Extreme Insulin Resistance From Insulin Antibodies (Not Insulin Receptor Antibodies) Successfully Treated With Combination Immunosuppressive Therapy

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A relationship between insulin resistance (IR) and insulin antibodies (IAs) was first described in the 1950s and was thought to be due to the use of nonhuman insulins (1). Since the introduction of human insulin, the presence of IAs and consequent IR was felt to be clinically insignificant (2).

The presence of high levels of IAs, associated with random hypoglycemia in insulin-naive patients, is termed insulin autoimmune syndrome or Hirata disease (3,4). In some cases, postprandial hyperglycemia (insulin bound to antibody) and fasting hypoglycemia (disassociation of bound insulin from antibodies) are both described as mechanisms of disease (5). These IAs are thought to be of low affinity and never lead to IR.

We present the case of a 65-year-old man with type 2 diabetes and extreme IR who was found to have IAs. The patient was never exposed to nonhuman insulins and was glutamic acid decarboxylase antibody (hallmark biomarker for type 1 diabetes) negative (6).

The patient's insulin regimen consisted of concentrated insulin (U-500) at 930 units/day; hemoglobin A_{1c} (HbA_{1c}) was 10%. Because of the many signs of IR, including acanthosis nigricans, the patient was assessed for type B insulin resistance with measurement of antibodies to the insulin receptor (6). Antibodies to the insulin receptor were undetectable; however, an insulin antibody titer was elevated at 8.7 units/mL (normal $<$0.4 units/mL) (Fig. 1*A*).

We noticed a modest decrease in insulin requirements with steroid treatment (1 month of prednisone 10 mg). However, because of the side effects of long-term glucocorticoid use, we offered the patient treatment with anti-CD20 monoclonal antibody (rituximab) aimed at controlling B-cell immune responses.

The patient received two rituximab infusions 1 month apart. The patient's insulin requirements significantly decreased to 220 units/day. A repeat IA titer after the first infusion was 7.6 units/mL (1:2 dilution was 6.5 units/mL) (Fig. 1*A*). A subsequent IA titer was even lower at 5.0 units/mL (1:2 dilution was 2.5 units/mL) (Fig. 1*A*). The patient's glucose control was steadily improving, with average insulin requirements $<$200 units/day (HbA_{1c} 8.7%) at 2 months. At 3 months after the second infusion of rituximab, the patient began to experience poor glycemic control again (HbA_{1c} 13.1% at 6 months).

The patient was then started on mycophenolate mofetil (MMF) (Fig. 1*B*). Repeat IA titers were 3 units/mL at 2 weeks and 0.4 units/mL at 1 month after the start of MMF (Fig. 1*A*). The patient also had remarkable improvement in glycemic control, with a $>$50% decrease in daily insulin requirements (Fig. 1*B*). After 5 months, glycemic control started to deteriorate again. A third dose of rituximab was given while the patient was on MMF. The IA titer returned low at 0.4 units/mL 2 weeks after the infusion, and total daily insulin requirements decreased again to 325 units daily (Fig. 1*A* and *B*). The patient is currently being followed on MMF alone.

Although rituximab or MMF has been used to treat anti-IA syndromes (7), this is the first report of "extreme" IR due to IAs successfully treated with combination immunosuppressive therapy. Our findings raise the question of the need for screening for the presence of IAs at least in similar patients.

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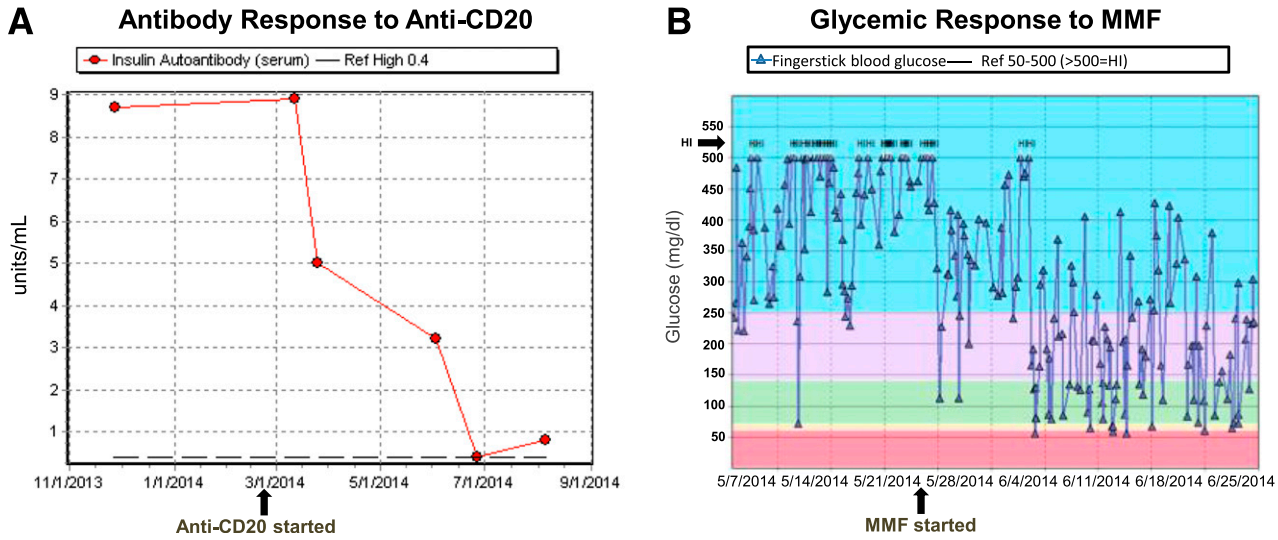

Figure 1—*A*: Decreasing insulin antibody levels after anti-CD20 (rituximab) therapy. *B*: Improved glycemic control after starting MMF therapy.

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