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Case Report

Mycophenolate Mofetil and Plasmapheresis: A Treatment Option for Severe Insulin Resistance caused by Insulin Antibodies

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ABSTRACT

Objective: Insulin antibody (IA)-mediated insulin resistance (IR) is a rare condition for which immunosuppressive regimens have been described. However, these raise the risk of infection, and the drugs may not be effectively metabolized in patients with liver disease. A 61-year old male with type 2 diabetes mellitus and antibody-mediated IR who required >800 units of daily insulin presented with acute decompensation of his preexisting cirrhosis from recurrent diabetic ketoacidosis. Laboratory tests confirmed an IA level of >625 μU/mL (reference: <5.0 μU/mL).
Methods: Centrifugal plasmapheresis and mycophenolate mofetil (MMF) were used to treat the patient to achieve glycemic control. Continuous glucose monitoring was implemented to monitor glycemic control pre- and posttherapy. Laboratory evaluation included levels of IA, C-peptide, insulin-like growth factor-1, growth hormone, salivary cortisol, zinc transporter 8, glutamic acid decarboxylase 65-kilodalton isoform antibody, and islet-cell antibodies.
Results: We initiated MMF followed by 5 sessions of plasmapheresis, leading to an overall 77.3% reduction from pretherapy insulin requirements after 6 months without further episodes of diabetic ketoacidosis or infection. The cirrhosis stabilized, and there was an improvement in HbA1C from 8.7% (72 mmol/mol) to 6.6% (49 mmol/mol) and time in euglycemic range from 30% to 61%.
Conclusion: This is the first report of MMF and centrifugal plasmapheresis use to mitigate the effects of IA-mediated IR in a patient with cirrhosis. We recommend further studies to determine the utility of this treatment to improve care for patients at high risk for IA-mediated IR.

Introduction

Insulin antibodies (IAs) slow the rise of plasma free insulin after subcutaneous injection, resulting in postprandial hyperglycemia and severe insulin resistance (IR).[1,2] Corticosteroids, immunosuppressants, and double-filtration plasmapheresis have been described to deplete antibody levels to achieve glycemic control in the treatment of IA-mediated IR. However, they have not been studied in patients with underlying liver disease or a higher risk of infections.[3-10] Furthermore, centrifugal plasmapheresis to rapidly deplete circulating IAs has not been previously described in patients with IA-mediated IR and cirrhosis. Mycophenolate mofetil (MMF) is an immunosuppressant that inhibits T- and B-cell proliferation and may reduce IA production.[5,11] We describe a case of IA-mediated IR in a patient with cirrhosis and type 2 diabetes mellitus (T2DM) resulting in recurrent diabetic ketoacidosis (DKA) leading to acute decompensation of his cirrhosis and a treatment approach using a combination of MMF and centrifugal plasmapheresis to achieve glycemic control.

Case Report

A 61-year-old male with a body mass index of 26 kg/m^2 and T2DM, hepatitis B, and nonalcoholic steatohepatitis cirrhosis presented to the emergency room with recurrent DKA and severe IR.

Abbreviations: CGM, continuous glucose monitoring; DKA, diabetic ketoacidosis; FSG, fingerstick glucose; IA, insulin antibody; IR, insulin resistance; MELD, Model for End-Stage Liver Disease; MMF, mycophenolate mofetil; TDD, total daily dose; T2DM, type 2 diabetes mellitus; U-500, concentrated human regular insulin 500 U/mL.

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The patient was diagnosed with T2DM at age 40 and was initially treated with glyburide/metformin 5/500 mg twice daily and sitagliptin 100 mg daily. He was diagnosed with cirrhosis at age 51 based on abnormal liver enzymes and findings of nodular liver morphology, splenomegaly, and esophageal varices on computed tomography scanning. He started insulin at 53 years old with varying regimens over the subsequent years. He had no exposure to animal-derived insulin preparations. His insulin exposure included insulin detemir, insulin degludec, insulin lispro, insulin glargine, and concentrated human regular insulin 500 U/mL (U-500). After his first admission for DKA at an outside institution, there was a dramatic rise in his total insulin requirements, with his regimen consisting of insulin degludec (160 units daily) and U-500 (100 units) with meals. His cirrhosis, which had been stable for over 10 years, became acutely decompensated after this DKA episode, leading to refractory ascites, severe muscle wasting, and hepatic encephalopathy, eventually requiring a transjugular intrahepatic portosystemic shunt. During his second admission for DKA, which occurred 6 months later, he required up to 110 units/hour of an insulin drip with concurrent dosing of up to 50 units every 3 hours of lispro and 90 units twice daily of insulin glargine for DKA resolution. His HbA1C at the time was 8.7% (72 mmol/mol). He was discharged on insulin degludec (190 units daily) and U-500 (100 units) with meals.

Laboratory workup revealed an elevated IA level >625 μU/mL (reference: <5.0 μU/mL) measured using an insulin-I125 binding capacity assay. C-peptide was 2.9 ng/mL (reference: 0.9-7.1 ng/mL), and serum glucose was 86 mg/dL. Zinc transporter 8, glutamic acid decarboxylase 65-kilodalton isoform antibodies, and islet-cell antibodies were negative. Other results included insulin-like growth factor-1, 52 ng/mL (reference: 54-194 ng/mL); growth hormone, 4.5 ng/mL (reference: 0.0-10.0 ng/mL); and normal midnight salivary cortisol testing. His Model for End-Stage Liver Disease (MELD) score at initial presentation was 17, increased from 15 three months prior.[12]

The patient was readmitted with presumed spontaneous bacterial peritonitis 2 months later, which was further complicated by a third occurrence of DKA. His MELD score increased to 25. Due to acute decompensation of his cirrhosis, the patient was evaluated for a potential liver transplant, but adequate glycemic control was required to be considered a candidate. He required up to 125 units/hour of an insulin drip, totaling >600 units of insulin for DKA resolution. He was discharged on 200 units of insulin degludec daily and U-500 (220 units) with meals. However, fingerstick glucose (FSG) levels remained uncontrolled, ranging from 170 to 300 mg/dL. The finding of an elevated IA level led to discussions between Endocrinology, Liver Transplant, and Transfusion Medicine personnel to implement a regimen involving MMF for generalized immunosuppression in combination with centrifugal plasmapheresis for the rapid removal of IA. This regimen would minimize the risk of infection while decreasing circulating IA levels both acutely and in the long term.

The patient started MMF (500 mg twice daily), with improvement in FSG in the range of 70-220 mg/dL. After 1 month of therapy with MMF, he was admitted to a monitored unit for a series of 5 plasmapheresis sessions with a single plasma volume exchange via central venous access every other day over 10 days with 5% albumin replacement using the Spectra Optia Apheresis System (Terumo BCT). The patient was placed on an insulin drip with hourly FSG testing to allow for rapid insulin titration in the event of any hypoglycemia during antibody clearance. He was transitioned to glargine and U-500, the doses of which were reduced daily due to hypoglycemia.

He continued MMF throughout the plasmapheresis course, with dosing following each session, and continued MMF monotherapy postdischarge. Continuous glucose monitoring (CGM) was utilized to monitor glycemic control pre- and posttherapy.

After 1 month of MMF alone, his total daily dose (TDD) of insulin was reduced by 27.3%. With the addition of 5 sessions of plasmapheresis, his TDD was reduced by an additional 29.7%, leading to a total reduction of 57.0% from pretherapy requirements. His insulin regimen currently includes 85 units U-500 with breakfast and lunch and 25 units of lispro with dinner, approximately 6 months after starting therapy, representing an overall 77.3% decrease from his pretherapy insulin requirements (Fig. 1). His IA titer remains >625 μU/mL. His HbA1C improved to 6.6% (49 mmol/mol), and time in range (defined as glucose levels between 80 and 180 mg/dL) by CGM improved to 61%, compared with 30% prior to treatment. Clinically, he has not had any further episodes of DKA or any more admissions for cirrhosis-related complications or infections. While he remains on MMF, his MELD score has decreased to 10, obviating the need for a liver transplant.

Discussion

We present a patient with T2DM who presented with progressively increasing insulin requirements and recurrent DKA with

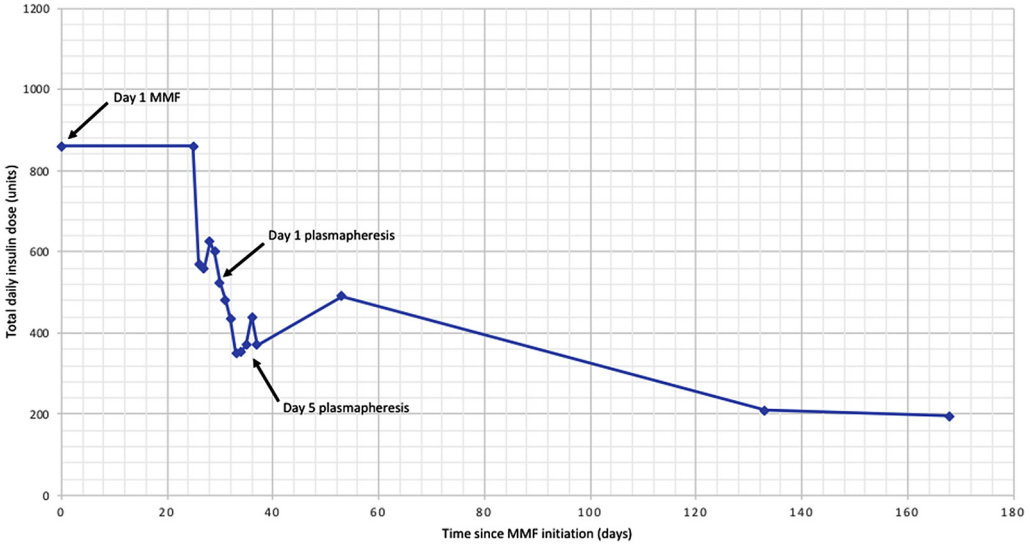

Fig. 1. Graph showing the decrease in total daily insulin dose over time after MMF initiation (day 1). Further reduction in insulin requirement is demonstrated after plasmapheresis occurring on days 29 through 37. *MMF* = mycophenolate mofetil.

associated decompensation of his pre-existing cirrhosis. High titers of IA were the suspected etiology of his presentation. MMF and centrifugal plasmapheresis led to significant improvement in his glycemic control and restored him to a compensated state of cirrhosis.

Despite changes made to the insulin manufacturing process, exogenous insulin can still lead to immunologic complications, such as IA production.[1] The presence of IA can be associated with severe IR in rare cases, but the mechanism underlying this syndrome is not yet fully understood.

The patient's severe IR due to IA caused recurrent DKA and likely contributed to acute decompensation of his cirrhosis. This hypothesis was supported by the drastic reduction in his TDD requirement and stabilization of his liver disease following plasmapheresis and 6 months of treatment with maintenance MMF. While his IA titer remains >625 μU/mL, it should be noted that because this assay is known to demonstrate considerable variability and is poorly associated with clinical status, glycemic control is a better overall indication of therapeutic effectiveness.[13] His TDD requirements have remained stable for several months without the need for repeat plasmapheresis, highlighting the long-lasting effects of this treatment approach.

Various immunosuppressive regimens have been described to treat IA-mediated IR, yet there is no consensus on the optimal treatment for these patients. This entity has not been described before in patients with cirrhosis. The patient in this case highlights additional factors to consider when there is underlying cirrhosis, including increased infection risk and impaired hepatic clearance of certain medications. The approach using MMF and plasmapheresis to deplete IA may be a particularly efficacious method to improve hyperglycemia in patients with IA-mediated IR. Furthermore, it could help to achieve glycemic control without requiring the use of corticosteroids or multidrug immunosuppression, thereby avoiding any potential additive infection risks.[14] MMF has increasingly been used to treat autoimmune conditions. It inhibits inosine monophosphate dehydrogenase, the enzyme responsible for the synthesis of guanine nucleotides for De Novo purine synthesis. As a result, T- and B-cell proliferation is blocked, and antibody production declines.[11] MMF was selected as part of this patient's treatment plan to decrease lymphocyte proliferation, which, in turn, would reduce IA production. Plasmapheresis was added to reduce circulating antibodies.[9,11,15] Examples to date of successful plasmapheresis in the setting of IA have focused on double-filtration plasmapheresis, a technique that is currently only available in Europe.[15] Here, we demonstrate the effectiveness of centrifugal plasmapheresis using the FDA-approved Spectra Optia Apheresis System.

This approach was efficacious, as evidenced by the overall 77.3% decrease from the patient's pretreatment insulin requirements, HbA1C improvement to 6.6% (49 mmol/mol), and an increase to 61% time in range by CGM. Furthermore, the patient has not had any further hospitalizations for DKA or cirrhosis-related complications, and the MELD score has decreased to 10. He has not experienced any significant infections since starting treatment and remains clinically well to date.

Conclusion

While no standard treatment has been established for IA-mediated IR, the approach of using plasmapheresis and MMF to deplete circulating IA and prevent further IA production may safely achieve glycemic control in vulnerable populations that are at increased risk of infection.

Acknowledgment

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Disclosure

The authors have no multiplicity of interest to disclose.

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