Case Report

SEVERE INSULIN RESISTANCE WITH DIABETIC KETOACIDOSIS AFTER BRENTUXIMAB TREATMENT

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ABSTRACT

Objective: To increase awareness of unusual inflammatory and other responses including severe insulin resistance (IR) associated with the use of targeted immunotherapies such as brentuximab.

Methods: We report the case of a man without any previous diagnosis of diabetes who developed diabetic ketoacidosis complicated by severe IR (unresponsive to >600 units of intravenous insulin per hour) after receiving brentuximab for Hodgkin lymphoma.

Results: Autoantibodies to the insulin receptor were not detected in the patient's serum, thus excluding a diagnosis of type B IR.

Conclusion: We hypothesize that brentuximab administration led to a rare reaction leading to systemic cytokine release with extreme IR in our patient. **(AACE Clinical Case Rep. 2020;6:e98-e100)**

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Abbreviations:
DKA = diabetic ketoacidosis; **IL** = interleukin; **IR** = insulin resistance; **IV** = intravenous

INTRODUCTION

Use of targeted immunotherapies including brentuximab have changed the landscape in cancer therapeutics but have also unveiled new drug toxicities from inducing inflammation and autoimmunity. We report a case of a patient who, after receiving his first dose of brentuximab, was admitted with new diabetic ketoacidosis (DKA) and severe insulin resistance (IR).

CASE REPORT

A 54-year-old Caucasian man with human immunodeficiency virus (CD4 count 199, viral load undetectable) on antiretroviral therapy and Hodgkin lymphoma but no history of diabetes or hyperglycemia, received his first dose of brentuximab for treatment of lymphoma. One week later, the patient presented to the emergency room with fatigue, polydipsia, and polyuria. Initial tests showed his glucose was 25.0 mmol/L or 450 mg/dL (normal ranges are 3.9 to 11.0 mmol/L and 70 to 198 mg/dL, respectively), bicarbonate was 7 mmol/L (normal range is 22 to 32 mmol/L), and serum ketones were 11.20 mmol/L (normal range is 0.02 to 0.27 mmol/L).

He was diagnosed with DKA and admitted to the intensive care unit. His physical exam was notable for a body mass index of 37 and no acanthosis nigricans, lipodystrophy, or signs of cortisol excess. Standard DKA protocol treatment was initiated with intravenous (IV) hydration and IV insulin. The patient's preadmission hemoglobin A1c was 5.4% (36 mmol/mol). The initial C-peptide

was 5.02 nmol/L (normal range is 0.27 to 1.02 nmol/L) and the insulin level was 6,024.1 pmol/L (normal range is 23.7 to 158.6 pmol/L) prior to IV insulin administration. Glutamic acid decarboxylase-65 antibody and insulin autoantibody were negative. The patient had no previous oral glucose tolerance testing prior to admission, and his total cholesterol was 112 mg/dL (normal range is <200 mg/dL), triglycerides were 141 mg/dL (normal range is <150 mg/dL), low-density lipoprotein was 65 mg/dL (normal range is <130 mg/dL), and high-density lipoprotein was 19 mg/dL (normal range is >39 mg/dL).

Within 12 hours of admission, the IV insulin had been titrated to >600 units/hour with only minor decreases in glucose to 21.9 mmol/L (394 mg/dL) and ketones to 7.35 mmol/L. The patient received 1,748 units of IV insulin in the first 24 hours of admission and 10,725 units in the following 24 hours. He subsequently developed cardiovascular, respiratory, and renal failure, while his lactate level rose to >28 mmol/L (normal range is 0 to 2 mmol/L). Regarding interleukin (IL) levels, his IL-6 concentration was 2,170 pg/mL (normal range is ≤5 pg/mL), the soluble IL-2 receptor level was 858.9 U/mL (normal range is <116.8 U/mL), the IL-8 concentration was 755 pg/mL (normal range is ≤5 pg/mL), and the IL-10 concentration was 123 pg/mL (normal range is ≤18 pg/mL). His tumor necrosis factor-α concentration was 100 pg/mL (normal range is ≤22 pg/mL), and a workup for infectious etiologies did not reveal any bacterial or fungal infections.

Due to the severity of his illness, the patient was treated for suspected type B IR and cytokine storm with 2 doses of IV methylprednisolone (1 gram each) followed by plasmapheresis. Twelve hours after plasmapheresis, the patient's insulin requirements decreased from 600 units/hour to 75 units/hour. Unfortunately, the patient ultimately died from multiple organ failure approximately 72 hours after admission.

Autopsy revealed a normal-appearing pancreas, a known malignant abdominal mass, and no infectious sources or major emboli as explanations of death. Samples of the patient's serum, which were collected before and after plasmapheresis, were analyzed after death. Both samples were tested for the presence of anti-insulin receptor autoantibodies by immunoprecipitation as previously described (1,2), and the results were negative.

DISCUSSION

This is the first report to our knowledge of the development of extreme IR in a patient without any previous diagnosis of diabetes or hyperglycemia after brentuximab infusion. Brentuximab is an anti-CD30 monoclonal antibody drug conjugate approved in 2011 for use in Hodgkin lymphoma. Brentuximab targets cells expressing CD30, leading to subsequent internalization of the anti-tubulin agent (monomethyl auristatin E) and cell death. CD30 is expressed on Hodgkin lymphoma cells but also is found on T-regulatory cells and on activated T cells producing Th2-type cytokines.

One previous case of severe cytokine release has been reported with brentuximab treatment (3). The reported case had a similar presentation to our patient with vasopressor-dependent shock, oliguria, and increase in inflammatory cytokines. Unlike our patient, the reported case patient had a reaction to brentuximab within 60 minutes of the infusion, survived, and did not develop severe IR. There may be milder cases that have been unreported. In fact, an August 2019 search of the U.S. Food and Drug Administration Adverse Events Reporting System (4) showed 70 reported reactions of "hyperglycemia" or "blood glucose increase", 10 reports of "DKA", and 7 cases of "cytokine release syndrome" or "cytokine storm".

Initially, we also suspected the presence of an insulin antibody or type B IR due to the massive amount of insulin required to treat the DKA, though specific antibodies to insulin and the insulin receptor were not identified in this patient. However, given the unusual presentation in this case, the patient may have developed antibodies that were not detected through traditional assays. We speculate that brentuximab administration led to a rare reaction leading to systemic cytokine release with extreme IR in our patient. We hypothesize that the combination of abnormal T cell function due to human immunodeficiency virus infection and possible attenuation of T cell regulation via the CD30 receptor led to an unleashing of a severe autoimmune response that included antibodies to the insulin receptor and a cytokine cascade, which ultimately resulted in the patient's death.

Our proposed mechanism for brentuximab contributing to severe cytokine release and extreme IR remains speculative. CD30 is part of the tumor necrosis factor receptor superfamily expressed on T-regulatory cells. It plays a role in protection from allograft rejection (5) and in autoimmune diseases such as rheumatoid arthritis (6). Depletion of CD30 can lead to compromise of negative selection in the thymus and increased T cell autoreactivity; blockade of the CD30 pathway reduces protection by T-regulatory cells from proinflammatory cytokine accumulation and T cell apoptosis (7). Interestingly, signaling through CD30 has also been shown in murine models as one pathway to protect against the development of autoimmune diabetes (8).

Other rare disorders have been described with brentuximab which may be related to immunomodulation or severe inflammation, including progressive multifocal leukoencephalopathy (9-11) and toxic epidermal necrolysis (12). This may point to a pattern in which brentuximab, in select patients, is related to a decrease in immune surveillance and an unleashing of autoimmunity.

CONCLUSION

We hope this case report increases clinician awareness and vigilance for unusual inflammatory and autoimmune manifestations, especially as use of targeted immunotherapies for cancers increase. More case reports and clinical trials will be needed to uncover the genetic, immune, and cancer profiles that may increase susceptibility to rare inflammatory or immune-related events from targeted immunotherapies.

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DISCLOSURE

The authors have no multiplicity of interest to disclose.

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