Diabetic Ketoacidosis Without Diabetes

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Context: Type B insulin resistance syndrome is a rare disease that occurs due to the development of autoantibodies to the insulin receptor and can result in either severe insulin resistance and hyperglycemia or, conversely, hypoglycemia. Diabetes mellitus is often severe, usually transient, and poorly responsive to exogenous insulin. Diabetic ketoacidosis is an unusual consequence of this most severe form of transient diabetes mellitus.

Case Description: A 39-year-old Nigerian woman presented with significant weight loss, severe diabetic ketoacidosis, and severe insulin resistance requiring massive doses of exogenous insulin. She was diagnosed with systemic lupus erythematosus and type B insulin resistance syndrome. She was treated by immunomodulation with rituximab and pulse dose dexamethasone, and she entered euglycemic remission after 4 months of treatment. She remains independent of exogenous insulin 1 year later on maintenance azathioprine therapy.

Conclusion: We report a case of severe type B insulin resistance syndrome complicated by severe diabetic ketoacidosis soon after the initial diagnosis of diabetes, despite large doses of exogenous insulin therapy. Our patient achieved euglycemic remission after combination immunomodulation. This case illustrates the severe catabolic state that may occur with high anti-insulin receptor antibody titers and that combination therapy with rituximab and dexamethasone, followed by maintenance azathioprine therapy for 1 year, is an effective treatment approach for the management of type B insulin resistance syndrome.

Case

A 39-year-old Nigerian woman presented with 25-kg weight loss over 6 months associated with new hyperglycemia. Her glycosylated hemoglobin 1 month earlier was 6.3%, but it had risen to 9.8%.

Her past medical history was significant for benign ethnic neutropenia with no history of gestational diabetes, pancreatic disease, endocrinopathy, or autoimmune disease. There was no family history of diabetes or autoimmune disease.

On physical examination, her vital signs were normal, weight was 45 kg, and body mass index was 16 kg/m². She appeared cachectic with marked “velvety” darkening of the skin behind her neck, around her ears and eyes, in both axillae and antecubital fossae, consistent with acanthosis nigricans. A comparison photograph from 1 year earlier confirmed significant weight loss and “new” prominent acanthosis nigricans (Figure 1). No violaceous abdominal striae were noted. Mild upper back acne was present without hirsutism. The remainder of the physical examination was unremarkable.

Diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic syndrome were excluded through laboratory testing at presentation. Glutamic acid decarboxylase, islet cell, and insulin antibody titers were below assay detection. Fasting C-peptide concentration was elevated to 8.56 ng/mL (reference range, 0.80–3.10 ng/mL). Contrast-enhanced computed tomography of the abdomen/pelvis did not reveal evidence of pancreatic or adrenal disease or intra-abdominal malignancy.

The patient was discharged home on metformin and insulin glargine. However, 1 month later she returned with...
strength, further weight loss, and decreased appetite, and her random glucose was 441 mg/dL with an anion gap metabolic acidosis and marked ketonuria. Her glycosylated hemoglobin was 12%. She met all diagnostic criteria for DKA. She was admitted to the intensive care unit on an insulin infusion. Despite receiving 1000 U/d of regular insulin in a continuous infusion, her hyperglycemia persisted. Further laboratory evaluation revealed a normal triglyceride concentration of 72 mg/dL, high-density lipoprotein cholesterol concentration of 36 mg/dL, and low-density lipoprotein cholesterol concentration of 160 mg/dL. Fasting blood glucose was 276 mg/dL, with a corresponding fasting insulin concentration markedly elevated to 300 U/mL (reference range, 2–15 U/mL). Although the insulin assay (ELISA; Quest Diagnostics) could not accurately distinguish between endogenous and exogenous insulin, concomitant fasting serum proinsulin was elevated to 79.9 pmol/L (reference range, 18.8 pmol/L), supporting endogenous hyperinsulinemia. The adiponectin concentration was in the normal range at 9 μg/mL (reference range, 5–37 μg/mL). Screening for common mutations responsible for maturity onset diabetes of the young was negative. Maturity onset diabetes of the young was considered during her initial outpatient evaluation, when her phenotype was still unclear, and prior to the return of her insulin, C-peptide, and proinsulin concentrations. C4 and C3 complement concentrations were low at 16 mg/dL (reference range, 17–48 mg/dL) and 54 mg/dL (reference range, 79–160 mg/dL), respectively. Antinuclear antibody titer was 1:2560 with a speckled pattern. Anti-smith, anti-ribonucleoprotein, and cardiolipin IgM antibodies were also present. Anti-double stranded DNA, anti-Sjögren’s Syndrome-related antigen A, and anti-Sjögren’s Syndrome-related antigen B were negative.

A working diagnosis of systemic lupus erythematosus and type B insulin resistance syndrome (TBIR) was considered. Markedly elevated titers of anti-insulin receptor antibodies (AIRAs) confirmed the diagnosis (Figure 2). The recently published National Institutes of Health (NIH) treatment protocol was initiated (1). Rituximab infusion was started in addition to pulse methylprednisolone therapy. Cyclophosphamide was offered as an additional immunosuppressant, but our patient declined citing concern for possible ovarian toxicity. Concentrated U-500 regular insulin was initiated at a dose of 1 mL U-500 insulin three times daily (1500 U/d). Oral dexamethasone 40 mg/d pulses for 4 days every month in addition to rituximab infusion every 4 months was planned upon discharge.

Four months later, U-500 insulin was tapered without any transition to U-100 insulin. U-500 insulin was completely discontinued 9 months after immunosuppression was initiated, and euglycemia was maintained. The patient had a fasting blood glucose concentration of 106 mg/dL with a corresponding fasting insulin concentration of 48 μU/mL and a proinsulin concentration of 22.1 pmol/L at the time of insulin discontinuation. Her acanthosis nigricans also improved but did not remit entirely. She contin-

Figure 1. The patient 1 year before presentation (A) and during her current presentation (B). The patient has lost a significant amount of weight over 1 year and has had significant darkening of her skin.

Figure 2. This semiquantitative assay based on the ability of the patient’s serum to immunoprecipitate a human insulin receptor antibody shows a strong positive result. Compared to the positive controls at titers of 1:5 and 1:50, the patient’s serum shows significantly darker bands, indicating the presence of large amounts of anti-insulin receptor antibodies.
ues to be followed closely on daily azathioprine maintenance immunosuppression with no significant hypoglycemia or recurrent hyperglycemia 1 year after presentation.

Discussion

TBIR is a rare disorder caused by polyclonal IgG autoantibodies to the insulin receptor. The exact prevalence is unknown. The largest longitudinal cohort has been reported from the NIH (2). There is no pathognomonic clinical feature defining the diagnosis. However, the biochemical triad of markedly elevated fasting insulin concentrations, hyperadiponectinemia, and low/normal fasting triglyceride concentrations in a typically lean individual with acanthosis nigricans and an underlying autoimmune disease should raise clinical suspicion (3, 4). The low/normal triglyceride concentration and hyperadiponectinemia are clues that help distinguish this condition from more common conditions associated with insulin resistance (3, 4). Hyperadiponectinemia in TBIR is postulated to result from hypersecretion of adiponectin or decreased adiponectin clearance, but the exact mechanism is not yet established. Hyperadiponectinemia is likely a reflection of a robust compensatory mechanism directed to increase insulin sensitivity in the setting of a hypofunctioning insulin receptor (4). The average age at diagnosis is 40 years, and the disease is more common among women and African Americans. Systemic lupus erythematosus is the most commonly reported concomitant autoimmune disorder. TBIR may also represent a paraneoplastic manifestation of certain malignancies including multiple myeloma or Hodgkin’s lymphoma. Mortality rates have traditionally been reported to be >50% within 10 years of diagnosis, even among patients achieving remission (2).

Refractory hyperglycemia is present in the majority of patients with TBIR. DKA rarely occurs and may signify a more severe presentation of disease and potentially markedly elevated AIRA. Remarkably, these patients have marked endogenous hyperinsulinemia but, given AIRA insulin receptor antagonism, can present with impaired insulin signaling to such an extent as to develop the consequences of severe insulin deficiency with ketogenesis and acidemia. We postulate that DKA occurred in our patient due to what may be construed as a severe “pseudo” insulin-deficient state, where extremely elevated AIRA titers resulted in markedly impaired insulin signaling, despite sufficient circulating endogenous insulin. The hyperglycemic phase of TBIR is often transient, but it is usually associated with significant catabolism such that most individuals are nonobese at the time of diagnosis (body mass index <30 kg/m²). Almost 30% of individuals develop spontaneous hypoglycemia during the course of the disease (2). Rarely, hypoglycemia occurs without hyperglycemia, but severe fasting hypoglycemia may occur, which may underlie the high reported mortality rates. The pathophysiological mechanism whereby AIRAs interact with the insulin receptor in humans is not completely understood, but receptor activation is clearly impaired as a direct result of the circulating AIRA. This may result from impaired insulin receptor recycling. Based on rodent studies, it may be postulated that at high concentrations the antibody acts as an antagonist at the receptor, whereas at low titers it has a stimulatory effect, resulting in varying degrees of hyperglycemia and/or hypoglycemia. Hypoglycemia may result from dose-dependent activation of the insulin receptor by AIRAs. Fasting rodents who were injected with an AIRA experienced hypoglycemia within 2 hours, and hypoglycemia persisted up to 24 hours, suggesting an acute insulin-like effect when administered periodically. In contrast, fed rodents who received AIRAs in high doses for many days paradoxically became hyperglycemic, presumably due to desensitization of the receptor (5, 6).

There are no placebo-controlled trials to guide therapy. However, the NIH has recently proposed a standardized therapeutic regimen consisting of a combination of rituximab infusion every 3–4 months, monthly high-dose pulse glucocorticoids, and cyclophosphamide, which has resulted in a drastic reduction in the previously reported mortality rates (1, 7). Rituximab, an antibody against the cell surface molecule CD-20 expressed by B cell progenitors, inhibits production of new antibodies working as an immunomodulator. Pulse glucocorticosteroids suppress activity of pre-existing AIRA-producing plasma cells. Cyclophosphamide is an adjunct agent augmenting suppression of B- and T-cell function. Mycophenolate mofetil, cyclophosphamide, azathioprine, and various glucocorticoids as monotherapy or combinations are of questionable consistent benefit. In some cases, cyclosporine may suffice in those who cannot tolerate cyclophosphamide (8, 9). Unfortunately, both cyclophosphamide and cyclosporine can result in ovarian toxicity. The role of insulin therapy in the hyperglycemic phase is amelioration of severe catabolism, rather than achievement of strict euglycemia, which is often extremely difficult to attain. U-500 concentrated regular insulin is often beneficial, with insulin doses frequently in excess of 5000 U/d (2). U-500 insulin typically has a similar half-life to NPH insulin, but in the setting of high AIRA titers, it has been reported to have a deranged and prolonged action, which may be explained by impaired receptor-mediated insulin degradation (10, 11). As a result, once fasting glucose levels normalize, the dose needs to be proactively reduced.
This case emphasizes the importance of correctly identifying the phenotype of patients with new-onset diabetes, and it is another example of short-term success (1 year) in achieving remission with a slightly modified NIH combination treatment protocol. It is currently unknown whether maintenance azathioprine therapy is essential to prevent recurrence or how long maintenance therapy should continue. It is important to recall that our patient was not treated with cyclophosphamide, given her concern for ovarian toxicity and the desire to preserve future fertility. Based on compelling data from the NIH, combination therapy, including cyclophosphamide, is recommended to reduce the risk of hypoglycemia and, by extension, mortality. Most patients in the NIH cohort suffered from lupus nephritis, for which cyclophosphamide therapy is indicated. Our patient did not have lupus nephritis so cyclophosphamide may not have been essential in her management, and this suggests that modification of the published NIH treatment approach may be appropriate for certain individuals. This case illustrates that remission can be achieved without the use of cyclophosphamide or cyclosporine in certain individuals with TBIR. This is crucial, considering that this disease mostly affects women of reproductive age and ovarian preservation is an important aspect to consider.

TBIR is an autoimmune disorder that may result in both autoimmune-mediated hypoglycemia and the most severe form of “transient” diabetes mellitus, and it may even result in DKA.

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