serve as a marker for prognosis and treatment response, although greater investigation is warranted. Moreover, it is important to note that this is the first case to our knowledge that describes a Mexican female presenting with TBIRS and concurrent IRAb and IAAb presence who also demonstrated a successful response to the National Institutes of Health treatment regimen described. Our case presentation may thus have significant implications regarding clinician access to IRAb immunoassay availability and use of the National Institutes of Health proposed management for TBIRS, and further studies should be conducted for more insight.

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Disclosure

The authors have no multiplicity of interest to disclose.

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