CLINICAL VIGNETTE

A 50-Year-Old Woman with B Insulin Resistance

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Introduction

Type B Insulin resistance (TBIR) is a rare autoimmune disorder caused by autoantibodies against the insulin receptor. Since its initial description by Kahn *et al*. in 1976, more than 120 cases have been reported.[1,2] At high concentrations, the antibodies act as receptor antagonists, reducing cellular response to insulin and resulting in hyperglycemia with elevated insulin requirements. Conversely, at low concentrations, the antibodies act as a partial receptor agonist and elicit hypoglycemia, which can rarely be the only presenting symptom. Mortality ranged from 15.8% to 54% in an NIH case series, largely due to hypoglycemia.[2]

Patients with TBIR present with markedly elevated fasting insulin levels, widespread acanthosis nigricans, hyperandrogenemia, and hypercatabolism with significant muscle wasting and weight loss.[2-4] TBIR is frequently associated with underlying autoimmune disease, including systemic lupus erythematosus, Sjogren syndrome, and mixed connective tissue disease. It has also been linked to paraneoplastic manifestations of Hodgkin's lymphoma and *Helicobacter pylori* infection.[2] Establishing the diagnosis of TBIR is difficult due to the lack of a simple and commercially available detection assay for insulin receptor autoantibodies. This may result in delays in treatment.[5]

No standard treatment regimen has been established for TBIR. The majority of cases have been treated with high-dose glucocorticoids. These can worsen hyperglycemia and have no proven long-term remission benefit.[2] Combinations of immunosuppressants, intravenous immunoglobulin, and plasmapheresis have also been used without consistent success.[2,4,6] Up to 30% of patients have spontaneous remission of their disease, making treatment efficacy difficult to establish.[4] TBIR treatment includes glycemic control and reversal of hypercatabolism until immunosuppression induces remission. Several strategies have been adopted to manage hyperglycemia including concentrated U-500 regular insulin, intravenous insulin infusion, sensor-augmented insulin pump therapy, recombinant insulin-like growth factor 1 (IGF-1), and insulin sensitizers metformin and pioglitazone without consensus.[2,4,6,7] Finally, as titers of insulin receptor autoantibodies decrease with treatment, patients are at increased risk of hypoglycemia and require increased surveillance to prevent mortality.[2,4]

We describe a case of TBIR that achieved rapid and sustained remission with combined immunosuppressive therapy of high-dose glucocorticoids, cyclophosphamide, and rituximab followed by maintenance azathioprine, based on a 2018 NIH protocol. She was treated with intravenous insulin infusion for optimal glycemic control and insulin sensitizers metformin and pioglitazone to reverse her hypercatabolic state. She was also given a continuous glucose monitor (CGM) to alert her of hypoglycemia.

Case

A 50-year-old woman with Sjogren syndrome and a one-year history of diabetes treated with insulin presented with DKA and was found to have TBIR. She was diagnosed with diabetes one year prior to admission and initially treated with metformin, glipizide, and empagliflozin. However, three months prior to admission, she developed DKA attributed to empagliflozin and was started on insulin but required escalating doses to achieve euglycemia. She had no known drug allergies and was taking sliding scale regular insulin 4-14 units with meals, neutral protamine Hagedorn (NPH) insulin 70 units twice daily, rosuvastatin, aspirin, and omeprazole. In the weeks preceding her admission, she had lost 100 lbs. She developed nausea and vomiting and presented for evaluation.

Initial laboratory testing demonstrated DKA with a blood glucose of 464 mg/dL (65–99 mg/dL), CO2 8 mmol/L (20–30 mmol/L), anion gap 16 (8–12), pH 7.08 (7.30–7.40) on venous blood gas, 2+ ketonuria, and a hemoglobin A1c of 11.7% (<5.7%). Additional tests included negative glutamic acid decarboxylase-65, insulin antigen-2, and insulin antibodies, positive C-peptide 2.7 ng/mL (1.1–4.3 ng/mL), elevated adiponectin 41 ug/mL (5–28 ug/mL), and low-normal triglycerides of 49 mg/dL (<149 mg/mL). Physical exam was notable for a weight of 49.8 kg, and extensive acanthosis nigricans, facial acne, and hirsutism (Figure 1). CT of the neck, chest, abdomen, and pelvis was unremarkable. She was started on intravenous insulin infusion with resolution of her DKA but

required over 2,000 units of insulin per day to obtain glycemic control.

Her overall picture was suspicious for TBIR, but her diagnosis could not be confirmed due to the lack of a commercially available assay. To avoid delays in treatment and further complications, she was given a functional diagnosis of TBIR based on Willard *et al.*'s clinical definition of fasting hyperinsulinism, hyperadiponectinemia, and low-normal fasting triglycerides in a person with a known autoimmune disease and acanthosis nigricans.

Our patient's hyperglycemia was managed with continuous intravenous insulin infusion, which allowed for rapid uptitration while receiving high-dose glucocorticoids and prompt de-escalation to prevent hypoglycemia during her therapy. To target her hypercatabolic state, she was treated with metformin 1000 mg twice daily and pioglitazone 30 mg daily that was increased to 45 mg daily after 2 weeks. To eliminate insulin receptor autoantibodies, she was given combined immunosuppressive therapy consisting of cyclophosphamide 100mg daily and 2 infusions of rituximab 750 mg/m^2 with dexamethasone 40mg for 4 days administered 14 days apart based on a 2018 NIH protocol. After receiving glucocorticoids, her hyperglycemia worsened, and her insulin requirements increased by 300% up to 5,367 units per day (Figure 2). However, over the next 30 days, her insulin requirements rapidly improved, and she began to develop overnight hypoglycemia attributed to decreased insulin receptor autoantibodies titers. She was given a continuous glucose monitor better monitor and alert her of hypoglycemia.

After 30 days, she achieved remission, defined by improvement in hyperglycemia, discontinuation of insulin, and normalization of hyperandrogenemia and hypercatabolic state (Figure 1). She was discharged on azathioprine 100 mg daily maintenance therapy, continued glucose monitoring, metformin 1000 mg twice daily, and pioglitazone 45 mg which was discontinued after 6 months. She has remained in sustained remission for 12 months with improvement of her hemoglobin A1c to 6.2% and without hypoglycemia detected on her CGM.

Discussion

This case highlights: 1) utility of a functional diagnosis of TBIR in the absence of commercially available testing, 2) successful use of combined immunosuppressive therapy, and 3) management of hyperglycemia and hypercatabolism with TBIR.

The absence of a commercially available assay to detect insulin receptor autoantibodies makes the diagnosis of TBIR challenging. Immunoprecipitation assays are the conventional method for diagnosis but are not readily available at most institutions due to the lack of necessary reagents.[5] More recently, novel detection assays have been developed including enzyme-linked immunoassay (ELISA), though yet to be widely adopted.[5] To aid in the diagnosis of TBIR, Willard *et al.* proposed a "functional" clinical definition comprising the triad of elevated fasting insulin, hyperadiponectinemia, and low-normal fasting triglycerides in patients with known autoimmune disease and acanthosis nigricans.[3] Hyperadiponectinemia and low-normal triglyceride concentrations distinguish TBIR from other forms of insulin resistance associated with type 2 diabetes. Antibody-mediated inhibition of the insulin signaling pathway blocks suppression of adiponectin synthesis and stimulation of *de novo* lipogenesis. This definition serves as an important tool to diagnose TBIR and identify candidates for therapy when insulin receptor autoantibody testing is not readily available.

Currently, no standardized therapy for TBIR has been established. Most data derived from case reports, have used various combinations of immunosuppressants (e.g. azathioprine, cyclophosphamide, cyclosporine, glucocorticoids, mycophenolate mofetil, and rituximab), intravenous immunoglobulin, plasmapheresis, and *Helicobacter pylori* eradication without consistent benefit.[2,8] In 2010, the NIH published a cohort of 7 patients successfully treated with combined immunosuppressive therapy that was expanded to the largest studied prospective cohort to date of 22 patients in 2018.[4,6] Using a regimen of rituximab, dexamethasone, and cyclophosphamide followed by azathioprine maintenance therapy at the time of remission, 86.4% of patients achieved remission, 13.6% developed disease recurrence, and no patients died.[4] Of the patients that did not achieve remission, one withdrew from the study, one was lost to follow-up, and one was only monitored for 2 months at the time of publication.[4] Glucocorticoids and cyclophosphamide are used for rapid induction of remission, but glucocorticoids exacerbate patients' hyperglycemia and cyclophosphamide can worsen pancytopenia, which may be present with lupus and other autoimmune conditions associated with TBIR. A recent case reported the success of double-filtration plasmapheresis in place of glucocorticoids and cyclophosphamide. This is increased risk of hemorrhage due to the loss of high molecular weight coagulation factors.[7] Given the success of combined immunosuppressive therapy including rituximab with 0% mortality, this treatment regimen was selected for our patient who achieved sustained remission after 30 days.

Similarly, no standardized regimen exists for the management of hyperglycemia. In a review of 119 cases of TBIR, insulin requirements ranged from 54 units to 57,600 units per day, with a median of 1,747 units per day.[2] One report successfully employed sensor-augmented pump therapy to manage a patient's hyperglycemia, with insulin requirements of only 120 units per day. This approach is not feasible in most patients.[7] Recombinant IGF-1 has also been proposed as an alternative pathway for glucose uptake but has had limited benefit due to the likelihood that insulin receptor autoantibodies also have an affinity for the IGF-1 receptor.[7] In the NIH's cohort of 22 patients, the majority were treated with U-500 regular insulin, with one requiring intravenous insulin infusion to control diabetic ketoacidosis (DKA) after pulse steroid treatment.[4] In our case, we chose to treat our patient's hyperglycemia with intravenous insulin infusion to allow for rapid adjustments while receiving glucocorticoids, which increased her insulin

requirements by over 300%, and for prompt de-escalation after immunosuppressive treatment to prevent hypoglycemia, especially overnight, as insulin receptor autoantibody titers improve. Finally, a continuous glucose monitor (CGM) should be administered to all patients to alert them of hypoglycemia.

Patients with TBIR typically present in a hypercatabolic state with significant weight loss and marked acanthosis nigricans. Although insulin sensitizer use has varied across case reports, we used metformin and pioglitazone, to reverse this condition. The glucagon-like peptide 1 receptor agonist, liraglutide, has also been successfully used in two cases of TBIR. Both cases demonstrated mild disease without typical features of hypercatabolism so its benefit remains unclear.[9,10] The extent of improvement of the hypercatabolic state from insulin sensitizers compared to immunosuppressive therapy is uncertain. We recommend metformin and pioglitazone given their overall tolerability to improve the hypercatabolic state until immunosuppressive therapy can take effect.

In conclusion, this patient with a functional diagnosis of TBIR was successfully treated with combined immunosuppressive therapy, insulin infusion, and insulin sensitizers metformin and pioglitazone. This approach has transformed this condition into a treatable form of diabetes and should be considered in all patients with TBIR.

Figures

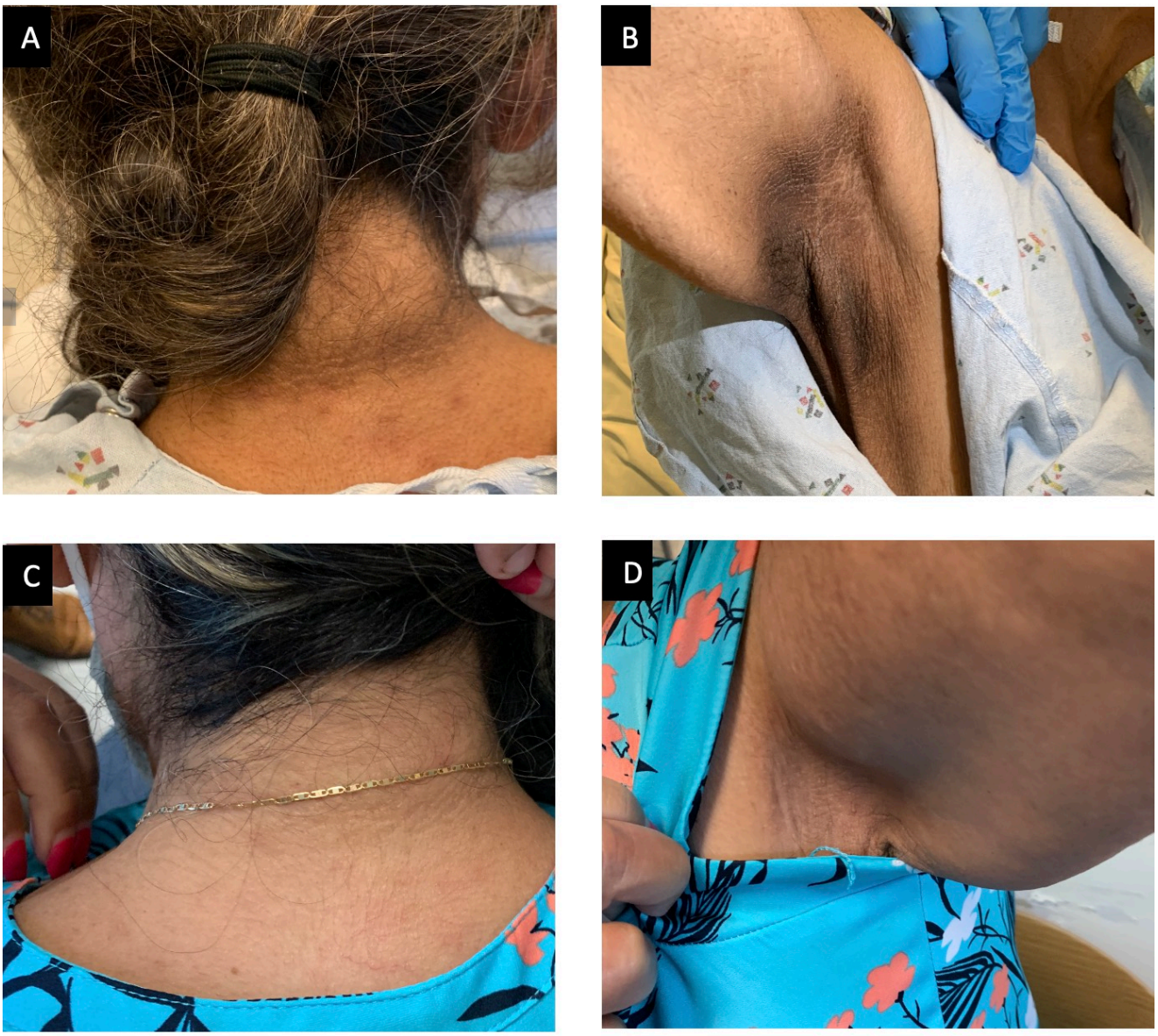

Figure 1. Improvement in Acanthosis Nigricans Prior to and 6 Months After Remission. A and B depict the patient's neck and underarm acanthosis nigricans, respectively, before treatment with combined immunosuppressive therapy. C and D show the rapid resolution in the patient's neck and underarm acanthosis nigricans, respectively, 6 months after remission.

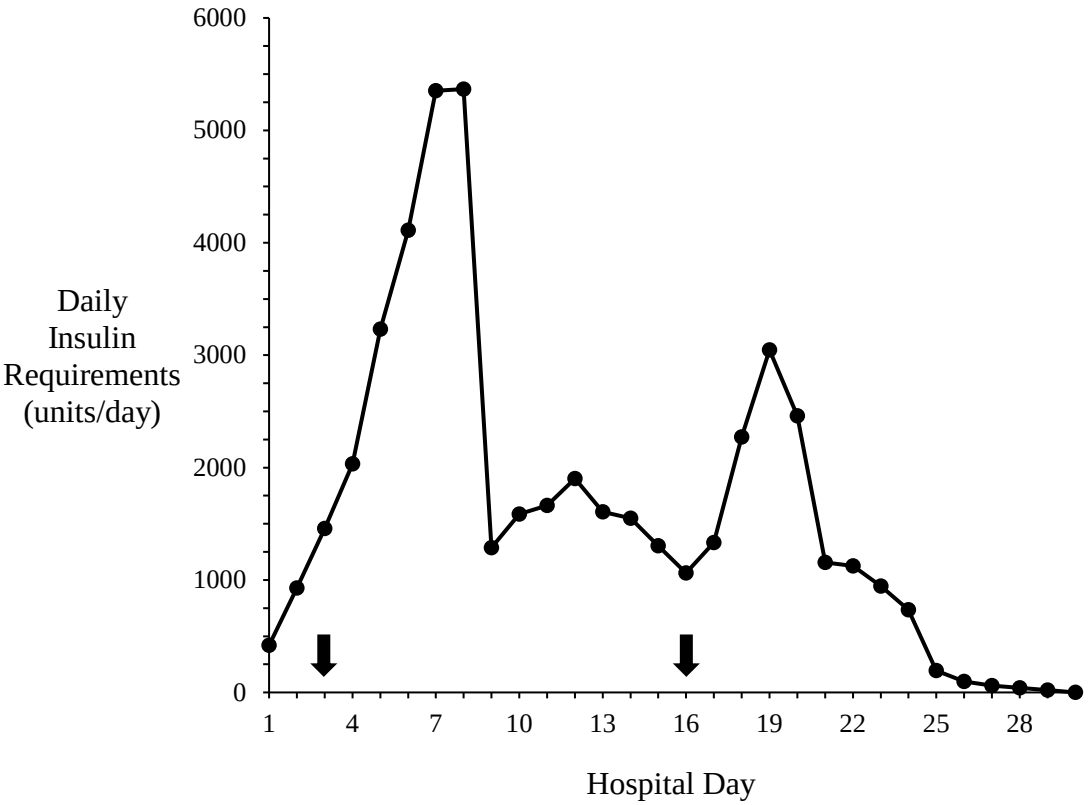

Figure 2. Daily Insulin Requirements. This figure depicts the daily insulin requirements of this patient throughout the course of her hospitalization. The black arrow (⬇) indicates each cycle of rituximab infusion and 4 days of dexamethasone 40mg.

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